Persons using assistive technology may not be able to fully access information in this file. For assistance, e-mail biolincc@imsweb.com. Include the Web site and filename in your message.

PVDOMICS MANUAL OF OPERATIONS TABLE OF CONTENTS – as of 05/04/2023		
Chapter #	**Manual of Operations Chapters**	**Version Date**

Chapter 4	General Recruitment Issues and Strategies
	• Consent Templates for Center Customization:
	  • Main/Comparator Groups Consent Template
	  • Healthy Volunteers Consent Template
	  • Biobank Consent Template
	• Genetics Discussion: Script for PH/Comparator and Control Groups Webinar
	• Documenting reasons for not approaching participants
	• Documenting reasons why participant did not consent
		11/02/2016

Chapter 5	Adjudication and Recruitment Committee • WHO Group Classification • Recruitment • Process • Appendix 1-Main/Comparator WHO Group Classification	11/05/2016
Chapter 6	Forms Completion, Data Entry and Computing Appendix A: Installing Java on PC Secure Portal Set-up Instructions Secure Document Transfer	11/28/2017 05/04/2018 11/03/2017
Chapter 7	Reporting of Incidental Findings	05/17/2016
Chapter 9	Quality Control and Site Monitoring	01/19/2017
Chapter 10	Protocol Changes	05/24/2016
Chapter 11	Publications and Presentations Policy Publications and Guidelines Addendum Appendix 11.1: Signature Page for Publications and Presentations Policy	05/05/2016 05/04/2023
Chapter 12	Ancillary Studies Policy	02/25/2016
Chapter 30	Participant Study Visits	03/03/2017
Chapter 31	Clinical Center Local Labs and Data Reporting	10/19/2016

PVDOMICS MANUAL OF OPERATIONS TABLE OF CONTENTS – as of 05/04/2023		
Chapter #	**Manual of Operations Chapters**	**Version Date**
Chapter 32	HRQOL Questionnaires • SF-36 • Minnesota Living with Heart Failure (MLHF) Questionnaire • EmPHasis-10	06/02/2016
Chapter 33	Biorepository Clinical Center Blood Collection Overview And Blood Drawing Procedures	05/23/2018
Chapter 34	Biorepository Clinical Center Blood Processing and Shipping Appendix 34.1: PVDOMICS OMICS Blood Collection 1: Processing, Aliquoting, Recording and Storing of Biospecimens Appendix 34.2: PVDOMICS OMICS Blood Collection 2: Processing, Aliquoting, Recording and Storing of Biospecimens Appendix 34.3: PVDOMICS OMICS Blood Collection: Healthy Controls Processing, Aliquoting, Recording and Storing of Biospecimens	05/23/2018 01/26/2017 04/11/2017 04/11/2017
Chapter 35	Biorepository Core Urine Specimens Collection, Processing and Shipping Appendix 35.1: Template for Female Urine Collection Instructions Appendix 35.2: Template for Male Urine Collection Instructions	09/21/2017
Chapter 36	Waist-to-Hip Circumference Measurements	10/25/2016
Chapter 37	Bioelectrical Impedance (BIA) Measurements Appendix 1-Tanita SC-240 Body Composition Analyzer	01/14/2017
Chapter 38	Blood Pressure and Vital Signs Measurements	10/13/2016
Chapter 39	Six-Minute Walk Test Summary Sheet of Recent Changes	06/15/2018 06/15/2018
Chapter 40	Electrocardiogram (ECG)	01/26/2017
Chapter 41	Clinical Center Sleep Study Processing and Review Appendix 1: General Participant Instructions Appendix 2: PAP Participant Instructions Appendix 3: Supplemental Oxygen Participant Instructions Nox T3 Ordering Supplies Information	02/03/2017 (App1- 01/17/2017 App2 & 3: 10/12/16) 11/30/2017

PVDOMICS MANUAL OF OPERATIONS TABLE OF CONTENTS – as of 05/04/2023		
Chapter #	**Manual of Operations Chapters**	**Version Date**
Chapter 42	Sleep Study Core	08/31/2016
Chapter 43	Arterial Blood Gases	01/25/2016
Chapter 48	Adverse Events and Serious Adverse Events Reporting	12/14/2016
Chapter 50	Pulmonary Function Testing Overview • PF Lab Exam	10/12/2016
Chapter 51	Clinical Centers PFT-Spirometry	10/12/2016
Chapter 52	Clinical Center PFT-Lung Volumes Plethysmography (Body Box)	10/12/2016
Chapter 53	Clinical Center PFT-Single-Breath Carbon Monoxide Diffusing Capacity (DLCO)	10/05/2017
Chapter 55	Lung Physiology Core PFT QC Parameters	10/12/2016
Chapter 60	ECHO Testing Overview and General Information	03/02/2017
Chapter 70	Cardiac MRI Testing Overview and General Information • CMR Acquisition Reference Guide	01/25/2017
Chapter 80	Clinical Center Chest CT Imaging: Ctr 11 Brigham & Women's Scanner Specifications Ctr 21 Columbia Scanner Specifications Ctr 22 Cornell Weill Scanner Specifications Ctr 31 Johns Hopkins Scanner Specifications Ctr 41 Mayo Clinic Scanner Specifications Ctr 51 Univ. of Arizona Scanner Specifications Ctr 61 Vanderbilt Scanner Specifications	11/03/2016 07/01/2019
Chapter 81	Lung Imaging Core Processing and Review	08/17/2016
Chapter 90	Ventilation/Perfusion (VQ) Scan	06/27/2017
Chapter 100	Clinical Center Right Heart Catheterization (RHC)	05/09/2018
Chapter 101	Clinical Center RHC Data Documentation and Transfer	01/31/2017

PVDOMICS MANUAL OF OPERATIONS TABLE OF CONTENTS – as of 05/04/2023		
Chapter #	**Manual of Operations Chapters**	**Version Date**
Chapter 110	Clinical Center Non-Invasive Cardiopulmonary Exercise Test (CPET) Appendix 1 Modified Borg Scale Appendix 2 Ramp Protocol Selection Appendix 3 Non-Invasive CPET Worksheet Appendix 4 Goldman Specific Activity Scale Appendix 5 CPET Calculations	06/13/2018
Chapter 111	Clinical Center Invasive Cardiopulmonary Exercise Test (iCPET)	06/13/2018

CHAPTER 4. GENERAL RECRUITMENT ISSUES AND STRATEGIES

4.1 Consent Forms

PVDOMICS has three informed consents: (1) main consent for participants with pulmonary vascular disease or those at-risk or suspected to have pulmonary vascular disease, (2) healthy controls consent, and (3) biobank consent for permission to retain and use samples from PVD and controls remaining at the end of the PVDOMICS study in future studies. All participants in PVDOMICS will be asked to sign two consent forms: PVD and at-risk PVD will be asked to sign (1) and (3), and healthy controls will be asked to sign (2) and (3). The main consent (1) and healthy control consent (2) describe the goals of PVDOMICS and are designed to allow sharing of data and samples across centers and with the DCC. The biobank consent (3) requests permission to use samples collected in this study in the future by researchers, who may be other than PVDOMICS researchers and/or possibly studying other diseases.

4.2 Consent Templates for Center Customization

The OSMB approved template consents will be customized by each site into the appropriate format for site-specific Institutional Review Boards (IRB). Once the consents are ready, they will be sent to the DCC for review, followed by NHLBI for review. Changes in consents will be provided to the study site. Once changes are made, consents may be submitted to their IRB. As soon as the site consent forms are IRB approved, they will be provided to the DCC for documentation of approval of the study. Recruitment will start at each site upon IRB-approval.

4.3 Recruitment

Recruitment is essential for the success of this study. Consider the following points when recruiting participants:

- Emphasize the importance of the study.
- Emphasize close follow-up of tests and results during the study, and the availability of findings to the participant.
- Explain that a stipend for participation will be provided.
- Approach potential participants more than once, if necessary.
- Be courteous, attentive and professional.
- Show interest and enthusiasm in the study.
- Make sure that potential participants fully understand the potential risks and benefits of the study. Explain all aspects of the study detailed in the informed consent. Make sure that participants understand the information you present. Allow the participant enough time to consider and sign the informed consent document.
- Emphasize that participation in the study will advance medical knowledge. Potential participants may be told, “We don’t know the answers, but there is a chance to help us all learn more about pulmonary vascular diseases.”

- Consider giving the consent to a potential participant for them to look over and then meet with them after they have had a chance to review the consent at home as this is a detailed protocol with multiple procedures and tests.

Some potential participants will be motivated by stressing that the results may benefit future generations of patients with lung diseases and that they may have a chance to help society.

4.4 Provider Cooperation

Providers are busy, and it is not their responsibility to recruit participants for this study. But you can ask for their support.

- Take the initiative. Do not wait for providers to contact you regarding potential participants.
- Mail a study brochure with a personal letter to providers requesting their cooperation.
- Ask providers for permission to contact their patients and ask them to encourage their patients to enroll.
- Reassure providers that their patients will be seen by investigators for study purposes only.
- Let the providers know that you will inform them of the participant's course in the study.

4.5 Contact with Providers

Direct involvement of site investigators with healthcare providers is important for successful recruitment. Possible strategies include:

- Formal and informal presentations (Grand rounds, research conferences, house staff rounds, clinic in-services)
- Distribution of brochures in clinics
- Direct conversations with physicians and other caregivers, such as physician assistants, nurse practitioners, and nurses
- Consistent and frequent screening in cardiology and pulmonary and other clinics
- Data base and Electronic Health Record searches and mailings

To promote collaboration, investigators should reassure providers that their patients will be seen by investigators for study purposes and that providers will be informed of the patient's status throughout the study if the participant wishes them to be notified.

4.6 The Study Information, Brochures

All participants will complete measurements, study tests, questionnaires, etc. All assessments will adhere to a standardized protocol and techniques. The net result is uniformity of data and adherence to uniform safety precautions. These data and samples are transferred to the DCC for collation and processing, respectively. The centralized data and samples will be utilized to answer questions approved by the Steering Committee.

Information about the study may be referred to online or printed. Study information and contacts will be on the Pulmonary Hypertension's website: www.phassociation.org. Informational brochures describe in easy-to-understand language the purpose of PVDOMICS and what is expected of the participants. This can be used as a tool to briefly review the study requirements with potential participants upon initial introduction, prior to the screening visit and the actual informed consent process. Sample participant brochures will be available on the study website and may be customized to reflect the local site IRB policies and investigators. This brochure requires approval by your local IRB before it can be distributed to potential participants or providers. The complete study is also registered in clinicaltrials.gov allowing widespread information availability to the public.

4.7 Letters to Patients and Providers

Letters mailed to potential participants require approval by your local Institutional Review Board before it should be distributed to potential participants or providers. Emails, telephone calls and letters may also be useful to engage providers in the study. These should be done according to your local policies and procedures.

4.8 Approach to Recruitment

Each site will develop a **recruitment plan** that may use some or all of the following recruitment strategies: clinic-based recruitment; referrals from providers; community-based recruitment campaigns.

Clinic-based recruitment:
After HIPAA waivers and waivers of Informed Consent are obtained, if required by local Institutional Review Boards, electronic medical records will be reviewed to identify potential patients who are eligible for participation.

Study staff will approach patients during their clinic sessions and invite them to learn more about the study. Recruitment letters may also be used instead of verbal contact during the course of providing medical care. Following introduction, study staff will communicate with interested individuals and set up a screening visit.

Referral from providers:
Providers will be introduced to the study and will be provided with a list of inclusion and exclusion criteria. The primary providers will be encouraged to discuss the study with potentially eligible participants, and to either provide the participant with contact information for the study, or alternative ask if study personnel may contact the participant to discuss the study in more detail. Study staff will initiate contact with interested and potentially eligible patients and describe the study to them. Recruitment letters may also be used instead of phone contact. Following introduction, study staff will set up screening visits with interested individuals.

Community-based recruitment:

The site investigators will initiate contact with community leaders and introduce them to the study. Community leaders will suggest possible ways to disseminate information regarding the study to potential participants in the community. Study staff will respond to contact initiated by interested individuals and briefly describe the study to them. Following introduction, study staff will communicate with interested individuals and set up a screening visit. Additional strategies, including targeted mailings, advertisements within healthcare settings and external promotions will also be considered.

Additional strategies may include:

- provider referrals
- participants referrals
- targeted mailings
- advertisements within local health care settings
- external promotion

Monitoring Recruitment Progress:
Investigators and study staff should meet weekly to discuss progress of weekly goals. Appropriate actions may include:

- Increase number of chart reviews
- Increase time in targeted clinics
- Determine what is working and what is not
- Review barriers and problems
- Revise the plan as necessary
- Consider other means of recruitment, including outside promotion

4.9 Documenting reasons for not approaching participants

Even if screening suggests a participant may be eligible for enrollment to the study, the final decision to approach the individual rests with the site PI and study team. There may be sound reasons to not approach the individual, most important of which is the individual's health stability or ability to safely participate. In every case, documentation of why the individual was not approached should be discussed and recorded by the study team in a local database. The DCC will not collect these data.

4.10 Documenting reasons why a participant did not consent

Study participation is voluntary. Upon understanding the risks of the study, the individual may decline to participate. Attempts to further influence the individual are not recommended. The study team should review and record each individual refusal and the reasons why participation was declined. The number of individuals screened and approached for consent will be recorded by the clinical center and reported to the DCC to determine success of site enrollment.

4.11 Documenting reasons why a participant does not consent to Biobank

Patients with pulmonary vascular diseases, or conditions that place them at risk for pulmonary vascular diseases may participate in this study even if they do not consent to the storage in the biobank and use of their samples after the end of the PVDOMICS study. Likewise healthy controls may participate in the study even if they do not consent to storage in the biobank and use of blood or urine samples at the end of the study. The reason(s) why the participant declined biobanking of samples should be documented and recorded by the clinical center. The DCC will ensure that these individuals' samples are not sent to the biobank. The consent to biobank is separate from consent for use of samples and data across the network during the study, and separate from data sharing (including DNA data) at the end of PVDOMICS. This use during the study, is a requirement for participation, and part of the consenting process in the PVD main consent and the healthy control consent.

Chapter 5: Adjudication and Recruitment Committee (ARC)

5.1 Overview

The Adjudication and Recruitment Committee (ARC) is tasked to review on-going recruitment, to minimizing inter-center variability with respect to WHO Group classification, assist in the difficult to discern overlap cases and adjudicate any study related events and complications. The committee membership consists of: Drs. Evelyn Horn (Chair), Robert Frantz, Jane Leopold, Stephen Mathai, Franz Rischard, Aaron Waxman and representatives from the Data Coordinating Center (DCC).

5.2 Enrollment of WHO Groups 1-5 PH Participants

While all institutions will strive for inclusion of participants in all WHO Groups there may be differences and institutional/network realignment of target population goals based on ongoing enrollment. Specifically, beyond the WHO Group 1 cohort, it is recognized that there will be some center specific strength in recruitment amongst the WHO Groups 2, 3, 4 and 5. Enrollment will be targeted to 3 – 3.5 years.

5.2.1 Primary WHO Group Diagnosis

- WHO 1: IPAH, HPAH, CTD, CHD, HIV, Portal hypertension, drug induced, PVOD, PCH, CTD (SSc, SLE, MCTD, Sjogren's, RA)
- WHO 2: HFrEF, HFpEF, VHD, RCM, HCM
- WHO 3: COPD, IPF, SSc ILD, other ILD, OHS, OSA, non-parenchymal lung diagnosis, CPFE
- WHO 4: CTEPH: surgery; non-surgical
- WHO 5: sarcoidosis, myeloproliferative disease, hemoglobinopathy (SS or Thalassemia)

WHO Group	1	2	3	4	5
Target/center	50	50	50	8-9	8-9
Target/total	300	300	300	50	50
Incident cases/total	75	75	75	12-13	12-13

5.2.2 Secondary WHO Group Diagnosis (if applicable)

Categorize under primary group and where appropriate include a secondary diagnosis utilizing same criteria for WHO Groups 1-5.

For the specific **overlap diagnosis** of WHO 2, 3 and WHO 1, 3 and possibly WHO 1, 2, 3 we will ask the center Principal Investigator (PI) to include a brief rationale to permit for quick review by committee call (3-4 ARC physician members).

The following criteria should be utilized:

WHO 2, 3: (PCW > 18, LAH, LAE, atrial fib) AND (COPD, IPF, SSC ILD, OHS, OSA, non- parenchymal restrictive lung diagnosis or CPFE);

Supporting rationale for 2 vs 3 primary diagnosis may include response to exercise or hemodynamic challenge such that acute worsening in filling pressures with exercise would prompt the primary WHO 2 diagnosis (and hence WHO 2, 3);

Acute worsening of oxygenation or only mild elevation of PCW would prompt the primary WHO 3 diagnosis (and hence WHO 3, 2);

WHO 1, 3: (features of WHO 1: i.e., autoimmune serology, positive family history) + mild (COPD, IPF, SSC ILD, OHS, OSA, non-parenchymal restrictive lung diagnosis, CPFE);

Stability and severity of hypoxemia/mild parenchymal lung disease in response to activity and/or over time with evidence of progressive PAH.

Within the primary diagnosis group, a running total of the numbers of secondary diagnosis will e maintained and included in the dashboard numbers.

5.2.3 Healthy Controls

- Target/center 16.7; Target/total = 100

5.2.4 Comparator Groups with Mild & Moderate Subclassification in Groups 2 and 3

- WHO 1: mild PH, ePAH, relative of heritable pulmonary arterial hypertension (HPAH), CTD with mild or no PH
- WHO 2: Iso-PH, no PVD
- WHO 3: mild to no PVD**,** mod PVD
- WHO 4: chronic PE with mild to no PVD

Target Enrollment for WHO Group Comparators

WHO Comparators	**1**	**2 mild-none**	**2 moderate**	**3 mild-none**	**3 moderate**	**4 mild-none**
Target/ctr	20	10.4	10.4	10.4	10.4	5
Target/total	120	62.5	62.5	62.5	62.5	30

5.3 Committee Responsibilities (ARC)

1. Ensure enrollment distributions across traditional groups as outlined in the protocol and in Section 5.2.1-5.2.4.
2. As long as the overall enrollment numbers are met across WHO Groups, comparators and controls, it is recognized that based on center-specific expertise each center may achieve somewhat different target group numbers Amongst the institutions we do have strength in different areas.
    a. Cardio-centric
    b. Pulmonary-centric
    c. CTEPH
    d. CTD
3. The Committee will monitor this every 3 months, establish and share a dashboard on current enrollment based on classification groups. This will be sent to centers on a regular basis and will be incorporated into the recruitment reports provided by the DCC.
4. The active dashboard will address deficiencies in a timely matter.
5. The ARC will ensure consistency across centers for WHO Group classification and classification of the mixed disease participants, incident vs prevalent disease, controls and comparators.
6. The ARC will specifically review participants with overlap of diagnoses (e.g., WHO Groups 2, 3 and 1, 3) with criteria as per protocol and outlined above.
7. The ARC will review difficult cases as requested by the center PI.
8. It is recommended that the ARC review all difficult cases for the first 6 months.
9. The ARC will adjudicate any complications that occur during the study evaluations.

CHAPTER 6: FORMS COMPLETION, DATA ENTRY AND COMPUTING

6.0 Introduction of data

The Study Coordinator will review all data forms for completeness and accuracy and to ensure timely submission of data to the Data Coordinating Center. Data forms should be filed in an area convenient for study personnel's access. To ensure that the study has quality data, team members must know the purpose of the study, the protocol design, and the sections of the Manual of Operations that are pertinent to their role in the study. If protocol expectations and study goals are clear and common to all team members, then protocol adherence by staff will help ensure quality data collection.

6.1 Form Completion

All study forms should be completed legibly using a blue or black pen. If an error occurs when completing an entry on a form, put an "x" through the incorrect entry and write the correct entry next to it. In the margin, next to the fixed entry, write your initials and the date the change was made. Never, try to place the correct entry over the incorrect entry. Do not transcribe a form from the original completed version onto another form. However, in the rare case that a form gets something like coffee spilled on it and you are worried that you will no longer be able to read some of the values, complete another form, let the coffee spill dry out and staple the coffee stained form to the transcribed form.

Each form has a "**Clinical Center Use Only**" box which is located at the end of every form. This box should only be completed once the form is successfully data entered into the database. If you receive an error message and are unable to commit the form, do not complete any of the information in this box. Once the form is successfully saved, write the username of the person entering the data and the date the form was entered into this box. This information will also be displayed on the database screen.

All data entered into the study database should always match the paper form. Data should be entered within 3 business days from the date the visit was held.

6.1.2 De-Identifying the Participant Consent and Forwarding to the DCC

In order for a participant to be randomized, the DCC will need to receive a de-identified copy of the signature page only of the consent form for the participant to be randomized. We do not need the entire consent; only the signature page. Please make sure that all participant information cannot be seen by DCC staff. This can be best done by using a black marker. The DCC should be able to see the date the participant signed the consent though.

Write the Participant ID and Alphacode in the middle of the page. This way, if it is scanned and emailed to the DCC, we will be able to see it and this information will not be cut off.

It is best if this document is scanned and emailed to pvd-systems@bio.ri.ccf.org. However, if you do need to fax it, please send an email to pvd-systems@bio.ri.ccf.org stating that you are doing this.

6.2 PVDOMICS Study Computing

The PVDOMICS Study Data Coordinating Center's recommended specifications for your PC are as follows:

Internet Explorer 7.0 or higher, Adobe Acrobat Reader, and the Sun JRE download for the Oracle 11g application. These can be downloaded from the DCC's website as specified in **Appendix A**.

6.3 Accessing the DCC Website to Enter Data

See Appendix A for instructions on how to set up your PC to access the DCC's database website.

https://qhsapps.ccf.org/forms/frmservlet?config=pvdomics

After you have successfully entered the website, you will see a menu titled 'PVDOMICS Study'. At this point, resize the window to the largest that will fit on the screen for optimal viewing. You can then choose a form or report from the menu, or you can go to the 'Inquiry' menu to answer or view your data inquiries.

6.4 Usernames and Passwords

You will have an Oracle database username and password. The usernames are assigned by the DCC's Database Administrators and are usually set up in the following format: first six letters of your last name followed by the first letter of your first name. There are up to seven letters in a username. Please do not share passwords. Passwords are not case sensitive.

Passwords will need to be changed every 75 days. You will be notified via email when your oracle password needs to be changed. If you do not change your password in the allotted time, you will need to send an email message to pvd-systems@bio.ri.ccf.org asking to have your password reset. A new temporary password will be sent to you in a secure e-mail and you will need to retrieve it from the secure site. This temporary password is only valid up until midnight of the same day.

6.4.1 Selecting a Good Password

Here are some good references for picking a good password:

- http://www.net.berkeley.edu/dcns/faq/good_pw.html
- http://www.msc.tamu.edu/services/cops/security/goodpasswd.html and
- http://www.cs.umd.edu/faq/Passwords.shtml

Please read them all as they all have good advice.

6.4.2 Changing Your Password

There is a menu option available to change your password.

1. Go into the PVDOMICS Study website http://qhsapps.ccf.org/pvdomics/ and click on 'Logon to the PVDOMICS System'

2. Enter your username and current password then hit 'enter' or click on 'connect'.
3. At the top of the screen, click on 'Change your password' and follow the prompts. Be sure to select 'RDP10' as the database. Passwords for the PVDOMICS Study will require:

    - 8 or more alphanumeric characters (no spaces or special characters).
    - An alpha character must always appear in the first position of the password.

6.5 Instructions: How to Enter Study Data into the Database

Press enter, tab or click your mouse to move from field to field within a form. Note that you will see bubble help when you move your mouse over the toolbar buttons. The upper left button should be the 'Save' button. When you are finished entering data for a form, click on the save button, or choose 'Save' from the 'Action' menu, or press the Ctrl+K to identify which key is the 'Save' or 'Commit' function key. The Ctrl+S key corresponds to the Oracle function 'Save' or 'Commit'.

Maximize window to see messages at the bottom of the screen. You will see a message indicating how many new records were added to the database. You can get out of a form by pressing the 'Exit' button or choosing 'Exit' from the 'Action' menu. 'F4' is the speed key to exit.

If you want to enter another form you should navigate to the top of the form, and press the 'Insert Record' button. 'Insert' can be selected from the 'Record' menu. You are not permitted to remove records once you have saved/committed them. You will need to send the DCC a data change request via the Inquiry System to delete a record (form). You are also not permitted to change certain key fields. (you will need to send a query to the DCC for these key fields).

When entering data, if you receive an error message stating the value is out-of-range, then back out of the form without saving the information and review the data with other staff members and PI if needed. If the value on the paper form is correct, notify the DCC with the information and we can investigate further. It may be that the range needs to be adjusted for that particular field. **Never** enter a value as a placeholder thinking that you will come back and fix the data at a later date.

If a form requires that all fields have a response but your paper version of the form has fields that are blank, **never** enter a value as a placeholder thinking that you will come back and fix the data at a later date. Instead, back out of the form without saving it. Discuss the form with other study personnel and the PI to obtain values for those fields that were missing. In the event that you do not have a value for a required field, contact the DCC for further instructions.

6.5.1 Obtaining the ID and Alphacode for a Participant

When data entering the Initial Enrollment Form for each study, question 1 "Identification Number" will have a list of values key (^), click on the "^". Select the first identification number that is listed. Once you have selected that number, that number will not be displayed the next time an initial enrollment is entered. The Alphacode will be populated once you have successfully committed and saved the

Screening Form. Make sure to write the Identification Number and the Alphacode on the Screening Form. This ID and alphacode will follow the participant throughout the study.

6.5.2 Keymappings

Ctrl+K means hold down the <Ctrl> key and then simultaneously press the 'K' key. Now release 'K' and then <Ctrl>. Another way to get to the key mappings is to choose 'Keys' from the 'Help' menu.

6.5.3 List of Values (LOV)

Note that you may see messages on the bottom of your screen. If you see 'List of Values', that means you can choose 'Display List' from the 'Edit' menu, or press Ctrl+L to retrieve a list of values to your screen which you can scroll through and make a selection. You can also click on the 'v' button next to the field to select the response you need.

6.5.4 Editing

If the box for the field is smaller than the text you are typing into it, you can choose 'Edit' from the 'Edit' menu, or press Ctrl+E when your cursor is in that field. This will open up a pop-up box containing a larger view of that field.

6.5.5 Navigation

Other useful Oracle functions that you can use are 'Next Record' and 'Previous Record'. You can find buttons and speed keys for these and they are also on the 'Record' menu. Use these to navigate between forms or detail records (for example, in the medication form).

6.5.6 Error Messages

If you skip over a required field, you will see the error message:

> Field must be entered.

If you enter a value that is not possible for that field, you will see the error message:

> Invalid value for field name.

If you enter a non-numeric character in a numeric field, you will see the error message:

> Legal characters are 0-9 - + E or Item must be formatted as, for example, 90.0 (or some specific format)

If you try to update previously entered data without using the [Change Value] button, you will see:

> Field is protected against update.

If you try to enter a Form that has already been entered, you will see the error message:

Error while inserting: ORA-00001: unique constraint (P201194.PVD_XX_PK) violated.

You will also see other various error messages as well. If you can't figure out why you are getting that particular error message, please write down the complete message, and also choose Help->Display Error while the message is on the screen to see if a further explanation pops up before contacting the DCC. If you get stuck, it may help to use Cancel Query or Query->Cancel (if you see 'Enter-Query' on the bottom of your screen), Action->Clear All or Record->Clear

6.6 Instructions: How to Change Study Data in the Database

6.6.1 Retrieving Data

Once the data has been entered, you can retrieve it to your screen for viewing:

- Access the form # you want to view.
- Press the F11 [Enter Query] key, query icon or use the pull down menu option under 'Query'.

Note the hint line will say 'Enter-Query'.

- Enter the Participant ID.
- Press the Ctrl+F11 [Execute Query] key, execute query icon or use click on the pull down menu option under 'Query' to execute query.

6.6.2 Data Change Within 7 Days

- Retrieve the form you want to view.
- Put the cursor on the field that needs to be updated.
- Press the [Change Value] button.
- Change the value by entering the appropriate value.
- Press 'enter' or [Save] button.
- A pop-up box will appear with a Data Change Number.
- Write the Data Change Number on your form next to the question that was changed.
- Press the [OK] button to return to the form.
- No further action is required.
- The database should <u>always</u> match the paper copy of the form you entered.

6.6.3 Clinical Center Change to Data After 7 Days (send 'Data Change Request' to DCC)

- Retrieve the verified data and the form you want to view.
- Position the cursor on the field to be changed.
- Press the [Change Value] button.
- A new screen will appear that will allow you to enter a 'New Value' and an explanation.
- Enter the new value in the 'New Value' field and text describing the desired change in the 'CC Text' field. Please give as much detailed information as possible as to why the value should be updated. (The DCC will use this response to investigate the request.)
- Press the [Save and Exit] button.
- You will receive an inquiry number or 'data change request' number after you save the request. Write this number on your form. You can use this number to check to see if the DCC signed off on your inquiry.
- The DCC will take the appropriate action, and then use the DCC Sign-Off screen to indicate the final status of the request.
- A 'DCC Sign-Off to CC Initiated Data Inquiry' will be sent to the DCC and CC.
- No further action is required.
- The database should <u>always</u> match the paper copy of the form you entered.

6.6.4 Data Change for Forms 9 and 10

- Data on Forms 9 and 10 can be changed at any time.
- Retrieve the data and the form you wish to view.
- Put the cursor on the field that needs to be updated.
- Change the value by entering the appropriate value
- Press the [Save] button.
- No further action is required.

6.7 Instructions: How to Initiate and Respond to Data Change Requests/Queries

6.7.1 Clinical Center Initiation of Queries

Queries, or Data Change Requests, can be initiated by the Clinical Center as described in the previous section on changing data.

6.7.2 Clinical Center Response to a DCC Initiated Inquiry

- You will receive a DCC initiated inquiry report through e-mail, or you can go to the 'Inquiries' menu and choose 'Center Response to DCC Inquiry' to find unanswered queries.

- To respond to an inquiry, you **must** use the database Inquiry System. The DCC is unable to accept e-mail responses.

- When the screen appears, press [Execute Query] to retrieve all unanswered queries, or press [Enter Query] and enter the specific query # and then press [Execute Query].

- If you do not enter an inquiry number, all unanswered queries will be retrieved. Press [Next Record] or use the 'up' or 'down' arrow' key to navigate to the other queries. Keep pressing [Previous Record] to get back to a previous query.

- Position the cursor on the 'DCC text' field'.

- Choose Edit->Edit to read the entire explanation from the DCC as to why you are being queried.

- Navigate to 'New Value'.

- Type a new value for the field being inquired. If a different field requires changing, leave it blank or enter N/A for not applicable.

- Navigate to 'CC text', and enter an explanation for the value. This field must be answered in order for the DCC to take action. Please make sure that the explanation is specific and complete.

- The explanation can be up to 2000 characters. Click on the [Save and Exit] button on the bottom of the screen to save the text. Click on [Exit and Don't Save] if you do NOT want to save the text.

- The DCC will make the appropriate update(s) to the database.

- It is very important that the CC respond within 3 business days.

6.8 Retrieving Data from Forms

6.6.1 Introduction

Data can be retrieved in several ways from the form application. In order to 'query' data available in the database for the information on a given form application, the [Enter Query] and [Execute Query] keys can be used. The screen will be populated with the first set of participant data for the form application being accessed. By pressing the [next record] or [previous record] keys, you will have the ability to view the next or previous set of data.

There are different ways to retrieve data. You can execute simple queries that meet specific criteria, as well as complex queries that satisfy several conditions. The following topics are discussed.

- Matching exact values
- Entering variable conditions
- Matching values that meet a specified pattern

6.6.2 Matching Exact Values

Suppose you want to check on all instances of visits of the 'B' or 'F' type for a given participant ID (110001 for example). The data entry screens can retrieve the record(s) that contains specifically these values. The following are general steps for retrieving records that match exact values:

1. Access the appropriate form via the menu system.
2. Press [Enter Query]
3. Type the values you want to match into the appropriate fields.
4. For this example, cursor to the Participant ID field and type 110001.
5. Press [Execute Query]
6. Press [Next Record] or [Previous Record] to view the retrieved data.

NOTE: If there is not any data that meets the specified criteria, the following message will be displayed on the status line of your screen:

'FRM-40301: Query caused no records to be retrieved. Re-enter.'

6.6.3 Entering Variable Conditions

Sometimes it is not practical to enter the exact values that you want retrieved data to match. For example, you might want to retrieve the following:

- A specific form with a visit date of 10/20/2016

To select data that have a visit date of 10/20/2016, press [Enter Query] and enter the participant ID number and visit date of 10/20/2016 and press [Execute Query]. This will bring up all of the forms with a visit date of 10/20/2016 for that participant.

6.6.4 Populating WHO Drug Data Fields

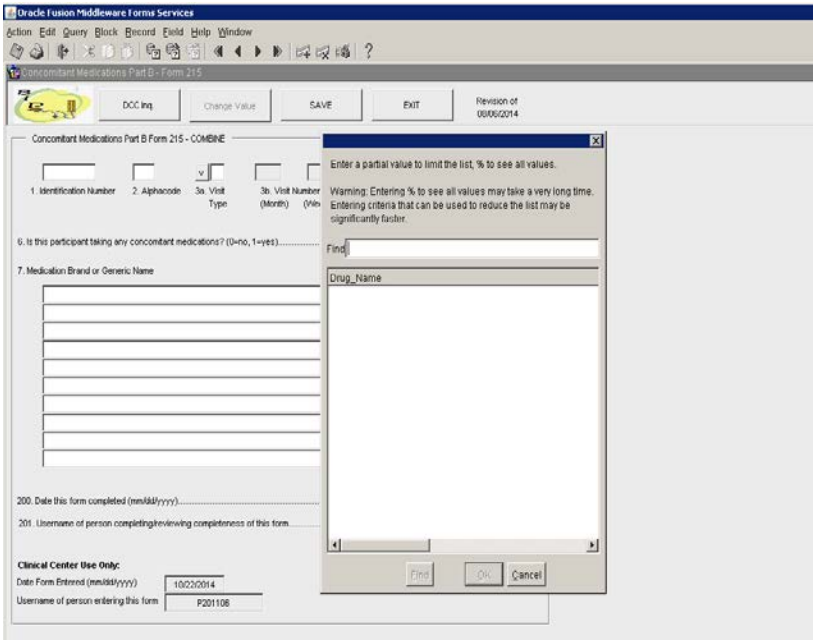
A. The WHO Drug database is used for recording medications on Form 110 Medications. You will need to select the name of the medication from a [List of Values] to populate these forms; you cannot type freehand the name of the medication as there is a chance of misspelling.

For example, a participant is taking a medication, Rolaids, on Form 110:

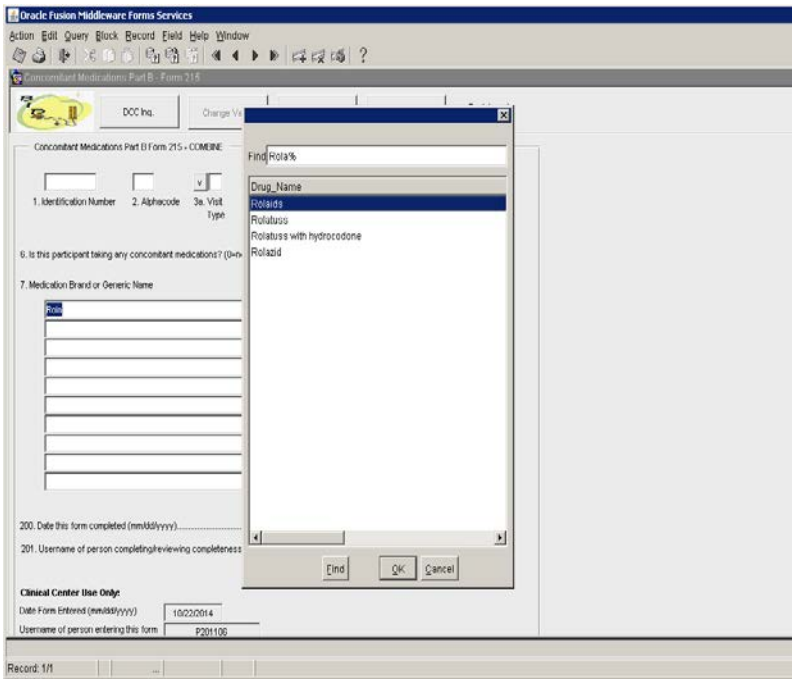
1. Access the Form 110 data entry screen and enter the participant information in Q1 - 3.

2. Database will automatically place the curser into a blank medication field.

3. Obtain the medication name by clicking on the [List of Values] box on the left side of the field and you should get an empty pop-up box. (Alternatively, you can just type in the name of the medication directly into the field.)



4. In the ‘Find’ box, type the first few letters of the medication name ‘Rolai’ (not case sensitive) and the window will automatically add the % sign. Either hit the ‘Enter’ key or click on the ‘Find’ button at the bottom of the window. The window will populate with all medications starting with those 5 letters.



5. Scroll through the list of medications to identify the name of the medication participant is taking.

6. You can further refine this same list of 413 medications by going to the 'Find' line and typing in the additional letters and the window will provide a smaller subset of medications.

7. With the mouse, highlight the medication name and click the 'OK' button. The blank medication field will now be populated with the medication name. Another option is to highlight the medication and double-click. The field will be populated.

8. **Note:** if you determine that the name of the medication is different than what you originally typed, you must click on the 'Cancel' button or the 'X' box and start over.

9. If there are no other medications to be entered, press the "enter" key twice to go to the next question or use the mouse to go to the next question. However, if you press "enter" and type something in the blank row and delete it, you will not be able to exit that row since the computer is expecting you to enter another medication. If there are no other medications to be entered, and the cursor will not go to the next field, select "Record" from the task bar, then select "Remove". You will then be able to use the mouse to get to the next question on the form.

6.9 Participant Confidentiality and Data Security

Participant confidentiality of medical records and identity will be maintained at the highest level. All participant data submitted to the DCC will be transmitted as secured encrypted files and reported anonymously with no names, Social Security numbers, etc. It will be emphasized to all staff at the clinical center, and any central cores, the need for strict confidentiality of all study data, with a specific plan for later data sharing as required by NIH. HIPAA privacy regulations will be followed carefully.

All forms, CDs and tapes will be kept in locked cabinets. All computerized files will be protected by means of a password system. All reports prepared by the Data Coordinating Center will be such that no individual participant can be identified. Any publication of data will be reported as a group, thus avoiding identification of an individual subject.

6.9.1 System Physical Security

The Server Room is located on the Cleveland Clinic main campus in the JJNorth Building. Building and department access is limited to authorized Cleveland Clinic IT and contracted maintenance employees via ID Badge swipe access device at building entrances. The Server room access is restricted to authorized personnel only via ID Badge swipe access device at the server room entrance.

Devices and systems for fire detection are installed and available. Server room undergoes periodic fire marshal inspection by the Department of Safety.

Temperature and humidity are automatically controlled by the heating and air conditioning equipment. Server and battery room temperatures are monitored automatically. Facility Engineering is notified of high temperature alerts for remediation automatically. The System Group is notified at the same time.

A UPS (uninterruptible power supply) is installed, maintained and tested periodically to allow for proper computer equipment shutdown in the case of extended power outages. The UPS automatically sends a page if it goes on.

6.9.2 Storage and Back-up

The database is backed up weekly in its entirety using Oracle Recovery Manager hot back-ups. Then incremental 'hot' back-ups are done on a daily basis. These are all written to disk where they are in turn copied to tape backup. In addition, transactions between backups are stored in archive logs that are also on hard disk. The tapes are kept in a fireproof safe on site for one month and then moved to Iron Mountain for long-term storage.

6.9.3 Auditing

PVDOMICS Study data are contained within an Oracle database. Access is through password protected user accounts. Passwords are forced to be changed at least every 75 days.

All inserted data records are stamped with the date, time and username of the person entering the information.

All changes to data records have a copy of the existing record saved in an audit table and the date, time and username of the person making the change is saved.

All data record deletions have the existing record copied into an audit table along with the date, time and username of the person deleting the record.

6.10 E-mail Alias Lists

There are several useful e-mail aliases, including:

pvd-systems@bio.ri.ccf.org = DCC Programming Staff

pvd-DCCclin@bio.ri.ccf.org = DCC Clinicians

pvd-steering@bio.ri.ccf.org – Steering Committee

pvd-dcc@bio.ri.ccf.org **– QHS** DCC Programming and Statistical Staff

Other alias listings can be found in the PVDOMICS Study Address Directory.

Appendix A

PVDOMICS Study - Instructions for Installing/Upgrading Java

Java is the application to run our Oracle Forms application for the PVDOMICS Study. Please follow the steps below to install or update your Java.

Please note that if you don't have permission, you may **need to contact your local IT support**.

A. Go to: http://www.java.com/en/

1. Click on the link "Do I have Java?" to obtain your computer's current version number.
2. Click on "Agree and Continue"
3. Click on "Download Java Now" to get current version
4. Click "Agree and Start Free Download"
5. If you get a pop-up box at the bottom of your screen that says "Do you want to run or save JavaSetup.exe from sdlc-esd.sum.com?, then click "Run"
6. On the "Welcome to Java" page click "install"
7. Uncheck the box "Install the Ask Toolbar in Internet Explorer" and click "Next"
8. Java will install
9. Uncheck "Restore Java security prompts" and click "Next"

You have successfully installed Java!

B. Please leave the check mark in "Restart my browser now to complete the installation" and click "Close"

1. Java will close and re-open in another window. Click "Enable" where it says "The Java™ Plug-In SSV Helper add-on from 'Oracle American, Inc.' is ready for use"

C. Go to the computer Start button, left click and select the Control Panel.

1. Select Java and click on the "Security" tab.
2. Click on "Edit Site List"
3. Click "Add" and type the following into the box labeled 'location': https://qhsapps.ccf.org and press "OK".
4. Close your browser and restart to access the PVD Database.

Appendix B

Key Mapping

FUNCTION	KEY
Block Menu	Ctrl+B
Clear Block	F7
Clear Field	F5
Clear Form	F8
Clear Record	F6
Commit	Ctrl+S
Count Query	F12
Delete Record	Ctrl+↑
Display Error	Shift+Ctrl+E
Down	↓
Duplicate Item	Shift+F5
Duplicate Field	Shift+F6
Edit	Ctrl+E
Enter Query	F11
Execute Query	Ctrl+F11
Exit	Action menu, select Exit
Help	Ctrl+H
Insert Record	Ctrl+↓
List of Values	Ctrl+L
List Tab Pages	F2
Next Block	Shift+PageDown
Next Field	Tab
Next Primary Key	Shift+F7
Next Set of Records	Shift+F8
Previous Block	Shift+PageUp
Previous Field	Shift+Tab
Print	Ctrl+P
Return	Return
Show Keys	Ctrl+K
Up	Up
Update Record	Ctrl+U

Appendix C

Instructions for Clearing your IE Cache

If you are unable to see an updated report, try cleaning out your ‘cache’ in your web browser and then try running the report again.

You can follow these steps:
a. Open Internet Explorer and then click on Tools.
b. Then click on Internet options.
c. Click the General tab, and then, under Browsing history, click Delete.
d. Here you can select history, cookies, temporary internet files and then click delete.
e. Refresh screen.

This will clear your Internet Explorer cache.

Chapter 6-Appendix 1: Securely Transferring Documents to PVDOMICS DCC Server

Overview

Some participant documents will be securely uploaded to the DCC server. Only those who have a DCC Systems-assigned account and password will be able to upload documents. If there is more than one person from each site who will be uploading documents, each person must have his/her own account. Never share your username and password with anyone.

Documents include:

- ECG summary page tracing (file format=pdf)
- CPET tracings (file format=cow files?)
- RHC documentation (file format=cow files?)
- Pulmonary Function Tracings (file format=pdf)
- Final Lung CT Report (file format=pdf)
- Sleep Study (file format=edf)
- Event (SAEs, deaths) review documentation (file format=pdf)
- Miscellaneous (consent signature page) (file format=pdf)

De-Identification and addition of PVDOMICS Study Identification

Any personal protected health information such as, but not limited to: name, SSN, clinical center medical record number and so on must be redacted prior to sending. New PVDOMICS Participant Identification must be present in a document and must include PVDOMICS identification number, alphacode and date of test.

The file may need to be printed out and redacted by hand using a black, permanent marker (like thick Sharpie) to cross through any identifying information. Then the file is re-identified with pvdomics identification as stated above. The file is then rescanned to a pdf format and uploaded.

Adobe PDF Pro X software has a redaction feature that eliminates de-identifying by hand and having to rescan the document.

Setting Up a Secure Copy Protocol (SCP) Account for the First Time

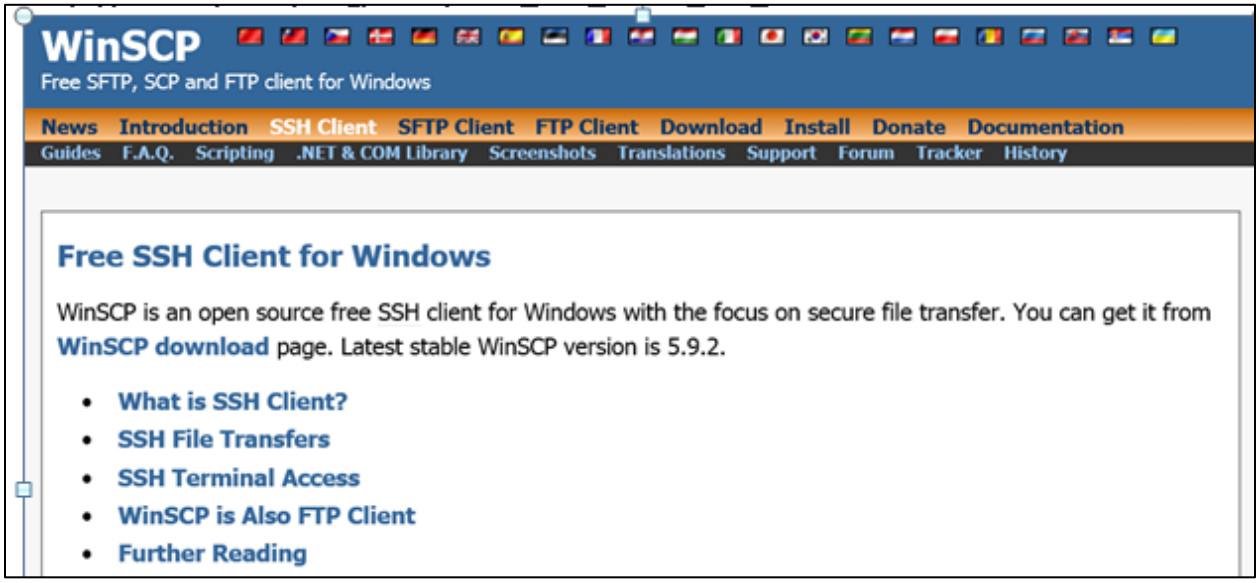
Open internet browser

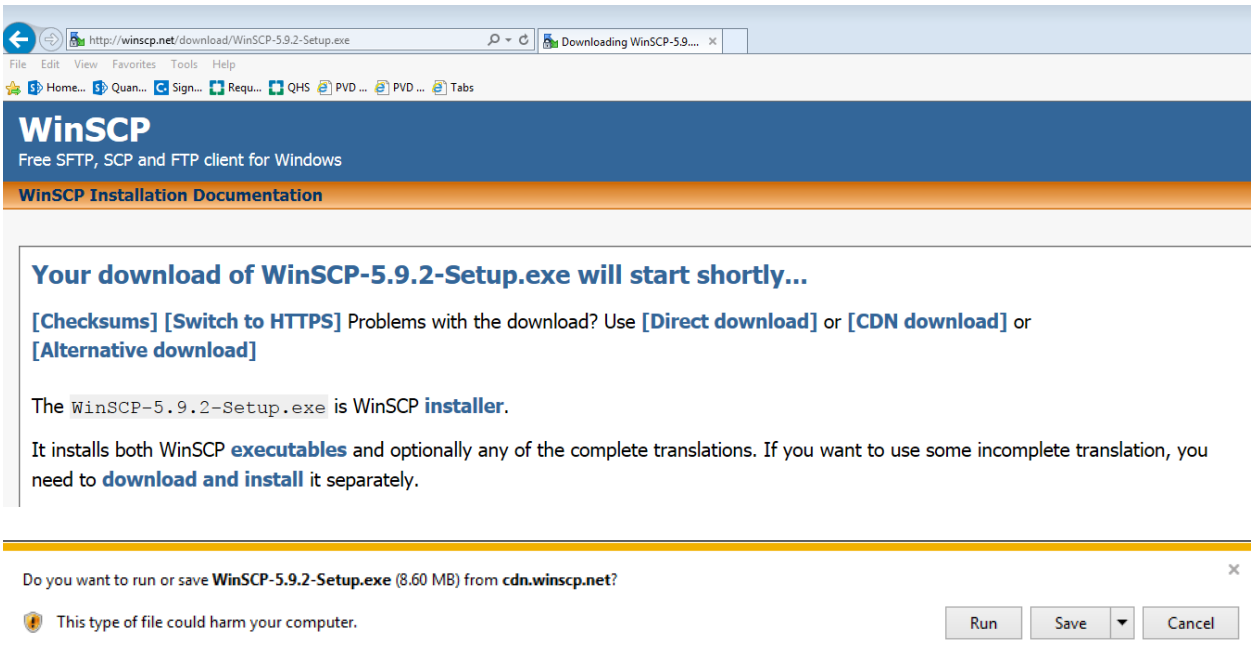
Type in www.winscp.net (free application) to install (you may need to get IT assistance to download)





http://winscp.net/eng/docs/free_ssh_client_for_windows

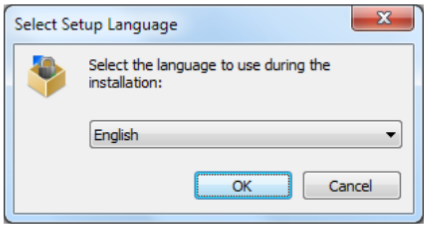




Installation

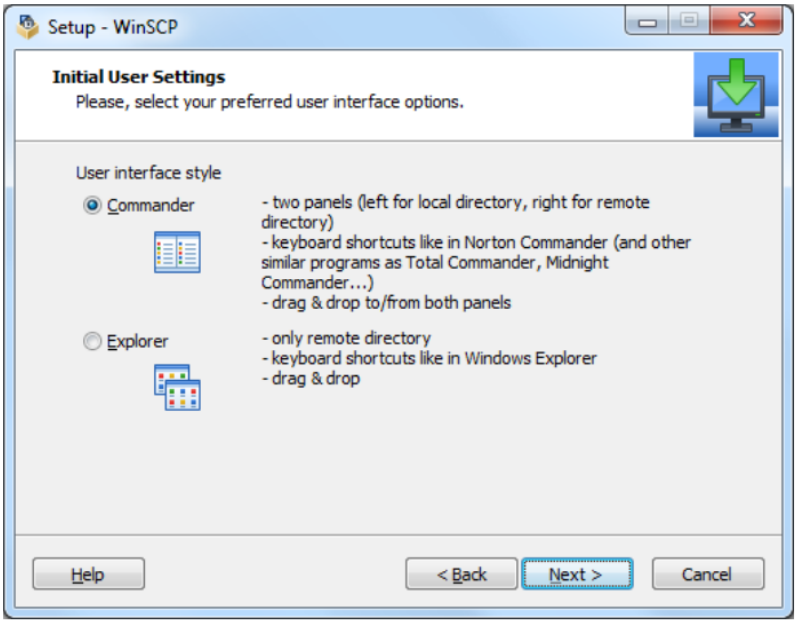
Edit

1. Open the **installation program** by double clicking on its icon.
2. If your Windows language is not supported by the installer, select an alternative **language** you want to use (both for installation and later when using WinSCP).



3. On the ***License Agreement*** screen click *Accept* after reviewing the license.
4. You will be prompted to select a **setup type**. For a basic setup, choose ***Typical installation***.
5. Then you will be prompted for ***Initial User Settings***. This allows you to select **user interface style**. If you have used (and enjoyed) file managers like Total Commander, Altap Salamander or Norton Commander before, keep default ***Commander interface***. Otherwise you will probably be more familiar with ***Explorer interface***.

Commander before, keep default ***Commander interface***. Otherwise you will probably be more familiar with ***Explorer interface***.

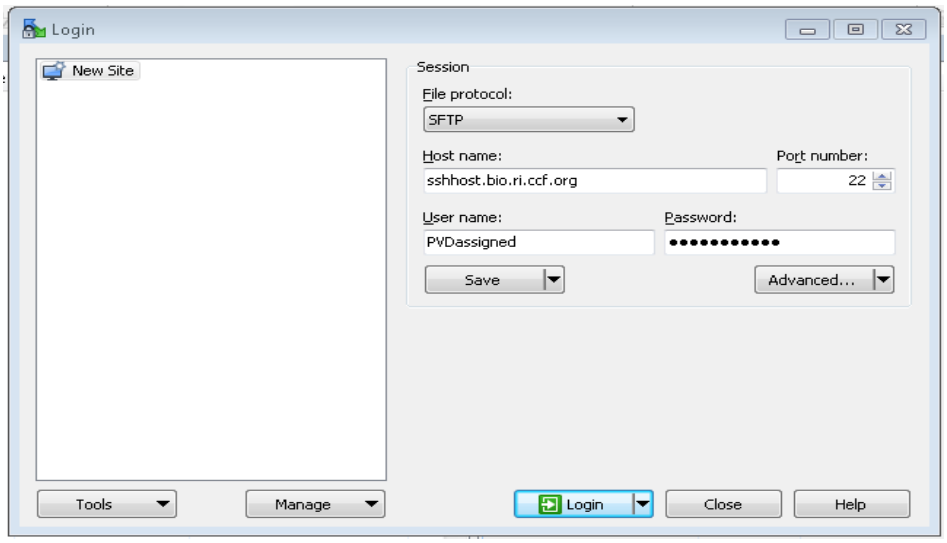


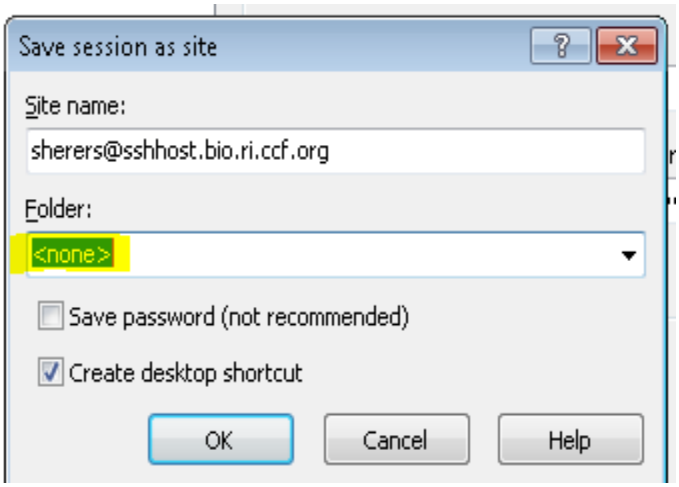
6. After you select the interface, the ***Ready to Install screen*** opens. On this screen, you can review the installation options you've selected. Click *Install* to start the installation.
7. A brief installation process will take place. You may have to restart Windows Explorer or your computer. If you choose not to restart, some WinSCP functions may not be available until you do so.

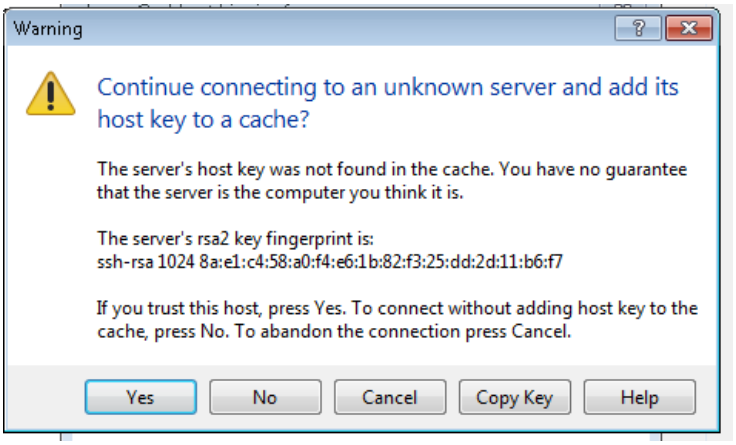
http://winscp.net/download/WinSCP-5.9.1-Setup.exe

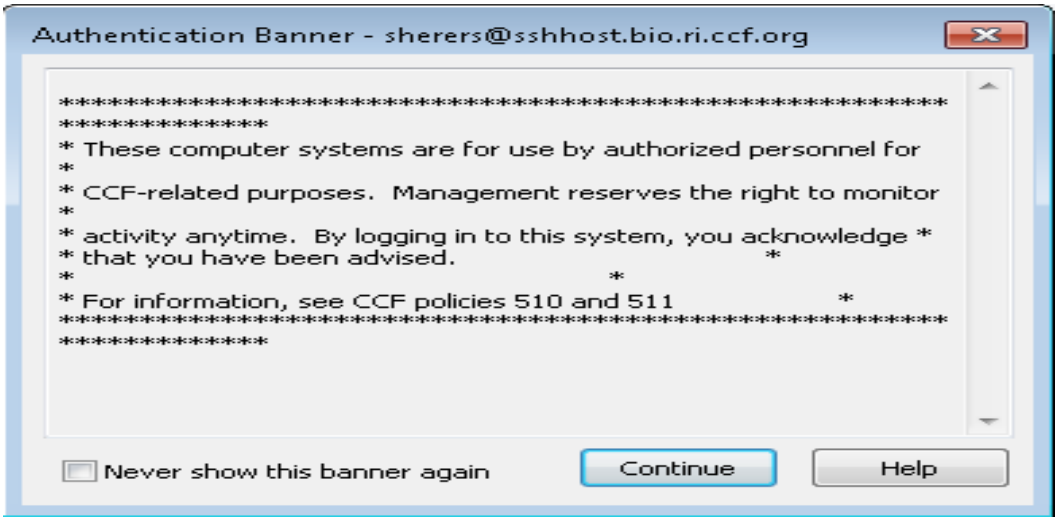
Locate the WinSCP shortcut on desktop

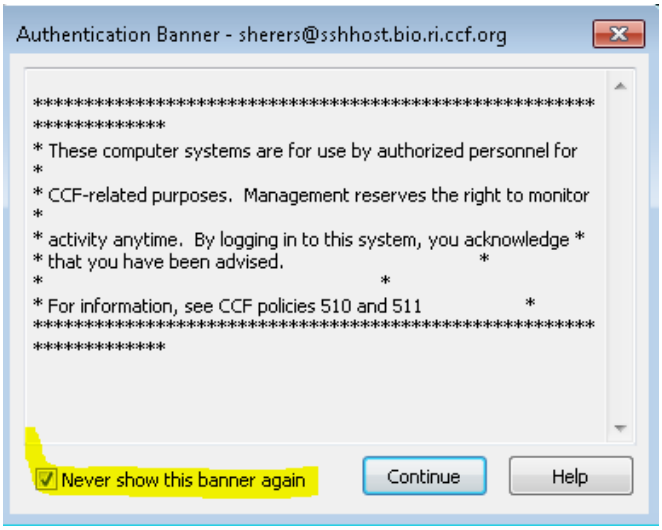



Login
New Site
Session
File protocol:
SFTP
Host name:
sshhost.bio.ri.ccf.org
Port number:
22
User name:
PVDassigned
Password:
Save
Advanced...
Tools
Manage
Login
Close
Help

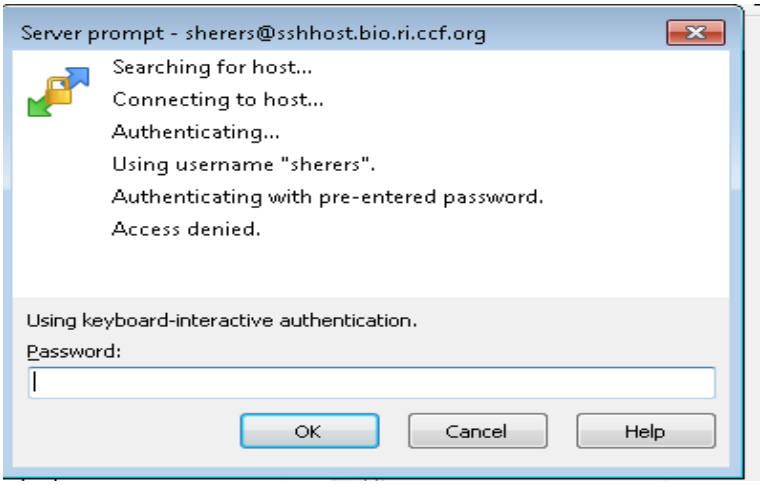

Save session as site
Site name:
sherers@sshhost.bio.ri.ccf.org
Folder:
<none>
Save password (not recommended)
Create desktop shortcut
OK
Cancel
Help

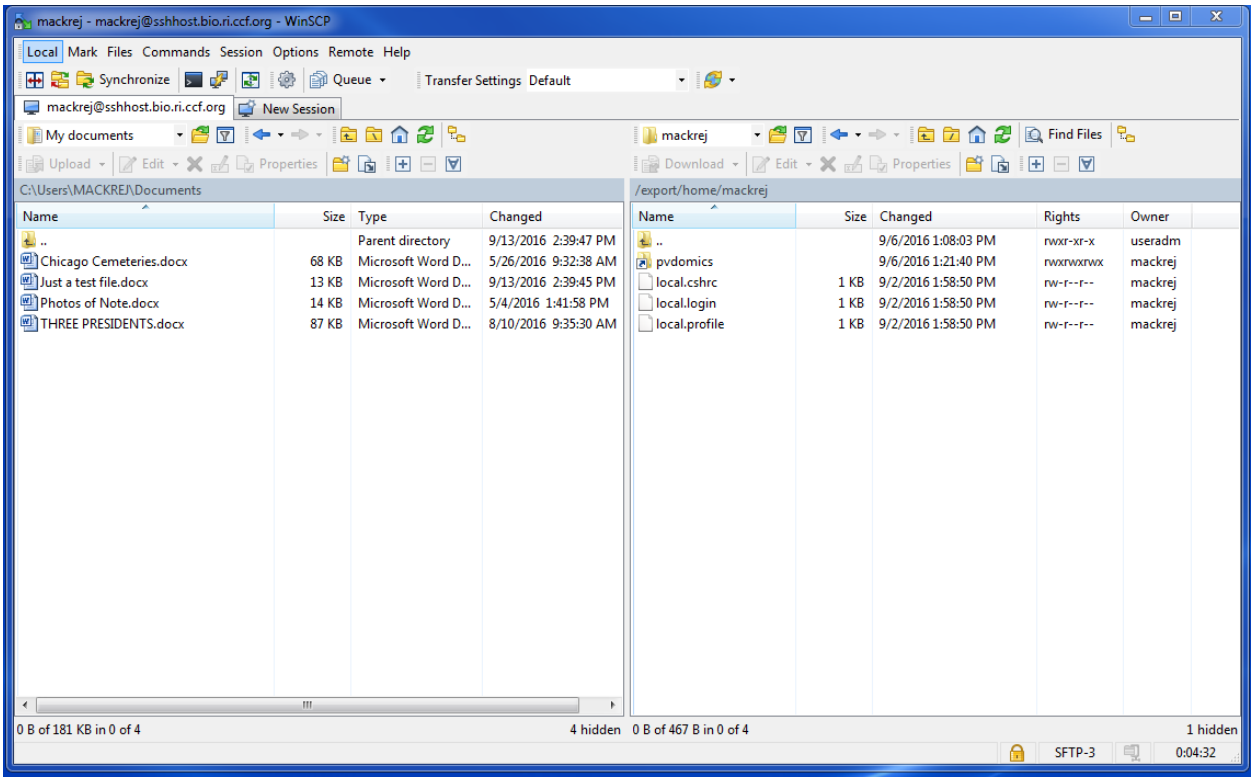

Warning
Continue connecting to an unknown server and add its host key to a cache?
The server's host key was not found in the cache. You have no guarantee that the server is the computer you think it is.
The server's rsa2 key fingerprint is:
ssh-rsa 1024 8a:e1:c4:58:a0:f4:e6:1b:82:f3:25:dd:2d:11:b6:f7
If you trust this host, press Yes. To connect without adding host key to the cache, press No. To abandon the connection press Cancel.
Yes
No
Cancel
Copy Key
Help

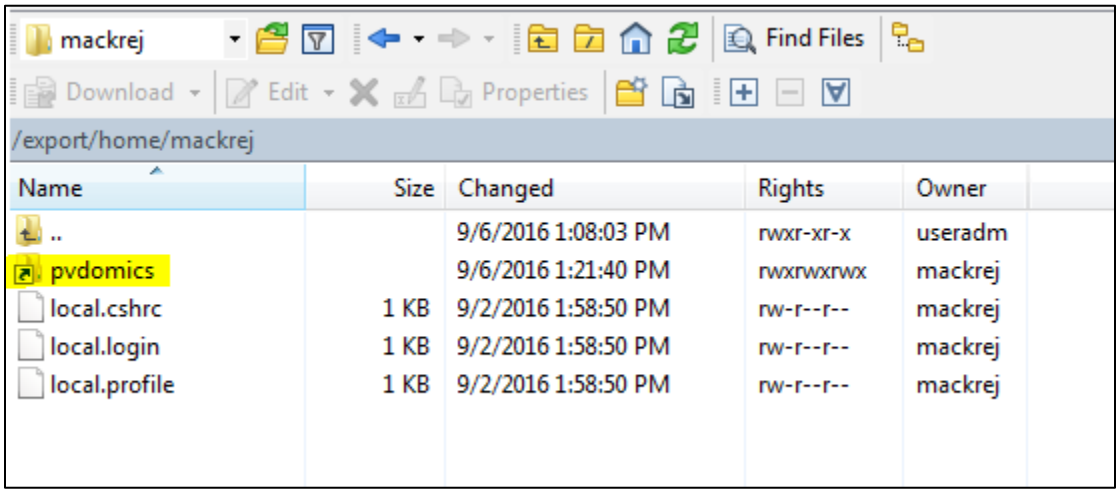




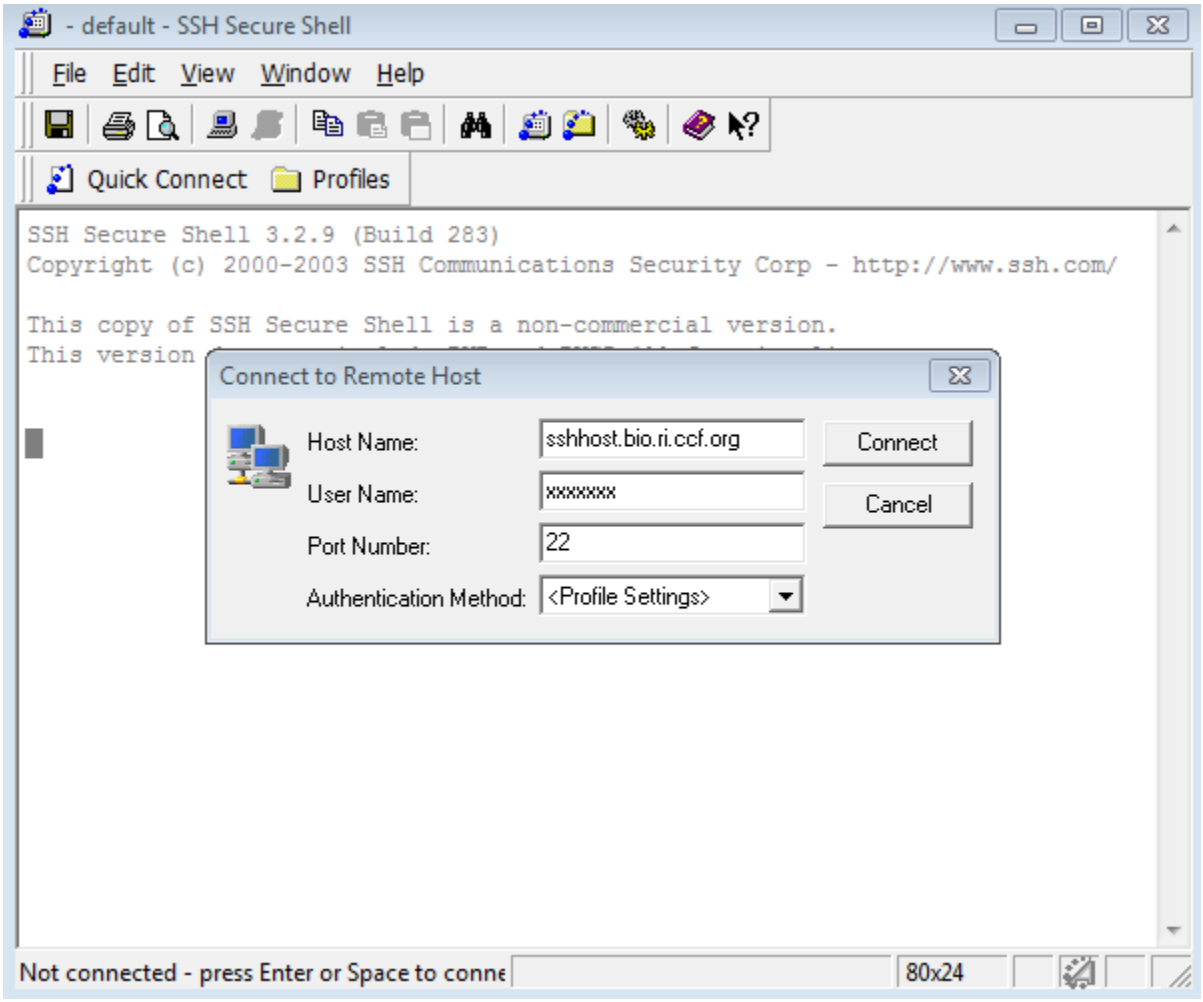
Make sure you type in the correct password or you will get an error box that looks like this:

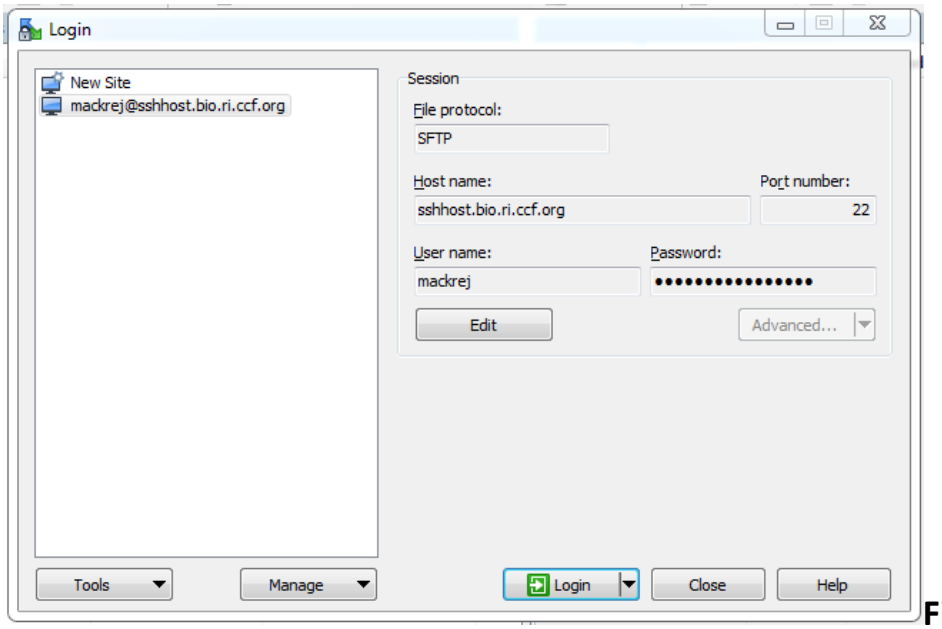




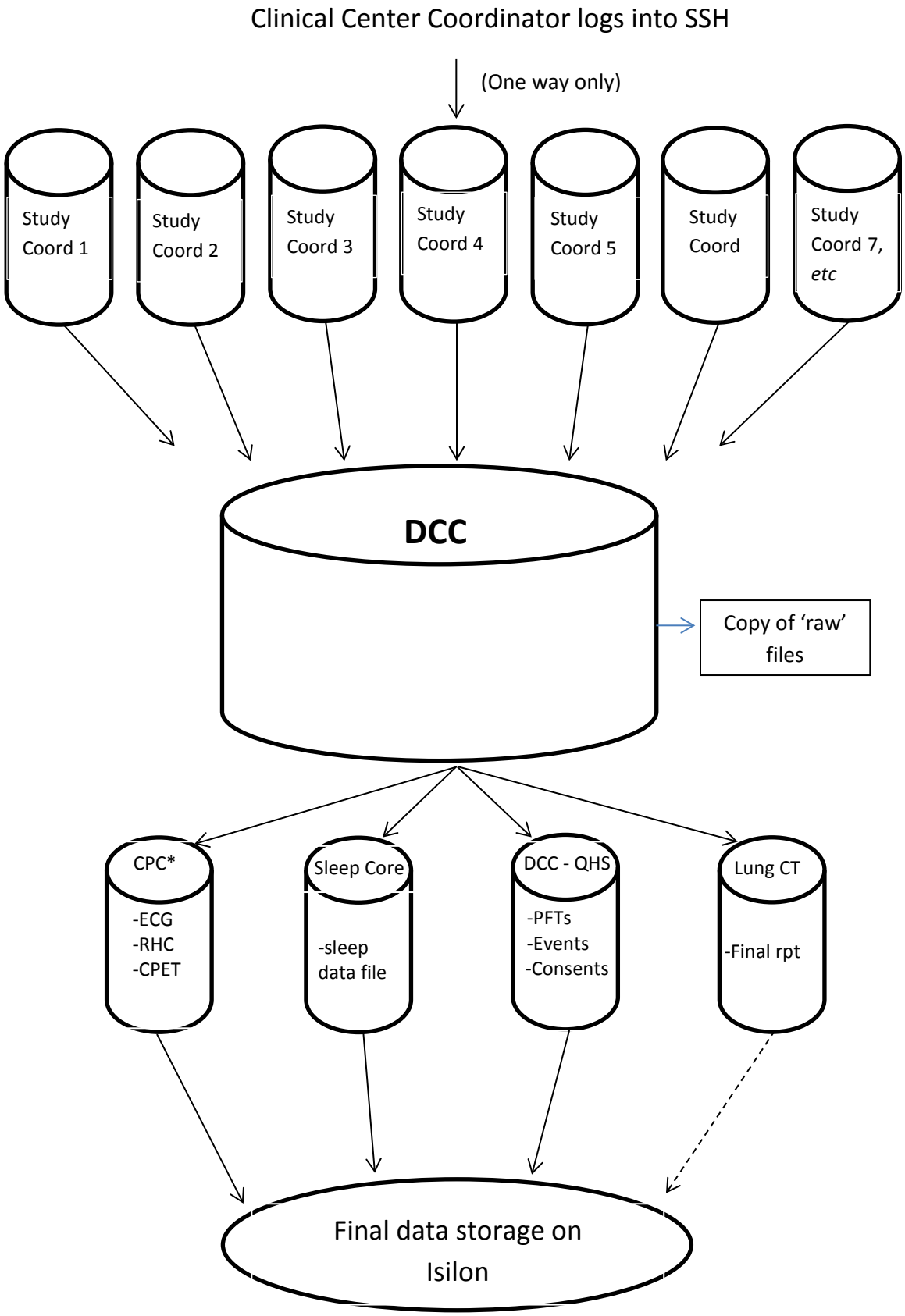


Accessing WinSCP following initial set-up





File Transfer from Clinical Centers to DCC Cores


Clinical Center Coordinator logs into SSH
(One way only)
Study Coord 1
Study Coord 2
Study Coord 3
Study Coord 4
Study Coord 5
Study Coord -
Study Coord 7, etc
DCC
Copy of 'raw' files
CPC*
-ECG
-RHC
-CPET
Sleep Core
-sleep data file
DCC - QHS
-PFTs
-Events
-Consents
Lung CT
-Final rpt
Final data storage on Isilon

PVDOMICS Study - Instructions for Installing/Upgrading Java

Java is the application to run our Oracle Forms application for the PVDOMICS Study. Please follow the steps below to install or update your Java.

Please note that if you don't have permission, you may **need to contact your local IT support**.

A. Go to: http://www.java.com/en/

1. Click on the link "Do I have Java?" to obtain your computer's current version number.
2. Click on "Agree and Continue"
3. Click on "Download Java Now" to get current version
4. Click "Agree and Start Free Download"
5. If you get a pop-up box at the bottom of your screen that says "Do you want to run or save JavaSetup.exe from sdlc-esd.sum.com?, then click "Run"
6. On the "Welcome to Java" page click "install"
7. Uncheck the box "Install the Ask Toolbar in Internet Explorer" and click "Next"
8. Java will install
9. Uncheck "Restore Java security prompts" and click "Next"

You have successfully installed Java!

B. Please leave the check mark in "Restart my browser now to complete the installation" and click "Close"

1. Java will close and re-open in another window. Click "Enable" where it says "The Java™ Plug-In SSV Helper add-on from 'Oracle American, Inc.' is ready for use"

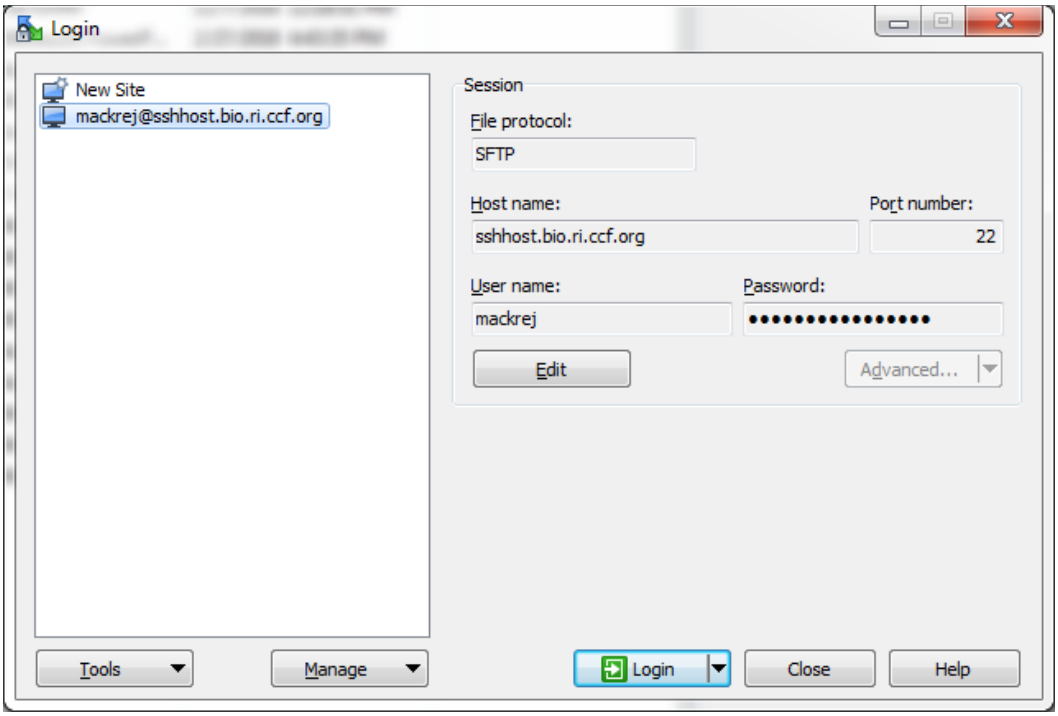
C. Go to the computer Start button, left click and select the Control Panel.

1. Select Java and click on the "Security" tab.
2. Click on "Edit Site List"
3. Click "Add" and type the following into the box labeled 'location': https://qhsapps.ccf.org and press "OK".
4. Close your browser and restart to access the PVD Database.

PVDOMICS Secure Portal

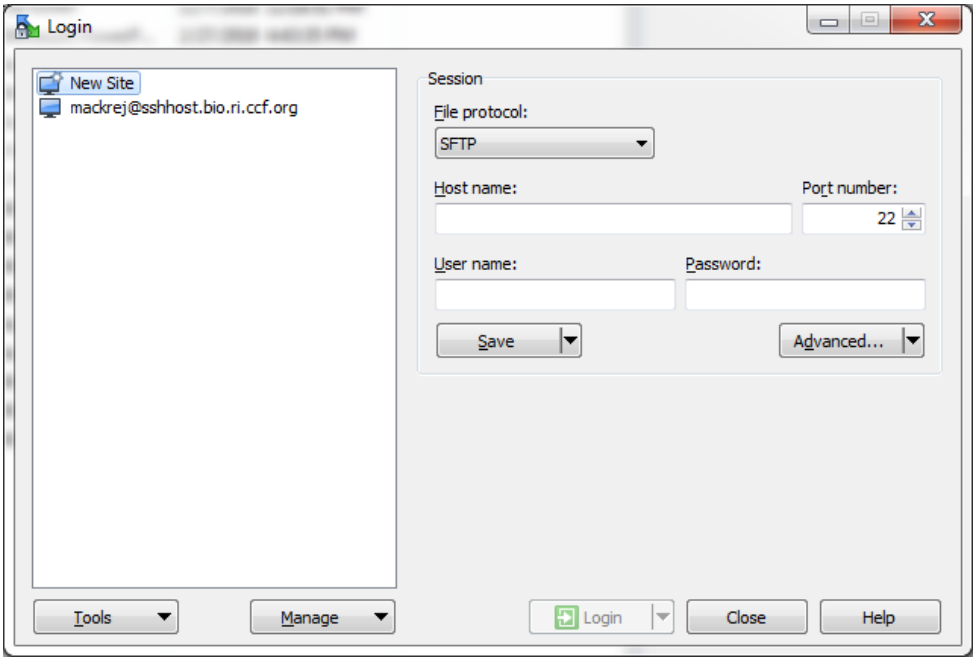
Create WinSCP Connection to the New PVDOMICS SFTP Site

Here is what your old connection looks like now:

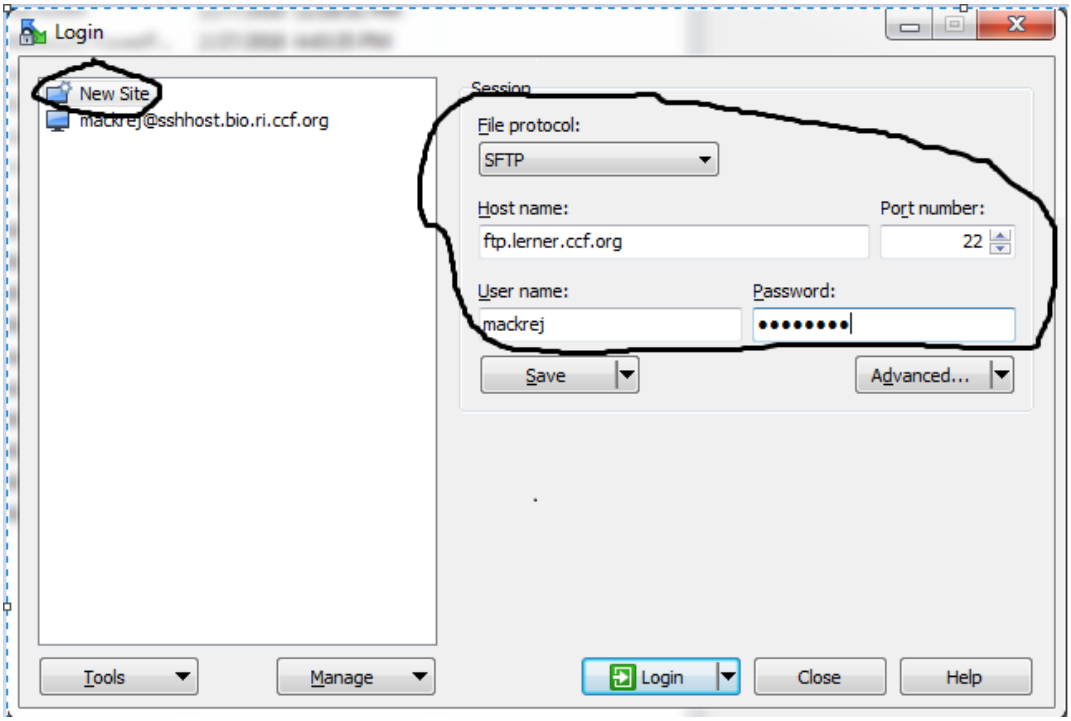


To create WinSCP Connection to the <u>New</u> PVDOMICS SFTP Site, do the following:

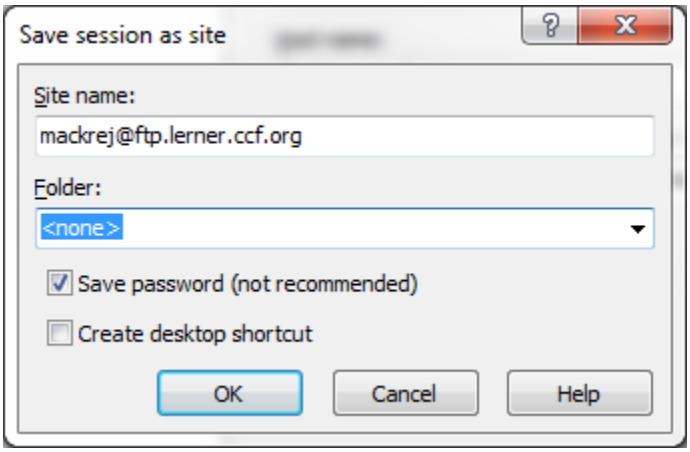
- **Make sure you have your old password available.**
- **Click on "New Site".**



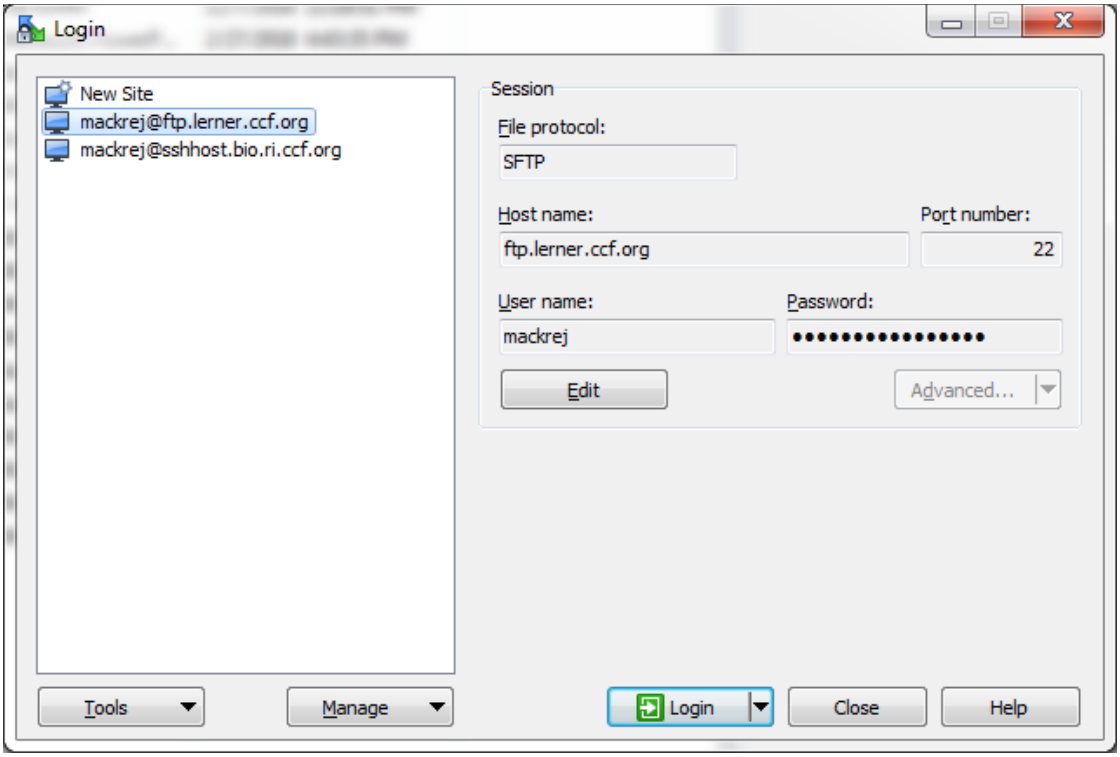
- **Fill in the Host name, User name and Password.**
  - **Host name is: *ftp.lerner.ccf.org***
  - **Your password is the same as when you first received it. Email DCC systems group at pvd-systems@ccf.org if you cannot remember your old password**
- **Make sure that 'Port Number' is '22'.**
- **Press 'Save'**



- **Check "Save password"**
- **Click on 'OK'**

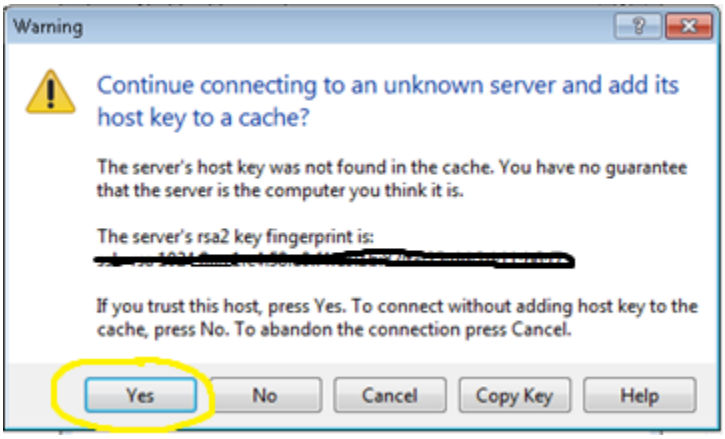


- **The new host link will appear on the login screen**
- **Click on 'Login' to test the connection**

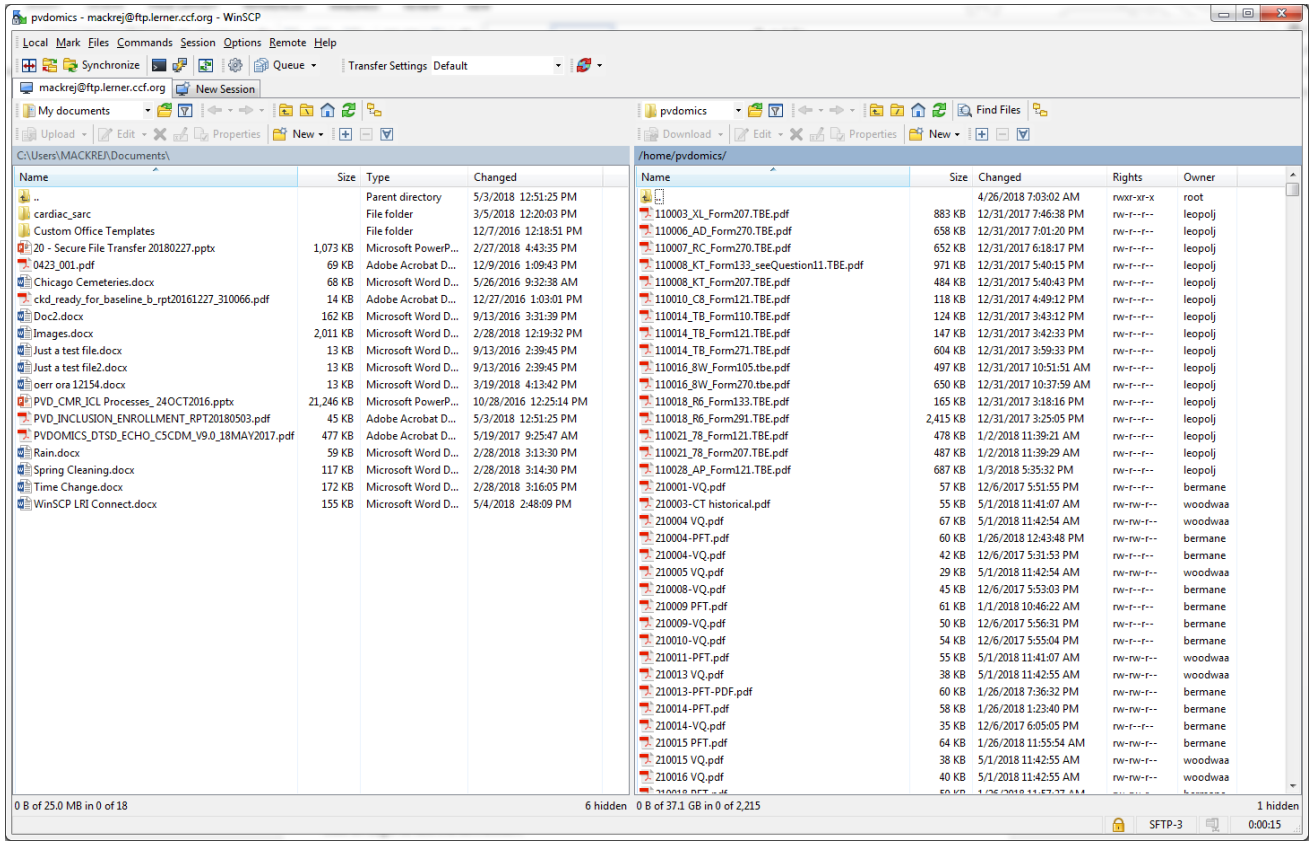


Note:

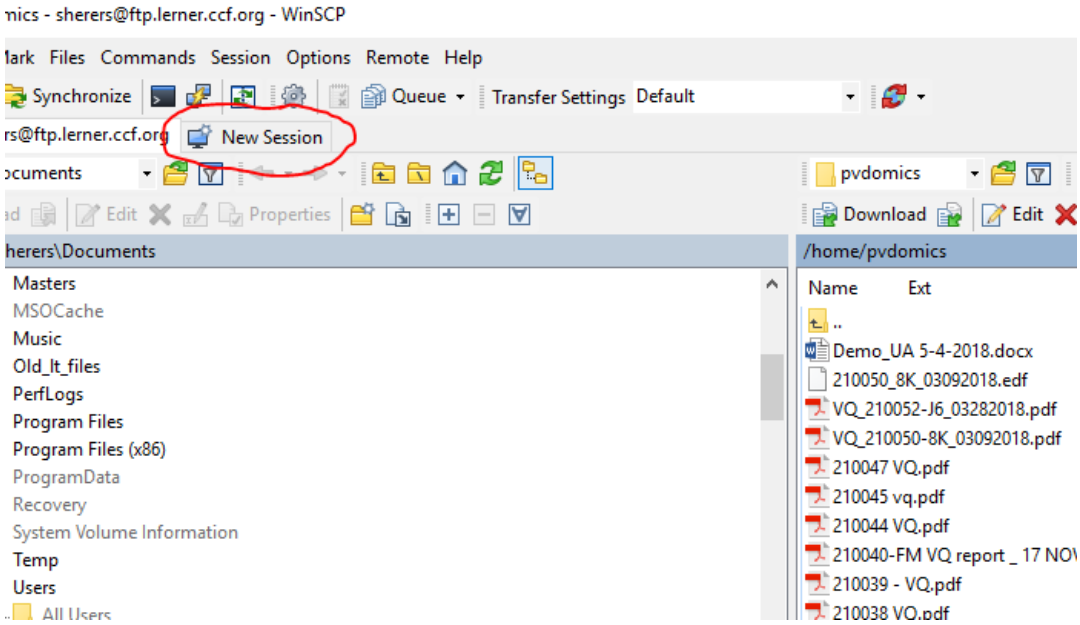
- **The very first time you try to login, it will show a warning message saying you are connecting to an unknown server. It will give you the option to connect and add the host key OR connect and not add the host key.**
- **Select "Yes"**



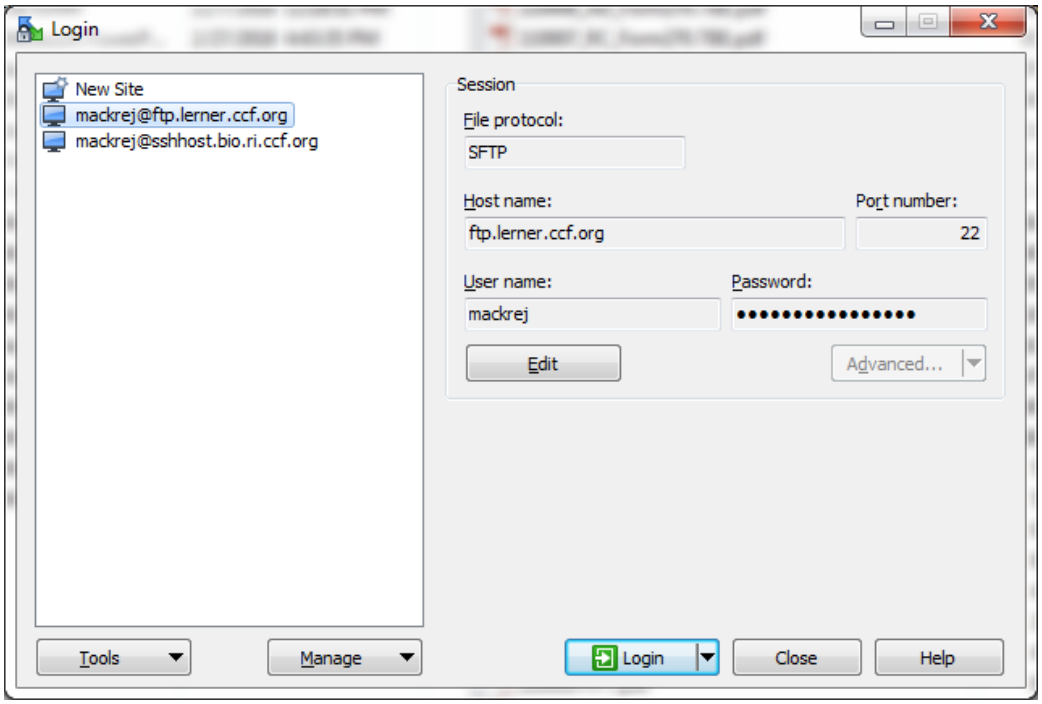
You're logged in! You can now transfer files into the portal again.



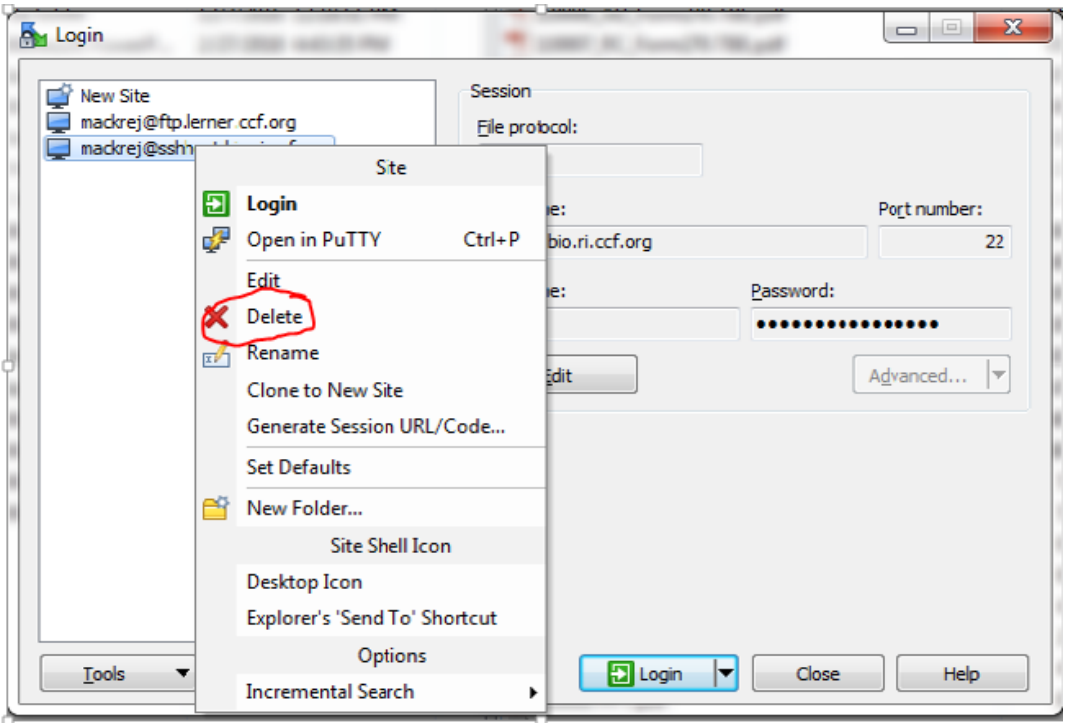
- **To delete the old portal session, click on the 'New Session'**



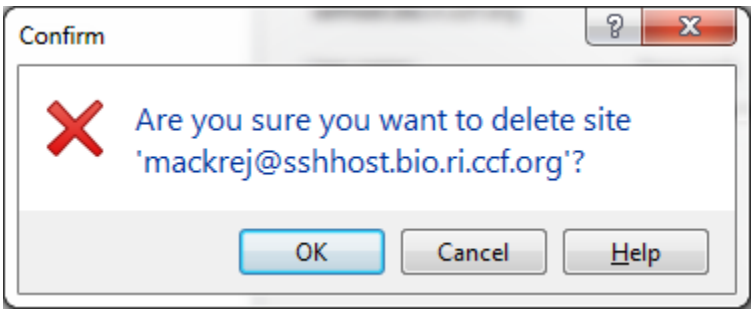
- **A new login screen will appear**



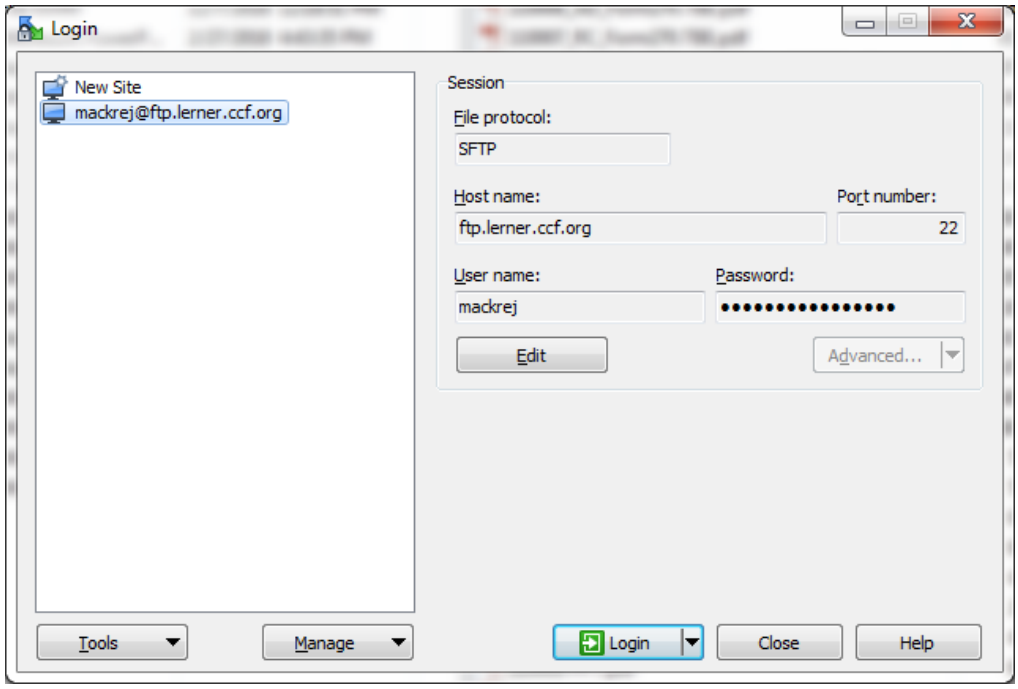
- **To delete the old portal session, right click on the old ssh host site (*sshhost.bio.ri.ccf.org*)**
- **Delete the old site**



- **Click OK.**



- **You're all set!**



7. Incidental Findings and Reporting

7.1 Introduction

The PVDOMIC protocol is designed to lead to a comprehensive understanding of patients with pulmonary vascular disease based on phenotypes and endophenotypes. In order to conduct this study, patients, at risk cohort comparators and true controls will be enrolled amongst the centers. All five WHO groups of pulmonary hypertension patients will also be recruited.

Subjects will undergo many tests as part of the study protocol, including but not limited to, overnight sleep monitoring, complete PFTs, echocardiography, cardiac MRI, chest CT, blood work and ventilation perfusion scan. Although these tests are part of a research protocol, they may reveal abnormalities in study subjects. This manual of procedures is designed to discuss the process of the identification of abnormalities and the dissemination of the information so that the patient can be made aware and receive the appropriate clinical work-up and treatment by their clinical health care provider.

7. 2 Incidental Findings Discovered at the Center

All subjects that are enrolled in PVDOMICs should identify a primary care provider or primary physician with contact information. This information should be kept in the study binder by the study coordinator. Testing conducted at the site may reveal an abnormality. The clinical site PI or his or her designee will notify the study subject within two weeks unless the finding is deemed critical by the PI, in which case it will be handled as described below. Findings will be highlighted and patients will be encouraged to check with their primary care providers regarding abnormalities. Findings deemed by the PI or designees to be clinically significant will be shared with the patient and primary care providers and other providers as designated by the patient. Critical abnormalities (such as severely abnormal blood tests) will be conveyed to the patient and primary care provider on an urgent basis (within 24 hours).. Although infrequent, an incidental finding may be found in a healthy control subject. The healthy subject will be notified and advised to check with their healthcare provider.

7.3 Incidental Findings Discovered at the DCC

Testing and samples collected at the clinical centers and sent to the DCC will be analyzed as outlined in the Manual of Procedures. Incidental findings that are discovered by Cores at the DCC of the PVDOMICs network will be reported (to the Principal Investigator and lead coordinator at the subject's site using only the subject's study ID. The PI or his or her designee will share this finding with the study subject at their clinical site. These findings will be highlighted and subjects will be encouraged to check with their primary care providers regarding the findings. Critical abnormalities (such as severely abnormal blood tests) will be conveyed to primary care providers on an urgent basis. During certain circumstances, primary care providers and other providers as designated by the patient will receive reports of significant abnormalities.

Results from genetic testing will only be reported if the subject agrees at the start of the study to have these findings reported. Only genetic results related to pulmonary hypertension risk or other clinically actionable genes (as defined by the American College of Medical Genetics) will be reported. The

central core laboratory that is doing genetic testing is a research facility and does not have the ability to provide genetic test results to the subjects. Therefore, the information will be conveyed to the site PI in general terms only. Site investigators will refer the subject to a genetic counselor to discuss options for clinical testing in a CLIA-approved laboratory. The cost of genetic counseling and clinical genetic testing is not covered under the research protocol.

The study site will provide acknowledgement to the DCC of their receipt of an incidental finding. The study site once notified by the DCC is responsible for the subject notification. We cannot forecast what incidental findings may be found on these tests or their clinical significance. That is why this information will be provided to the clinical center Principal Investigator who is familiar with the subject.

7.4 Placement in Medical Records

Many of the studies performed locally at a site will likely be placed into the subject's medical record, which means they would be available to the subjects and their healthcare providers. If an abnormality is found by a PVDOMICs core lab during research analyses, the results will not be placed into the subject's medical record.

CHAPTER 9. Quality Control and Site Monitoring

9.1 Quality Control Committee

The Quality Control (QC) Committee will oversee the monitoring of clinical sites as far as completeness and accuracy of the data being collected. Site visits can enhance the collaborative relationship between clinical centers (CC) and DCC personnel and provide an opportunity to discuss outstanding questions regarding individual patients or study procedures. Site visits will include sample data audits, reviews of data and lab QC, inspection of facilities, and discussions of recruitment, retention, and adherence as required. Additional "virtual site visit" conference calls can be held and have been a cost-effective approach in our recent studies for reviewing participant recruitment and data completeness/quality.

9.2 Data Edit Checks

Throughout the course of the study, each clinical center's performance will be monitored by a series of data quality reports. These include reports of enrollment, number of missing forms, rates of invalid data and data quality. These reports will routinely be sent to the clinical centers, the Steering Committee, and the NHLBI Program Office.

Edit checks are applied upon data entry and discrepant data will not be accepted into the study database. If data already in the study database appear to be discrepant, a data discrepancy inquiry will be sent to the clinical center. The DCC will track when the inquiry was sent, what item was questioned, who responded to the inquiry, what was the response, whether the database was changed, and if so, when.

9.3 Site Visits

Site visits are to be made to each of the clinical centers during the first two years of recruitment. The primary goals of the site visits are: 1) to observe the clinic under normal operating conditions for adherence to protocol; 2) to provide an opportunity for face-to-face questions and answers on any outstanding problems a clinical center is having with individual patients or with study procedures in general; 3) to increase/improve communication between the study administration, the clinic personnel and the DCC; and 4) to demonstrate the study's concern for the quality of data collection. Site visit teams consist of a site visit chair from the Quality Control Committee, a DCC staff member familiar with the PVDOMICS protocol and procedures (usually a coordinator), a NIH representative, and a study coordinator from another clinical center. Pre-site visit reports will be compiled by the DCC. All site visit teams will compile a post-site visit report which is given to the clinical center PI and to the NIH. These reports are reviewed by the Quality Control Committee.

At the site visits, the DCC will monitor the clinical center's performance in following the protocol by observing PVDOMICS Study procedures. Study patient files will be inspected, and a sample of PVDOMICS Study data forms will be checked against original source documents in the patients' medical records.

9.4 Remote Site Visits

In addition to on-site site visits, remote or virtual site visits will be made to clinical centers. These are done as conference calls between the site visit team and the clinical center. These are done usually on a as needed basis so can occur at any time during the course of the study. The primary goals of these type of visits are to check on the progress and operation of the center and address any specific concerns. A possible agenda is given in Appendix 1.

Appendix 1

Study Site Visit Call Example

Draft agenda for the call, which will be held from 1 to 3 p.m. Eastern Time on XXX

Toll free number: xxxxx Conference code: xxxxxx

Welcome and introductions
Note all members of STUDY SITE staff
Purpose of this call

Summaries from the weekly reports
Ready to enroll: Feb 15, 20xx. First enrollment: March 15, 20xx
Current goal for participants enrolled: XX (based on total enrollment goal of YY)
Percent of goal for randomized patients: ZZ%

Review of individual participants who have enrolled
990001

990002

990003

Promoting recruitment
How is the clinical center publicizing the study to referring physicians?
How is the clinical center publicizing the study to participants?
How will this clinical center team promote recruitment?

Considering which participants to enroll
How does the consent process work?
How does/will the "team meeting" work?

Promoting adherence to the protocol
How are participants scheduled and flow through upcoming visits and procedures?
How does the clinical center staff make sure no forms or procedures are missed?
How will this clinical center team promote adherence?

Issues with central cores
Would the clinical center like to raise any issues/points about the central cores?

Issues with DCC and Study Cores
Would the clinical center like to raise any issues/points where the DCC could be more helpful?

Quality control and review of data from the weekly QC report

Logistics
How often does this clinical center team meet as a group?
What other methods of communication are used?
When the PI is not available, who serves as the back up PI?
When the study coordinator is not available, who serves as the backup study coordinator?
Are there enough computers available for data entry, and is the internet connection good?
Any issue with contracts or budgets?
Have payments been received as expected?

Institutional support
Member of the institution states that this institution supports the study

Final comments from the clinical center

Closed session for the site visit team

CHAPTER 10: PROTOCOL CHANGES

10.1 General Principles

Version 1.1, May 12, 2016 of the PVDOMICS Study Protocol was approved by the Observational Safety and Monitoring Board (OSMB) and NHLBI. This version was used for submission to IRBs at the start of the study.

Protocol changes during the course of a study are not desirable and should not be made unless new information (from inside or outside the study) becomes available and strongly suggests that a change would strengthen the scientific validity of the study or protect the safety of study participants.

Recommendations for essential protocol changes may originate from the OSMB, the Data Coordinating Center (DCC), or any one of the clinical centers or study committees. Proposed changes will be submitted to the Steering Committee for consideration. The Steering Committee will decide whether the proposed modifications merit consideration and will determine the method of incorporating the proposed changes in the protocol.

If a major change is considered, the Steering Committee will receive a document showing the wording of the current protocol and the revised wording proposed.

There are nine voting members of the Steering Committee. These nine voting members are the six clinical center PI's, a DCC PI, the Steering Committee Chair, and the NHLBI Project Officer. A protocol change will be considered approved by the Steering Committee if *two-thirds* of the voting members are in favor of the change.

The Steering Committee Chair and the NHLBI Project Officer will judge whether a protocol change is considered major. If the Steering Committee approves what is considered to be a major change to the study protocol, this change will be presented to the OSMB who will advise the NHLBI as to whether the protocol change is acceptable. The NHLBI may seek further advice from other experts outside of the PVDOMICS Study before making the final decision as to whether the recommended protocol change is approved.

Corrections in numbering, paging, and format will be considered minor, non-essential changes, as will corrections of typographic errors. The DCC will keep track of the need for any non-essential changes needed and these changes will be made to the study protocol at the time an essential protocol change is needed.

11. Publications and Presentations Policy

11.1 Group Definitions

PVDOMICS Investigators

For the purposes of this policy, *PVDOMICS Study Investigators* are all individuals affiliated with the PVDOMICS Study to whom this policy will apply. The *PVDOMICS Study Investigators* are categorized into three groups:

1) PVDOMICS Study PIs
    a) PVDOMICS Study Principal Investigators at the Clinical Centers, Data Coordinating Center and Central Cores
    b) NHLBI Project Scientist
    c) Steering Committee Chair
2) PVDOMICS Study Investigators
    a) Typically, investigators who are at the Clinical Centers, Data Coordinating Center and Central Cores, other than *PVDOMICS Study Principal Investigators.*
    b) Research staff and study coordinators
    c) Trainees
        i) Trainees funded to maintain an active role on the PVDOMICS Study.
        ii) Students or fellows with an active but temporary role.
        iii) *PVDOMICS Study Principal Investigators* will be responsible for identifying *Trainees* at their sites annually or more often if changes in this group occur.
3) Ancillary Study Investigators
    a) Individuals who propose, receive approval from the PAS Committee, and obtain funding for a PVDOMICS ancillary study.

Publications and Ancillary Studies (PAS) Committee

The PVDOMICS PAS Committee will be chaired by the Steering Committee Chair. Other members are:

1) PVDOMICS Study PIs or Co-PIs at the Clinical Centers
2) DCC PI
3) NHLBI Project Scientist

[Note: Above makes the PAS the same as the Steering Committee. PAS does not include Core PIs.]

11.2 Publication Policy Principles

1) Publication of scientific research papers is a central and critical aspect of the PVDOMICS Study because:
    a) Scientific publications will be the principal mechanism by which the PVDOMICS Study will communicate its scientific findings.
    b) Scientific publications represent one of the most important mechanisms for PVDOMICS Study Investigators to achieve scientific and academic recognition for their participation in PVDOMICS Study.
2) Research questions and hypotheses to be addressed using PVDOMICS Study data should be formulated *a priori* and clearly stated in a manuscript proposal to reduce the likelihood that study results are attributable to Type I error.
    a) When an approved manuscript activity diverges from the established analytical plan, the authors of any resulting manuscript are urged to be transparent in their discussion

of the possible implications for the level of Type I error and assessments of statistical significance.

b) In the event that a new research question and hypothesis is generated during analyses, the authors are similarly urged to be transparent in their discussion of the possible implications for the level of Type I error and assessments of statistical significance.

3) Publication policies should promote scientific inquiry within and productivity from the PVDOMICS Study.
4) To avoid premature publication of results that might compromise the performance of the study (such as by publication of trends of results before such trends become statistically convincing) or that might compromise the ability to publish the results in high-quality peer-reviewed journals (as by premature release to the lay press).
5) Publication of scientific findings from the PVDOMICS Study should proceed in a timely fashion once relevant analyses are complete.
6) Abstracts, presentations, and publications based on PVDOMICS Study material must be accurate and objective and must not compromise the scientific integrity of the PVDOMICS Study.
7) The publications arising from the PVDOMICS Study should avoid overlap (except for review articles) and conflicting representation of PVDOMICS Study findings.
8) Recognition through authorship will be distributed among the *PVDOMICS Study Investigators* so that:
    a) *PVDOMICS Study PIs* have equitable opportunity to lead and co-author PVDOMICS Study publications.
    b) *PVDOMICS Study Investigators* have opportunity to lead and be co-authors on publications resulting from analyses made possible through their collaboration, and participate in publications reporting scientific findings to which they have contributed.
    c) *Ancillary Study Investigators* have the opportunity to lead and be co-authors on publications resulting from analyses made possible through their collaboration.
9) The PVDOMICS Study promotes the career development of trainees and junior faculty by providing them opportunity to lead and to be recognized as co-authors of PVDOMICS Study publications, as appropriate.
10) Authorship on PVDOMICS Study publications will adhere to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the Inter Committee of Medical Journal Editors.

To adhere to these principles, it is the policy of the Study that preparation of all publications or presentations, other than materials prepared for local publicity purposes (see Section 11.3), must be assigned by the Chair of the Publications and Ancillary Studies (PAS) Committee to specifically appointed writing committees. Materials must be reviewed and approved by the PAS Committee and/or the Steering Committee before publication or presentation.

The PVDOMICS PAS Committee will operate as long as the DCC is functioning in providing support to the analysis and reporting of study results. This may include operating under no cost extensions of the DCC grant.

11.3 Scope of Policy, and Exception for Local Informational Materials

All material to be presented orally, as poster, or submitted for publication for dissemination by individuals associated with the Study and dealing with any aspect of the Study must receive prior review and approval by the PAS Committee with the following exception:

Material prepared for informational purposes within the recruitment region of a PVDOMICS Clinical Center, or presented orally or as handouts or posters to local professional audiences solely for the purposes of informing the profession of the Study and its objectives, need not be reviewed by the PAS Committee. Such material must be limited to a background discussion of pulmonary hypertension and a description of the Study organization, objectives, and entrance criteria, and to results of the Study that have previously been presented to a scientific body or published in a scientific journal. It must not include discussion of any study data not previously presented or published. Informational material for dissemination, including lay summaries, does need to be reviewed and approved by the PAS Committee

11.4 Source of Suggestions for Publications of the Study

Suggestions for topics appropriate for preparation of abstracts or peer-reviewed papers are made by the PAS Committee. In addition, all investigators and staff in the Study are invited to suggest topics appropriate for preparation as abstracts and peer-reviewed papers from the Study. Such suggestions should be made to the DCC and the Chair of the PAS Committee, who shall review the request to be certain that there is no overlap with materials previously assigned, or planning to be assigned, to other writing committees. Where such overlap exists, the Chair of the PAS Committee may make recommendations that the suggestion be referred to an existing writing committee, that additional study investigators be added to existing writing committees, or make other suggestions to resolve the overlap. However, final decision in this matter will be made by the Chair of the PAS Committee.

It is the intent of this policy to encourage non-physician professionals to prepare scientific presentations to their own professional meetings and to prepare scientific papers for their own professional journals in addition to participating in the preparation of papers for medical journals. Since the subject matter of these reports and papers may well overlap with material being prepared by writing committees for medical journals, it is the policy of the Study that under these circumstances, rather than forming a new writing committee, such non-physician professionals should be added to the existing writing committee concerned with related matters, specifically for the purposes of preparing such reports. The authors of these presentations and reports will be the members of the writing committee, with first author being the individual added to the committee for this purpose, using the appropriate authorship style described in Section 11.7.

It is also the intention of this policy to promote the conversion of as many abstracts as possible into full manuscripts and to discourage the production and presentation of abstracts that do not represent an intermediate step towards the preparation of a full scientific manuscript.

In addition, the PAS Committee will formulate and maintain a list of suggested topics that should be prepared for publication, to assure that all completed aspects of the work of the Study are reported to the scientific community in a timely fashion.

11.5 Assignment of Writing Committees

Topics suggested for presentation or publication that do not overlap with an existing committee will be circulated to PVDOMICS Study PIs and PVDOMICS Study investigators. Writing committees should be formed with the intent of writing a paper for publication. This committee can also prepare abstracts for submission to professional meetings. Volunteers for the writing committee solicited are from all investigators. Persons are requested to suggest and justify names for lead authors (Chair of writing committees) and co-authors. This information will be collated and reviewed by the Chair of the PAS Committee and the DCC PI. The Chair of the PAS Committee will decide on the final composition of the writing committee.

If a topic is suggested by an investigator of the Study, and approved by the PAS, the writing committee will be formed as just described and the person making the suggestion will be considered as the potential lead author. The Principal Investigator of an ancillary study should be considered for lead author of material derived from that ancillary study. If only a subset of clinical centers participate in an ancillary study, only investigators from these centers should be considered to be on writing committees relating to this study.

Appointments of writing committee chairs will be made fairly to all professionals -- physicians, study coordinators, nurses, statisticians, and others -- in a manner that recognizes the unique contributions of each member of the Study to its performance. Any dispute about the selection of the lead author or co-author will be settled by the Chair of the PAS Committee. In all cases, writing committees requiring analysis of data by the Data Coordinating Center will have at least one member of the DCC assigned to it.

From time to time it may be expedient for the chairmanship of a writing committee to be reassigned to another member of that committee, or for members to be dropped from or added to a writing committee. The Chair of the PAS Committee is authorized to make such changes with the consensus of the members of the writing committee, or on his own authority where there is clear cause.

11.6 Classes of Reports of the Study

There are four types of reports of the PVDOMICS Study:

A. Reports of the major outcomes of the Study. It is assumed that there will generally be only a few of these reports.

B. Reports addressing in detail one aspect of the Study, but in which the data are derived from the entire study.

C. Reports of data derived from a subset of centers by members of the Study (e.g., substudies or ancillary studies), or originally conceived analyses of data from the entire Study (original analyses).

D. Reports of investigations initiated outside the Study, but using data or samples collected by the Study. The investigators may be PVDOMICS or other investigators, but the source of the ideas and the funding for the study will have been derived outside the Study itself. Writing committees for this type are formed and presentations and publications made in accordance with the general policy rules for PVDOMICS publications. However, the Principal Investigator of an ancillary study should be assigned the prerogative and should take primary responsibility in publishing the results of the study.

11.7 Authorship Policy

The authorship policy of the Study must achieve two somewhat conflicting goals. First, it is recognized that the findings of the study, especially the findings reported in Type A and B reports, are derived from the efforts of the entire PVDOMICS professional staff. Thus, reports of Types A and B must give recognition to all the investigators of the Study, and other Types must give primary recognition to those participating in the specific investigation. On the other hand, it is recognized that the preparation of a manuscript places special demands on the assigned writing committee, and especially on the Chair of the writing committee. Further, recognition of special effort and achievement is important in the professional careers of the study staff, and specific listing as an author is a significant motivating factor that will help assure prompt completion of writing assignments and timely publication of the results of the Study. The PVDOMICS authorship policy

attempts to recognize each of these goals. The authors of PVDOMICS Study publications will be listed as detailed below for each type of publication.

Type A publications:

Abstracts: the PVDOMICS Study Group[1], presented by XXXX.

Papers: the PVDOMICS Study Group[1], prepared by XXXX.

[1]The PVDOMICS participant box, detailed below, must be included in these papers. If a society's or journal's policy does not allow authorship by a group, the authors will be listed first as in Type B publications.

Type B publications:

Abstracts and papers: Authors' names, and the PVDOMICS Study Group[1]

[1]The PVDOMICS participant box will be included in all papers if this can be arranged with the publisher. Otherwise it will be referenced to one of the Type A papers. It will not be practical to publish the entire list of participants in abstracts.

Type C and Type D publications:

Abstracts and papers: authors' names for the PVDOMICS Study

[1]The participant box will be included in all Type C papers if this can be arranged with the publisher. Otherwise it will be referenced to one of the Type A papers. In Type D papers, the list of research personnel will be referenced in all cases. It will not be practical to publish the entire list of participants in abstracts.

11.8 Listing of Professional Participants in the Participant Box

The PVDOMICS Study participant box will list all professionals who have participated in the Study for a minimum of one year. The participants for each participating center will be listed together, with the center Principal Investigator listed first, and identified as "P.I." followed by the other center or investigators listed alphabetically. Each participant will be listed only by his/her professional and academic degrees, not by the specific position that he/she held in the study. The centers will be listed in the following order:

Steering Committee Chair
Clinical Centers (in alphabetical order by center name)
DCC
Cores/Repositories
NHLBI

Prior to the publication of any papers from the Study, each center will be asked to confirm and approve the listing of the personnel from that center in the Participant Box.

11.9 Acknowledgement of Support

Acknowledgement of grant support to be used in all papers reporting results of the Study. (In the case of ancillary studies, additional sources of support should be cited as appropriate).

The Study is supported by the National Heart, Lung, and Blood Institute, and the Pulmonary Hypertension Association. Additional support is provided by the (list of any industrial or other support).

11.10 Schedule for Completion of Writing Assignments and Resolution of Overlaps Between Writing Committees

At the time that a writing committee is constituted, the PAS Committee will establish a timetable for the completion of the writing assignment that takes into account deadlines for the publication, the amount of time that will be required for data analysis, the other commitments of the DCC, and the priority of the publication. The Chair of the Writing Committee should provide the Chair of the PAS Committee a general outline of the proposed publication within a month of receiving its assignment, to permit the PAS Committee to identify any overlap with the assignments of other writing committees, and to permit establishment of an appropriate timetable. Where overlaps of materials to be covered by different writing committees are detected, the Chair of the PAS Committee will attempt to resolve these informally with the chairs of the involved writing committees. In the event that this effort at mediation fails, the issue will be resolved by the Chair of the PAS Committee. The Chair of the PAS Committee will report at each meeting of the Steering Committee on the progress of the various writing committees.

11.11 Review of Abstracts and Presentations by the PAS Committee

To expedite review of abstracts, oral presentations, and any other material for which there is an explicit deadline for submission, the following procedure will be used:

1) The writing committee shall contact the Chair of the PAS Committee and the DCC P.I. should be contacted. The Chair (or designee) will name a subcommittee of <u>two members</u> of the PAS Committee to review the submitted material and will inform the submitter and this subcommittee of their appointment. The submitted material should be sent by the submitter directly to these two reviewers so as to reach them no fewer than seven (7) days prior to the deadline for submission.
2) The members of the subcommittee shall review the material and notify the Chair (or designee) of their approval or disapproval. If there is unanimous approval, the PAS Committee Chair (or designee) shall inform (through the DCC) the submitter that he/she has approval for the submission.
3) All materials submitted for approval in this fashion will be distributed, together with notice of the disposition, to all members of the PAS Committee.

Approval for submission of an abstract or oral presentation does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval in accordance with the above rules at least seven (7) days prior to the scheduled oral or poster presentation. Normally this review will be done by the same subcommittee of the PAS Committee that reviewed the initial abstract.

1) In the case of an oral presentation, an outline of the talk and a copy of any slides to be used must be submitted for review.
2) In case of a poster presentation, the content of the poster material must be submitted for review.

Also, if there is a meeting proceedings paper, the lead author must notify the PAS Chair at the time the abstract is proposed and receive approval for both abstract and the affiliated proceeding paper.

11.12 Review of Papers by the PAS Committee

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference (including book chapters and reviews), whether or not there is a deadline for submission, must be submitted to the Chair of the PAS Committee for formal review by the entire

Committee. If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the Chair, PAS Committee, at least 30 days prior to the deadline, to permit such review. This review will be conducted as follows:

1) The Chair of the PAS Committee, shall appoint at least two primary reviewers, one of which must be a PAS Committee member, and one of whom may be any professional member of the Study Group with appropriate expertise. The Chair (through the DCC) shall distribute the material to all members of the PAS Committee. The two primary reviewers shall each prepare and send to the Chair a written critique of the submitted material for distribution to the entire PAS Committee. The PAS Committee will be given a deadline by which any comments or critiques must be received by the Chair of the PAS Committee.

2) The Chair of the PAS Committee may schedule a conference call of the PAS Committee, to review papers and other non-time critical materials as agenda items. The reviews of the panel members and any comments received from the center PIs will be distributed to the committee with the agenda. Alternatively, the Chair can decide if the review can be done by email input, rather than by conference call.

3) While discussion of the submitted paper(s) and other materials will be led by the two appointed reviewers, all members of the PAS Committee will be invited to participate and all shall vote on final disposition.

4) In keeping with medical editorial traditions, there are three possible dispositions: approval of the material as submitted (possibly with some recommendations for revision that do not require re-review), non-acceptance of the material as submitted but with recommendations to the authors for revisions and resubmission, and disapproval of the material.

5) The Chair of the PAS Committee shall be responsible (through the DCC) for communicating the decision of the Committee to the authors, together with a summary of suggestions for revision, if any.

6) In the event that editors of a scientific journal to which an approved PVDOMICS scientific manuscript is submitted suggest or require revisions of the manuscript, the revised manuscript must be reviewed again by the PAS Committee prior to resubmission in the same manner as described above. Generally, the Chair will appoint the same reviewers who first read the paper to review the revision, and every effort will be made to expedite such repeat reviews.

11.13 Criteria for Review of Materials by the PAS Committee

All materials submitted to the PAS Committee will be reviewed for acceptability on two grounds:

1) Materials shall be evaluated for scientific accuracy, quality, importance, and style. The intent is to assure that all approved PVDOMICS materials reflect well on the Study.

2) Materials shall be reviewed to assure appropriateness of the content. The material shall be reviewed to assure that it conforms to the assignment to the writing committee, addressing satisfactorily the assigned topics and not encroaching on material assigned to other writing groups. In addition, the material shall be reviewed to assure that it does not divulge prematurely the outcomes or findings of the Study or compromise the eventual publication of PVDOMICS findings in high quality peer-reviewed journals

11.14 Maintenance of Records of Publications and Presentations

The DCC will maintain a record of all publications and presentations of the PVDOMICS Study, separated into the following categories:

1) Peer-reviewed accepted or published papers in professional journals

2) Abstracts published in citable journals
3) Presentations at regional, national or international meetings

This listing will be updated at least every six months and will be distributed to the all investigators in the Study, together with copies of any scientific papers or abstracts published since the last update. This is intended to inform investigators of all study findings and to facilitate the updating of curricula vitae.

11.15 Acknowledgement and Acceptance of PVDOMICS Study Policies on Publications and Presentations by the Study Investigators

To assure that all investigators (the three groups defined in Section 11.1) involved with the Study are aware of the policies of the Study, and to minimize the possibilities of misunderstandings after initiation of the Study, each investigator (except vascular function personnel, sonographers) will be given a copy of this Chapter and will be asked to sign a Statement of Understanding Form (see next pages) listing the major provisions of the Chapter and attesting to his/her acceptance of these policies. The original of the signed Statement of Understanding Form should be returned to the DCC. A copy of the Chapter and their signed Statement of Understanding Form should be kept by each PVDOMICS investigator.

PVDOMICS STUDY

Statement of Understanding of Policy
Concerning Publications and Presentations

To assure that all professionals involved with the PVDOMICS Study know and understand the policies of the PVDOMICS Study regarding publications and presentations, and to preclude the possibilities of misunderstandings after initiation of the Study, each professional member will be given a copy of the Manual of Operations Section 11 detailing these policies and will be asked to sign this form attesting to his/her acceptance of these policies, which are summarized below.

I. Material Covered by These Policies

All material to be presented at meetings or submitted for publication or dissemination by individuals associated with the PVDOMICS Study and dealing with any aspect of the PVDOMICS Study must receive prior review and approval by the Publications and Ancillary Studies (PAS) Committee with the following exception:

Material prepared for publicity purposes within the recruitment region of a PVDOMICS Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of the PVDOMICS Study and its objectives, need not be reviewed by the PAS Committee. Material for dissemination does need to be reviewed and approved by the PAS Committee. Such material must be limited to a background discussion of the issue involved and a description of the PVDOMICS Study organization, objectives, and entrance criteria, and to results of the Study that have previously been presented to a scientific body or published in a scientific journal. It must not include discussion of any previously unpresented or unpublished PVDOMICS Study outcomes or results, and must not itself result in publication of an abstract or other citable professional reference.

II. Assignment of Writing Committees for Publications

The PAS Committee will solicit volunteers for each writing committee for abstracts and publications and make a recommendation on the writing committee and topic to the PVDOMICS Steering Committee Chair. The PVDOMICS PAS Chair will decide on the final composition and topic of the committee. All interested individuals will be given a chance to request appointment to the various writing committees, but the final appointments will be determined by the Chair of the PAS Committee.

III. Authorship

The PVDOMICS policies specify the authorship for each of the four different classes of publication or abstract (See Section 11.6 of the Manual of Operations). These policies are binding and must be followed in all publications derived from the PVDOMICS Study.

IV. Review of Abstracts

All abstracts must be reviewed and approved by the PAS Committee before being submitted (See Section 11.11 of the Manual of Operations). These abstracts must be delivered to the reviewers at least seven (7) days before the submission deadline to permit time for this review. Abstracts not approved in this fashion will be withdrawn by the PVDOMICS Study.

V. Review of Materials for Presentations

Approval for submission of an abstract does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval by members of the PAS Committee at least seven (7) days prior to the scheduled oral or poster presentation.

VI. Review of Papers

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PAS Committee for formal review by the entire Committee (see Section 11.12 in the Manual of Operations). If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the Chair of the PAS Committee at least 30 days prior to the deadline, to permit such review.

VII. Certification by PVDOMICS Study Investigators

This is to certify that I have read the above statement of policies of the PVDOMICS Study with regard to publications and presentations, understand it, and agree to abide by it in matters of all publications and presentations derived from the PVDOMICS Study.

_____ _____

(Signature) (Date)

_____

(Print or Type Name and Institution)

PVDOMICS STUDY

Statement of Understanding of Policy
Concerning Publications and Presentations

To assure that all professionals involved with the PVDOMICS Study know and understand the policies of the PVDOMICS Study regarding publications and presentations, and to preclude the possibilities of misunderstandings after initiation of the Study, each professional member will be given a copy of the Manual of Operations Section 11 detailing these policies and will be asked to sign this form attesting to his/her acceptance of these policies, which are summarized below.

I. Material Covered by These Policies

All material to be presented at meetings or submitted for publication or dissemination by individuals associated with the PVDOMICS Study and dealing with any aspect of the PVDOMICS Study must receive prior review and approval by the Publications and Ancillary Studies (PAS) Committee with the following exception:

Material prepared for publicity purposes within the recruitment region of a PVDOMICS Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of the PVDOMICS Study and its objectives, need not be reviewed by the PAS Committee. Material for dissemination does need to be reviewed and approved by the PAS Committee. Such material must be limited to a background discussion of the issue involved and a description of the PVDOMICS Study organization, objectives, and entrance criteria, and to results of the Study that have previously been presented to a scientific body or published in a scientific journal. It must not include discussion of any previously unpresented or unpublished PVDOMICS Study outcomes or results, and must not itself result in publication of an abstract or other citable professional reference.

II. Assignment of Writing Committees for Publications

The PAS Committee will solicit volunteers for each writing committee for abstracts and publications and make a recommendation on the writing committee and topic to the PVDOMICS Steering Committee Chair. The PVDOMICS PAS Chair will decide on the final composition and topic of the committee. All interested individuals will be given a chance to request appointment to the various writing committees, but the final appointments will be determined by the Chair of the PAS Committee.

III. Authorship

The PVDOMICS policies specify the authorship for each of the four different classes of publication or abstract (See Section 11.6 of the Manual of Operations). These policies are binding and must be followed in all publications derived from the PVDOMICS Study.

IV. Review of Abstracts

All abstracts must be reviewed and approved by the PAS Committee before being submitted (See Section 11.11 of the Manual of Operations). These abstracts must be delivered to the reviewers at least seven (7) days before the submission deadline to permit time for this review. Abstracts not approved in this fashion will be withdrawn by the PVDOMICS Study.

V. Review of Materials for Presentations

Approval for submission of an abstract does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval by members of the PAS Committee at least seven (7) days prior to the scheduled oral or poster presentation.

VI. Review of Papers

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PAS Committee for formal review by the entire Committee (see Section 11.12 in the Manual of Operations). If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the Chair of the PAS Committee at least 30 days prior to the deadline, to permit such review.

VII. Certification by PVDOMICS Study Investigators

This is to certify that I have read the above statement of policies of the PVDOMICS Study with regard to publications and presentations, understand it, and agree to abide by it in matters of all publications and presentations derived from the PVDOMICS Study.

_____ _____

(Signature) (Date)

_____

(Print or Type Name and Institution)

PVDOMICS Network

Manual of Procedures, Chapter 11 Addendum (5/4/23)

Authorship of papers

Main considerations

Authorship is to recognize contributions of PVDOMICS participants to manuscripts as well as to the network generally.

Manuscripts require the contributions of many individuals who have participated in creation and organization of the network including data and biosample collection, collating data and assuring its quality, analysis of data, writing of the paper, critiquing and editing of the manuscript and many other roles.

Distribution of authorship on manuscripts arising from the Network should be fair in recognizing these contributions, inclusive and flexible.

Named authors on the title page of manuscripts will be as follows:

First author will be the author who takes the lead in pulling the first draft of the manuscript together and takes the major role in overseeing subsequent drafting through submission. This will usually be the writing committee lead, but could be delegated to a junior writing committee member. There may be 2 first authors who exert comparable effort

The last named author will usually be a senior member of the WC who has provided major oversight of drafting and may have delegated first authorship.

Other members of the WC may be listed according to the contributions they made or alphabetically

Clinical PIs who were not members of the writing committee will be named next, followed by the DCC PIs and Steering Committee Chair.

Core Leaders and members who made substantial contributions to cleaning, interpretation and analysis of data for the manuscript should also be included

Other members of the Steering Committee who made notable contributions to the manuscript can also be listed

The last author will be followed by “and the PVDOMICS Study Group” which will be linked to an authorship box which, along with the named authors on the title page, will be citable by PubMed

Chapter 12: PVDOMICS Study Ancillary Studies

12.1 Purpose

To enhance the value of the PVDOMICS Study, the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies in collaboration with the PVDOMICS Study investigators.

12.2 Definition of Ancillary Study

An ancillary study is one based on information, images or biospecimens from the PVDOMICS Study participants in an investigation that is relevant to, yet not part of the main goals of the PVDOMICS parent study, and derives support from non-PVDOMICS Study funds. It is anticipated that a typical ancillary study will propose the collection of additional data not collected or analyzed as part of the PVDOMICS Study parent data set.

12. 3 Ancillary Study Principles

1) Participation in, and approval of, an ancillary study is subject to review by the PVDOMICS Steering Committee. Also, the PVDOMICS Study Observational Study Monitoring Board (OSMB) will be notified of all ancillary studies and will provide oversight. Namely, the OSMB will determine if there are any safety concerns and if the study impacts the parent PVDOMICS study. The OSMB will monitor ancillary studies in a similar manner as the parent study.

2) Approval by the Steering Committee will be defined as a majority of votes in favor of the proposal. In the case of an ancillary study which includes subject participation at all clinical centers, two-thirds approval of the Steering Committee membership will be required. Furthermore, the centers participating must each approve.

3) An ancillary study must receive Steering Committee approval before a grant to support it is submitted to a funding agency or to local institutional authorities (e.g., IRB), and before the study is permitted to begin.

4) All PVDOMICS ancillary study proposals initiated by a non-PVDOMICS investigator as PI must include as a Co-investigator at least one PVDOMICS Study PI or Co-investigator.

5) Ancillary studies require external (non-PVDOMICS Study) funding. Any ancillary study must have sufficient funding to cover the costs incurred by the PVDOMICS Study Clinical Centers and Cores (e.g., to process or ship samples), and the Data Coordinating Center (DCC) (for tasks such as sample selection, data management, preparing and documenting analysis files, participating in statistical analysis, and integrating the new ancillary data into the combined PVDOMICS Study database). Also, studies using Repository biospecimens must have adequate support for handling and using the specimens. Special consideration will be given to requests for ancillary

studies to be funded through training grants or career development awards through the NIH or other peer-reviewed funding sources.

6) Considerations for approval of ancillary studies

   The proposed study:

   A) must meet requirements of the highest scientific merit.
   B) must not, or minimally, interfere with the completion of the main objectives of PVDOMICS Study.
   C) must not, or minimally, adversely affect participant cooperation or compliance with PVDOMICS Study.
   D) must not create a serious diversion of PVDOMICS Study resources.
   E) must put minimal demand on scarce PVDOMICS Study resources, such as blood samples.
   F) must require the unique characteristics of the PVDOMICS Study patient data to accomplish its goals.
   G) must have adequate resources to effectively complete the project.
   H) must agree to provide the ancillary data to the PVDOMICS Study (also see 10 and 13).
   I) must not jeopardize the public image of the PVDOMICS Study.
   J) consider using the entire cohort for testing, rather than individual centers or isolated subgroups when appropriate.

7) Once an ancillary study is approved, if a change occurs in the structure or concept of the study (for example as a result of the NIH review process), including any change in data elements to be collected or analyzed, or any change to study aims, such changes must be disclosed to the PVDOMICS Study Steering Committee, for review and approval before the proposal is (re-)submitted to a funding agency.

8) A written progress report on ancillary studies must be made periodically (e.g., at time of Steering Committee meetings) to the Steering Committee.

9) All data collected under the auspices of an ancillary study is expected to adhere to the same high standards of quality applied to data collected in the core PVDOMICS Study. A plan for quality control must be submitted to the DCC for funded studies. In addition, once the ancillary study is initiated, periodic quality control reports must be sent to the DCC.

10) Data from ancillary studies will be made available to the DCC either on a real time basis using direct data entry into the DCC's computer server or through periodic transfers of ancillary data to the DCC.

11) Images, tracings and biosamples may usually be kept by the ancillary study investigators. During the PVDOMICS Study operation, further use of the samples beyond the objectives that have been approved by the PVDOMICS Steering Committee is prohibited without additional consent from the Steering Committee. The restrictions on specimens imposed by the Veterans Affairs for specimens

collected at any VA sites must be observed. Also, the NHLBI has the option to require that the images, tracings (or copies of) and remaining biosamples be transferred to the NHLBI Biological Specimen and Data Repository Information Coordinating Center (BioLINCC) Repository at the end of the PVDOMICS Study.

12) Unless specifically arranged, all analyses will take place at the DCC and be conducted under the supervision of its biostatistician-investigators in collaboration with the ancillary study investigators. Under specifically approved circumstances, datasets will be released to external investigators for local analysis.

13) Proposals for abstracts and manuscripts resulting from all ancillary studies shall be submitted to the Steering Committee for review and approval before establishment of a writing committee or a submission for publication or presentation. It is anticipated that principal investigators of approved ancillary studies will lead at least one scientific paper emerging from the ancillary study analyses.

14) An archival copy of the collected data and/or laboratory results not already held at the DCC will be sent to the PVDOMICS Study Data Coordinating Center at the conclusion of the data analysis and publication of the main ancillary study results. This transfer is the responsibility of the ancillary study PVDOMICS Study collaborator(s). Once transferred back to the PVDOMICS, these ancillary data will become part of the aggregate PVDOMICS Study data.

15) Information about proposed ancillary studies, and progress and results from approved ancillary studies are considered to be confidential and are not to be shared with others outside of the PVDOMICS Study except as provided for by the PVDOMICS Study Publications and Ancillary Studies Policy. Ancillary study investigators can share information among their co-investigators and with PVDOMICS Study investigators.

12.4 Funding of Ancillary Studies

Ancillary studies will not be funded by the PVDOMICS Study, but will require an independent source of funding.

12.5 Approval Procedures

1. Proposals may be generated by a participating clinical center or by other interested investigators providing at least one PVDOMICS Study PI or Co-investigator is included as a co-investigator. These applications are submitted to the Data Coordinating Center for review by the PVDOMICS Steering Committee.

2. There will be a two-step review by the Steering Committee. The first step is to have the proposal reviewed for its concept and general acceptability. This will be done in 2-4 weeks after submission. A short description of the study including the following information should be submitted.

a. Hypotheses to be tested.
Specific outcome variables that will be assessed.
Need for data and specimens from the DCC or Repositories.

b. Significance of the proposed ancillary study.

c. How will performance of this ancillary study affect the PVDOMICS Study? Specifically:

i. Will there be any data/specimen/image collection beyond that specified in the PVDOMICS Study protocol? If so, what additional information/samples will be obtained? What, if any, impact will this additional information/sample have on the main study?

ii. How much additional participant burden and time will be required to complete this ancillary study?

iii. Will additional funds be requested for the study and what will their source be?

3. If this proposal is acceptable in concept to the Steering Committee, a more detailed proposal should be written and submitted for review. This proposal should include detailed information on:

a. Hypotheses to be tested.
b. Background and significance of the study.
c. Conduct and performance of the study including specifying the study population and the data to be collected.
d. PVDOMICS Study staff and DCC burden. Costs for this work need to be included in the project's support.
e. Sample size justification.
f. Quality control of the data.
g. Data analysis methods.

4. The Steering Committee will review the proposal within 2-4 weeks. The decision can be for approval, modifications with further review, or disapproval.

12.6 Publication of Ancillary Study Results

The policies regarding publications and presentations of the result of ancillary studies are the same as those governing the publications and presentations of results of the main study (see Manual of Operations). These policies are designed to:

1. Assure timely publication of the results to the appropriate professional audiences.
2. Avoid premature publications of results that might compromise the performance of the main study or that might compromise the ability to publish the results in high quality peer reviewed journals.
3. Maintain high standards of the published material.
4. To guard against duplicate publication of results, unless in review articles after the results have been published in a peer-reviewed article.
5. Assure equitable attribution of credit to all of the professionals participating in the ancillary study and the PVDOMICS Study.

CHAPTER 30. Participant Study Visits

30.1 Introduction: This Manual of Operations chapter describes study visits for all three groups of participants who consented to participate in the PVDOMICS Study. These three groups of participants include:

- Pulmonary vascular disease (PVD)
- PVD comparators
- Healthy controls

Note: PVD and PVD comparators will undergo the same study protocol. Healthy controls will NOT undergo right heart catheterization (RHC) and V/Q scan.

The PVDOMICS Study is not a treatment trial, other drugs considered necessary for any participant's welfare may be given at any time. Participation in PVDOMICS will not prohibit access to new or novel therapies, but participants will be asked to refrain from participating in a clinical trial involving biologic medications or other PH therapies during the time of participation in PVDOMICS. Medications will not be withheld except for the conduct of specific procedures where withhold of medications is part of routine care.

30.2 Study Visit(s) Overview: PVDOMICS Study visits need to be completed within 6 weeks and participants will undergo many tests and procedures during this time. Some of these tests and procedures will be for clinical care as well as for the PVODMICS Study. In some cases, historical test data may be used.

Procedures that participants will undergo at each recommended study visit are shown in the table below. The number of visits held will depend on each clinical center's scheduling procedures. The complexity of procedures requires careful planning and scheduling of participants.

IMPORTANT: There are specific tests that MUST be completed before or after other tests:

- CBC, CMP, PT/INR, pregnancy test (if applicable) must be completed and resulted before right heart catheterization
- OMICS blood draw #1 must be completed <u>before</u> RHC , CPET, CT (with contrast), and V/Q scan
- All blood draws need to be done either before the V/Q scan or at least 3 days following V/Q
- Pregnancy testing (either blood or urine) needs to be completed and resulted <u>prior</u> to completion of any other testing at each study visit.

It is anticipated that research coordinators and investigators will have screened and contacted the participant in advance of visit 1 in anticipation of testing. For example: Visit 1 requires blood draw in fasting conditions. Thus participants should be asked to come to Visit 1 fasting for a minimum of 8-10 hours.

Table 30.21. RECOMMENDED VISIT SCHEDULE – Note: times are approximate

Test/Procedure	Historical	Visit 1 5 hours	Visit 2 6-8 hours	Visit 3 3-4 hours	Visit 4 1-2 hours	Notes
Consent		X				
Medical and Medication History		X				
Vital Signs: pulse, BP, temperature, respiratory rate		X	X	X		Rest for 15 minutes prior to vital signs
Bioelectrical Impedance/Waist Hip		X				
HRQOL surveys (SF-36, MLHF, emPHasis-10)		X				Completed on site
6MWT		X				
Overnight oximetry	X	X (give)	(return)			Up to one year prior to enrollment
Research labs - (OMICS) blood and urine		X (venous blood)	X			• Cath blood for PVD and comparators • Venous blood for healthy controls • Must be fasting for at least 8-10 hours for OMICs bloods
*Center-measured clinical labs (CBC, CMP, INR,HIV, hepatitis panel, ANA)	See specific test	X				Hgb for DLCO should must be done within 2 wks of PFTs but up to 30 days is allowed
Center-measured pregnancy test (urine or blood)		X	X	X	X	Must be done in all women by CLIA certified lab or by study personnel with CLIA waiver per local institutional protocol
ECG		X				
Spirometry, DLCO, Lung Volumes	X	X				Historical acceptable if within 1 year of enrollment, or 3 months if lung disease is present
Echocardiogram		X				
Right heart catheterization (RHC)			X			Not done in healthy controls
CPET, non-invasive -OR- CPET, invasive (iCPET)			X	X(non-invasive)		• iCPET is center-specific; only on PVD/comparators • May be done at visit 3 if *not* doing iCPET
Cardiac MRI/MRA			X			
Lung CT	X			X		Historical acceptable if within 1 year of enrollment
**Ventilation-perfusion scan (V/Q)	X			X-last	X	Historical acceptable if within 1 year of enrollment; not done in healthy controls.

*

*Center CBC w Diff Results and CMP Results	*Lab draw must be no more than 1 month before the Form 100 date.*
Center Antinuclear Antibody (ANA) Results	*Lab draw must be no more than 45 days before the Form 100 date.*
Center Prothrombin Time (PT) Results	*Lab draw must be on or after the Form 100 date.*
Center HIV Antigen/Antibody Screen and Hepatitis Screen Results	If HIV and Hepatitis screens were positive then no need to repeat; if either HIV and/or Hepatitis screen was negative but more than one year ago, then repeat; If either screen was completed within the past year, no need to repeat screen.

VQ scan required if the participant has lung parenchymal disease and has had a CT angiogram (CTA) in the past year from which the results (images) are provided to the Lung Imaging Core. If needed, VQ scan can be done after lung CT. VQ Scan Tracer (radioactive) is detectable for 1 week in blood and can affect HRCT and may expose lab to radiation. Suggest VQ scan be done last after all blood samples and urine are obtained to avoid tracer exposure of lab personnel to radiation. If urine or blood products are collected after the VQ scan, these samples should be collected a minimum of 3 days after the scan.

30.3
Visit 1, 2 or 3 procedures and tests may be performed over more than one day. For example, the site may choose to consent and perform some of the study items (QOL and history), and schedule the fasting blood draws and other testing on a separate day. These are all still considered visit 1, but dates of testing will be recorded for each item. Visit 1 and 2 could be combined if local IRB allows for total quantity of blood to be drawn.

30.7 Telephone calls
Frequent phone contact with participants will facilitate adherence with visits. Suggested frequency of phone call contact is listed below:

- Reminder phone calls one day prior to each study visit and to remind participants to fast and/or hold certain medications.
- Check-up phone calls at least once (at the mid-point) between consecutive study visits
- Other phone calls may include calls to retune missed calls from participants and any phone calls in response to labs that necessitate scheduling an unscheduled visit.

Visits and Windows
There is no rigid timing between visit 1 and 2 and 3, but it is requiredthat completion of all visits will occur within 6 weeks. Timely visit adherence should be encouraged. **Right heart catheterization (with invasive CPET at centers performing this), echocardiogram, MRI and omics blood draws should be performed within two weeks of each other.**.

30.8 Retention
Because this is a procedure-intensive study, some attrition is possible. Therefore retention efforts will focus on ease of visits and informational rewards. Visits will occur at times convenient to the participants. Sites will make every effort to minimize parking inconveniences and other limitations to visits. A monetary compensation for time will be given for each visit. A study coordinator and physician will be available by phone during off-hours to aid in management of procedure or study-related adverse events.

30.9 Priority of Requirements for Passive or Partially Compliant Participants
Once a participant is enrolled, the center will need to continue to follow the participant through all study visits. If the participant at any time states that they no longer want to participate or does not want a specific study procedure done, the Principal Investigator should speak with the participant. If at the end of the discussion, the participant still does not want to be in the study or does not want a specific study procedure done, then complete all data that the participant is willing to complete. It is important that communication with the participant continue. It may be that the participant will return to full procedure capabilities after a period of rest.

30.10 Longitudinal Follow-up
All patients, or their designated contacts, will be contacted by telephone and/or letter at least annually after enrollment up to the end of the study (maximum of 3.5 years) if not seen at the enrolling center

for follow-up. Vital status and occurrence/date of any lung, heart or heart-lung transplantation will be determined from this contact or by using center medical records. Cause of death will be ascertained by the site investigators.

30.11 Adverse Events

Participants will be followed for adverse events occurring during the PVODMICS Study visits and up to 2 weeks after the last study visit. MOP Chapter 48 provides details on reporting adverse events.

Participants experiencing minor illnesses may continue in the study if the nature, severity, and duration of the illness are recorded. Examples of minor illnesses include gastroenteritis and skin disorders. Medications are allowed for treatment of these conditions.

30.11.1 Risk-benefit ratio

It is the belief of the investigators involved in this research that risks of the tests and procedures associated with this study are justifiable given the knowledge to be gained.

Chapter 31. Clinical Center Local Labs

31.1 Overview

Clinical Centers will be asked to provide one-time local lab values that have been analyzed locally and enter results into the PVDOMICS Study database. All labs must have been analyzed by a CLIA certified laboratory. In some instances, historical data may be used (see section 31.4 below).

31.2 Blood Collection and Supplies

If blood is collected for the PVDOMICS Study, each clinical center will need to follow their own local laboratory guidelines for collecting blood.

It is important to note that blood collection tubes for blood analyzed locally are **NOT** provided by the PVDOMICS Study. The Biorepository provides blood kits for collecting Clinical Chemistry Blood (tubes are labeled as PRL) and OMICS bloods only. Please keep these tubes separate from what is used locally.

31.3 Clinical Center Local Labs drawn for PVDOMICS Study

The table below identifies specific local labs must be done on or after PVDOMICS Form 100-Initial Enrollment date at the clinical center's local laboratory. No historical values will be accepted for these labs.

Form #	Form Name	Data Timing
205	Clinical Center Prothrombin Time (PT) Results	*Lab draw must be on or after the Form 100 date*
206	Clinical Center Pregnancy Test Results	*Urine (or blood) for pregnancy test must be on or after the Form 100 date*
207	Clinical Center Arterial Blood Gases (ABG) Results (not required but if collected, results requested)	*Lab draw must be on or after the Form 100 date*

31.4 Historical Labs

Historical lab work can be used in certain circumstances for the PVDOMICS study. Acceptable results for use in the PVDOMICS Study must have been analyzed by a CLIA certified laboratory and should be done at clinical center.

Form #	Form Name	Historical Data Timing
200	Clinical Center CBC w Diff Results	*no more than 1 month before the Form 100 date*
201	Clinical Center Complete Metabolic Panel (CMP) Results	*must be no more than one month before the Form 100 date.*
202	Clinical Center Antinuclear Antibody (ANA) Results	*Lab draw must be no more than 45 days before the Form 100 date*
203	Clinical Center HIV Antigen/Antibody Screen Result	*Within past year from 100 date*
204	Clinical Center Hepatitis Screen Result	*Within past year from 100 date*

CHAPTER 32. QUALITY OF LIFE

Participant Reported Outcomes in PVDOMICS: Instructions for Study Coordinators

32.1 Introduction

Health-related Quality of Life (HRQOL) will be assessed using three different instruments:

- self-administered MOS SF-36 version 2 (SF-36v2)
- self-administered Minnesota Living With Heart Failure (MLHF)
- self-administered emPHasis-10

HRQOL is defined as the subjects' perception of their physical, functional, emotional and mental well-being. The SF-36v2 is one of the most commonly used instruments to measure global HRQOL), and its eight subscales have been tested extensively for reliability, validity against mortality, and responsiveness to interventions in HD participants.) The survey is well-accepted by participants, taking only 5 to 10 minutes to complete. In addition, norms for the general U.S. population have been reported.) A licensing agreement is required and is on file at the DCC.

The 21-question Minnesota Living with Heart Failure (MLHF) instrument was designed as a self-administered measure of the effects of heart failure and treatments for heart failure on participants' quality of life. The content of the questionnaire was selected to be representative of the ways heart failure can affect important physical, emotional, social and mental dimensions of a participant's life without being too long to administer during clinical trials or practice. A licensing agreement is required and is on file at the DCC.

Emphasis-10 is designed to determine how pulmonary hypertension (PH) affects a participant's life. The instrument was jointly developed by The Pulmonary Hypertension Association UK ("PHA") and The University of Manchester ("Manchester") as an output of a PHA funded study (2011-2013). The English and Spanish versions are a copyrighted quality of life instrument used by the PVDOMICS study with full permission of Dr. Janelle York of University of Manchester and The Christie NHS Foundation Trust.

32.2 Forms to be Used

The PVDOMICS study participants will complete the SF-36v2, MLHF, and emphasis-10. The participant can chose whichever language they prefer if they speak English or Spanish. Depending on the language preferred by the participant, the QOL forms to be completed include:

English:

F170 36-Item Short Form Survey Instrument (SF-36v2)
F171 Minnesota Living with Heart Failure
F172 EmPHasis-10

Spanish

QOL Packet includes:

F170 Admin – MOS 36-Item Short Form Survey Instrument (SF-36) Administrative Form
F170S-MOS 36-Item Short Form Survey Instrument (SF-36v2)

F171 Admin – Minnesota Living with Heart Failure Administrative Form
F171S- Minnesota Living with Heart Failure

F172 Admin – EmPHasis-10 Administrative Form
F172S- EmPHasis-10

The PVDOMICS Study's Forms webpage will allow the Spanish QOL forms to be printed out as a packet of forms or by clicking on individual documents at:

http://qhsapps.ccf.org/pvdomics/open_web/FORMS/Forms_TOC.htm

32.3 Timing of Questionnaire Administration

The three QOL instruments can be administered anytime during the PVDOMICS visits. It is recommended that the instruments be completed during the clinic visit to minimize the chance a participant will forget to bring them back if taken home to complete.

32.4 Mode of Administration

The primary mode of completion for the above forms will be self-administered by the study participant. Self-administered questionnaires may be more difficult to complete for the elderly, minority groups, and those with high comorbidity. In these participants, the questionnaire may be administered by the study coordinator. The mode of administration will be noted in Forms 170-172.

If the participant does not answer all of the questions, the Study Coordinator may ask the participant to respond to the questions that were missed. It is very important that the Coordinator does not interpret or rephrase any of the questions for the participant. There is no right or wrong response to the questions on this questionnaire.

The forms should be completed during a study visit in the clinic. This information will be recorded on Forms 170-172. Follow institution's guidelines for illiterate or visually-impaired participants.

a. For self-administration, participants should be instructed to read the brief directions at the top of the page. After the participant's correct understanding has been confirmed, he/she should be encouraged to complete every item in order without skipping any.

b. During interviewer-administration, the Study Coordinator will read the questions and answer choices to the participants and mark their answer. The Coordinator should not

translate or re-interpret the questions for the participants, as these are validated questionnaires and doing so will invalidate the findings. The Coordinators will be trained to administer the questionnaires so as to elicit non-biased participant responses.

The Coordinator should administer the questionnaires in person at a clinic visit. However, exceptions can be made (e.g., phone interview) in certain circumstances in which the questionnaires cannot be completed otherwise.

32.5 Data Entry and Scoring

Study Coordinators will enter the responses for Forms 170, 171, and 172 into the database. The forms will then be scored by the Data Coordinating Center.

32.6 References

Maruish ME. (Ed.). 2011. *User's manual for the SF-36v2 Health Survey* (3rd ed.). Lincoln, RI: QualityMetric Incorporated.

Rector TS, Kubo SH, Cohn JN. 1987. Patients' Self-Assessment of Their Congestive Heart Failure: Content, Reliability and Validity of a New Measure, the Minnesota Living With Heart Failure Questionnaire. *Heart Failure* 3: 198-209.

Yorke J, Corris P, Gaine S, Gibbs JS, Kiely DG, Harries C, Pollock V Armstrong I. 2014. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *Eur Respir J* 43: 1106-1113.

33. BIOREPOSITORY CORE BLOOD COLLECTION OVERVIEW AND BLOOD DRAWING PROCEDURES

33.1 Purpose and Background

Participants who enroll in the PVDOMICS study will be asked to provide biological samples (blood and urine) for OMICS analysis (Genomics, Proteomics, Metabolomics, Coagulomics and Cell Biomics). If participants agree to storage of their biological samples for use in possible future studies, a separate Biorepository informed consent will be signed.

Among those participants who consent for storage of biological specimens, serum, plasma, buffy coat, and urine samples will be collected at various time points depending on required samples. This document describes the collection of blood specimens. Chapter 34 describes processing and shipping of blood specimens.

Chapter 35 describes collection, processing and shipment of urine specimens.

33.2 Biorepository Contacts

The Biorepository under supervision of Suzy Comhair, PhD, is part of the DCC and is located at the Cleveland Clinic, Cleveland, Ohio. Laura Peterson is the Biorepository manager. Their contact information can be found in the PVDOMICS Address Directory. For general questions, e-mail pvd-biorepos@bio.ri.ccf.org.

33.3 Collection Schedule, Type and Volume of Samples

Blood is collected twice during the study. Collection 1 (C1) should be at time of enrollment during Visit 1 and Collection 2 (C2) should be done at the time of the Right Heart Catheterization (RHC) with or without invasive Cardiopulmonary Exercise Testing (iCPET).

During the study, the following blood will be collected:

- Venous blood
- Systemic artery blood (optional)
- Pulmonary capillary blood (Wedge)
- Pulmonary artery blood (Mix)

Table 33.1 provides the blood volumes needed for the OMICS studies.

(see table on next page)

Table 33.1 PVDOMICS Blood Samples Volumes (number of tubes x tube size) Collected for OMICS

Vacutainer™ Blood Tubes	Collection 1 (C1)	Collection 2 (C2)	
		RHC with/without iCPET: Rest	RHC with iCPET: Rest, Peak and Post
Gold top (SST)	2 x 5 ml	1 x 5 ml	1 x 5 ml
Green top (Na-Heparin)	1 x 4 ml		
Lavender top (EDTA)	1 x 10 ml 1 x 4 ml	2 x 10 ml 3 x 4 ml	2 x 10 ml 7 x 4 ml
Red top (*PAXgene*®)		4 x 2.5 ml	8 x 2.5 ml
Blue top (Na-Citrate)	1 x 4.5 ml		
TOTAL Blood Collected	32.5 ml	47 ml	73 ml

33.4 Personnel Blood Collection Training Requirements

The Biorepository and the DCC will conduct a webinar and an in–person training session prior to the beginning of the study. In addition, persons collecting and processing specimens for PVDOMICS will be certified by written exam to ensure samples are uniformly handled prior to analyses. Each PVDOMICS center will designate a study staff member who will be responsible for training the appropriate personnel.

33.5 Supplies for Blood Collection and Shipment

The Biorepository provides sample collection/shipping kits. Five collection/shipping kits will be shipped to each center at the beginning of the study. Additional kits will be shipped to centers monthly or as needed. The number of the additional kits will be determined by the actual center recruitment. If kits are not received for any reason, or extra supplies are needed, centers should enter an Emergency Supplies Request Form 340 in the database.

Table 33.2 PVDOMICS Blood Collection 1 (C1) Kit

Item Number	Description	Quantity
Fisher: 02-683-97 BD: 367986	5 ml Serum Separator Gold top Vacutainer™ blood tube (gel barrier)	2
Fisher:02-689-5 BD: 367871	4 ml NA-Heparin Green top Vacutainer™ blood tube	1
Fisher: 02-687-107 BD: 367862	4 ml EDTA Plasma Lavender top Vacutainer™ blood tube	1
Fisher: 02-688-26 BD: 369714	4.5 ml NA-Citrate Blue top Vacutainer™ blood tube	1
Fisher: 02-657-32 BD: 366643	10 ml EDTA Plasma Lavender top Vacutainer™ blood tube	1

Table 33.3 PVDOMICS Blood Collection 2 (C2) Kit: RHC with or without iCPET at Rest

Item Number	Description	Quantity
Fisher: 23-02101 BD: 762165	2.5 ml *PAXgene*® Red top Vacutainer™ blood tube	4
Fisher: 02-657-32 BD: 366643	10 ml EDTA Plasma Lavender top Vacutainer™ blood tube	2
Fisher: 02-683-97 BD: 367986	5 ml Serum Separator Gold top Vacutainer™ blood tube (gel barrier)	1
Fisher: 02-687-107 BD: 367862	4 ml EDTA Plasma Lavender top Vacutainer™ blood tube	3

Table 33.4 PVDOMICS Blood Collection 2 (C2) Kit: RHC with iCPET during Rest, Peak and Post

Item Number	Description	Quantity
Fisher: 23-02101 BD: 762165	2.5 ml *PAXgene*® Red top Vacutainer™ blood tube	8
Fisher: 02-657-32 BD: 366643	10 ml EDTA Plasma Lavender top Vacutainer™ blood tube	2
Fisher: 02-683-97 BD: 367986	5 ml Serum Separator Gold top Vacutainer™ blood tube (gel barrier)	1
Fisher: 02-687-107 BD: 367862	4 ml EDTA Plasma Lavender top Vacutainer™ blood tube	7

Standard phlebotomy kits that include items such as: alcohol wipes or swabs, adhesive tape, gloves, tourniquets and 21 gauge needles are not part of the collection kit and must be purchased using local center funds.

The peripheral venous blood collection needs to occur with a 21 gauge needle.

In addition, the following materials are needed for Collection 2 which occurs during RHC and are not provided by DCC:

- BD Vacutainer Blood transfer device BD 364880
- BD 10 ml Syringe Luer-Lok™ tip: BD 309604
- BD 30 ml Syringe Luer-Lok™ tip: BD 309650

33.6 Preparation for Each PVDOMICS Blood Collection

Blood will be collected 2 times during the study. The first blood draw (C1) will generally occur at the first study visit. The second blood draw (C2) takes place during RHC with or without iCPET visit. It is strongly recommended to avoid scheduling Collection 1 draw on a Friday. Additional instructions for the timing of blood Collection 1 and Collection 2 are provided in Chapter 33 Addendum 1.

Several days prior to each collection, the study coordinator prepares the collection kit for the participant and the data collection forms. The coordinator needs to check expiration dates on the Vacutainer™ blood tubes included in the kit, and the participant ID and collection number. If the Vacutainer™ blood tubes included the kit have expired or any other issues are discovered, the coordinator should enter an Emergency Supplies Request Form 340 in the study database.

The coordinator contacts the participant the day prior to the collection to remind them to avoid all food and liquids except for small sips of water for pills, for 8-10 hours prior to blood collection. Every effort should be made to schedule the biospecimen collections in the morning to avoid potential diurnal effects of measures.

Specific instructions for blood collection for healthy control subjects are included in Chapter 33, Addendum 2.

33.7 Blood Draw Collection 1 (C1) Procedure

- All participants will need to ***avoid all food and liquids*** except water for 8-10 hours prior to blood collection. Record the number of hours the participant fasted on Form 300.
- Blood collection needs to occur after vital signs and prior to physical exam.
- Before beginning the blood collection, participants need to be resting in a chair for 15 min. This time should be in a quiet area with minimal talking and the participant should not be doing questionnaires or other study components.
- Complete Form 300 to document the blood draw.

Procedure

1. Apply tourniquet.
    - Wrap the tourniquet around the arm 3 to 4 inches (7.5 to 10.0 cm) above the venipuncture site. Tuck the end of the tourniquet under the last round. If a Velcro tourniquet is used adhere the ends to each other.
2. Identify vein.
    - Palpate and trace the path of veins several times with the index finger. Unlike veins, arteries pulsate, are more elastic, and have a thick wall. Thrombosed veins lack resilience, feel cord-like, and roll easily – these should be avoided. If superficial veins are not readily apparent, lowering the extremity over the arm of the chair will allow the veins to fill to capacity. Identify the best available vein.

3. Assemble the butterfly-Vacutainer™ set, if butterfly is used. If a straight phlebotomy needle is used, confirm that it is a 21g and then attach it to the Vacutainer™ holder with the Luer adapter.
   - Attach the Luer adapter to the Vacutainer™ holder.
   - Attach the Luer end of the butterfly needle (21 gauge needle) set to the Luer adapter.
4. Cleanse the venipuncture site.
   - Remove alcohol prep from its sterile package.
   - Cleanse the vein site with the alcohol prep using a circular motion from the center to the periphery.
   - Allow the area to dry to prevent possible hemolysis or contamination of the specimen and a burning sensation to the participant when the venipuncture is performed.
5. If venipuncture becomes difficult, the vein may need to be touched again with a gloved hand. If this happens, cleanse the site again with alcohol and allow the skin to dry.
6. Perform venipuncture.
   - Grasp the participant's arm firmly, using your thumb to draw the skin taut. This anchors the vein. The thumb should be 1 or 2 inches (2.5 or 5.0 cm) below the venipuncture site.
   - With the 21 gauge needle bevel upward, enter the vein in a smooth continuous motion.
   - Once blood appears in the butterfly tubing, place the first Vacutainer™ blood tube into the Vacutainer™ holder (Table 33.5). Grasp the flange of the needle holder and push the Vacutainer™ blood tube forward until the butt end of the needle punctures the stopper, exposing the full lumen of the needle.
   - Make sure the participant's arm is in a flat or downward position while maintaining the Vacutainer™ blood tube below the site when the needle is in the vein. It may be helpful to have the participant make a fist with the opposite hand and place it under the elbow for support. DO NOT HAVE THE PARTICIPANT MAKE A FIST IN THE HAND OF THE ARM FROM WHICH BLOOD IS TO BE DRAWN.
   - Remove the tourniquet after Vacutainer™ blood tube #1 fills. Once the draw has started, do not change the position of a tube until it is withdrawn from the needle. The tourniquet may be reapplied if blood flow is slow without it. If the color of the arm turns red or blue, the tourniquet is applied too tightly. Loosen it and continue.
   - Keep a constant, slight forward pressure (in the direction of the adapter) on the end of the Vacutainer™ blood tube. This prevents release of the shutoff valve and stopping of blood flow. Do not vary pressure nor reintroduce pressure after completion of the draw.
   - Fill remaining Vacutainer™ blood tubes in the order specified in Table 33.5.
   - Fill all Vacutainer™ blood collection tubes as completely as possible, i.e., until the vacuum is exhausted and blood flow ceases. If a Vacutainer™ tube fills only partially, remove the Vacutainer™ blood tube and attach another without removing needle from vein.
   - When the blood flow into the Vacutainer™ blood tube ceases, remove the Vacutainer™ blood tube from the holder. The shutoff valve covers the point, stopping blood flow until the next Vacutainer™ blood tube is inserted (if necessary).

- To remove the needle, lightly place clean gauze over venipuncture site. Remove the needle quickly and immediately apply pressure to the site with a gauze pad. Discard needle with its cap into needle box. DO NOT ATTEMPT TO RECAP NEEDLES. Have the participant hold the gauze pad firmly for one to two minutes to prevent bruising.
- If the blood flow stops before collecting all of the Vacutainer™ blood tubes, repeat the venipuncture on the participant beginning with the first unfilled Vacutainer™ blood tube. As always, the tourniquet must never be on for longer than two minutes.

Order of Peripheral Venous Blood Collection 1 at Visit 1

Clinical Blood Collection: This blood is collected and analyzed at each clinical center. Vacutainer™ blood tubes are not provided by the DCC. **Do not send** to Biorepository. For details about clinical blood collection refer to Chapter 30 and Chapter 31.

Center CBC w Diff Results	Note: Lab draw must be no more than 1 month before the Form 100 date.
Center Complete Metabolic Panel (CMP) Results	Note: Lab draw must be no more than one month before the Form 100 date.
Center Antinuclear Antibody (ANA) Results	Note: Lab draw must be no more than 45 days before the Form 100 date.
Center HIV Antigen/Antibody Screen Result	If there is a historical positive HIV test, no need to repeat screen. If HIV screen was completed **within the past year,** no need to repeat screen.
Center Hepatitis Screen Result	If there is a historical positive hepatitis test, no need to repeat screen. If hepatitis screen was completed **within the past year,** no need to repeat screen.
Center Prothrombin Time (PT) Results	Note: Lab draw must be on or after the Form 100 date.

- The following clinical bloods done locally: CBC, CMP, PT/INR, and pregnancy test (if applicable) must be completed and **resulted before** right heart catheterization.
- OMICS Collection 1 blood draw must be completed before CPET, CT with contrast, RHC and V/Q scan.
- All clinical and OMICS blood draws need to be done either before the V/Q scan or at least 3 days following V/Q.
- Pregnancy testing (either blood or urine) needs to be completed and resulted prior to completion of any other testing at each study visit.

OMICS Blood Collection: Vacutainer™ blood tubes are provided by the DCC.

1. The order of blood draw is shown in Table 33.5
2. Immediately after drawing the samples, gently invert the Vacutainer™ blood collection tubes 10 times to mix the clot activator or anticoagulant with the blood.
3. Place all Vacutainer™ blood tubes on wet ice **except** the Green top (4ml) Plasma "Genomics" and Lavender top (10ml) "Cell Biomics" which will remain at room temperature and can be placed into a biohazard bag for transport.
4. Transport all Vacutainer™ blood tubes to the laboratory. All blood needs to be transported to the lab **within 1 hour of collection**.

Table 33.5 Order of OMICS Blood Draw Collection 1

Order	Color	Additive	Volume	Core	Transport to Lab
1	Gold	SST	5 ml	CC-PRL	Wet ice
2	Gold	SST	5 ml	CC-PRL	Wet ice
3	Green	Na-Heparin	4 ml	Genomic	Room temperature
4	Lavender	EDTA	4 ml	OMICS	Wet ice
5	Blue	Na-Citrate	4.5 ml	OMICS	Wet ice
6	Lavender	EDTA	10 ml	Cell Biomics	Room temperature

*** If you are unable to obtain all the blood in one venipuncture, please try another time on the same visit. **YOU WILL NEED TO HAVE THE PARTICIPANT REST FOR 15 MINUTES PRIOR TO BLOOD COLLECTION AGAIN** - If you are still unable to obtain all the blood after two attempts, then you will have to have the participant come in for another visit to obtain the blood. If you are unable to obtain the blood at visit one, you may attempt to obtain the clinical and OMICS blood at visit 2 only if you will not exceed your institution's policy for maximum amount of blood drawn at one visit. If you were unable to draw due to volume limit constrains, the OMICS blood collection can than occur at Visit 3. Remember that the participant will need to **avoid all food and liquids** except water for 8-10 hours prior to each blood collection and needs to be resting 15 minutes prior each blood collection.

33.8 Blood Draw Collection 2 (C2) Procedure

- All participants will need to ***avoid all food and liquids*** except water for 8-10 hours prior to blood collection. Record the number of hours the participant fasted on Form 304 (Form 307 if Invasive CPET center).
- Before beginning the blood collection, participants need to be resting in a chair for 15 min. This time should be in a quiet area with minimal talking and the participant should not be doing questionnaires or other study components.
- Non-invasive CPET Clinical centers **21, 22, 31, and 61** complete Blood Draw Form 304. Invasive CPET Clinical centers **11, 41, and 51** complete Blood Form 307 for **all participants**.

During the RHC procedure with or without iCPET, venous blood, pulmonary capillary blood (Wedge), and pulmonary artery blood (Mix) will be collected. In some cases, systemic artery blood will also be collected.

The order of blood collection is as follows:

1. Venous blood
2. Systemic artery blood (optional)
3. Pulmonary capillary bed blood (Wedge)
4. Pulmonary artery blood (Mix)

Blood Collection During RHC with/without iCPET

Venous Blood Collection 2

1. After the introducer has been placed but before any other procedures or measurements are performed, draw the venous blood sample from the side port of the sheath. Remember participant needs to be resting for 15 min prior to this blood draw.
2. Draw back 3mL of blood in a sterile syringe and waste the sample.
3. Then, using a second 30 ml sterile syringe with a Luer-Lok™ tip, draw 27.5 ml of blood from the side port.
4. Transfer the blood in the syringe into the appropriate Vacutainer™ blood collection tubes using the Vacutainer™ blood transfer device system.
5. Order of *Venous Blood Collection 2* is shown in Table 33.6.
6. Immediately after filling the Vacutainer™ blood tubes, gently invert the Vacutainer™ blood tubes 10 times to mix the clot activator or anticoagulant with the blood.
7. Place all Vacutainer™ blood tubes on wet ice **except** the Red *PAXgene*® tube.
8. All blood needs to be transported to the lab within 1 hour of collection.
9. A study team member should be designated to transport blood samples to the lab.

Table 33.6 Order of Blood Draw Collection 2: Venous Blood Draw

Order	Blood Type	Color	Additive	Volume	Core	Transport to Lab
1	Venous	Red *PAXgene*®	RNA Preservative solution	2.5 ml	Genomic	Room temperature
2	Venous	Lavender	EDTA	10 ml	OMICS	Wet ice
3	Venous	Lavender	EDTA	10 ml	OMICS	Wet ice
4	Venous	Gold	SST	5 ml	Bank	Wet ice

NO VENOUS BLOOD WILL BE DRAWN DURING THE CHALLENGES (INCLUDING PEAK OR POST EXERCISE)

Systemic Artery Blood Collection (optional)

Collection of systemic artery blood (radial or femoral) is optional and is preferred to collect the blood after the venous blood draw. This blood collection is not required. If arterial blood collection for arterial blood gases (ABG) occurs at the time of spirometry, there is no need to repeat ABG collection during RHC. If collecting at the time of spirometry, remember to collect the OMICS systemic artery blood **before** spirometry starts.

1. Draw back 3 ml of blood and waste the sample.
2. Draw at least 1 ml of blood into a sterile heparinized syringe for arterial blood gas analysis per protocol at local center.
3. Use a second 10 ml non-heparinized sterile syringe with a Luer-Lok™ tip, draw back 6.5 mL of blood from the arterial line for OMICS analysis.
4. Transfer the arterial blood from this second syringe into the appropriate Vacutainer™ blood collection tubes using the Vacutainer™ blood transfer device system.
5. Order of *Systemic Artery Blood Collection 2* is shown in Table 33.7.
6. Immediately after filling the Vacutainer™ blood tube, gently invert the Vacutainer™ blood tube 10 times to mix the clot activator or anticoagulant with the blood.
7. Place all Vacutainer™ blood tube on wet ice **except** the Red *PAXgene*® tube.
8. All blood needs to be transported to the lab within 1 hour of collection.

Table 33.7 Order of Blood Draw Collection 2: Systemic Artery Blood

Order	Blood Type	Color	Additive	Volume	Core	Transport to Lab
1	Systemic artery	Lavender	EDTA	4 ml	OMICS	Wet ice
2	Systemic artery	Red *PAXgene*®	RNA Preservative solution	2.5 ml	Genomic	Room temperature

Pulmonary Capillary Blood (Wedge) and Pulmonary Artery Blood (Mix) Collection

Pulmonary capillary wedge and pulmonary artery mixed blood must be drawn after all hemodynamic measurements except thermodilution cardiac output and prior to any of the challenges.

1. During the right heart catheterization, there will be two different blood draws:
   a. Pulmonary capillary (Wedge) blood, drawn while the catheter is in the wedge position, after the pulmonary capillary wedge pressure measurements are complete.
   b. Pulmonary artery (Mix) blood, drawn while the catheter is in the pulmonary artery position, after the pulmonary artery pressure measurements are complete.
2. Blood will be drawn from the distal port in both cases.
3. Pulmonary capillary (Wedge) blood.

a. After all pulmonary capillary wedge pressure measurements are completed, and while the tip of the catheter is still in the capillary wedge position with the balloon inflated, draw back 3 mL of blood using a sterile syringe and waste the sample. Then, using a second 10 ml sterile syringe with a Luer-Lok™ tip, draw back 6.5mL of blood per your institution's guidelines for drawing from a Swan-Ganz catheter.
b. Transfer the blood in the syringe into the appropriate Vacutainer™ blood collection tubes using the Vacutainer™ blood transfer device system.

4. Pulmonary artery (Mix) blood.
   a. Similarly, after all pulmonary artery pressures are completed, and while the tip of the catheter is still in the pulmonary artery position, draw back 3 mL of blood using a sterile syringe and waste the sample. Then, using a second 10 ml sterile syringe with a Luer-Lok™ tip, draw back 6.5 mL of blood per your institution's guidelines for drawing from a Swan Ganz catheter.
   b. Transfer the blood in the syringe into the appropriate Vacutainer™ blood collection tubes using the Vacutainer™ blood transfer device system.
5. Order of blood draw during Collection 2 is shown in Table 33.8.
6. Immediately after filling the Vacutainer™ blood tube, gently invert the Vacutainer™ blood tubes 10 times to mix the clot activator or anticoagulant with the blood.
7. Place all Vacutainer™ blood tubes on wet ice **except** the Red *PAXgene*® tube.
8. All blood needs to be transported to the lab within 1 hour of collection.

Table 33.8 Order of Blood Draw Collection 2: Procedure for Pulmonary Artery Blood (Mix) and Pulmonary Capillary Blood (Wedge)

Order	Blood type	Color	Additive	Volume	Core	Transport to lab
1	Pulmonary Capillary "Rest Wedge"	Lavender	EDTA	4 ml	OMICS	Wet ice
2	Pulmonary Capillary "Rest Wedge"	Red *PAXgene*®	RNA Preservative solution	2.5 ml	Genomics	Room Temperature
3	Pulmonary Artery "Rest Mix"	Lavender	EDTA	4 ml	OMICS	Wet ice
4	Pulmonary Artery "Rest Mix"	Red *PAXgene*®	RNA Preservative solution	2.5 ml	Genomics	Room Temperature

If OMICS blood is collected during PEAK and POST exercise, the blood draw should be done following the procedure for the collection during REST outlined above. The recommended order of the blood draw is specified in Table 33.9.

Table 33.9 Recommended Order of Collection 2 Blood Draw During Right Heart Catheterization

Blood type	Order	Color	Additive	Volume	Cat # Fisher or BD	Core	Transport to lab
Venous	1	Red	RNA Preservative solution	2.5ml	Fisher: 23-02101 BD:762165	Genomic	Room temperature
Venous	2	Lavender	EDTA	10ml	Fisher:02-657-32 BD #366643	OMICS	Wet ice
Venous	3	Lavender	EDTA	10ml	Fisher:02-657-32 BD #366643	OMICS	Wet ice
Venous	4	Gold	SST	5ml	Fisher:02-683-97 BD:367986	BANK	Wet ice
Systemic Artery "Rest"	5*	Lavender	EDTA	4ml	Fisher:02-687-107 BD:367862	OMICS	Wet ice
Systemic Artery "Rest	6*	Red	RNA Preservative solution	2.5ml	Fisher: 23-02101 BD:762165	Genomics	Room temperature
Pulmonary Capillary "Rest Wedge"	7	Lavender	EDTA	4ml	Fisher:02-687-107 BD:367862	OMICS	Wet ice
Pulmonary Capillary "Rest Wedge"	8	Red	RNA Preservative solution	2.5ml	Fisher: 23-02101 BD:762165	Genomics	Room Temperature
Pulmonary Artery "Rest Mix"	9	Lavender	EDTA	4ml	Fisher:02-687-107 BD:367862	OMICS	Wet ice
Pulmonary Artery "Rest Mix"	10	Red	RNA Preservative solution	2.5ml	Fisher: 23-02101 BD:762165	Genomics	Room Temperature
Pulmonary Artery "Peak Mix"	11**	Lavender	EDTA	4ml	Fisher:02-687-107 BD:367862	OMICS	Wet ice
Pulmonary Artery "Peak Mix"	12**	Red	RNA Preservative solution	2.5ml	Fisher: 23-02101 BD:762165	Genomics	Room Temperature
Systemic Artery "Peak	13**	Lavender	EDTA	4ml	Fisher:02-687-107 BD:367862	OMICS	Wet ice
Systemic Artery "Peak"	14**	Red	RNA Preservative solution	2.5ml	Fisher: 23-02101 BD:762165	Genomics	Room Temperature
Pulmonary Artery "Post Mix"	15**	Lavender	EDTA	4ml	Fisher:02-687-107 BD:367862	OMICS	Wet ice
Pulmonary Artery "Post Mix"	16**	Red	RNA Preservative solution	2.5ml	Fisher: 23-02101 BD:762165	Genomics	Room Temperature
Systemic Artery "Post"	17**	Lavender	EDTA	4ml	Fisher:02-687-107 BD:367862	OMICS	Wet ice
Systemic Artery "Post"	18**	Red	RNA Preservative solution	2.5ml	Fisher: 23-02101 BD:762165	Genomics	Room Temperature

Notes: Blood tubes 1-4 and 7-10 will be collected on all participants.

* Some participants will have blood tubes 5 and 6 collected before the resting right heart catheterization, at the same time as the initial venous collection.

** Some participants will have blood tubes 11-18 collected during the iCPET.

Addendum 1: Timing of OMICS and CLINICAL Blood Collection 1 and Collection 2

The timing of Collection 1 blood draw needs to be BEFORE Collection 2 blood draw. Blood draw is performed for clinical/safety reasons, and for OMICS analyses. Collection 1 results can be skewed by the RHC and CPET procedures, and should not be done after these procedures.

If both OMICS Collection 1 and 2 are done on the same day, the following should be done:

1. This needs to be approved by the local IRB as this may exceed local policies regarding quantity of blood draw at one visit for a research study.
2. The clinical results need to be reviewed prior to the RHC procedure by the PI or doctor performing procedure.
3. Participant rests for vitals (before blood draw)
4. Participant rests for each blood draw for 15 minutes and is fasting

Remember:

- No testing intervention (e.g., RHC, CT, MRI, VQ, etc.) before collection of blood
- Participant needs to be resting for 15 min and must be fasting prior to blood draw

Addendum 2: Biorepository Blood Collection: Healthy Controls

Healthy participants who enroll in the PVDOMICS study will be asked to provide Clinical and OMICS blood and urine. All procedures needs to be performed as described at Biorepository Core blood collection overview and blood drawing procedures (Chapter 33). Participant identification numbers for healthy control subjects will have "9" as third digit, i.e. a healthy control from center 51 would have an ID "51**9**001". The blood collection kits for healthy control participants will be marked with an orange sticker.



Clinical Blood Collection: This blood is collected and analyzed at the clinical center. Vacutainer™ blood tubes are not provided by the DCC. **Do not send** to Biorepository. For details about clinical blood collection refer to Chapter 30 and Chapter 31.

Center CBC w Diff Results	Note: Lab draw must be no more than 1 month before the Form 100 date.
Center Complete Metabolic Panel (CMP) Results	Note: Lab draw must be no more than one month before the Form 100 date.
Center Antinuclear Antibody (ANA) Results	Note: Lab draw must be no more than 45 days before the Form 100 date.
Center HIV Antigen/Antibody Screen Result	If there is a historical positive HIV test, no need to repeat screen. If HIV screen was completed **within the past year,** no need to repeat screen.
Center Hepatitis Screen Result	If there is a historical positive hepatitis test, no need to repeat screen. If hepatitis screen was completed **within the past year,** no need to repeat screen.
Center Prothrombin Time (PT) Results	Note: Lab draw must be on or after the Form 100 date.

- Pregnancy testing (either blood or urine) needs to be completed and resulted prior to completion of any other testing at each study visit.

OMICS Blood Collection: Only Resting Venous Blood will be collected at Collection 1 (C1) and Collection 2 (C2).

If approved by IRB, the clinical blood collection and OMICS blood collection 1 and 2 can occur at one visit as described in Addendum 1. The blood volumes and the order of the blood draws are described in Tables 33.1, 33.5 and 33.6. The tables are listed below again for convenience:

This subset of Table 33.1 provides the blood volumes needed for the OMICS studies

Vacutainer™ Blood Tubes	Collection 1 (C1)	Collection 2 (C2)
Gold top (SST)	2 x 5 ml	1 x 5 ml
Green top (Na-Heparin)	1 x 4 ml	
Lavender top (EDTA)	1 x 10 ml 1 x 4 ml	2 x 10 ml
Red top (*PAXGene*®)		1 x 2.5 ml
Blue top (Na-Citrate)	1 x 4.5 ml	
TOTAL Blood Collected	32.5 ml	27.5 ml

Table 33.5 Order of OMICS Blood Draw Collection 1

Order	Color	Additive	Volume	Core	Transport to Lab
1	Gold	SST	5 ml	CC-PRL	Wet ice
2	Gold	SST	5 ml	CC-PRL	Wet ice
3	Green	Na-Heparin	4 ml	Genomic	Room temperature
4	Lavender	EDTA	4 ml	OMICS	Wet ice
5	Blue	Na-Citrate	4.5 ml	OMICS	Wet ice
6	Lavender	EDTA	10 ml	Cell Biomics	Room temperature

Table 33.6 Order of Blood Draw Collection 2: Venous Blood Draw

Order	Blood Type	Color	Additive	Volume	Core	Transport to Lab
1	Venous	Red *PAXgene*®	RNA Preservative solution	2.5 ml	Genomic	Room temperature
2	Venous	Lavender	EDTA	10 ml	OMICS	Wet ice
3	Venous	Lavender	EDTA	10 ml	OMICS	Wet ice
4	Venous	Gold	SST	5 ml	Bank	Wet ice

Processing of samples for healthy controls is the same as the processing of samples for pulmonary hypertension participants and is described in Chapter 34.

34. PVDOMICS BIOSPECIMEN BLOOD PROCESSING AND SHIPPING

34.1 Purpose and Background

Participants who enroll in the PVDOMICS study will be asked to provide biological samples (blood and urine) for OMICS analysis (Genomics, Proteomics, Metabolomics, Coagulomics and Cell Biomics). If participants agree to storage of their biological samples for use in possible future studies, a separate Biorepository informed consent will be signed.

Among those participants who consent for storage of biological specimens, serum, plasma, buffy coat, and urine samples will be collected at various time points depending on required samples. This document describes the collection of blood specimens. Chapter 33 describes collection of blood specimens.

Chapter 35 describes collection, processing and shipment of urine specimens.

34.2 Logistics for Biorepository

The Biorepository under supervision of Suzy Comhair, PhD, is part of the DCC and is located at the Cleveland Clinic, Cleveland, Ohio. Laura Peterson is the Biorepository manager. The contact information can be found in the PVDOMICS Address Directory. For general questions and biosample shipment notification, e-mail pvd-biorepos@bio.ri.ccf.org.

All samples collected at the specific centers will be shipped at room temperature or on dry ice to the Biorepository for processing, storage, and distribution of samples to PVDOMICS cores and investigators for genome, proteome, metabolome, coagulome, and advanced cell biome analyses upon approval by the Steering Committee. At the end of the study, any remaining biological samples will be transferred to a central biobank or to the National Heart, Lung and Blood Institute (NHLBI) Biological Specimen and Data Repository Information Coordinating Center (BioLINCC) biobank.

34.3 Collection Schedule, Type and Volume of Samples

Blood is collected twice during the study. Collection 1 (C1) should be at time of enrollment during Visit 1 and Collection 2 (C2) should be done at the time of the Right Heart Catheterization (RHC) with or without invasive Cardiopulmonary Exercise Testing (iCPET). Table 34.1 provides the blood volumes needed for the OMICS studies.

(see table on next page)

Table 34.1 PVDOMICS Blood Samples Volumes (number of tubes x tube size) Collected for OMICS

Vacutainer™ blood tubes	Collection 1 (C1)	Collection 2 (C2)	
		RHC with/without iCPET: Rest	RHC with iCPET: Rest, Peak and Post
Gold top (SST)	2 x 5 ml	1 x 5 ml	1 x 5 ml
Green top (Na-Heparin)	1 x 4 ml		
Lavender top (EDTA)	1 x 10 ml 1 x 4 ml	2 x 10 ml 3 x 4 ml	2 x 10 ml 7 x 4 ml
Red top (*PAXgene*®)		4 x 2.5 ml	8 x 2.5 ml
Blue top (Na-Citrate)	1 x 4.5 ml		
TOTAL Blood Collected	32.5 ml	47 ml	73 ml

34.4 Personnel Blood Processing and Shipping Training Requirements

The Biorepository and the DCC will conduct a webinar with video and an in–person training session prior to the beginning of the study. In addition, persons collecting and processing specimens for PVDOMICS will be certified by written exam to ensure samples are uniformly handled to analyses.

Each person shipping specimens to the DCC PVDOMICS Biorepository needs to be certified according to Department of Transportation (DOT) and International Air Transportation Authority (IATA) regulations.

Each PVDOMICS center will designate a study staff member who will be responsible for training the appropriate personnel and maintaining the certifications locally.

34.5 Supplies for Processing, Storing and Shipment Blood

The Biorepository provides pre-labeled processing and shipping kits (Table 34.2-34.6). Five processing kits will be shipped to each center at the beginning of the study. Additional kits will be shipped to centers monthly or as needed. The number of additional kits will be determined by center recruitment. If kits are not received, or extra kits are needed, centers should enter an Emergency Supplies Request Form 340 in the study database.

Table 34.2 PVDOMICS Blood Collection 1 (C1) Processing Kit

Description	Quantity
0.5 ml Yellow top cryovial	14
0.5 ml Blue top cryovial	13
0.5 ml Lavender top cryovial	13

Table 34.3 PVDOMICS Blood Collection 2 (C2) Processing Kit: RHC with or without iCPET at Rest

Description	Quantity
0.5 ml Yellow top cryovial	10
0.5 ml Lavender top cryovial	73
2 ml Clear top cryovial	1

Table 34.3HC PVDOMICS Blood Collection 2 (C2) Processing Kit: Healthy Controls

Description	Quantity
0.5 ml Yellow top cryovial	10
0.5 ml Lavender top cryovial	40
2 ml Clear top cryovial	1

Table 34.4 PVDOMICS Blood Collection 2 (C2) Processing Kit: RHC with iCPET during Rest, Peak and Post

Description	Quantity
0.5 ml Yellow top cryovial	10
0.5 ml Lavender top cryovial	117
2 ml Clear top cryovial	1

The catalog numbers for the Fisher scientific items above are as follow: 0.5ml cryovial 02-681-333; Yellow cap, 02-681-360, Purple cap, 02-681-366; Clear cap, 02-681-358; Blue cap, 02-681-359; 2ml tube, 02-681-343.

Table 34.5 PVDOMICS Storage Kit

Description	Quantity
Pre-labeled cardboard box with 9x9 cell dividers for cryovials with absorbent sheet for monthly shipping	12 for non-exercise centers 15 for exercise centers

Table 34.6 PVDOMICS Shipping Kit: Room Temperature

Description
Big specimen box (2.5” x 9.5” x 12.5”) with insulated envelope inside
Gel pack
95kPa Specimen Transport Bag
Absorbent sheet tube holder
UN 3373 Category B label

Table 34.7 PVDOMICS Blood / Urine Shipping Kit: Dry Ice

Description	Notes
2 Big specimen foam box (16” x 16” x 16”) with innerbox	
6 Biohazard bags	
Big specimen foam box (15” x 13” x 14”) with innerbox	This additional box will be sent only to centers collecting blood at Peak and Post
2 Biohazard bags	These additional bags will be sent only to centers collecting blood at Peak and Post
UN 3373 Category B label	
Class 9 miscellaneous dangerous goods label	
Blue UPS Dry Ice for Diagnostic or Medical Purposes sticker	

Note that the big specimen shipment boxes will be reused and should not be discarded.
In addition, centers should have the following supplies and equipment for sample collection and shipment:

- Refrigerated centrifuges with capacity of spinning at 2200g
  (recommended: Allegra™ X-12R Centrifuge, Beckman Coulter)
- -70°C/-80°C freezer
- -20°C freezer
- Laboratory supplies such as biohazard bags, gloves, sterile pipettes, pipettors, and sterile pipette tips
- Dry ice pellets
- Permanent black marker
- Packing tape
- Clear parafilm
- Conical tube rack (Fisher: 14-791-6D) is highly recommended to avoid tube breakage
- Pipetman set: 1000ul and 200ul
- Barcode scanner
  (recommended: Datalogic Gryphon GD4430-BK-HD and can be purchased through:
  RACO Industries
  Contact – Judith Maria
  888-433-1274
  jmaria@racoindustries.com

It is recommended to calibrate pipettes used in the study twice per year.

Each lab must compute the appropriate rpm using this target xg force and the radius of their centrifuge rotor. This can be done by using the website: http://insilico.ehu.es/mini_tools/rcf_rpm.php, which calculates the RPM from input of target xg and centrifuge rotor radius.

All cryovials included in the collection kits are pre-labeled. The label is a preprinted barcode (8 alpha numeric digits), study participant ID number (6 alpha numeric digits), collection number (2 alpha numeric digits), sample type, and collection scenario (Figure 34.1).

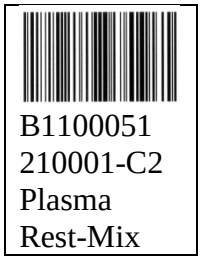


Figure 34.1: Example of a cryovial label

34.6. Specimen Storage Log Overview

All samples aliqouted during Collection 1 and Collection 2 must be logged into the Biological Tracking System (BST) in the study database before stored in –70°C/–80°C freezer. Instructions for creating a specimen storage log are provided in Sections 34.8.1 and 34.9.1 respectively for each collection.

34.7 Specimen Shipping Log Overview

Before samples are shipped to Biorepository, a separate shipping log must be created in the Biological Tracking System (BST) in the study database for each box sent to the Biorepository. Instructions are provided in Section 34.10 of the MOP.

34.8 PVDOMICS COLLECTION 1: PROCESSING, STORING and SHIPPING

The blood draw for Collection 1 will generally occur at the first study visit (for details see MOP Chapter 33). The processing of all 6 Vacutainer™ blood tubes needs to start within 1 hour of collection.

Table 34.8 Vacutainer™ Blood Tubes Collection 1 (C1)

Description	Quantity
5 ml Gold top (SST)	2
4 ml Green top (Na-Heparin)	1
4 ml Lavender top (EDTA)	1
4.5 ml Blue top (Na-Citrate)	1
10 ml Lavender top (EDTA)	1

At arrival of Vacutainer™ blood tubes into the lab:

- Check if participant ID number on the Vacutainer™ blood tubes matches with ID number on the screw cap tubes and ID sticker provided in processing kit. Coordinator must also check expiration date on Vacutainer™ blood tubes.Place ID sticker on Form 301: Center Blood Collection 1- Processing Sample.
- Complete questions 1-6 on Form 301 before processing the Vacutainer™ blood tubes and the rest of the form as you process the tubes.

34.8.1 Processing

1. Two Gold tops "Serum CC-PRL": Allow the blood to clot in an upright position at room temperature for 30 minutes.
2. Green top "Genomics" and Lavender top (10ml) "Cell Biomics": Do not centrifuge. Do not refrigerate or freeze at any time. Leave at room temperature and ship **the same day** to Biorepository (see below).
3. Centrifuge Lavender top "Plasma" and Blue top "Plasma-Cit" at 2200g at 4ºC for 10 minutes for Swing-Bucket Centrifuge or for 15 minutes if using a Fixed Angle unit. After centrifugation of Lavender top "Plasma".
   - Immediately pipet 200 ul of plasma into 13 pre-labeled "Plasma" cryovials (0.5ml) with purple screw cap.
     NOTE: Place a black dot with permanent marker on the screw cap if the volume is less than 200 ul.
   - Place samples on dry ice until all samples from Collection 1 are aliquoted
4. After centrifugation of Blue top "Plasma-Cit":
   - Immediately pipet 200 ul of plasma into 13 pre-labeled "Plasma-Cit" cryovials (0.5ml) with blue screw cap.

NOTE: Place a black dot with permanent marker on the screw cap if the volume is less than 200 ul.

- Place samples on dry ice until all samples from Collection 1 are aliquoted

5. 30 minutes after 2 Gold tops "Serum CC-PRL" are placed in upright position, centrifuge at 2200g at 4ºC for 10 minutes for Swing-Bucket Centrifuge or for 15 minutes if using a Fixed Angle unit.
6. After centrifugation of the two Gold tops:
   - Immediately pipet **400 ul of serum** into 4 pre-labeled "Serum CC-PRL" cryovials (0.5ml) with yellow screw cap.
   - Pipet **200 ul** of serum into 10 pre-labeled "Serum" (0.5ml) with yellow screw cap.
     NOTE: Place a black dot with permanent marker on screw cap in volume is less than 200ul.
   - Place samples on dry ice until all samples from Collection 1 are aliquoted.
7. Access the PVDOMICS Biological Sample Tracking (BST) system online and input the participant ID and blood collection date in order to connect the specimens to the correct participant ID and collection in Form 330. Scan the barcodes of all cryovials to insert one record for each cryovial. Indicate whether the cryovial was marked with a black dot due to insufficient volume of blood. Once information is entered, print a copy of the specimen storage log for the participant's study records to keep a record of the barcode associated with each cryovial.
8. Store all cryovials in an upright position in the pre-labeled cardboard boxes with 9 x 9 cell dividers provided by the Biorepository and place in -70ºC/-80ºC freezer (Table 34.9). The 9 x 9 boxes need to be filled to capacity and could contain cryovials from more than one participant.

Table 34.9 Processing and Storage of Cryovials of Collection 1 (C1)

Cryovial label	Color Cryovial Screw cap	Volume	Number of cryovials	Storage box
Serum-CC-PRL	Yellow	400ul	4	SERUM/BC/Urine
Serum	Yellow	200ul	10	SERUM/BC/Urine
Plasma	Purple	200ul	13	PLASMA
Plasma-Cit	Blue	200ul	13	PLASMA

34.8.2 SHIPPING of Green top (4ml) "Genomics" and the Lavender top (10ml) "Cell Biomics" Plasma Vacutainers™ to Biorepository at ROOM TEMPERATURE

Creating a shipping log

Green top (4ml) "Genomics" and the Lavender top (10ml) "Cell Biomics" Vacutainers™ blood tubes are scanned into the PVDOMICS Biological Sample Tracking (BST) system. Access the BST system online and input the participant ID and blood collection date in order to link the specimens to the correct participant ID and collection in Form 335. Scan the barcodes of tubes to insert one record for each. Once information is entered, print two copies of the specimen log: one for the participant's study records to keep a record of the barcode associated with each tube and one to be enclosed in the shipment box.

Shipping Vacutainers™ blood tubes to Biorepository

The Green top (4ml) "Genomics" and the Lavender top (10ml) "Cell Biomics" Vacutainers™ blood tubes must be shipped at room temperature **on the day of blood draw** for arrival to the Biorepository Core within 24 hours. Complete Form 302 and enclose a copy with the shipment.

To pack the specimen properly for shipment in the boxes provided as part of the shipping kit (Table 34.7).

1. Ensure rubber stopper of each filled specimen tube is tight.
2. Secure with parafilm.
3. Verify tube is labeled correctly and label is well adhered to tube surface. Secure with packing tape if necessary.
4. Verify tube label matches label placed on associated paperwork (shipping log, specimen collection form).
5. Place each tube into the absorbent sheet tube holder.
6. Place the tubes in the 95kPa Specimen Transport Bag.
7. Remove white adhesive liner from the bag and discard.
8. Place bag in gel wrap (the gel pack should NOT be frozen).
9. Place gel wrap into insulated envelope.
10. Snap close envelope.
11. Place envelope into box.
12. Include copy of the specimen shipment log as required by Federal regulations.
13. Close box.
14. Use package-sealing tape over the locking tabs of the mailer.
15. Place provided UN3373 diagnostic specimen sticker (IATA 650 compliance) on the top of the box on the upper right corner.

If shipping occurs during Monday through Thursday, **Priority Overnight UPS Courier** is the required shipping method and provided by the DCC:

Address: Cleveland Clinic
Lerner Research NB2-037
Attn: Laura Peterson
2111 E. 96th St.
Cleveland, Ohio 44106
(216) 445-6625

Study personnel should be aware when the last UPS pick up of the day is since the blood needs to be shipped on the day of collection.

Please provide advance notice as soon as possible by emailing **pvd-biorepos@bio.ri.ccf.org** if Collection 1 occurs before a non-working day in order to arrange staff to receive and process the samples. The package will need to be sent to a residential address since our dock is not open on the weekend or holidays.

If shipping occurs on Friday, email the DCC and we will create the UPS shipping bill. An orange UPS "Saturday Delivery" label needs to be affixed to the package. These stickers will be provided. Again, please notify the Biorepository as soon as possible if this occurs.

If shipping occurs the day before a holiday, Sterling Courier will need to be used. Contact the DCC and we will help to arrange the shipment. Please notify the Biorepository as soon as possible.

NOTE: If a Friday shipment (for Saturday delivery) will NOT occur, please notify the Biorepository as soon as possible so that lab personnel will not be required to come in to the lab on a Saturday.

34.8.3 SHIPPING of Frozen Cryovials to Biorepository

Frozen vials from Collection 1 and Collection 2 that are stored at local centers must be shipped to the Biorepository. They can be shipped Monday-Wednesday as long as the next day is not a holiday. Email **pvd-biorepos@bio.ri.ccf.org and include the tracking number.** See Section 34.10 for shipping instructions.

34.9 PVDOMICS COLLECTION 2: PROCESSING, STORING and SHIPPING

The blood draw for Collection 2 takes place during the Right Heart Catheterization (RHC). Some centers will perform a RHC without invasive Cardiopulmonary Exercise testing (iCPET) and some centers will perform a RHC with iCPET at rest, while others will perform a RHC with iCPET at rest, peak and post exercise. The amount of Vacutainer™ blood tubes and processing depends if RHC is performed during "rest" or "rest, peak and post" exercise.

During the RHC procedure, Venous blood, Systemic artery blood (Syst Art) (OPTIONAL), Pulmonary capillary blood (Wedge) and Pulmonary artery blood (Mix) will be collected.

Blood Processing Protocol A: RHC blood with or without CPET at rest
Blood Processing Protocol B: RHC blood with Invasive CPET (iCPET) at rest, peak and post exercise

Forms

Non-invasive CPET Clinical centers **21, 22, 31, and 61** complete Blood Processing Forms 305 and 306 for **all participants** who had C2 blood collected.
Invasive CPET Clinical centers **11, 41, and 51** complete Blood Processing Forms 308 and 309 for **all participants** who had C2 blood collected.

OMICS Blood Collection	**CPET-type Center**	**Participant type**	**Biorepository Forms Used**
Collection 1	All Centers	Everyone (PH, comparator, healthy control)	Use forms F300, F301 and F303.
Collection 2	Non-Invasive CPET Centers (21,22,31,and 61)	Everyone (PH, comparator, healthy control)	Use forms F304, F305 and F306
	Invasive CPET Centers (11, 41, and 51)	Everyone, *even if only 'rest' blood was obtained or non-invasive CPET was done or a healthy control* (PH, comparator, healthy control)	Use forms F307, F308 and F309

34.9.1 Blood Processing Protocol A: RHC with or without iCPET at rest

The blood draw for Collection 2 will generally occur at the second study visit (for details see MOP Chapter 33) during the RHC with or without iCPET. The systemic artery blood collection is optional and clinical center dependent.

The processing of the Vacutainer™ blood tubes needs to start within 1 hour of collection. Depending on the procedure time, some Vacutainer™ blood tubes may need to be brought to the laboratory for processing before the end of the collection procedure.

Table 34.10 Vacutainer™ Blood Tubes Collection 2: RHC with/without iCPET at Rest

Description	Quantity
Red top *PAXgene*®	4
5 ml Gold top (gel barrier)	1
10 ml Lavender top	2
4 ml Lavender top (EDTA)	3

At arrival of Vacutainer™ blood tubes into the lab:

- Check if participant ID number on the Vacutainer™ blood tubes matches with ID number on the screw cap tubes and ID sticker provided in processing kit.
- Place ID sticker on Form 306.
- Complete questions 1-5 on From 305 and Form 306 before processing the Vacutainer™ blood tubes. Complete the rest of the forms as you process the samples.

34.9.1.1 Processing

1. Place all Red top *PAXgene*® tubes, i.e., Genomic Rest Venous, Genomic Rest Mix, Genomic Rest Wedge, and Genomic Rest Syst Art upright at room temperature for 2 hours.
2. Gold top "Rest Venous Serum": Allow the blood to clot in an upright position at room temperature for 30 minutes.
3. Centrifuge the two Lavender tops (10ml) "Plasma Rest Venous" and the three Lavender top (4ml) i.e. Plasma Rest Mix, Plasma Rest Wedge, Plasma Rest Syst Art at 2200g at 4ºC for 10 minutes for Swing-Bucket Centrifuge or for 15 minutes if using a Fixed Angle units.
4. After centrifugation of all Lavender tops, start processing as follows:

   Two <u>Lavender top (10ml) labeled with Plasma-Rest Venous</u>

   - Pipet 200 ul of plasma into 40 pre-labeled "Plasma Rest Venous" cryovials (0.5ml) with violet screw cap.

     NOTE: Place a black dot with permanent marker on screw cap in volume is less than 200ul.
   - Remove the buffy coat from two Lavender tops "Plasma Rest Venous" using a Pasteur pipette.
   - Ensure that you collect all of the white cells. You will also draw up a little of the plasma from above the cells and red blood cells from below – this is normal, but try to collect as little "extra" fluid as possible.
   - Place the two buffy coats in one pre-labeled "Buffy coat Rest Venous" cryovials (2.0ml) with clear screw cap.
   - Place cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

Lavender top (4ml) labeled with Plasma Rest Mix

- Pipet 200 ul of plasma into 11 pre-labeled "Plasma Rest Mix" cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap in volume is less than 200ul.
- Place all cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

Lavender top (4ml) labeled with Plasma Rest Wedge

- Pipet 200 ul of plasma into 11 pre-labeled "Plasma Rest Wedge" cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap in volume is less than 200ul.
- Place cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

Lavender tops (4ml) labeled with Plasma Rest Syst Art

- Pipet 200 ul of plasma into 11 pre-labeled "Plasma Rest Syst Art" cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap if the volume of plasma is less than 200ul.
- Place all cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

5. 30 minutes after the Gold top "Rest Venous Serum" is placed in upright position, centrifuge at 2200g at 4ºC for 10 minutes for Swing-Bucket Centrifuge or for 15 minutes if using a Fixed Angle unit.
6. After centrifugation of the Gold top "Rest Venous Serum":
   - Immediately pipet 200 ul of serum into 10 pre-labeled "Serum Rest Venous" cryovials (0.5ml) with yellow screw cap.
   - Place Samples on dry ice until all samples from Collection 2 are aliquoted.
7. 2 hours after all the Red tops *PAXgene*® tubes are placed in upright position
   - Access the PVDOMICS Biological Sample Tracking (BST) system online and input the participant ID and blood collection date in order to connect the specimens to the correct participant ID and collection in Form 330. Scan the barcodes of all cryovials to insert one record for each cryovial. Indicate whether the cryovial was marked with a black dot due to insufficient volume of blood. Once information is entered, print a copy of the specimen storage log for the participant's study records to keep a record of the barcode associated with each cryovial.
8. After scanning

- Transfer the Red top *PAXgene*® tube upright to the -20ºC freezer for 24 hours.
- Do not freeze tubes upright in a styrofoam tray as this may cause the tubes to crack. A 15ml Conical Tube rack (Fisher: 14-791-6D) is recommended.
- After 24 hrs, transfer the Red top *PAXgene*® tube upright to at -70ºC/-80ºC Freezer. A 15ml Conical Tube rack (Fisher: 14-791-6D) is recommended.

9. Store all cryovials in an upright position in the respective pre-labeled "PLASMA" and "SERUM/BC/Urine" cardboard boxes with 9 x 9 cell dividers provided by the Biorepository and place in –70ºC/-80ºC freezer (Table 34.11). The 9 x 9 boxes need to be filled to capacity and may contain cryovials from more than one participant.

34.9.2 Blood Processing Protocol B: RHC with iCPET at rest, peak and post exercise

Blood draw Collection 2 will generally occur at the 2nd visit (for details see MOP Chapter 33) during the RHC with iCPET. The systemic artery blood collection is optional and clinical center dependent.

The processing of the Vacutainer™ blood tubes needs to start within in 1 hour of collection. Depending on the procedure time, some Vacutainer™ blood tubes need to be brought to the laboratory for processing before the end of the collection procedure.

Table 34.11 Vacutainer™ Blood Tubes Collection 2: RHC with/without iCPET at Rest

Description	Quantity
Red *PAXgene*®	8
5 ml Gold top (gel barrier)	1
10 ml Lavender top	2
4 ml Lavender top (EDTA)	7

At arrival of Vacutainer™ blood tubes into the lab:

- Check if participant ID number on the Vacutainer™ blood tubes matches with ID number on the screw cap tubes and ID sticker provided in processing kit.
- Place ID sticker on Form 308.
- Complete questions 1-5 on Form 308 and Form 309 before processing the Vacutainer™ blood tubes. Complete the rest of the forms as you process the samples.

34.9.2.1 Processing

1. Place all eight Red top *PAXgene*® tubes, i.e., Genomic Rest Venous, Genomic Rest Mix, Genomic Peak Mix, Genomic Post Mix, Genomic Rest Wedge, Genomic Rest Syst Art, Genomic Peak Syst Art, and Genomic Post Syst Art upright at room temperature for 2 hours.
2. Gold top "Serum Rest Venous": Allow the blood to clot in an upright position at room temperature for 30 minutes.
3. Centrifuge the two Lavender tops (10ml) "Plasma Rest Venous" and seven Lavender tops (4ml) collected during **Rest** (Mix, Wedge and Syst Art), during **Peak** (Mix and Syst Art), and during **Post** (Mix and Syst Art) at 2200g at 4°C for 10 minutes for Swing-Bucket Centrifuge or for 15 minutes if using a Fixed Angle unit.

Two Lavender tops (10ml) labeled with Plasma Rest Venous

- Pipet 200 ul of plasma into 40 pre-labeled "Plasma Rest Venous" cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap in volume is less than 200ul.

- Remove the buffy coat from two Lavender tops (10ml) “Plasma Rest Venous” by using a Pasteur pipette.
- Ensure that you collect all of the white cells. You will also draw up a little of the plasma from above the cells and red blood cells from below – this is normal, but try to collect as little “extra” fluid as possible.
- Place the two buffy coats in one pre-labeled “Buffy coat Rest Venous” cryovials (2.0ml) with clear screw cap.
- Place cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

Lavender top (4ml) labeled with Plasma Rest Mix

- Pipet 200 ul of plasma into 11 pre-labeled “Plasma Rest Mix” cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap if the volume of plasma is less than 200ul.
- Place all cryovials immediately on dry ice until all samples of Collection 2 are aliquoted.

Lavender top (4ml) labeled with Plasma Rest Wedge

- Pipet 200 ul of plasma into 11 pre-labeled “Plasma Rest Wedge” cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap if the volume of plasma is less than 200ul.
- Place all cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

Lavender top (4ml) labeled with Plasma Rest Syst Art

- Pipet 200 ul of plasma into 11 pre-labeled “Plasma Rest Syst Art” cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap if the volume of plasma is less than 200ul.
- Place all cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

Lavender top (4ml) labeled with Plasma Peak Mix

- Pipet 200 ul of plasma into 11 pre-labeled “Plasma Peak Mix” cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap if the volume of plasma is less than 200ul.
- Place all cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

Lavender top (4ml) labeled with Plasma Peak Syst Art

- Pipet 200 ul of plasma into 11 pre-labeled "Plasma Peak Syst Art" cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap if the volume of plasma is less than 200ul.
- Place all cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

Lavender top (4ml) labeled with Plasma Post Mix

- Pipet 200 ul of plasma into 11 pre-labeled "Plasma Post Mix" cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap if the volume of plasma is less than 200ul.
- Place all cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

Lavender top (4ml) labeled with Plasma Post Syst Art

- Pipet 200 ul of plasma into 11 pre-labeled "Plasma Post Syst Art" cryovials (0.5ml) with violet screw cap.

  NOTE: Place a black dot with permanent marker on screw cap if the volume of plasma is less than 200ul.
- Place all cryovials immediately on dry ice until all samples from Collection 2 are aliquoted.

4. 30 minutes after the Gold top "Serum Rest Venous" is placed in upright position, centrifuge at 2200g at 4ºC for 10 minutes for Swing-Bucket Centrifuge or for 15 minutes if using a Fixed Angle unit.
5. After centrifugation of the Gold top "Serum Rest Venous".
   - Immediately pipet 200 ul of serum into 10 pre-labeled "Serum Rest Venous" cryovials (0.5ml) with yellow screw cap.
   - Place Samples on dry ice until all samples of Collection 2 are aliquoted.
6. 2 hours after all the Red tops *PAXgene*® tubes are placed in upright position
   - Access the PVDOMICS Biological Sample Tracking (BST) system online and input the participant ID and blood collection date in order to connect the specimens to the correct participant ID and collection in Form 330. Scan the barcodes of all cryovials to insert one record for each cryovial. Indicate whether the cryovial was marked with a black dot due to insufficient volume of blood. Once information is entered, print a copy of the specimen storage log for the participant's study records to keep a record of the barcode associated with each cryovial.
7. After scanning
   - Transfer the *PAXgene*® Blood tube upright to the -20ºC freezer for 24 hours.

- Do not freeze tubes upright in a styrofoam tray as this may cause the tubes to crack. A 15 ml Conical Tube rack (Fisher: 14-791-6D) is recommended.
- After 24 hours, transfer the *PAXgene*® Blood tube upright at –70°C/-80°C freezer. A 15 ml Conical Tube rack (Fisher: 14-791-6D) is recommended.

8. Store all cryovials in an upright position in the respective pre-labeled "PLASMA" and "SERUM/BC/Urine" cardboard boxes with 9 x 9 cell dividers provided by the Biorepository and place in –70°C/-80°C freezer (Table 34.11). The 9 x 9 boxes need to be filled to capacity and may contain cryovials from more than one participant.

Table 34.11 Storage of Cryovials of Collection 2

Cryovial label	Color Cryovial Screw cap	Number of cryovials	Storage box
Serum Rest Venous	Yellow	10	SERUM/BC/URINE
Plasma Rest Venous	Lavender	40	PLASMA
Plasma Rest Mix	Lavender	11	PLASMA
Plasma Rest Wedge	Lavender	11	PLASMA
Plasma Rest Syst Art	Lavender	11	PLASMA
Buffy coat Rest Venous	Clear	1	SERUM/BC/URINE
Plasma Peak Mix	Lavender	11	PLASMA
Plasma Peak Syst Art	Lavender	11	PLASMA
Plasma Post Mix	Lavender	11	PLASMA
Plasma Post Syst Art	Lavender	11	PLASMA
PAXgene® Tubes	Red	- 4 tubes for non-exercise sites - 8 tubes for exercise sites	PAXgene

SHIPPING of Collection 2 Cryovials and *PAXgene*® to Biorepository

All samples from Collection 1 and Collection 2 stored at the centers should be shipped to the Biorepository on Monday – Wednesday as long as the following day is not a holiday.

Email pvd-biorepos@bio.ri.ccf.org PRIOR to shipping to confirm the lab is able to receive packages the next day. See Section 34.10 for details.

34.10 Shipping of All Collected Biospecimen Samples on Dry Ice to Biorepository

NOTE: Since the shipping instructions for biospecimens refer to blood and urine specimens, MOP Chapter 34.10 and MOP Chapter 35.11 are identical.

All frozen cryovials, *PAXgene*® and urine stock tubes must be shipped to the Biorepository Core according to the instructions below. Shipping can occur on Monday-Wednesday as long as the following day is not a holiday. Email **pvd-biorepos@bio.ri.ccf.org** PRIOR to shipping to confirm the lab is able to receive packages the next day. Personnel shipping samples must adhere to IATA and Dept. of Transportation shipping regulations. Please check with your institution for guidelines. Failure to comply may result in fines.

The *PAXgen*e® tubes will be taken out of the racks, placed in the labeled "*PAXgene*®" cardboard box and covered with an absorbent sheet to minimize moving of tubes.

Shipping log instructions:
A shipping log must be created on the day the samples will be shipped. Access the PVDOMICS Biological Sample Tracking (BST) system online and scan the barcodes of all cryovials in Form 336 to insert one record for each. A shipment inventory will be generated that contains: date of shipment, site of origination, shipment ID, and an inventory detailing all the tubes in the shipment with their barcode numbers and participant information (participant ID number, collection number, specimen collection date). Please note that serum, plasma and urine shipments for several participants, blood draws and urine collections can be combined in the same large shipping box, but a separate shipping inventory must be created for each large box. A maximum of 7 boxes (9x9) can go into one large shipping box. Once 7 (9x9) boxes have been scanned, save the log, make note of the auto-populated Shipment Box ID and start a new shipment log if necessary. Print 2 copies of the shipment inventory (ies): one to include in each shipment box, and one to retain for the study records at the originating site.

Once the shipment information is completed in the BST system, an e-mail will automatically be sent to the Biorepository notifying them that a shipment should be expected. A copy of that e-mail will sent to the originating site. The e-mail message will include the originating site, the name of the person preparing the shipment and the shipment box ID in the body and a complete shipment inventory as an attachment.

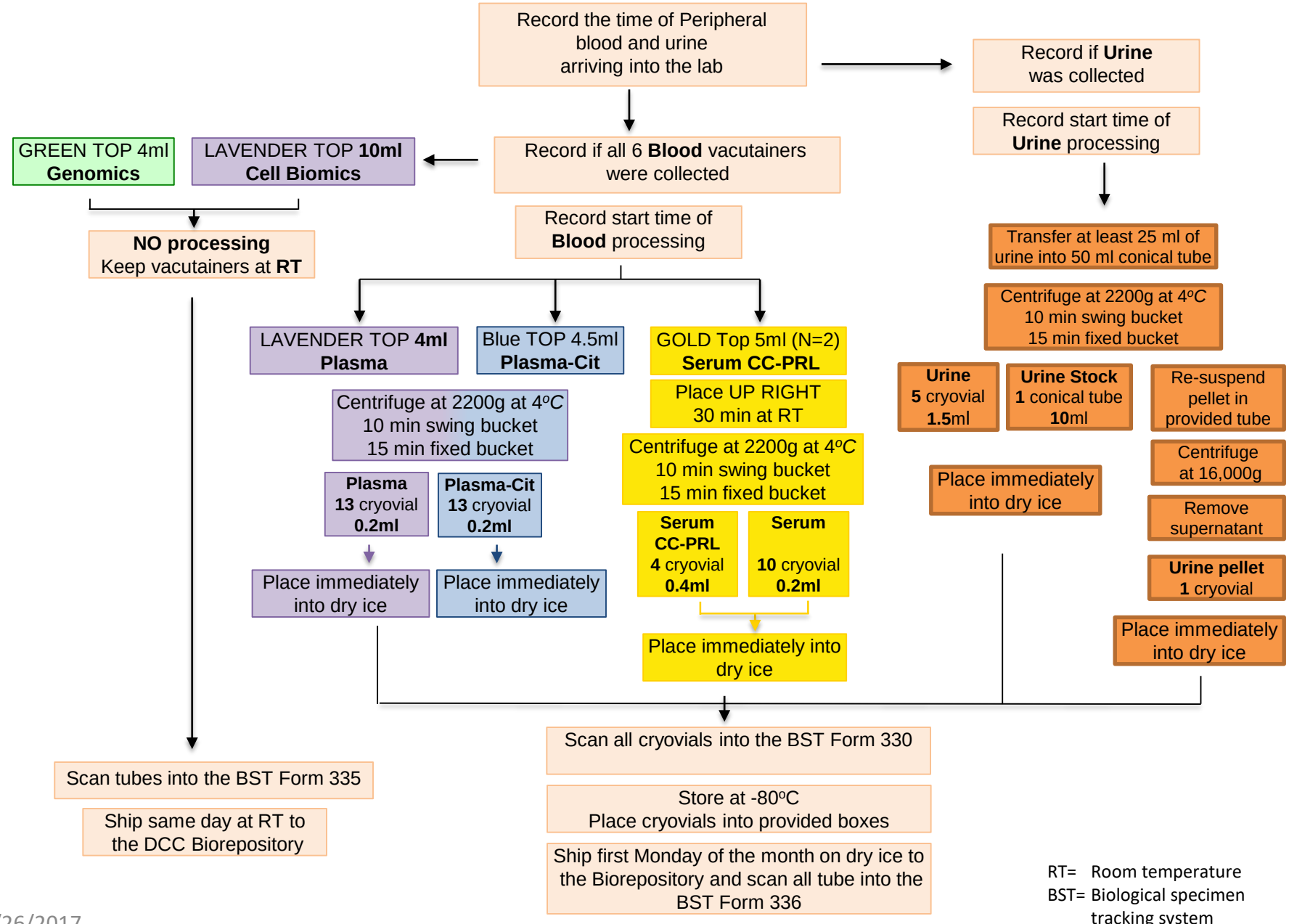
Complete Form 303 and enclose a copy with the shipment.

Packing instructions:
1. Wrap rubber band around each specimen box and place inside biohazard bag. Up to 2 boxes can be in each bag. Seal the bag when full.
2. Place a thin layer of dry ice pellets in the bottom of the shipper.

3. Place up to 7 boxes in the plastic biohazard bag containing specimen on the dry ice.
4. Fill the rest of the space in the shipper with dry ice pellets. Leave 3.5" (height) empty in the top of the shipper for the lid's foam insert.
5. Place the foam insert on top of the dry ice. Place a copy of the shipment log. Close and tape the outer box.
6. Affix the Biorepository **"To:"** address label to the side of the box in the upper left corner.
7. Affix the dry ice label **(UN1845)** to the same side of the box in the upper right corner. Enter the weight of dry ice on the label in kilograms.
8. Affix the "UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B" label to the left of the dry ice label.
9. Affix the blue UPS "Dry Ice for Diagnostic or Medial Purposes Only" sticker. Enter weight of dry ice in kg, must be the same as on the dry ice label
10. Create a UPS airbill to ship specimens to BIOREPOSITORY at Cleveland Clinic.
11. Send a shipment notification to the Biorepository via email at pvd-biorepos@bio.ri.ccf.org on the day the package is dropped for UPS pickup. Include the UPS tracking number in the notification.
    Note: You should be able to setup your UPS account to send an automated message to pvd-biorepos@bio.ri.ccf.org when a shipment label is created.

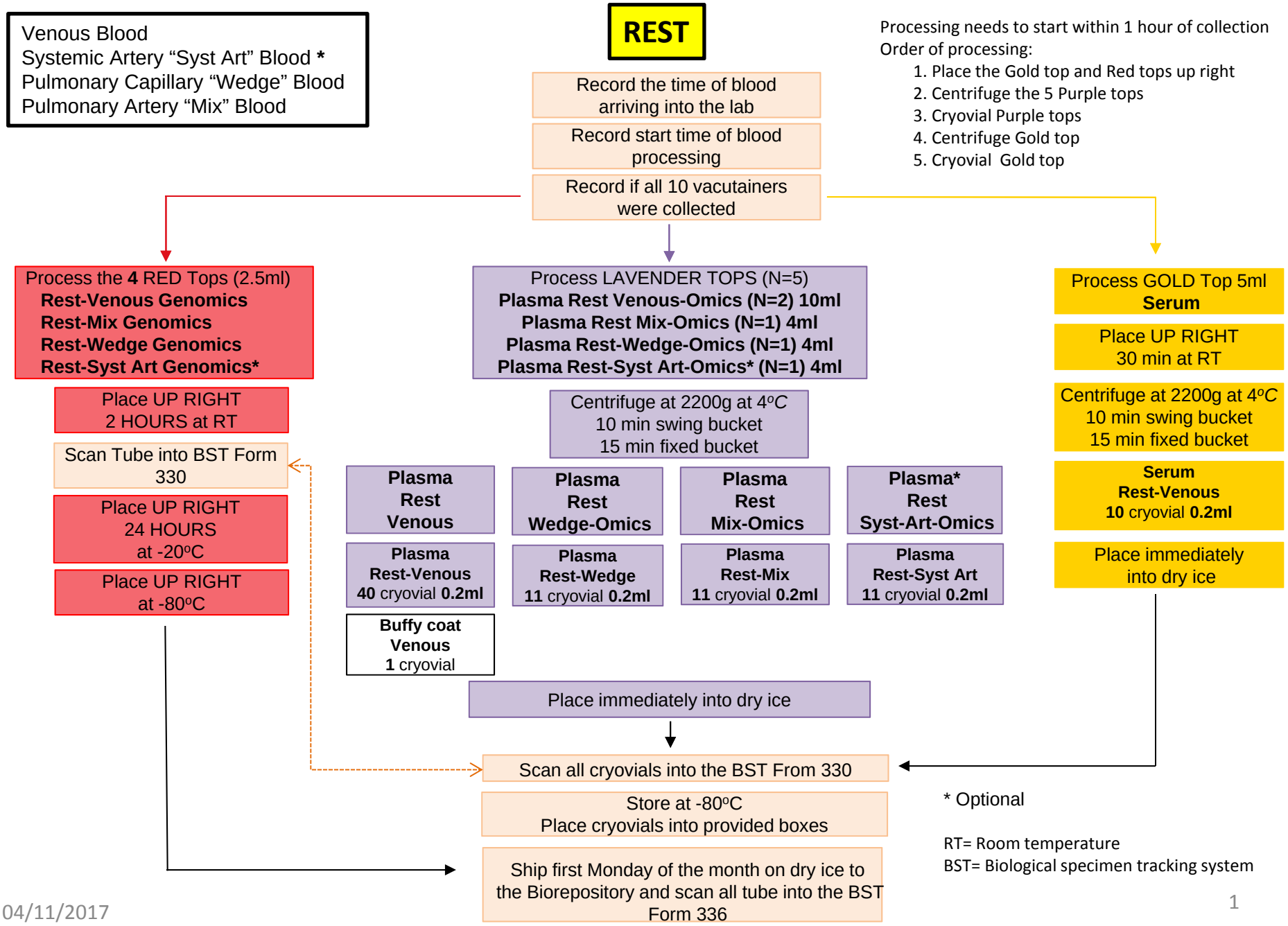
Appendix 34.1: PVDOMICS OMICS Blood and Urine Collection 1:
Processing, Aliquoting, Recording and Storing of Biospecimens

Processing needs to start within 1 hour of collection



RT= Room temperature
BST= Biological specimen tracking system

Appendix 34.2: PVDOMICS OMICS Blood Collection 2: Processing, Aliquoting, Recording and Storing of Biospecimens



Appendix 34.2: PVDOMICS OMICS Blood Collection 2: Processing, Aliquoting, Recording and Storing of Biospecimens

Pulmonary Artery "Mix" Blood
Systemic Artery "Syst Art" Blood

PEAK and POST

Only sites doing exercise portion

Record the time of blood arriving into the lab

Record start time of blood processing

Record if all 8 vacutainers were collected

Process the 4 RED Tops (2.5ml)
Peak-Mix Genomics
Peak-Syst Art Genomics
Post-Mix Genomics
Post-Syst Art Genomics

Place UP RIGHT
2 HOURS at RT

Scan Tube into BST Form 330

Place UP RIGHT
24 HOURS
at -20ºC

Place UP RIGHT
at -80ºC

Process LAVENDER TOPS (N=4) 4ml
Plasma Peak Mix-Omics
Plasma Peak-Syst Art-Omics
Plasma Post Mix-Omics
Plasma Post-Syst Art-Omics

Centrifuge at 2200g at 4ºC
10 min swing bucket
15 min fixed bucket

Plasma Peak Mix-Omics	**Plasma Peak Syst Art-Omics**	**Plasma Post Mix-Omics**	**Plasma Post Syst Art-Omics**
Plasma Peak-Mix **11** cryovial **0.2ml**	**Plasma Peak-Syst Art** **11** cryovial **0.2ml**	**Plasma Post-Mix** **11** cryovial **0.2ml**	**Plasma Post-Syst Art** **11** cryovial **0.2ml**

Buffy coat Peak-Mix **1** cryovial

Place immediately into dry ice

Scan all cryovials into the BST Form 330

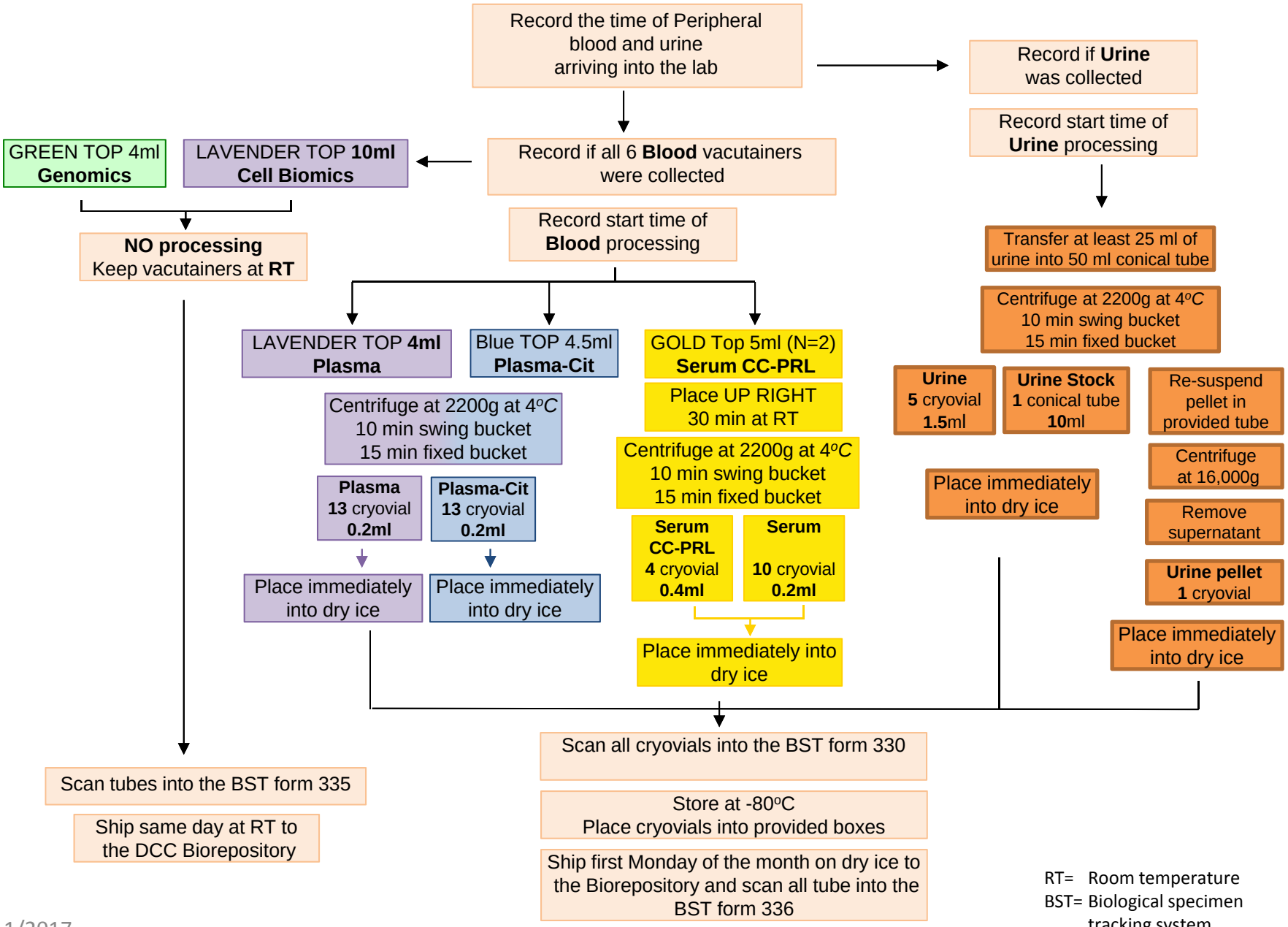
Store at -80ºC
Place cryovials into provided boxes

Ship first Monday of the month on dry ice to the Biorepository and scan all tube into the BST Form 336

RT = Room temperature
BST = Biological specimen tracking system

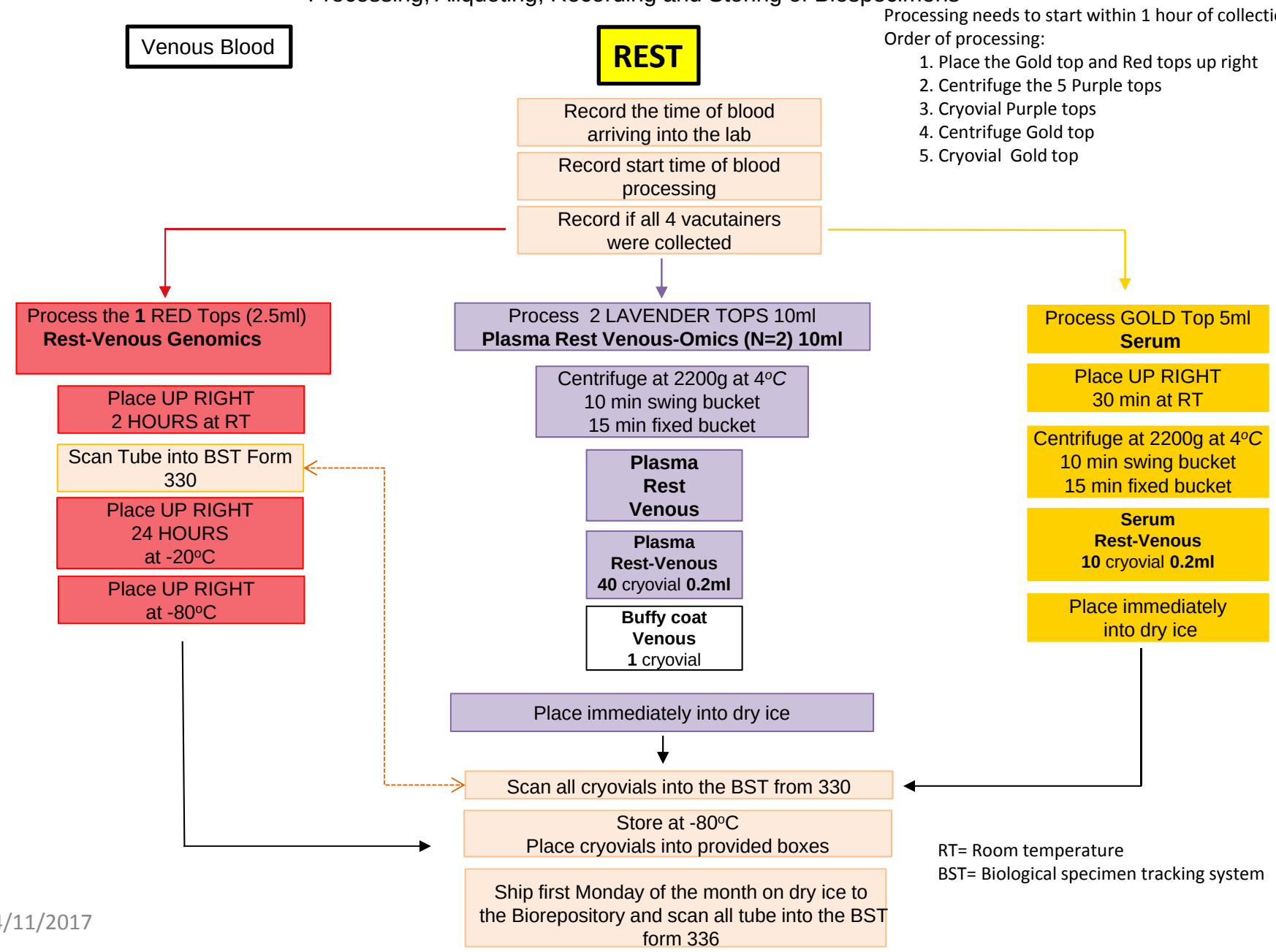
Appendix 34.3: PVDOMICS OMICS HEALTHY CONTROLS Blood and Urine Collection 1:
Processing, Aliquoting, Recording and Storing of Biospecimens

Processing needs to start within 1 hour of collection



RT= Room temperature
BST= Biological specimen tracking system

Appendix 34.3: PVDOMICS OMICS Blood Collection 2 HEALTHY CONTROLS:
Processing, Aliquoting, Recording and Storing of Biospecimens



35. BIOREPOSITORY CORE URINE SPECIMENS COLLECTION, PROCESSING AND SHIPPING

35.1 Purpose

Participants who enroll in the PVDOMICS study with be asked to provide biological specimens (blood and urine). The urine specimens will be used to assess urine biochemical biomarkers to determine whether a panel of biomarkers, including nitrate and nitrate in conjunction with uBrY and urinary F2isoP, can be used as a surrogate for PAH classification. If participants agree to storage of their biological samples for use in possible future studies, a separate repository informed consent will be signed.

Among those participants who consent for storage of biological specimens, serum, plasma, and urine samples will be collected at various time points. This document describes the collection of urine. Chapter 33 describes collection of blood specimens. Chapter 34 describes processing and shipping of blood specimens.

35.2 Biorepository Contacts

The Biorepository under supervision of Suzy Comhair, PhD, is part of the DCC and is located at the Cleveland Clinic, Cleveland, Ohio. Laura Peterson is the Biorepository manager. Their contact information can be found in the PVDOMICS Address Directory. For general questions, e-mail pvd-biorepos@bio.ri.ccf.org.

35.3 Collection Schedule, Type and Volume of Samples

Urine will be collected one time during the study, at the time of enrollment.

35.4 Personnel Training Requirements

Each person shipping repository specimens should be trained according to Department of Transportation (DOT) and International Air Transportation Authority (IATA) regulations. Each PVDOMICS center will assign a study staff member who will be responsible for training the appropriate personnel.

The Biorepository and the DCC will conduct an in–person training session prior to the beginning of the study.

35.5 Supplies for Urine Collection and Shipment

The Biorepository will provide sample collection/shipping kits (Tables 35.1-35.2). Five collection/shipping kits will be shipped to each center at the beginning of the study. Additional kits will be shipped to centers monthly or as needed. The number of the additional kits will be determined by the actual site recruitment. If kits are not received for any reason, or extra supplies are needed, sites should send an Emergency Supplies Request Form 340 in the study database.

The Biorepository provides the following materials for sample collection and shipment:

Table 35.1 PVDOMICS Urine Collection Kit 1

Item number	Description	Quantity
Fisher: NC9867141 Sarstedt:75562105CS200	SC Urine Cup 57x76mm 100ml PP Label Sterile	1
Fisher: 02-681-343	2 ml cryovial	6
Fisher: 12-565-268 Thermo Scientific: 339650	Thermo Scientific™ Nunc™ 15mL Conical Sterile Polypropylene Centrifuge Tubes	1
Fisher: 12-565-270 Thermo Scientific: 339652	Thermo Scientific™ Nunc™ 50mL Conical Sterile Polypropylene Centrifuge Tubes	1

Table 35.2 PVDOMICS Blood / Urine Shipping Kit: Dry Ice

Description	Notes
2 Big specimen foam box (16” x 16” x 16”) with innerbox	
6 Biohazard bags	
Big specimen foam box (15” x 13” x 14”) with innerbox	This additional box will be sent only to centers collecting blood at Peak and Post
2 Biohazard bags	These additional bags will be sent only to centers collecting blood at Peak and Post
UN 3373 Category B label	
Class 9 miscellaneous dangerous goods label	
Blue UPS Dry Ice for Diagnostic or Medical Purposes sticker	

In addition, sites should have the following supplies and equipment for sample collection and shipment:

- Refrigerated centrifuges with capacity of spinning at 2200g (recommended: Allegra^{TM} X-12R Centrifuge, Beckman Coulter)
- -70°C/-80°C freezer
- -20°C freezer
- Laboratory supplies such as biohazard bags, gloves, sterile pipettes, pipettors, and sterile pipette tips
- Pipetman set: 1000ul
- Collection cleansing wipes
- Dry ice pellets
- Packing tape

- Barcode scanner
  (recommended: Datalogic Gryphon GD4430-BK-HD and can be purchased through:
  RACO Industries
  Contact – Judith Maria
  888-433-1274
  jmaria@racoindustries.com

Each lab must compute the appropriate rpm using this target xg force and the radius of their centrifuge rotor. This can be done by using the website: http://insilico.ehu.es/mini_tools/rcf_rpm.php, which calculates the RPM from input of target xg and centrifuge rotor radius.

It is recommended to calibrate pipettes used in the study twice per year.

All tubes and cryovials included in the collection kit are pre-labeled. The label is a preprinted barcode (8 alpha numeric digits), study participant ID number (6 alpha numeric digits), collection number (C1), and sample type (Figure 35.1)

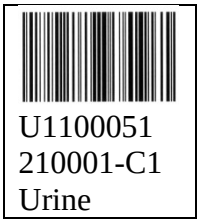


Figure 35.1: Example of a urine cryovial / tube label

35.6 Preparation for each PVDOMICS Urine Collection

Urine collection should occur at the first study visit (C1). Several days prior to collection the study coordinator prepares the urine collection kit for the participant and the data collection forms.

The coordinator contacts the participant the day prior to the collection to remind them to avoid all food and liquids except water, for 8-10 hours prior to collection only if the urine collection will occur on the day of blood collection. Every effort should be made to schedule the collections in the morning to avoid potential diurnal effects of measures. Time of collection will be recorded for all samples collections.

35.7 Specimen Storage Log Overview

All aliquoted urine samples aliqouted must be logged into the Biological Sample Tracking System (BST) in the study database before stored in -70°C/-80°C freezer. Instructions for creating a specimen storage log are provided in Section 35.9.3.

35.8 Specimen Shipping Log Overview

Before urine samples are shipped to Biorepository, a shipping log must be created in the BST. Instructions are provided in Section 35.11 of the MOP.

35.9 PVDOMICS COLLECTION 1: URINE COLLECTION, PROCESSING, STORING

35.9.1 Collection

Ideally blood Collection 1 and urine collection should occur in the same day. Urine must be collected at the time of visit in a clinical setting only and cannot be collected prior to coming to visit. Encourage the participant to fill up cup about 1/2 - 2/3 full. Urine collection will not be repeated at another time irrespective of quality and quantity of collected specimen. Specimen collection instruction templates for females and males are provided in Appendix 35.1 and 35.2 respectively. If your institution already has established guidelines, you can follow those.

1. To obtain urine, the participant will void into the provided sterile collection container labeled with participant's study ID number.
2. Make sure to obtain a "clean catch" sample.
3. Follow "Universal Precautions" throughout the collection procedure; discard all contaminated material in biohazard container.
4. Complete Form 320 to document the urine collection.
5. Transport the urine container to the lab for processing.

35.9.2 Processing

1. Transfer at least 25 ml of urine into a 50 ml conical tube with sterile transfer pipette.
2. Centrifuge the 50 ml conical tube at 2200xg at 4°C for 10 minutes for Swing-Bucket Centrifuge or 15 minutes for Fixed Angle Centrifuge (balance the tube in centrifuge).
3. After centrifugation of the 50 ml conical tube:
    - Immediately pipet 1.5 ml of urine into 5 pre-labeled 2 ml "Urine" cryovials with orange O-ring screw caps (Fisher Scientific; cap# 02-681-364).
    - Transfer 10ml of urine into a 15ml pre-labeled "Urine" conical tube with sterile transfer pipette. Do not fill to the top of the tube, urine expands when frozen.
    - Pour off most of the urine supernatant (leave a proximal 500ul of urine behind).
    - Re-suspend the pellet in the urine that is left behind.
    - Transfer the re-suspended pellet into pre-labeled 2 ml "Urine Pellet" cryovials with orange O-ring screw caps labeled "P" on the top (Fisher Scientific; cap# 02-681-364).
    - Centrifuge at 16,000g (or top speed on microcentrifuge) for 4 minutes at room temperature.
    - Pipet off remaining urine supernatant.
4. Place cryovials and 15 ml conical tube immediately on dry ice.

Complete Form 321 to document the details about urine processing. Use MOP Appendix 34.1 for quick reference for urine processing.

35.9.3 Creating Storage Log

All samples will be logged into the PVDOMICS Biological Sample Tracking (BST) system as part of the study database before storing in -70ºC/-80ºC freezer.

Access the PVDOMICS Biological Sample Tracking (BST) system online and input the participant ID and urine collection date in Form 330 in order to connect the specimens to the correct participant ID and collection. Scan the barcodes of all cryovials and tubes to insert a record for each of them. Once you have entered the information, print a copy of the specimen storage log for the participant's study records to keep a record of the barcode associated with each cryovial/tube.

35.9.4 Storage of Urine Cryovials and Tubes

After scanning the samples into PVDOMICS study BST, the samples must be stored at -70ºC/-80ºC. Store all cryovials in an upright position in the appropriate size cardboard boxes with 9 x 9 cell dividers provided by the Biorepository.

Place in -70ºC/-80ºC freezer. Place 15 ml tubes in cardboard box without cell divider.

35.10 SHIPPING of Frozen Aliquots and Tubes to Biorepository

SHIPPING of Collection 2 Cryovials and *PAXgene*® to Biorepository

All samples from Collection 1 and Collection 2 stored at the centers should be shipped to the Biorepository on Monday – Wednesday as long as the following day is not a holiday.

Email pvd-biorepos@bio.ri.ccf.org PRIOR to shipping to confirm the lab is able to receive packages the next day. See Section 35.11 for details.

35.11 Shipping of All Collected Biospecimen Samples on Dry Ice to Biorepository

NOTE: Since the shipping instructions for biospecimens refer to blood and urine specimens, MOP Chapter 34.10 and MOP Chapter 35.11 are identical.

All frozen cryovials, *PAXgene*® and urine stock tubes must be shipped to the Biorepository Core according to the instructions below. Shipping can occur on Monday-Wednesday as long as the following day is not a holiday. Email **pvd-biorepos@bio.ri.ccf.org** PRIOR to shipping to confirm the lab is able to receive packages the next day.

Personnel shipping samples must adhere to IATA and Dept. of Transportation shipping regulations. Please check with your institution for guidelines. Failure to comply may result in fines.

The *PAXgen*e® tubes will be taken out of the racks, placed in the labeled "*PAXgene*®" cardboard box and covered with an absorbent sheet to minimize moving of tubes.

Shipping log instructions:
A shipping log must be created on the day the samples will be shipped. Access the PVDOMICS Biological Sample Tracking (BST) system online and scan the barcodes of all cryovials in Form 336 to insert one record for each. A shipment inventory will be generated that contains: date of shipment, site of origination, shipment ID, and an inventory detailing all the tubes in the shipment with their barcode numbers and participant information (participant ID number, collection number, specimen collection date). Please note that serum, plasma and urine shipments for several participants, blood draws and urine collections can be combined in the same large shipping box, but a separate shipping inventory must be created for each large box. A maximum of 7 boxes (9x9) can go into one large shipping box. Once 7 (9x9) boxes have been scanned), save the log, make note of the auto-populated Shipment Box ID and start a new shipment log if necessary. Print 2 copies of the shipment inventory (ies), one to include in each shipment box, and one to retain for the study records at the originating site.

Once the shipment information is completed in the BST system, an e-mail will automatically be sent to the Biorepository notifying them that a shipment should be expected. A copy of that e-mail will sent to the originating site. The e-mail message will include the originating site, the name of the person preparing the shipment and the shipment box ID in the body and a complete shipment inventory as an attachment.

Packing instructions:
1. Wrap rubber band around each specimen box and place inside biohazard bag. Up to 2 boxes can be in each bag. Seal the bag when full.
2. Place a thin layer of dry ice pellets in the bottom of the shipper.
3. Place up to 7 boxes in the plastic biohazard bag containing specimen on the dry ice.

4. Fill the rest of the space in the shipper with dry ice pellets. Leave 3.5” (height) empty in the top of the shipper for the lid’s foam insert.
5. Place the foam insert on top of the dry ice. Place a copy of the shipment log. Close and tape the outer box.
6. Affix the Biorepository **“To:”** address label to the side of the box in the upper left corner.
7. Affix the dry ice label **(UN1845)** to the same side of the box in the upper right corner. Enter the weight of dry ice on the label in kilograms.
8. Affix the “UN3373 BIOLOGICAL SUBSTANCE, CATEGORY B” label to the left of the dry ice label.
9. Affix the blue UPS “Dry Ice for Diagnostic or Medial Purposes Only” sticker. Enter weight of dry ice in kg, must be the same as on the dry ice label
10. Create a UPS airbill to ship specimens to BIOREPOSITORY at Cleveland Clinic.
11. Send a shipment notification to the Biorepository via email at pvd-biorepos@bio.ri.ccf.org on the day the package is dropped for UPS pickup. Include the UPS tracking number in the notification.
    Note: You should be able to setup your UPS account to send an automated message to pvd-biorepos@bio.ri.ccf.org when a shipment label is created.

PVDOMICS Study
Instructions for Collecting Urine Sample – Female

Collecting clean-catch urine sample is an important part of the PVDOMICS study. A 'clean catch' is a method of collecting a urine sample to be tested. The 'clean-catch' urine method is used to prevent germs from the surrounding tissue from getting into a urine sample.

~Ask your coordinator any questions you may have before collecting your urine.~

Before starting:

Your coordinator will give you the following items:

- 1 urine cup with lid and pre-labelled with your specific PVDOMICS Study ID
- 2 cleansing wipes



How the urine is collected:

- If possible, collect the sample when urine has been in your bladder for 2 to 3 hours
- You will use the items given to you to collect the urine
- Wash your hands with soap and warm water.

Collection procedure:

- Wash the area surrounding the urethra (where urine comes out of the body) called the labia.
- Sit on the toilet with your legs spread apart. Use two fingers to spread open your labia.
- Use the first wipe to clean the inner folds of the labia. Wipe from front to back.
- Use a second wipe to clean over the opening where urine comes out (urethra) - just above the opening of the vagina.
- Urinate into the toilet, stop the flow and then put the open urine container under the stream to catch the urine.
- Collect as much urine as you can up to about 1/2 - 2/3 of the cup.
- You may finish urinating into the toilet bowl.



After collecting the sample:

- Screw the lid tightly on the cup. Do not touch the inside of the cup or the lid.
- Return the sample to your study coordinator.

Thank you!

PVDOMICS Study
Instructions for Collecting Urine Sample – Male

Collecting clean-catch urine sample is an important part of the PVDOMICS study. A 'clean catch' is a method of collecting a urine sample to be tested. The 'clean-catch' urine method is used to prevent germs from the surrounding tissue from getting into a urine sample.

~Ask your coordinator any questions you may have before collecting your urine.~

Before starting:

Your coordinator will give you the following items:

- 1 urine cup with lid and pre-labelled with your specific PVDOMICS Study ID
- 1 cleansing wipe



How the urine is collected:

- If possible, collect the sample when urine has been in your bladder for 2 to 3 hours
- You will use the items given to you to collect the urine
- Wash your hands with soap and warm water.

Collection procedure:

- Clean the head of the penis with a cleansing wipe. If you are not circumcised, you will need to pull back (retract) the foreskin first.
- Urinate into the toilet, stop the flow and then put the open urine container under the stream to catch the urine.
- Collect as much urine as you can up to about 1/2 - 2/3 of the cup.
- You may finish urinating into the toilet bowl.



After collecting the sample:

- Screw the lid tightly on the cup. Do not touch the inside of the cup or the lid.
- Return the sample to your study coordinator.

Thank you!

Chapter 36. Waist Circumference and Waist-Hip Ratio

36.1 Introduction

During the PVDOMICS study each participant will undergo waist circumference and waist-hip ratio measurements. These measurements may been studied and thought be an indicator of increased disease risk if both are increased. Although the level of association may vary, it was found that waist circumference and waist to hip ratio correlated with Body Mass Index (BMI). In fact, these measures may provide different information and therefore are not interchangeable with BMI. Abdominal obesity and waist circumference have been included as one of the elements of metabolic syndrome. According to the WHO Report in 2008 from Geneva, abdominal obesity is defined as waist-hip ratio above 0.90 for males and above 0.85 for females.

World Health Organization Cut-off Points and Risk of Metabolic Complications

Indicator	Cut-off points	Risk of metabolic complications
Waist circumference	>94cm (M); >80cm (W)	Increased
Waist circumference	>102cm (M); >88cm (W)	Substantially increased
Waist-hip ratio	≥90cm (M); ≥85cm (W)	Substantially increased

M=Men W=Women

36.2 Preparations for Taking Measurements

- Identify a room (or space) preferably with a closed door to allow privacy and prevent interruptions during the measurements.
    - Exam area should be comfortable and free of drafts.
    - A chair or coat stand should be provided for participants to place their clothing and take off their shoes. Feet need to be flat on the floor during measurements.
- A constant-tension tape measure(s) (to measure waist and hip circumferences) – It is recommended that each center order more than one tape measure. Examples of constant-tension, cleanable tape measures include Gulick II and Figure Finder Tape.
- Disinfecting wipes to clean tape measure after use.

36.3 Participant Exclusions

Do not take participant's measurements if either of the following condition(s) exist:

- Wheelchair bound and unable to stand up straight for any length of time
- Significant kyphoscoliosis

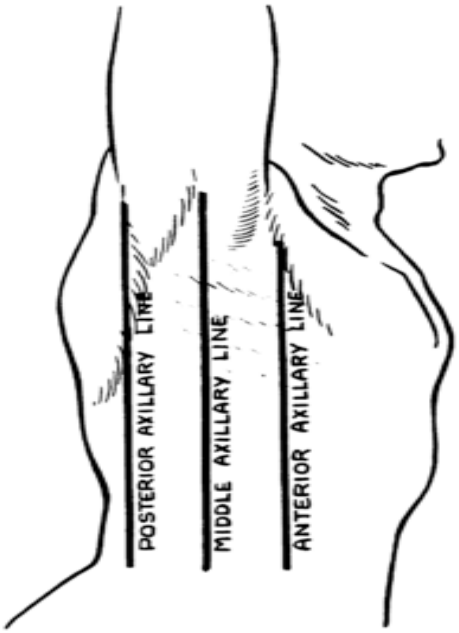
Record on Form 131 that test could not be completed.

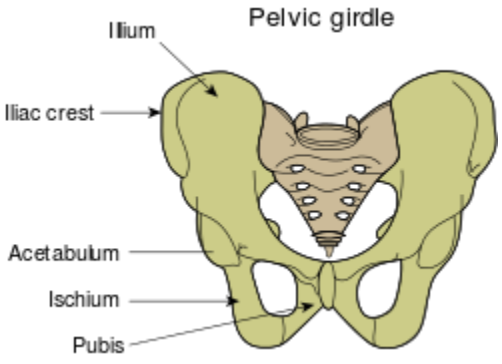
36.4 Participant Preparation

- Study testing procedure should be explained to the participant.
- Ask the participant to urinate prior to measuring.
- Ask participant not use a cell phone or mobile device while having a measurement done.
- Participant should remove clothing over their abdominal and hip areas for this testing. A participant's privacy should be protected during this portion. If it is not possible for a participant to remove all of their clothing in this area, measurements must be taken over thin/light clothing.
- Use the constant-tension stretch-resistant tape measure that can be wrapped snugly around a participant but it should never be constricting. The tape should be kept level and parallel to the examination room floor.
- When measuring the <u>waist circumference</u>, a participant should take several natural breaths and then measurement taken at the end of these breaths. The measurement should be conducted with the tape level to the examination floor, midpoint between the top of the iliac crest and lower margin of the last palpable rib at the mid axillary line.
- Participant should stand during testing, if possible.

.

Reference Points





36.3 Performing a Waist Circumference

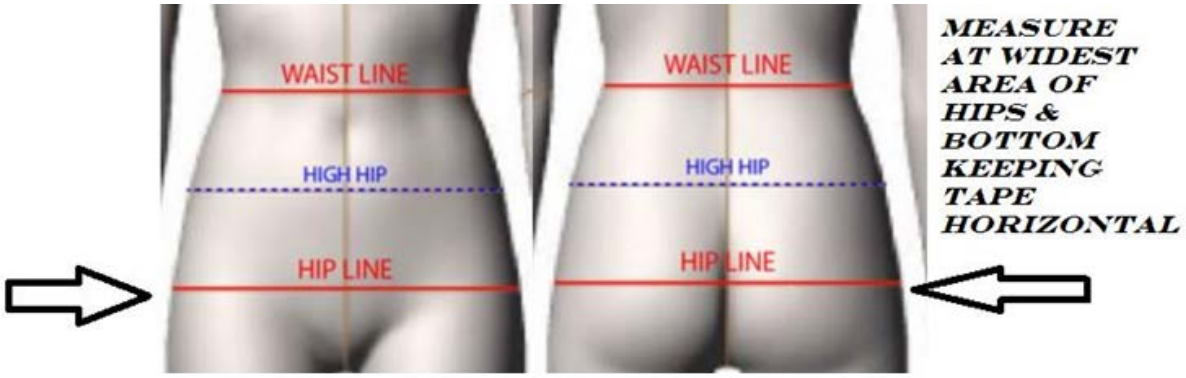
After the participant has removed the clothing around their waist and hips and are barefoot, approximate the midpoint between the lower margin of the last palpable rip and the top of the iliac crest.

- Arms should be at their sides and relaxed.

- Ask the participant to wrap the measuring tape around the waist, and then position the tape midway between the last palpable rib and the top of the iliac crest or hip bone. Make sure that the tape is located over the same spot on the other side. The tape should appear level with the floor.
- Participant should stand with their feet together with weight evenly distributed.
- Participant should breathe several natural breaths and the measurement should be recorded in centimeters (cm) to the nearest 0.1cm after a normal expiration and recorded on PVDOMICS Form 131. This measurement should be done only once.

36.4 Performing a Hip Circumference Measurement

- Arms should be at sides and relaxed.
- Ask participant to wrap the measuring tape around them, and then position the tape at the maximum circumference over the buttocks. Make sure that the tape is located over the same spot on the other side. The tape should appear level with the floor and should be snug without constricting.
- Participant should stand with their feet together with weight evenly distributed.
- Measurement should be recorded in centimeters (cm) to the nearest 0.1 cm on the PVDOMICS Form 131. This measurement should be done only once.



References

Wikipedia-Iliac Crest and Mid Axillary Definitions

Waist Circumference and Waist-Hip Ratio, Report of a WHO Expert Consultation Geneva 8-11 December 2008

Hip measurement image from s3.amazonaws.com

Waist circumference and waist–hip ratio: Part 3: Training and Practical Guides 3-3-4
Section 3: Guide to Physical Measurements (Step 2) WHO STEPS Surveillance 12 December 2008

Chapter 37. Bioelectric Impedance Assessment (BIA)

37.1 Introduction

During the PVDOMICS study each participant will undergo Bioelectrical Impedance Assessment using the Tanita SC-240 Body Composition Analyzer. This device is intended to measure weight and impedance, estimation of body mass index (BMI), total body fat percent, and total body water percent for the purposes of this study. Please refer to the manual provided with the device in addition to this MOP prior to operating the device (See Appendix 37.1).

37.2 Preparations for Taking Measurements

- Tanita SC-240 Body Composition Analyzer (BIA machine)
- Identify a room (or space) for the Tanita SC-240 Body Composition Analyzer to sit on a flat surface (a carpeted floor is not ideal).
- Exam area should be comfortable and free of drafts.
- Device must be plugged directly into wall outlet. Do not use power strips.
- Perform daily device check prior to participant's arrival.
- Provide a chair for participants to place their bulky clothing, remove phones and other devices, coins, etc., and take off shoes and socks.
- Appropriate disinfectant to clean scale platform after each use.
- Wipes for bottom of feet, if needed.

37.3 Participant Exclusions and Preparation

- Explain the testing procedure to the participant.
- Participant should be asked whether he or she has an implantable defibrillator or pacemaker. Participants with an implantable defibrillator or pacemaker should not undergo the BIA procedure.
- Make sure that each participant has refrained from hard exercise (any physical activity where a participant breaks a sweat or becomes breathless) or taken a sauna within 12 hours prior to measurement. Test should be rescheduled if possible.
- Participants should wait 3 hours after waking or eating prior to have a measurement done. If a participant has experienced over-eating or over-drinking (i.e., greater than 8 oz.), has drank alcohol in the last 12 hours. Test should be rescheduled if possible.
- If a female participant is menstruating then the measurement should be rescheduled if possible, as test would be inaccurate.
- If participant is dehydrated, the measurement should be rescheduled.
- Participant should not have a fever or be in shock.
- Participant's height and weight should be accurately obtained; height using centimeters and weight using kilograms. The maximum weight for an accurate test is 440 pounds.
- If participant has a leg or arm that has been amputated, this must be recorded on the PVDOMICS BIA Form 132. If a double leg amputee, test cannot be done.
- Ask the participant to urinate prior to measuring.
- Ask the participant to use a wipe to clean off bottom of feet, if needed.

- Ask the participant to sit quietly before test and not use cell phones or other mobile devices.

37.4 Measuring Safely

- This device cannot be used in participants who have pacemakers or other mechanical implants of any kind. If a participant has such a device, this test will not be done. There is a weak electrical current that flows through the body during a measurement that could interfere with the medical device, resulting in serious injury or consequence. Also, avoid use of this device in any participant who is allergic to metals.
- When operating the device avoid using near any flammable gases or wet or oxygen rich areas, and make sure to use dry hands when plugging the device into the outlet.
- Please disinfect the scale platform prior to use and between participants.
- Do not touch participant during a measurement.
- Unplug the device from the wall outlet when not in use for long periods of time.

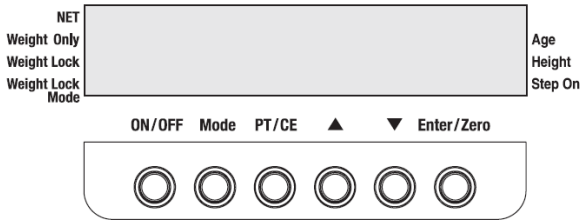
37.5 Initializing Device - Display Panel and Keys on Tanita SC-240

- On/Off key is located on the left hand of the display.
- Mode selection key is next to the ON/OFF key on the left hand side of the display-you may choose the body composition analyzer or weight scale
- PT/CE key is after the Mode selection key and used to clear input values or set preset.
  - ▲ The up key is next and is used to increase the numerical values
  - ▼ The down key follows and is used to decrease numerical values
- Enter/Zero key is the last key and is used to enter the input value/reset the scale to zero/mode setting.

Please refer to the Tanita SC-240 Manual for Common Symbols and their meanings, common display messages and for proper insertion of batteries into the device and/or insertion of AC adapter.

Figure 1. See next page.

Names and Functions of Display Panel & Operation Keys



ON/OFF	**ON / OFF key**	: turn the power ON / OFF
Mode	**Mode selection key**	: Select Body composition analyzer / Weigh scale
PT/CE	**PT / CE**	: Set preset tare / Clear input values
▲	**UP**	: Increase numerical values
▼	**DOWN**	: Decrease numerical values
Enter/Zero	**Enter / Zero reset**	: Enter input value / Scale reset to zero / Mode setting

NET	: Indicates that the clothes weight is input
Weight Only	: Indicates that the Weight Only (Scale) Mode
Weight Lock	: Indicates that the Weight is locking
Weight Lock Mode	: Indicates that the Weight Lock function is activated
Age	: Indicates that the age is input
Height	: Indicates that the height is input
Step On	: Indicates that the measuring start

37.6 Performing a BIA Measurement

- Bare feet must be used when taking a measurement and the feet must be over the electrode panels during measurements.
- The soles of the feet should be clean and free of dirt, and the participant should not be wet from sweat or urine.

<u>Scale Mode</u>

- Turn on Tanita SC-240 device, using the ON/OFF key.
- Use the MODE key and select the scale mode. Check that the weight only mode is selected. Input 1 kilogram for clothes weight. This is the standard weight for all clothes for each participant. So make sure all unnecessary clothing is removed and all shoes and socks are off. Use the up and down keys to input 1 kg. and then press the enter/zero key.
- Once the “Step on” is displayed and is flashing, have the participant step on the Tanita platform over the electrodes. Make sure the participant is not touching anything and that no one is touching the participant. The measurement will be displayed and the participant may step off of the platform (and seated until composition mode is accessed, if needed).
- Record the height in centimeters and weight in kilograms on PVDOMICS Form 132.

Body Composition Mode

- Press mode button on the device and choose body composition mode.
- Re-enter the clothes weight if needed (1 kg) and press 'enter/zero' key.
- Select the body type standard or athletic using the up and down keys. Press "Enter/Zero" key.
- Select the gender and use the "Enter/Zero" key.
- Input participant's age using the up and down keys and press "Enter/Zero" key.
- Input the height in centimeters using the up and down keys and press "Enter/Zero" key.
- Have the participant step on the platform again when the "Step On" is flashing. Make sure the participant is not touching anything, is standing still and that no one is touching the participant.
- Record the measured body fat percentage display, measured body mass index (BMI), total body water % and impedance on PVDOMICS Form 132.
- Participant is free to leave for other testing procedures.

Refer to the manual if any error messages display and attempt to re-perform the reading if needed.

37.7 Maintenance of Tanita SC-240 BIA Device

Prior to use and on a daily basis, make sure the device is on a stable and level surface, away from moisture and is in an environment with a stable temperature.

Each week, visually inspect the display, cables, electrodes, cords and connectors, to make sure there that they are free from damage, soiling and contamination. Do not use equipment that appears damaged.

37.8 Information about the Tanita SC-240 BIA Device

The URL for the Tanita website is: http://www.tanita.com/es/tanita-health-ware/

This website identifies that the Tanita BIA device works with Windows XP (32-bit and 64-bit English version) *[Note: Windows XP is no longer supported by Microsoft]*, Vista (32-bit and 64-bit English version), Windows 7 (32-bit and 64-bit English version), Windows 8 (32-bit and 64-bit English version) and Windows 10(32-bit and 64-bit English version). Tanita 240 software is not compatible with Mac and not compatible with some netbooks. Cables are sold separately.

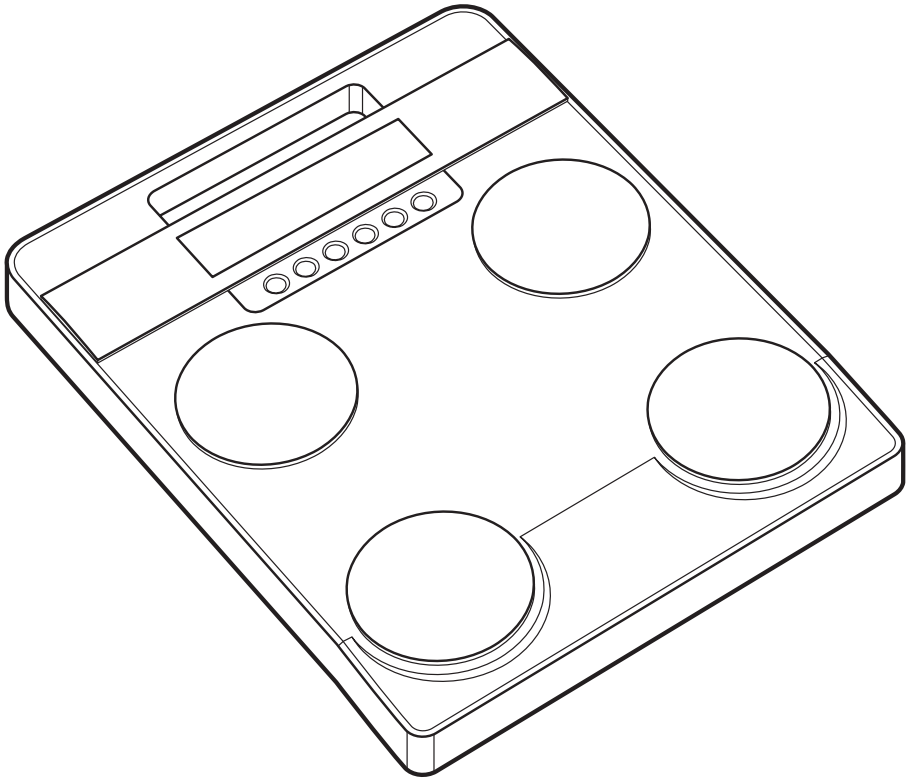
There 1 license per CD per computer. Additional licenses must be purchased separately if more than one computer will use the software. Local funds must be used by Clinical Center to purchase additional licenses and/or equipment.

TANITA®
Monitoring Your Health

BODY COMPOSITION ANALYZER

SC-240 / SC-240IM

Instruction manual



<Usage Conditions>

Temperature Range for Use	: 0°C – 35°C (32F° – 95°F)
Relative Humidity	: **30% – 80%** (without condensation)
Max Altitude	: 2,000m ASL (6,500ft ASL)
Pressure Range of Environment	: **86kPa - 106kPa**

<Storage Conditions>

Temperature Range of Environment : **-10°C – 60°C (14°F – 140°F)**
Range of Relative Humidity : **10% – 90%** (without condensation)
To avoid malfunctions, avoid storing the equipment where there is direct sunlight, significant temperature changes, the risk of dampness, a large amount of dust, in the vicinity of fires, or where there is the risk of receiving vibrations or shocks.

Please read this Instruction Manual carefully and keep it for future reference.

Intended use

- This equipment can be used in the screening of certain adult diseases and conditions related to body weight and composition.
- It can be used in the monitoring and prevention of conditions caused by excessive deposits of fat tissue such as diabetes, hyperlipidemia, cholelithiasis and fatty liver.
- It can be used in the monitoring of changes in individuals' body composition related to differences in the ratio of fat tissue to lean.
- It can be used to assess the effectiveness of individuals' nutrition and exercise programmers, both for health and physical fitness.
- The TANITA Body Composition Analyzer is indicated for use in the measurement of weight and impedance , and the estimation of body mass index (BMI), total body fat percent, total body water percent and weight , muscle mass (skeletal and smooth), physique rating, bone mass, visceral fat rating with healthy range, basal metabolic rate (BMR), and metabolic age, using B IA (Bioelectrical Impedance Analysis).
  The device is indicated for use for healthy children 5-17 years old and healthy adults with active, moderately active, to inactive lifestyles.

Efficacy

1. This product is simple to use, and requires no specialized facilities or expertise to take measurements.
2. Measurements can be taken quickly and easily, causing minimal inconvenience to the patient during measurments.



Contents

Before use (safety precautions)

Safety Notes 3
Part Names & Accessories 6
Names and Functions
of Display Panel & Operation Keys 7
Preparation (Power supply).....8
Various setting.....9

How to use (cautions for safety)

How to use (Mode selection).....10
How to use (Body composition mode).....11
How to use (Scale mode).....14
How to use (Scale / Weight lock mode).....15
How to use (Scale / BMI mode).....16

When necessary (cautions for safety)

Troubleshooting.....17
Various criteria.....18
Connection with a personal computer.....22
Technical notes.....26
Specifications.....30

How to Measure Correctly

The following outlines precautionary measures to be taken to avoid injury to the users of this device and others, and to prevent damage to property. Please familiarise yourself with the contents to ensure the safe operation of this equipment.

⚠Warning	**Ignoring instructions highlighted with this mark could result in death or severe injury.**
⚠Caution	**Ignoring instructions highlighted with this mark could result in injury or damage to property.**
⃠	**This mark indicates actions that are prohibited.**
❗	**This mark indicates instructions that must always be adhered to.**

⚠ Warning

Prohibited



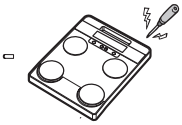
Do not handle the plug with a wet hand.
Such action may result in electric shock, fire, or leakage.



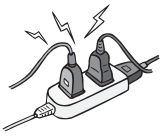
Keep this equipment away from flammable gas and oxygen rich environment.



No modification of this equipment is allowed.
There is a risk of electrocution or injury. Nor can precise analysis be guaranteed.



Do not use double adapters.
May result in fire.



Always…

Use only a correctly wired outlet.
Only genuine cables and equipments are allowed.

⚠Caution

Prohibited

Keep off wet circumstance.

Avoid using on subjects with allergies to metals.
Allergic reactions may be caused by the stainless steel used in the electrodes of this device.

Do not jump on the equipment.

Do not lean on the equipment.
Do not use this equipment near other products that emit electromagnetic waves.

Do not insert fingers into gaps and holes.

Avoid impacts on the display.
The screen panel may split and cause injury.

Ensure disabled persons do not attempt to use the equipment by themselves.
A companion must perform the measurements.

Always…

Be sure to clean the scale platform with appropriate disinfectant after each use.

For your safety to avoid the risk of electric shock and to secure the accuracy, keep a clearance with patients during measuring.

Continually monitor both the subject and the equipment for anomalies.
Should an anomaly with the subject or the equipment be discovered, take appropriate action, such as stopping the equipment, while ensuring the safety of the subject.

Unplug the equipment from the wall outlet when it will not be in use for long periods of time.

Do not interpret analysis results yourself (including evaluating measurements and formulating exercise programmes based on results, etc.).
Weight loss and exercise based on self-analysis could be detrimental to you health. Always follow the advice of a qualified professional.

This equipment is designated a Class B IT equipment (mainly for systems intended to be used in domestic environments) and CE (EMC), but weak equipment may be affected.
If you connect your computer or peripherals, please use the compliance with IEC60601-1 (EN60601-1). Or if using the compliance with IEC60950 (EN60950), power must be supplied from themedical isolating transformer. Keep at a distance of 1.5m between each equipment during operation. If you ignore this requirement, may cause electrical shock of patients or operation.

How to Measure Correctly

For Accurate Measurements

Prohibited

Avoid measuring after hard exercise.

May result in measurement errors. Please take measurements after sufficient rest.



Avoid measuring after over-eating or over-drinking, and when severely dehydrated.

May result in measurement errors. For greater accuracy, avoid using directly after waking up. Use at the same time on each occasion, at least three hours after eating.



Do not take measurements while using transmitters, such as mobile phones, which may affect readings.

Always…

Use the device under the same conditions and in the same position as much as possible to track changes.

Readings are greatly affected by the level of hydration and position of the body. Please use at the same time each day, under the same conditions and in the same body position.



Avoid measuring in locations of greatly differing temperature.

May result in measurement errors. When the equipment has been moved to a location ±20ºC (±36˚F), allow to stand for at least 2 hours before using.



Bare feet should be placed correctly on the electrode panel for measurement.

Also, make sure the soles of feet are free of excess dirt, as this may also act as a barrier to the mild current.

Use in a stable location.

Errors in measurements may occur when the device is used in an unstable location.

Scheduled Maintenance

Always…

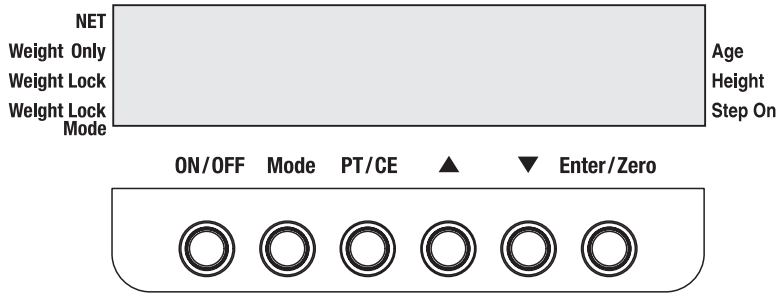
Perform periodic checks TANITA recommends that each facility conduct periodic checks of each unit.

1. Check the following at least daily:
   - Place the unit on a stable and level surface.
2. Visually inspect the following at least weekly:
   - the display for any damage or contamination
   - all cables, cords, and connector ends for damage or contamination
   - all safety-related labeling for legibility
   - all accessories (sensors,electrodes) for wear or damage
   - documentation for current revision of the unit
3. Visually inspect the following at least monthly:
   - Screws on unit

Update settings, replace items, or call for service as necessary based on results of visual inspection. Do not use the equipment if you see any signs of damage. Qualified service personnel must check any equipment that is damaged for proper operation before putting the equipment back into use.

The equipment should only be inspected in accordance with the regulations in each country.

Names and Functions of Display Panel & Operation Keys



ON/OFF **ON / OFF key** : turn the power ON / OFF

Mode **Mode selection key** : Select Body composition analyzer / Weigh scale

PT/CE **PT / CE** : Set preset tare / Clear input values

▲ **UP** : Increase numerical values

▼ **DOWN** : Decrease numerical values

Enter/Zero **Enter / Zero reset** : Enter input value / Scale reset to zero / Mode setting

NET : Indicates that the clothes weight is input

Weight Only : Indicates that the Weight Only (Scale) Mode

Weight Lock : Indicates that the Weight is locking

Weight Lock Mode : Indicates that the Weight Lock function is activated

Age : Indicates that the age is input

Height : Indicates that the height is input

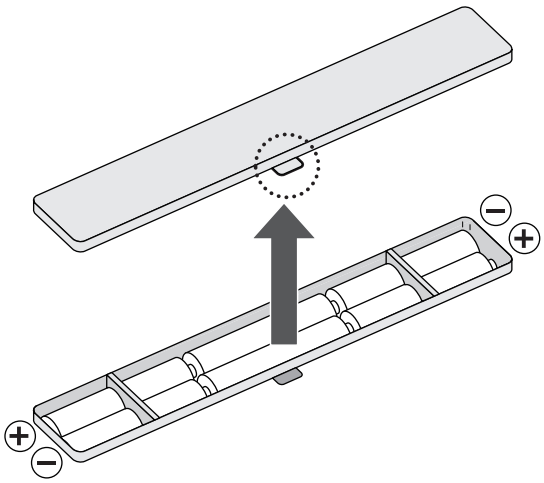
Step On : Indicates that the measuring start

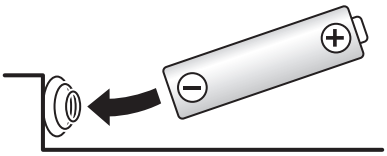
<Symbols and their Meanings>

P T	Preset tare (Clothes weight)		Male		Female
	Athletic mode		Direct current		Input, Output
	Caution. Refer to the attached information		Alternating current		Negative polarity
⊕ LR6,15A,"AA" ⊖	⊕ for positive polarity				

Preparation (Power supply)

<Using batteries>

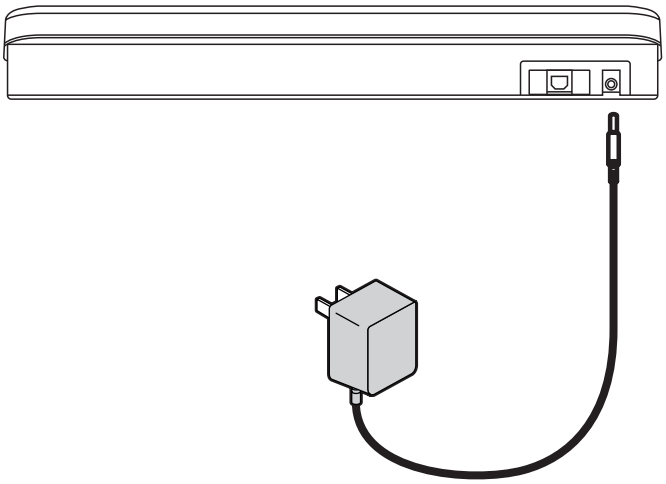




⚠
- Please change the batteries LR6 (AA) carefully to avoid dropping them on your feet.
- Ensure that the batteries are inserted with the correct polarity⊕/⊖. If the polarity is incorrect, then the batteries may leak and damage the equipment.
- When not in use for a long time, remove the batteries before storing the equipment.

<Using the AC adapter>

(1) Insert the AC adapter jack into the AC adapter inlet on the right side of the main unit.
(2) Plug the AC adapter into the power outlet.



⚠Caution

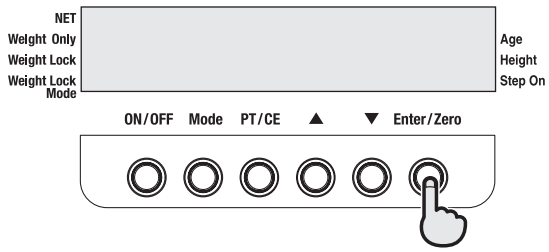
- This equipment must be used with the included AC adapter.
- Please observe the following instructions for accurate measurement.
  Measurement may not be possible on the unstable environment.
  During weight measurement, please don't touch any connecting cable "such as a AC Adapter cable and PC communication cable" to avoid causing unstable scale installation.

Various setting

Call up the setting mode.

1 Press ON/OFF to turn on the power.

2 Press Enter/Zero for 1 second.

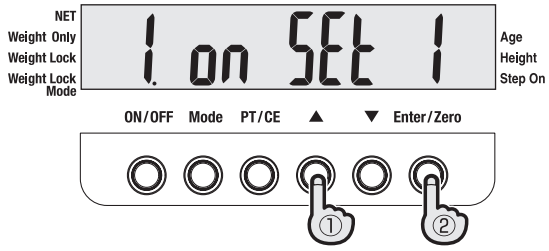


SET 0 is displayed.



3 Select the setting items.

1) by ▲ or ▼,
2) and **Enter/Zero** key.



SET1 Set ON / OFF of the beep sound.
(0.off or 1.on, default: 1.on)

SET2 Set ON / OFF of the athlete selection.
(0.off or 1.on, default: 1.on)

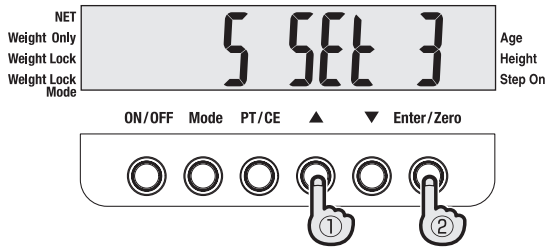
SET3 Set the automatic acceptance time when inputting.
(input range 0-9 seconds, default: 5 seconds)
* "0" automatic acceptance function deactivate.

SET4 Set the automatic power off time.
(0, 5, 10, 30, 60 minutes, default: 5 minutes)
* "0" automatic power off function deactivate.

SET5 Set the unit.
(0kg or 1.lb, default: 1.lb)

4 Input the setting value.

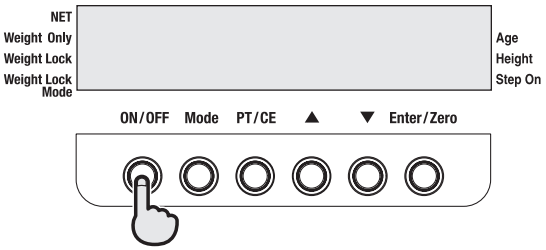
1) by ▲ or ▼,
2) and **Enter/Zero** key.

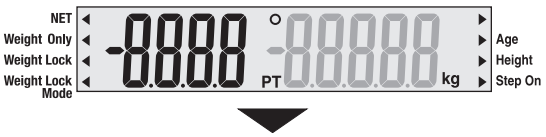


5 Press ON/OFF to turn the power off.

How to use (Mode selection)

1 Press ON/OFF to turn on the power.

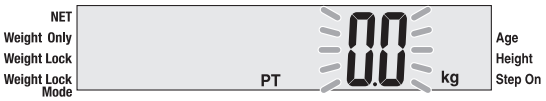




Model name is displayed.

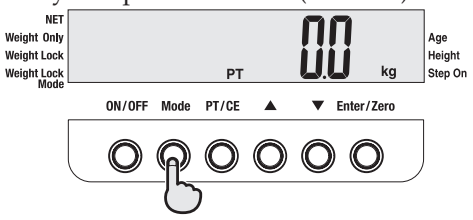


00 „ is displayed (Body composition analyzer).

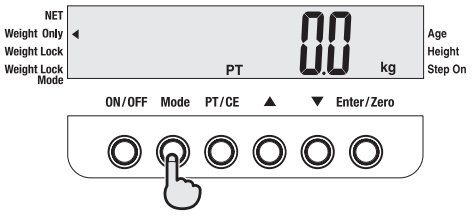


Mode is selected by **Mode** key.

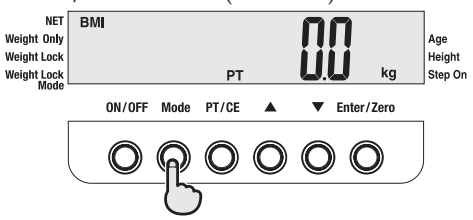
Body composition mode (☞P.11)



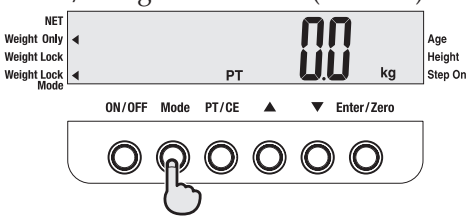
Scale mode (☞P.14)



Scale / BMI mode (☞P.16)



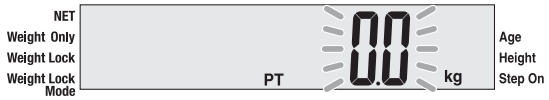
Scale / Weight lock mode (☞P.15)



How to use (Body composition mode)

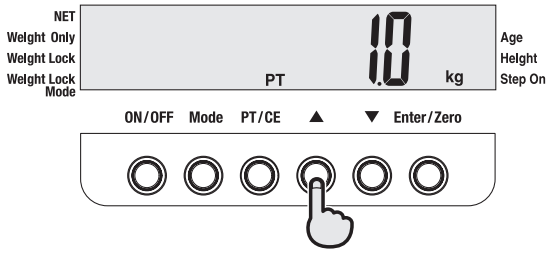
1 Press ON/OFF to turn on the power.

2 Check that the Body composition analyzer mode is selected (☞P.10).



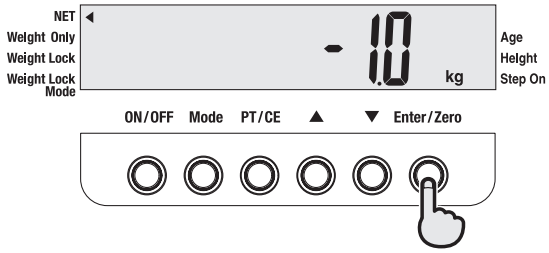
3 Input the clothes weight.

1) by ▲ or ▼,



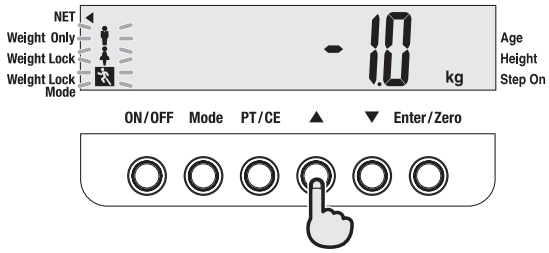
2) and **Enter/Zero** key

* **PT/CE** ➡ clear the input.



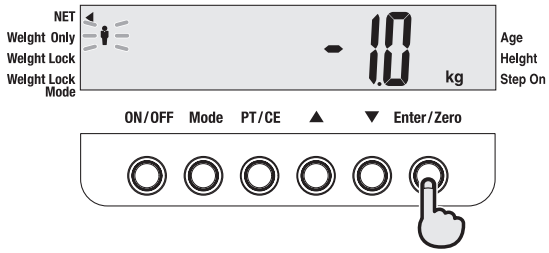
4 Select the Body type and Gender.

1) by ▲ or ▼,



2) and **Enter/Zero** key

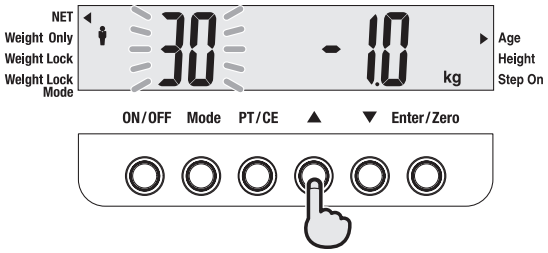
* **PT/CE** ➡ return to previous status.



How to use (Body composition mode) (continued)

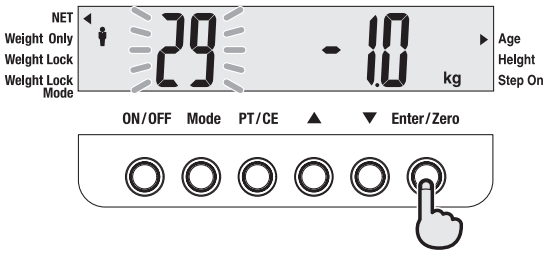
5 Input the age

1) by ▲ or ▼,



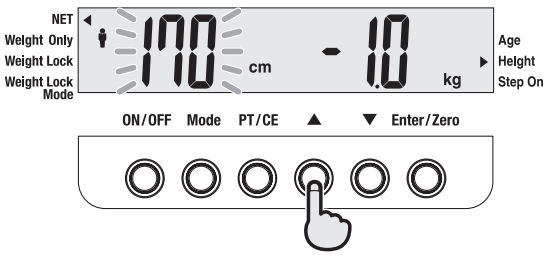
2) and **Enter/Zero** key

* **PT/CE** ➡ return to previous status



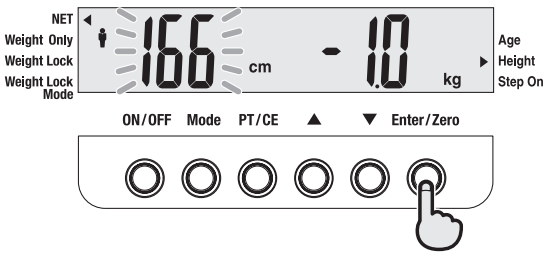
6 Input the height

1) by ▲ or ▼,



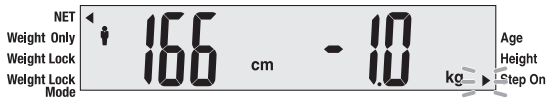
2) and **Enter/Zero** key

* **PT/CE** ➡ return to previous status



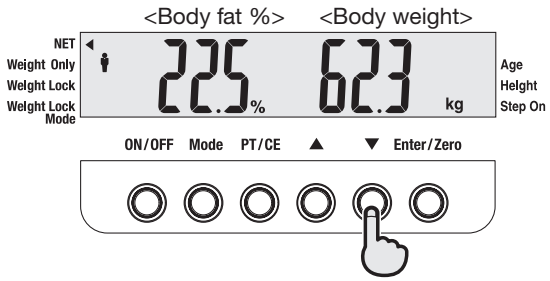
How to use (Body composition mode)

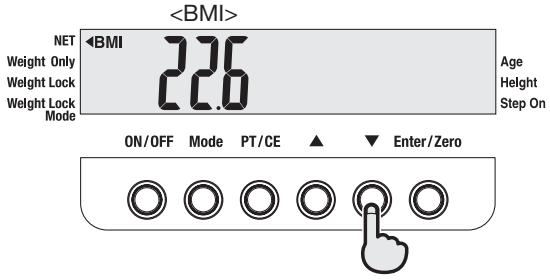
7 **Step on the platform with bare feet, after "Step on" flashing.**

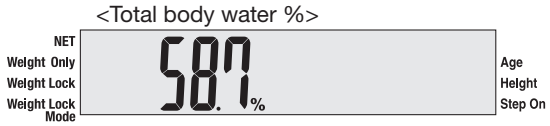




8 **Measurement completion.**







* **PT/CE**, **Enter/Zero** ➡ Clear the displayed result

Eng

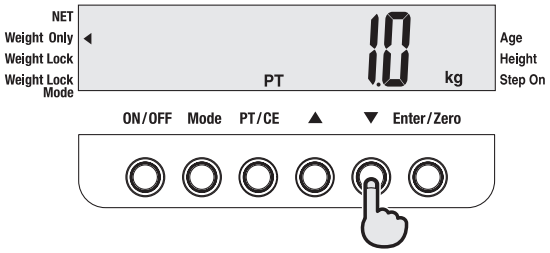
How to use (Scale mode)

1 **Press ON/OFF to turn on the power.**

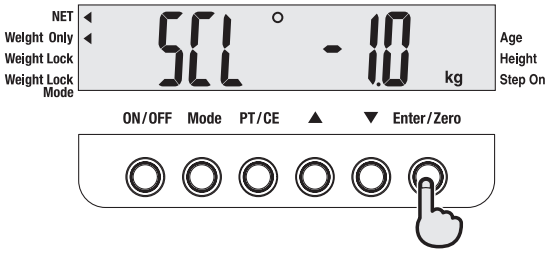
2 **Check that the Weight only mode is selected (☞P.10).**



3 **Input the clothes weight.**
1) by ▲ or ▼,

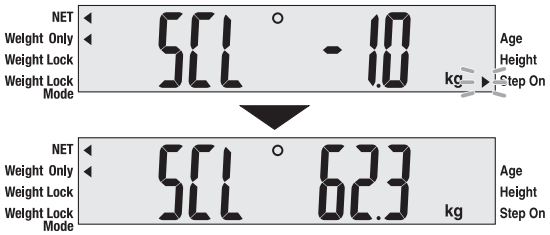


2) and **Enter/Zero** key
* **PT/CE** ➡ clear the input.



4 **Step on the platform, after "Step on" flashing.**

5 **Measurement completion.**



How to use (Scale / Weight lock mode)

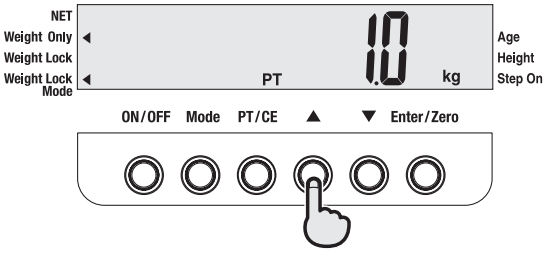
Activation of Weight lock function.

1 **Press ON/OFF to turn on the power.**

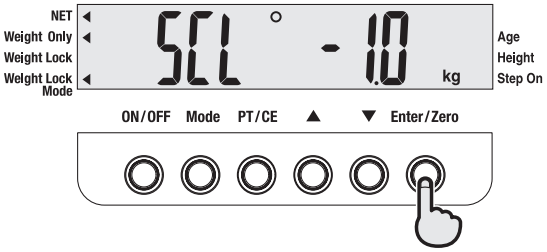
2 **Check that the Weight only mode (Weight lock mode) is selected (☞P.10).**



3 **Input the clothes weight.**
1) by ▲ or ▼,

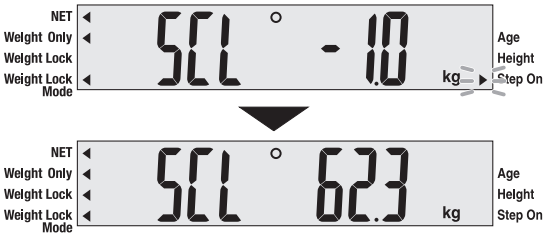


2) and **Enter/Zero** key
* **PT/CE** ➡ clear the input.



4 **Step on the platform, after "Step on" flashing.**

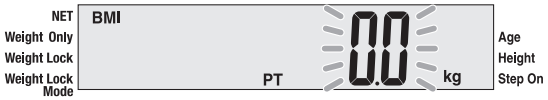
5 **Measurement completion.**
* **Enter/Zero** ➡ Clear the displayed result



How to use (Scale / BMI mode)

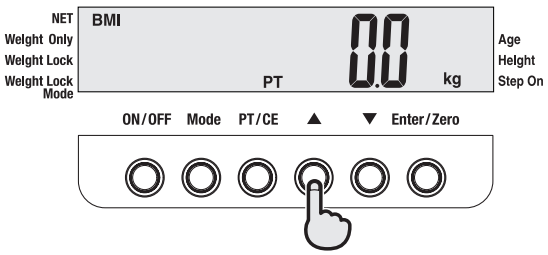
1 Press ON/OFF to turn on the power.

2 Check that the BMI mode is selected (☞P.10).



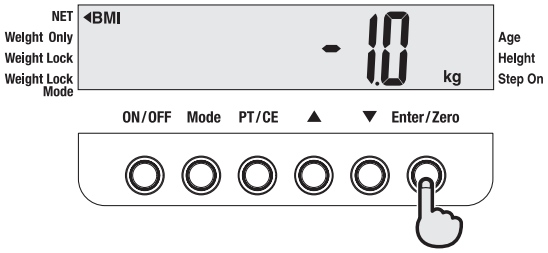
3 Input the clothes weight.

1) by ▲ or ▼,



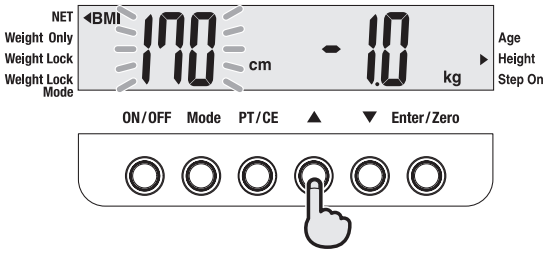
2) and **Enter/Zero** key

* **PT/CE** ➡ clear the input.



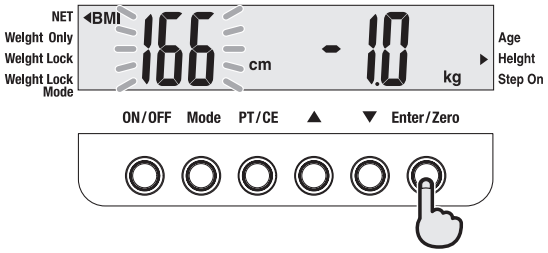
4 Input the height

1) by ▲ or ▼,



2) and **Enter/Zero** key

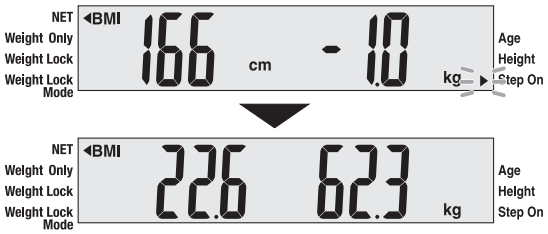
* **PT/CE** ➡ return to previous status



5 Step on the platform, after "Step on" flashing.

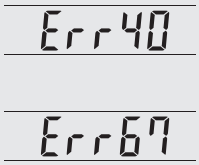
6 Measurement completion.

* **PT/CE**, **Enter/Zero** ➡ Clear the displayed result



Troubleshooting

- Please check the following before asking for repair.

	Symptom	Please check
How to measure	**Impedance measurement error** 	• Measure with bare feet. • When the soles of your feet are dry, drop water for about 0.5 ml with the attached dropper on the electrodes before measurement. • Check the input information.
	Zero point error 	• Turn off the power, and remove the items on the platform and turn on the power again, and then redo the measurement.
	The measured weight is not stable.	• Is it installed at a place with vibrations? • Is the platform inclined? ⇨ Keep the platform horizontal. • Is anything caught in the gaps of the platform? ⇨ Remove anything caught in the gaps.
Display part	**Nothing is displayed even after turning on the power.**	• Check that the power supply is connected correctly.
	 **is displayed.**	• The weight to measure exceeds the measurement range.

Note

- In the case that an error is displayed other than the above, turn off the power once, and then measure again.
  If the same error is displayed repeatedly, contact our customer service center.

Various criteria

What is body fat percentage? (Applicable age 5 - 99)

Body fat percentage is the amount of body fat as a proportion of your body weight.

Reducing excess levels of body fat has shown to reduce the risk of certain conditions such as high blood pressure, heart disease,diabetes and cancer. The chart below shows the healthy ranges for body fat.

Body Fat Ranges for Standard Children [1]
Body Fat Ranges for Standard Adults [2]

[1] *Susan Jebb et al. Obesity Reseach[o2] 2004;12:A156-157 "New Body Fat Reference Curves for children"*

[2] *Gallagher D et al. Am J Clin Nutr 2000,72:694-701. "Healthy percentage body fat ranges:an approach for developing guidelines based on body mass index."*

| Female Age | Underfat | | | | | | | | | Healthy | | | | | | | | | | Overfat | | | | | Obese | | | | | | | | | |

- What is total body water percentage? (Applicable age 18 - 99)

Total Body Water Percentage is the total amount of fluid in a person's body expressed as a percentage of their total weight.

Water plays a vital role in many of the body's processes and is found in every cell, tissue and organ. Maintaining a healthy total body water percentage will ensure the body functions efficiently and will reduce the risk of developing associated health problems.

Your body water levels naturally fluctuate throughout the day and night. Your body tends to be dehydrated after a longnight and there are differences in fluid distribution between day and night. Eating large meals, drinking alcohol, menstruation, illness, exercising, and bathing may cause variations in your hydration levels.

Your body water percentage reading should act as a guide and should not be used to specifically determine your absolute recommended total body water percentage. It is important to look for long-term changes in total body water percentage and maintain a consistent, healthy total body water percentage.

Drinking a large quantity of water in one sitting will not instantly change your water level. In fact, it will increase your body fat reading due to the additional weight gain. Please monitor all readings over time to track the relative change.

Every individual varies but as a guide the average total body water percentage ranges for a healthy adult are:

Female : 45 to 60%
Male : 50 to 65%
Source : Based on Tanita's Internal Research

Note: The total body water percentage will tend to decrease as the percentage of body fat increases. A person with a high percentage of body fat may fall below the average body water percentage. As you lose body fat the total body water percentage should gradually move towards the typical range given above.

- What is visceral fat rating? (Applicable age 18 - 99)

This feature indicates the ratingof visceral fat in your body.

Visceral fat is the fat that is in the internal abdominal cavity, surrounding the vital organs in the trunk (abdominal) area. Research shows that even if your weight and body fat remains constant, as you get older the distribution of fat changes and is more likely to shift to the trunk area especially post menopause. Ensuring you, have healthy levels of visceral fat my reduce the risk of certain diseases such as heart disease, high blood pressure, and the onset of type 2 diabetes.

The Tanita Body Composition Analyzer will provide you with a visceral fat rating from 1 – 59.

Rating from 1 to 12

Indicates you have a healthy level of visceral fat. Continue monitoring your rating to ensure that it stays within the healthy range.

Rating from 13 –59

Indicates you have an excess level of visceral fat. Consider making changes in your lifestyle possibly through diet changes or increasing exercise.

Source: 1) Tanita Institute Contract Study. Algorithm Development for Estimating Visceral Fat Rating. SB Heymsfield MD. Columbia University College of Physicians and Surgeons 2004.
2) Wang, Z., et al. Japanese-American Differences in Visceral Adiposity and a Simplified Estimation Method for Visceral Adipose Tissue. North American Association for the Study of Obesity. Annual Meeting. Abstract 518-P. 2004

Note:

- Even if you have a low body fat rate, you may have a high visceral fat level.
- For medical diagnosis, consult a physician.

Various criteria (continued)

- What is basal metabolic rate (BMR)? (Applicable age 18 - 99)

WHAT IS BMR?

Your Basal Metabolic Rate(BMR) is the minimum level of energy your body needs when at rest to function effectively including your respiratory and circulatory organs, neural system, liver, kidneys, and other organs. You burn calories when sleeping.

About 70% of calories consumed every day are used for your basal metabolism. In addition, energy is used when doing any kind of activity however; the more vigorous the activity is the more calories are burned. This is because skeletal muscle (which accounts for approximately 40% of your body weight) acts as your metabolic engine and uses a large amount of energy. Your basal metabolism is greatly affected by the quantity of muscles you have, therefore increasing your muscle mass will help increase your basal metabolism.

By studying healthy individuals, scientists have found that as people age, their metabolic rate changes. Basal metabolism rises as a child matures. After a peak at the age of 16 or 17, it typically starts to decrease gradually.

Having a higher basal metabolism will increase the number of calories used and help to decrease the amount of body fat. A low basal metabolic rate will make it harder to lose body fat and overall weight.

HOW DOES A TANITA BODY COMPOSITION ANALYZER CALCULATE BMR?

The basic way of calculating Basal Metabolic Rate BMR is a standard equation using weight and age. Tanita has conducted in-depth research into the relationship of BMR and body composition giving a much more accurate and personalized reading for the user based on the impedance measurement. This method has been medically validated using indirect calorimetry (measuring the breath composition).*

* Reliability on equation for Basal Metabolic Rate: At 2002 Nutrition Week : A Scientific and Clinical Forum and Exposition Title: International Comparison: Resting Energy Expenditure Prediction Models: The American Journal of Clinical Nutrition

- What is metabolic age? (Applicable age 18 - 99)

This feature calculates your BMR and indicates the average age associated with that type of metabolism.

If your BMR Age is higher than your actual age, it is an indication that you need to improve your metabolic rate. Increased exercise will build healthy muscle tissue, which will improve your metabolic age.

You will obtain a reading between 12 and 90. Under 12 will be displayed as “12” and over 90 displayed as “90”.

- What is muscle mass? (Applicable age 18 - 99)

This feature indicates the weight of muscle in your body. the muscle mass displayed includes the skeletal muscles, smooth muscles (such as cardiac and digestive muscles) and the water contained in these muscles.

Muscles play an important role as they act as an engine in consuming energy. As your muscle mass increase, your energy consumption increases helping you reduce excess body fat levels and lose weight in a healthy way.

- What is bone mass? (Applicable age 18 - 99)

This feature indicates the amount of bone (bone mineral level, calcium or other minerals) in the body.

Research has shown that exercise and the development of muscle tissue are related to stronger, healthier bones. While bone structure is unlikely to make noticeable changes in a short period, it is important that you develop and maintain healthy bones by having a balanced diet and plenty of exercise. People worried about bone disease should consult their physician. People who suffer from osteoporosis or low bone densities due to advanced age, young age, pregnancy,hormonal treatment or other causes, may not get accurate estimations of their bone mass.

Below is the result of estimated bone masses of persons aged 20 to 40, who are said to have the largest amounts of bone masses, by weight. (Source : Tanita Body Weight Science Institute)

Please use the below charts as a guide to compare your bonemass reading.

Women : Average of estimated bone mass

Weight (lb)		
Less than 110 lb	110lb - 165 lb	165 lb and up
4.3 lb	5.3 lb	6.5 lb

Weight (kg)		
Less than 50 kg	50 kg - 75 kg	75 kg and up
1,95 kg	2,40 kg	2,95 kg

Men : Average of estimated bone mass

Weight (lb)		
Less than 143 lb	143 lb - 209 lb	209 lb and up
5.9 lb	7.3 lb	8.1 lb

Weight (kg)		
Less than 65 kg	65 kg - 95 kg	95 kg and up
2,66 kg	3,29 kg	3,69 kg

Note: Persons described below may obtain varying readings and should take the values given for reference purposes only.

- Elderly persons
- Women during or after menopause
- People receiving hormone therapy

"Estimated bone mass" is a value estimated statistically based on its correlation with the fat-free amount (tissues other than the fat). "Estimated bone mass" does not give a direct judgment on the hardness or strength of the bones or the risks of bone fractures. If you have concerns over your bones, you are recommended to consult a specialist physician.

Connection with a personal computer

The USB interface enables input and output from this equipment.

- Specifications

Communication standards	USB
Communication method	Asynchronous Transmission
Signal speed	9600 baud
Data bit length	8 bits
Parity	None
Stop bit	1 bit
Flow control	None
Terminator	CR+LF

Note

- USB connector (B - Type 4 - pin female) are located on the back of the control box.
- Please provide your own cable as necessary as none are included.
  USB cable : A - Type 4 - pin (male) - B - Type 4 - pin (male)
- You must install the necessary driver onto your PC, available download from http://www.tanita.com or on the enclosed CD-Rom.

- Transmit data

⚠Caution Transmission Data is output immediately after measurement regardless of the status of the receiving equipment (personal computer, etc.). Therefore the receiving equipment needs to be ready to accept the data before measuring.

(1) Output example (in the case to kg unit)

Note

- The data are divided with commas (,) for each data.
- The terminator (end of the data) is CR (ASCII code 0DH), LF (ASCII code 0AH).
- The control data for the items 1 –4 are for expansion. They are not used presently so the receiving side can ignore them.
- Because of its specifications, the scale will output an irrelevant signal approximately 0.1 second after data output. Make sure you ignore this signal and do not import it.

Entire body data

Model number		Serial number		Body type		Gender		Age	
MO	"XXXXXX"	SN	"XXXXXXXX"	Bt	0or2	GE	1or2	AG	XX

Height		Preset tare		Body weight		Fat %		Fat mass	
Hm	XXX.X	Pt	XX.X	Wk	XXX.X	FW	XX.X	fW	XXX.X

Fat free mass		Muscle mass		Muscle score		Bone mass		Body water	
MW	XXX.X	mW	XXX.X	sW	XX	bW	XXX.X	wW	XXX.X

Body water %		BMI		Ideal body weight		Degree of obesity		Visceral fat rating	
ww	XX.X	MI	XXX.X	Sw	XXX.X	OV	XXX.X	IF	XX

BMR (kJ)		BMR (kcal)		BMR score		Metabolic age		Impedance (50kHz)	
rb	XXXXX	rB	XXXXX	rJ	XX	rA	XX	ZF	XXXX.X

Checksum	
CS	XX

Connection with a personal computer (continued)

(2) Output data items

<kg / cm mode>

Item	Header	format	kg / cm mode	Order of output				
				Body composition			Scale	BMI
				Adult	Athlete	Child		
Control data	{0		2 bytes fixed length	1	1	1	1	1
Control data	~0		1 byte fixed length	2	2	2	2	2
Control data	~1		1 byte fixed length	3	3	3	3	3
Control data	~2		1 byte fixed length	4	4	4	4	4
Model number	MO	"XXXXXX"	8 bytes fixed length ("SC-240")	5	5	5	5	5
Serial number	SN	"XXXXXXXX"	10 bytes fixed length	6	6	6	6	6
Body type	Bt	0 or 2	1 byte fixed length (0: Standard 2: Athletic)	7	7	7		
Gender	GE	1 or 2	1 byte fixed length (1: Male 2: Female)	8	8	8		
Age	AG	XX	1-2 bytes variable length	9	9	9		
Height	Hm	XXX.X	4-5 bytes variable length (cm)	10	10	10		7
Preset tare	Pt	XX.X	3-4 bytes variable length (increments 0.1 kg)	11	11	11	7	8
Body weight	Wk	XXX.X	3-5 bytes variable length (increments 0.1 kg)	12	12	12	8	9
Fat %	FW	XX.X	3-4 bytes variable length (increments 0.1%)	13	13	13		
Fat mass	fW	XXX.X	3-5 bytes variable length (increments 0.1 kg)	14	14	14		
FFM	MW	XXX.X	3-5 bytes variable length (increments 0.1 kg)	15	15	15		
Muscle mass	mW	XXX.X	3-5 bytes variable length (increments 0.1 kg)	16	16			
Muscle score	sW	XX	1-2 bytes variable length (1-24)	17	17			
Bone mass	bW	XXX.X	3-5 bytes variable length (increments 0.1 kg)	18	18			
Body water	wW	XXX.X	3-5 bytes variable length (increments 0.1 kg)	19	19			
Body water %	ww	XX.X	4 bytes fixed length (increments 0.1%)	20	20			
BMI	MI	XXX.X	3-5 bytes variable length (increments 0.1)	21	21	16		10
Ideal body weight	Sw	XXX.X	3-5 bytes variable length (increments 0.1 kg)	22				
Degree of obesity	OV	XXX.X	3-5 bytes variable length (increments 0.1%)	23				
Visceral fat rating	IF	XX	1-2 bytes variable length	24	22			
BMR (kJ)	rb	XXXXX	1-5 bytes variable length (increments 1 kJ)	25	23			
BMR (kcal)	rB	XXXXX	1-5 bytes variable length (increments 1 kcal)	26	24			
BMR score	rJ	XX	1-2 bytes variable length (1-24)	27	25			
Metabolic age	rA	XX	2 bytes fixed length	28	26			
Impedance (50 kHz)	ZF	XXXX.X	1-2 bytes variable length (4-55)	29	27	17	9	
Checksum	CS	XX	2 bytes fixed length	30	28	18	10	11

Output sample

Standard, Male, 30 years old, Height 170 cm

{0, 16, ~0, 1, ~1, 1, ~2, 1, MO, "SC-240", SN, "00000002", Bt, 0, GE, 1, AG, 30, Hm, 170, Pt, 0.0, Wk, 82.7, FW, 18.6, fW, 15.4, MW, 67.3, mW, 64.0, sW, 19, bW, 3.3, wW, 48.0, ww, 58.0, MI, 28.6, Sw, 63.6, OV, 30.0, IF, 6, rb, 8255, rB, 1973, rJ, 12, rA, 28, ZF, 369.4, CS, FD

<lb / ft-in mode>

Item	Header	format	lb / ft-in mode	Order of output				
				Body composition			Scale	BMI
				Adult	Athlete	Child		
Control data	{0		2 bytes fixed length	1	1	1	1	1
Control data	~0		1 byte fixed length	2	2	2	2	2
Control data	~1		1 byte fixed length	3	3	3	3	3
Control data	~2		1 byte fixed length	4	4	4	4	4
Model number	MO	"XXXXXX"	8 bytes fixed length ("SC-240")	5	5	5	5	5
Serial number	SN	"XXXXXXXX"	10 bytes fixed length	6	6	6	6	6
Body type	Bt	0 or 2	1 byte fixed length (0: Standard 2: Athletic)	7	7	7		
Gender	GE	1 or 2	1 byte fixed length (1: Male 2: Female)	8	8	8		
Age	AG	XX	1-2 bytes variable length	9	9	9		
Height	Hm	XXX.X	4 bytes variable length (in)	10	10	10		7
Preset tare	Pt	XX.X	3-4 bytes variable length (increments 0.2lb)	11	11	11	7	8
Body weight	Wk	XXX.X	3-5 bytes variable length (increments 0.2 lb)	12	12	12	8	9
Fat %	FW	XX.X	3-4 bytes variable length (increments 0.1%)	13	13	13		
Fat mass	fW	XXX.X	3-5 bytes variable length (increments 0.2 lb)	14	14	14		
FFM	MW	XXX.X	3-5 bytes variable length (increments 0.2 lb)	15	15	15		
Muscle mass	mW	XXX.X	3-5 bytes variable length (increments 0.2 lb)	16	16			
Muscle score	sW	XX	1-2 bytes variable length (1-24)	17	17			
Bone mass	bW	XXX.X	3-5 bytes variable length (increments 0.2 lb)	18	18			
Body water	wW	XXX.X	3-5 bytes variable length (increments 0.2 lb)	19	19			
Body water %	ww	XX.X	4 bytes fixed length (increments 0.1%)	20	20			
BMI	MI	XXX.X	3-5 bytes variable length (increments 0.1)	21	21	16		10
Ideal body weight	Sw	XXX.X	3-5 bytes variable length (increments 0.2 lb)	22				
Degree of obesity	OV	XXX.X	3-5 bytes variable length (increments 0.1%)	23				
Visceral fat rating	IF	XX	1-2 bytes variable length	24	22			
BMR (kJ)	rb	XXXXX	1-5 bytes variable length (increments 1 kJ)	25	23			
BMR (kcal)	rB	XXXXX	1-5 bytes variable length (increments 1 kcal)	26	24			
BMR score	rJ	XX	1-2 bytes variable length (1-24)	27	25			
Metabolic age	rA	XX	2 bytes fixed length	28	26			
Impedance (50 kHz)	ZF	XXXX.X	5-6 bytes variable length (increments 0.1)	29	27	17	9	
Checksum	CS	XX	2 bytes fixed length	30	28	18	10	11

Output sample

Standard, Male, 30 years old, Height 67.0 in

{0, 16, ~0, 1, ~1, 1, ~2, 1, MO, "SC-240", SN, "00000003", Bt, 0, GE, 1, AG, 30, Hi, 67.0, Pt, 0.0, Wp, 182.2, FW, 18.7, fW, 34.0, MW, 148.2, mW, 140.8, sW, 19, bW, 7.4, wW, 105.6, ww, 58.0, MI, 28.5, Sw, 140.4, OV, 29.8, IF, 6, rb, 8247, rB, 1971 ,rJ, 12, rA, 29, ZF, 372.8, CS, 2A

Technical notes

Body composition measurement by the BIA method.

Introduction

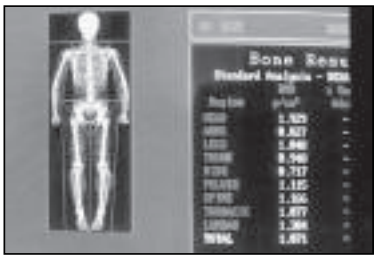
This equipment provides estimated values for each measured value of body fat percentage, fat mass, fatfree mass, muscle mass and bone mass by the DXA method, estimated value for the total body water measured value by the dilution method and estimated value for the visceral fat rating by MRI method using the Bioelectrical Impedance Analysis (BIA method).
For measurement, a mode must be selected based on body type.
1) Standard (for 5-99 years of age)
2) Athletic (for Athletic persons who exercise considerably more than non-athlete)
Making a distinction by body type in the measurement mode produces more reliable body composition measurements for athletic persons, whose body compositions differ from those of average persons.

- Principles of body composition measurement

BIA is a means of measuring body composition – fat mass, predicted muscle mass, etc. – by measuring bioelectrical impedance in the body. Fat within the body allows almost no electricity to pass through, while electricity passes rather easily through water, much of which is found in muscles. The degree of difficulty with which electricity passes through a substance is known as the electrical resistance, and the percentage of fat and other body constituents can be inferred from measurements of this resistance.
The Tanita Body Composition Analyzer measures body composition using a constant current source with a high frequency current (50 kHz, 90 µA). The 8 electrodes are positioned so that electric current is supplied from the electrodes on the tips of the toes of both feet, and voltage is measured on the heel of both feet. The current flows into the upper limbs or lower limbs, depending on the body part(s) to be measured.

- What is the DXA method?

DXA was originally designed to measure bone mineral content, but in the full-body scan mode the body fat percentage, fat mass, and fat free mass of individual body parts (arms, legs, trunk) can also be measured. The image below shows one example of body composition measurement results obtained by DXA.



Body composition measurement results obtained by DXA (Lunar Co., Ltd; DPX-L)

- What is dilution method?

In the dilution method, a labeled substance for a known amount is given and the concentration in equilibrium diffusing evenly is measured to obtain the total amount of the solvent that dilutes the labeled substance.
To measure the total body water (TBW), deuterium oxide (D2O) is generally used as the labeled substance. Deuterium oxide uses the overall total body water as dilution space so the total body water can be obtained. To obtain the extracellular fluid amount, sodium bromide (NaBr) is used as a labeled substance. Bromine (Br) is said to not enter the inside of cells, and uses extracellular fluid as the dilution space.

- What is the visceral fat?

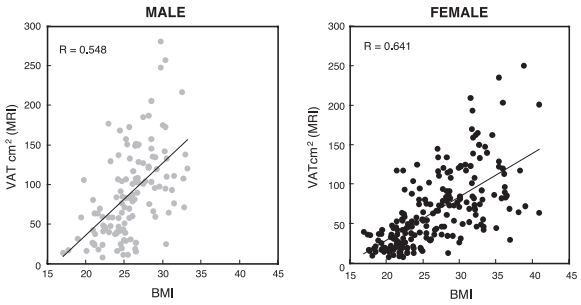
Visceral Adipose Tissue (VAT) has been associated with increased risk of developing lifestyle-related diseases. Accordingly, knowing and periodically checking the estimated VAT accumulation serves as one factor of a number of factors in assessing the prevention of lifestyle related diseases.

Tanita has developed the technology for measuring the VAT accumulation risk through bioelectrical impedance analysis (BIA) in comparison with image analysis applied to magnetic resonance imaging (MRI), in addition to the established technology for measuring the percent of body fat. The VAT accumulation risk is calculated by estimating the VAT area by the BIA method on the basis of MRI image processing. This method has a higher correlation than the estimation of the VAT accumulation risk based on BMI or abdominal circumference (waist circumference), allowing estimation that corresponds more precisely to individuals.

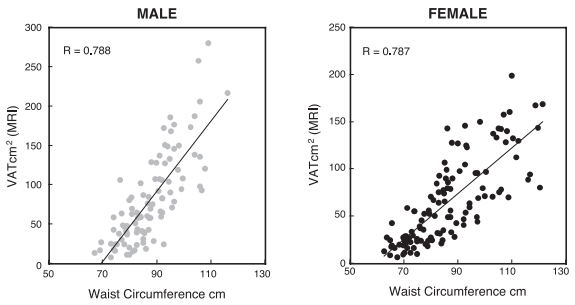
* The VAT area by MRI is calculated by carrying out an image processing of the cross section of the lumber vertebra L4-L5 regions.

(Fig. 1 - Fig. 3: Research results by N. Y. Columbia University and Jikei University Published by the North American Association for the Study of Obesity [NAASO] in 2004.)

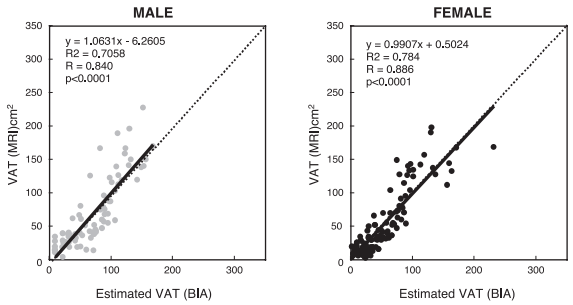
<Fig. 1> Relationship between VAT Area and BMI



<Fig. 2> Relationship between VAT Area and Waist Circumference



<Fig. 3> Relationship between VAT Area by MRI and Estimated VAT Area by Tanita's BIA



Technical notes (continued)

- Factors giving errors in measurement

In the BIA method, impedance is measured and the body composition is calculated based on the value. It is known that impedance changes by the amount of the total body water that occupies about 60% of weight and the change in its distribution and temperature change. Therefore, for the purpose of research or for daily repeating of measurements, the measurement conditions must be kept constant. Measurement under the changing conditions of temperature and total body water distribution or blood flow volume of extremities due to exercising, taking a bath, etc., affects the measurement result since the electric resistance in the body also changes.
Therefore, it is recommended to measure under the following conditions forstable measurement.

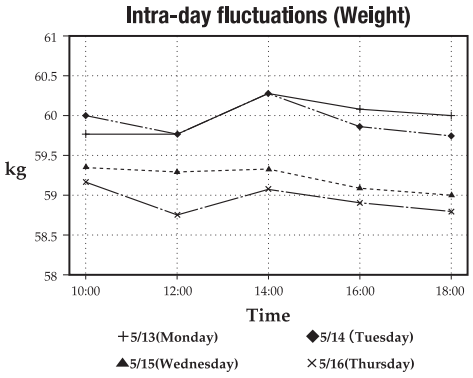
1) 3 hours have passed after getting up and normal lifestyle activities are carried out during this period. (The impedance transits staying at a high level if you remain sitting after getting up or drive acar, etc.)
2) 3 hours or more have passed after eating. (For 2 – 3 hours after eating, the impedance has a tendency to decrease.)
3) 12 hours or more have passed after vigorous exercise for measurement. (The tendency toward changes in impedance is not stable depending on the type and rigorousness of the exercise.)
4) If possible urinate before taking measurement.
5) For repeated measurements, measure at the same hour as much as possible. (At the same time of measurement of weight, the measurements can be made more stable by measuring at the same time of the day)

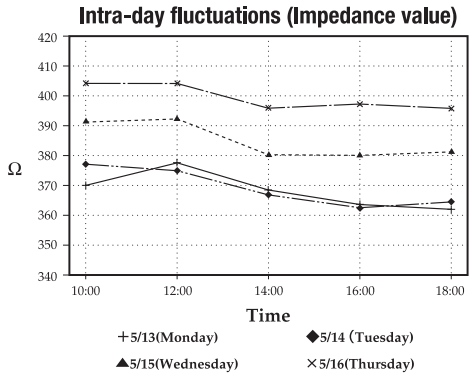
Very stable measured values can be obtained by measuring under the above conditions.
And in the development of this equipment, the following 6 items were set as conditions for the regression equation.

1) Prohibition of alcohol intake for 12 hours before measurement
2) Prohibition of excessive exercise for 12 hours before measurement.
3) Prohibition of excessive eating and drinking the day before measurement
4) Prohibition of eating and drinking for 3 hours before measurement
5) Urination just before measurement
6) Avoid measurements during menstruation (for female)

Inter-day changes

The diagrams below offer examples of actual measurements made of inter-day changes. A study was done to determine the degree of change in the impedance between the feet during dehydration; the first two days represent a normal daily routine, while in the latter two days a state of dehydration was induced using a sauna.





No significant inter-day change was measured in body weight, impedance between the feet, or body fat percentage during the normal daily routine. During the dehydrated state, however, a drop in body weight of 1kg was noted, with the impedance between the feet rising approximately 15Ω on the first day of dehydration and 30-35Ω on the second day. As a result, body fat percentage was up by around 1% on the first day of dehydration and by 1.5-2% on the second day.

As mentioned earlier, impedance increases when body weight is reduced (such as by dehydration), and decreases when body weight is increased through excess consumption of food and drink. The inter-day change in impedance is thus inversely proportional to the change in body weight.

These inter-day changes stem from such causes as:

1) Temporary increases in body weight (total body water) through overeating and overdrinking
2) Dehydration due to heavy sweating during vigorous exercise
3) Dehydration due to alcohol consumption or the use of diuretics
4) Dehydration due to heavy sweating during saunas, etc.

Accordingly, it is recommended that instructions be provided to the subject to help eliminate these causes when accurate measurements are needed.

Specifications

Model		SC-240 / SC-240IM	
Power source	**AC adapter**	Centre minus	
	Battery	LR6 (AA) x 6	
Power Consumption		0.5 W	
Impedance Measurement	**Measurement System**	Tetra polar Bioelectrical Impedance Analysis	
	Measurement Frequency	50 kHz	
	Measurement Current	90 µA	
	Measurement Range	150-1200 Ω	
Weight Measurement	**Measurement System**	Strain Gauge Load Cell	
	Maximum Capacity	440 lb	200 kg
	Minimum Graduation	0.2 lb	0.1 kg
Input Items	**Clothes Weight**	0-44 lb / 0.2 lb increments	0-10 kg / 0.1 kg increments
	Gender	Female / Male	
	Body Type	Standard / Athletic	
	Age	5-99 years (Standard) / 18-99 years (Athletic)	
	Height	3 ft-7 ft 11.5 in / 0.5 in increments	90-249 cm / 1 cm increments
Output Items (Display)	**Weight**	0-440 lb/0.2 lb increments	0-200.0 kg/0.1 kg increments
	Body Fat %	3-75% / 0.1% increments	
	BMI	0.1 increments	
	Total body water %	15 - 85% / 0.1% increments	
Interface Connections		USB	
Weight of Equipment		10.0 lb	4.5 kg
Size		13.4×17.2×2.1 in	341×437×54 mm

USA and Canada

Federal Communications Commission and Canadian ICES Notice

This equipment has been tested and found to comply with the limits for a Class B digital device, pursuant to Part 15 of the FCC Rules and Canadian ICES-003. These limits are designed to provide reasonable protection against harmful interference in a residential installation. This equipment generates, uses and can radiate radio frequency energy and, if not installed and used in accordance with the instructions, may cause harmful interference to radio communications. However, there is no guarantee that interference will not occur in a particular installation. If this equipment does cause harmful interference to radio or television reception, which can be determined by turning the equipment off and on, the user is encouraged to try to correct the interference by one or more of the following measures:

• Reorient or relocate the receiving antenna.
• Increase the separation between the equipment and receiver.
• Connect the equipment into an outlet on a circuit different from that to which the receiver is connected.
• Consult the dealer or an experienced radio or television technician for help.

Modifications

The FCC requires the user to be notified that any changes or modifications made to this device that are not expressly approved by Tanita Corporation may void the user's authority to operate the equipment.

<U.S.A. representative>

TANITA® Corporation of America, Inc.

2625 South Clearbrook Drive, Arlington Heights, Illinois 60005, U.S.A. TEL: 1-847-640-9241 FAX: 1-847-640-9261 http://www.tanita.com

<Manufacturer>

TANITA® Corporation

1-14-2, Maeno-cho, Itabashi-ku, Tokyo 174-8630 , Japan TEL: +81 (0) 3-3968-7048 FAX: +81 (0) 3-3967-3766 http://www.tanita.co.jp

TANITA Europe B.V.
Hoogoorddreef 56-E,
1101 BE Amsterdam, the Netherlands
TEL: +31-20-560-2970
FAX: +31-20-560-2988
http://www.tanita.eu

TANITA Health Equipment H.K.LTD.
Unit 301-303, Wing On Plaza, 3/F., 62 Mody Rord,
Tsimshatsui East, Kowloon, Hong Kong
TEL: +852-2834-3917
FAX: +852-2838-8667
www.tanita.asia

TANITA India Private Limited
A-502, Mittal Commercia, Off. M.V. Road(Andheri Kurla Road),
Marol, Andheri-East, Mumbai 400 059 INDIA
TEL: +91-22-3192-6107
FAX: +91-22-2859-9143
www.tanita.co.in

TANITA (Shanghai) Trading Co., Ltd.
Room 8005, 877 Huai Hai Zhong Lu, Shanghai,
The People's Republic of China
TEL: +86-21-6474-6803
FAX: +86-21-6474-7901
www.tanita.com.cn

Copyright © 2013 TANITA Corporation. All Rights Reserved.

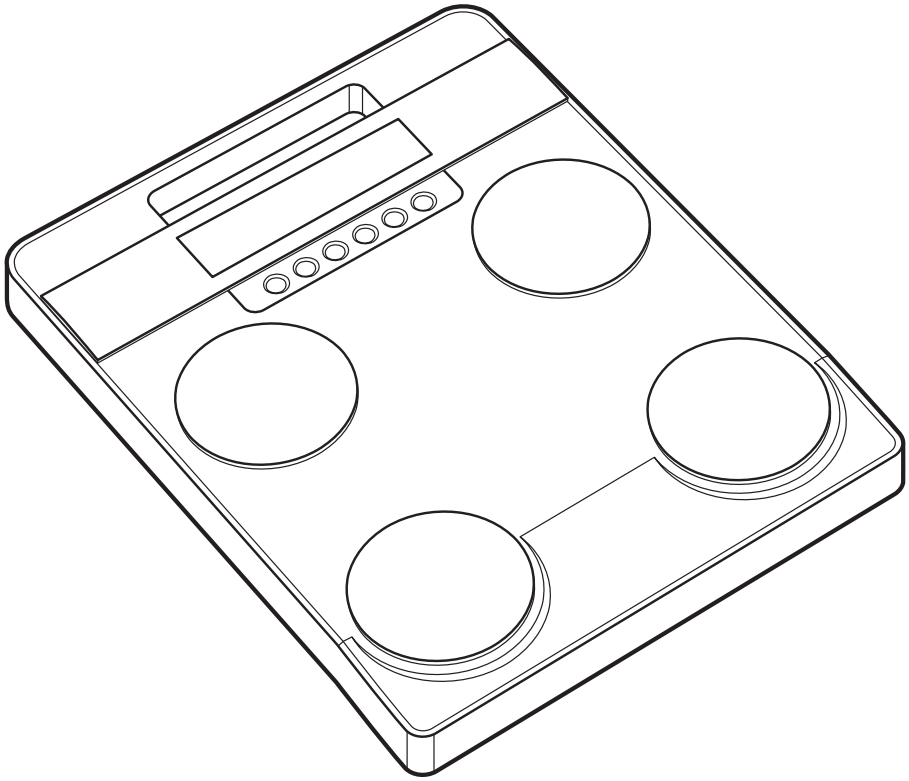
Feb 2013.TY.C.SC2407611(1)

TANITA®
Monitoring Your Health

ANALIZADOR DE COMPOSICIÓN CORPORAL

SC-240 / SC-240IM

Manual de instrucciones



<Condiciones de uso>

Intervalo de temperatura de uso	: 0°C – 35°C (32F° – 95°F)
Humedad relativa	: 30% - 80% (sin condensación)
Altitud máxima	: 2,000m ASL (6,500ft ASL)
Gama de presión de Medio Ambiente	: 86kPa - 106kPa

<Condiciones de almacenamiento>

Intervalo de temperatura ambiental : -10°C – 60°C (14°F – 140°F)
Intervalo de humedad relativa : 10% – 90% (sin condensación)
Para evitar problemas de funcionamiento no almacene este equipo donde haya luz solar directa, cambios significativos de temperatura, riesgo de humedad, mucho polvo, fuego cercano o donde haya riesgo de que reciba choques o vibraciones.

⚠ Lea atentamente este MANUAL DE INSTRUCCIONES y téngalo a mano para posibles consultas.

Uso previsto

- Este equipo puede usarse en la detección de ciertas enfermedades de los adultos y condiciones relacionadas con el peso y composición corporal.
- El equipo puede usarse en el control y prevención de afecciones causadas por depósitos excesivos de tejido graso, tales como diabetes, hiperlipidemia, colelitiasis (cálculos biliares) e hígado graso.
- El equipo puede usarse en el control de cambios en la composición corporal de las personas relacionados con la razón de tejido graso a tejido magro.
- El equipo puede usarse para evaluar la efectividad de los programas de nutrición y ejercicios de las personas para la salud y el bienestar físico.
- El analizador de composición corporal Tanita Body Composition Analyzer es indicado para uso en la medición de peso e impedancia y el presupuesto del índice de masa corporal (BMI), el porcentaje de grasa corporal total agua corporal, la masa muscular (esquelétal y lisa) , Tipo de cuerpo, la masa osea, el nivel de grasa visceral con margen saludable, el indice del metabolismo basal (BMR), y la edad metabolica, usando BIA (análisis de la impedancia Bioelectrica).
  El dispositivo es indicado para el uso para niños sanos de 5-17 años y adultos sanos con vidas activas, vidas moderadas, o de vidas inactivas.

Eficacia

1. Este equipo es fácil de usar y no requiere instalaciones especializadas ni experiencia para tomar las mediciones.
2. Las mediciones pueden tomarse en forma rápida y sencilla, causando un mínimo de binconvenientes al paciente durante la medición.



Índice

Antes de utilizar

Notas sobre seguridad.....63
Piezas y accesorios.....66
Denominación y funciones de la pantalla y de las teclas operativas.....67
Preparación (Suministro eléctrico).....68
Configuración Varios.....69

Instrucciones de uso

Modo de empleo (Selección de modo).....70
Modo de empleo (Analizador de composición corporal).....71
Modo de empleo (Báscula).....74
Modo de empleo (Báscula / Modo Bloqueo de peso).....75
Modo de empleo (Modo IMC).....76

Cuando sea necesario

Daño a la unidad.....77
Diversos criterios.....78
Conexión a un ordenador personal.....82
Aspectos técnicos.....86
Especificaciones.....90

Para su seguridad

Esta sección explica las medidas de precaución que deben tomarse para evitar lesiones a los usuarios de este dispositivo y a otras personas, así como para evitar daños a la propiedad. Es recomendable que se familiarice con esta información para garantizar la operación segura de este equipo.

⚠Advertencia	**No seguir las instrucciones resaltadas con este símbolo podría producir la muerte o una lesión grave.**
⚠Precaución	**No seguir las instrucciones resaltadas con este símbolo podría producir una lesión o daño a la propiedad.**
⊘	**Este símbolo indica las acciones que están prohibidas.**
❗	**Este símbolo indica las instrucciones que siempre deben seguirse.**

⚠ Advertencia

⊘ Prohibido

Este equipo no debe usarse en personas con marcapasos o cualquier otro implante mecánico.

Este equipo envía una pequeña corriente eléctrica a través del cuerpo, la cual podría interferir o causar el mal funcionamiento de los implantes médicos eléctricos, produciendo un grave daño.



No manipule el enchufe con las manos húmedas.

Esto puede producir un choque eléctrico, incendio o fuga.

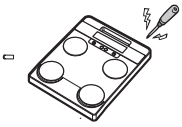


Mantenga este equipo lejos de los gases inflamables y ambientes ricos en oxígeno.



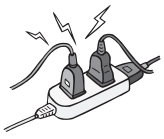
No modifique este equipo de ninguna forma.

Esto puede producir un choque eléctrico o lesión, o puede afectar la precisión del análisis.



No utilice un adaptador para múltiples enchufes.

Esto puede producir un incendio.



❗ Siempre…

Utilice sólo una toma correctamente cableada.

Sólo los cables originales y los equipos se les permite.

⚠Precaución

Prohibido

Manténgalo lejos del agua.

Evite usar el equipo en personas con alergias a los metales.
Las reacciones alérgicas pueden ser causadas por el acero inoxidable utilizado en los electrodos de este dispositivo.

No salte en el equipo.

No se apoye en el equipo.
No use este equipo cerca de otros productos que emitan ondas electromagnéticas.

No meta sus dedos en las aberturas ni huecos.

No aplique fuerza a la pantalla.
El panel de la pantalla puede romperse o producir una lesión.

Ayude a las personas con discapacidades.
Otra persona debe realizar las mediciones para las personas con discapacidades que afecten su capacidad de hacerlo ellas mismas.

Siempre…

Asegúrese de limpiar la plataforma de la balanza con un desinfectante adecuado después de cada uso.

Manténgase lejos de la persona durante la medición para evitar un choque eléctrico y para garantizar la precisión.

Controle continuamente tanto a la persona como al equipo para detectar anomalías.
Si se detecta alguna anomalía en la persona o en el equipo, tome la acción adecuada, tal como detener el equipo a la vez que garantiza la seguridad de la persona.

Desenchufe el cable de corriente alterna (CA) cuando mueva el equipo.

La interpretación de los resultados del análisis (por ejemplo, evaluación de las mediciones y formulación de los programas de ejercicios basada en los resultados) debe ser realizada por un profesional.
Las medidas para perder peso y los ejercicios basados en el autoanálisis podrían ser dañinos para su salud.

Este equipo está designado como un dispositivo de Clase B IT (principalmente para sistemas diseñados para utilizarse en ambientes domésticos) y tiene la certificación de CE (EMC), pero puede afectar a los dispositivos que son sensibles a las ondas electromagnéticas.
Si va a conectar una computadora o dispositivos periféricos a este equipo, utilice los dispositivos cumpliendo con IEC60601-1 (EN60601-1). La energía debe suministrarse desde un transformador de aislamiento para uso médico para los dispositivos IEC60950 (EN60950). Mantenga una distancia de 1,5 m entre las unidades durante la operación. No hacerlo puede producir un choque eléctrico a las personas o un mal funcionamiento.

Para su seguridad

Para realizar una medición precisa

Prohibido

Evite realizar mediciones después de un ejercicio extenuante.

Esto puede producir mediciones inexactas. Realice las mediciones después de un descanso suficiente.



Evite realizar mediciones después de una ingesta de alimentos o líquido en exceso o cuando esté deshidratado.

Esto puede producir mediciones inexactas. Para una mayor precisión, evite usar el equipo directamente después de levantarse. Utilícelo a la misma hora en cada ocasión, por lo menos tres horas después de cada comida.



No tome medidas cuando utilice transmisores, como los teléfonos móviles, que pueden afectar las lecturas.

Siempre…

Use el equipo bajo las mismas condiciones y en la misma posición, en la medida de lo posible, para registrar en forma precisa los cambios.

Les lectures sont très affectées par le niveau d'hydratation et la position du corps.Veuillez utiliser l'appareil chaque fois au même moment de la journée, dans les mêmes conditions et avec le corps dans la même position.



Evite las mediciones en múltiples ubicaciones con grandes diferencias de temperaturas.

Esto puede producir mediciones inexactas. Deje que el equipo descanse por lo menos dos horas antes de usarlo, si ha sido llevado a una nueva ubicación con una diferencia de temperaturas de ±20°C (±36˚F) o más.



Los pies desnudos deben colocarse correctamente sobre la plataforma de electrodos.

Asegúrese de que las plantas de sus pies estén libres de exceso de suciedad, ya que esto puede actuar como un obstáculo para el paso de la suave corriente eléctrica.

Use una ubicación estable.

Pueden producirse errores en las mediciones si el dispositivo se utiliza en una ubicación inestable.

Mantenimiento programado

Siempre…

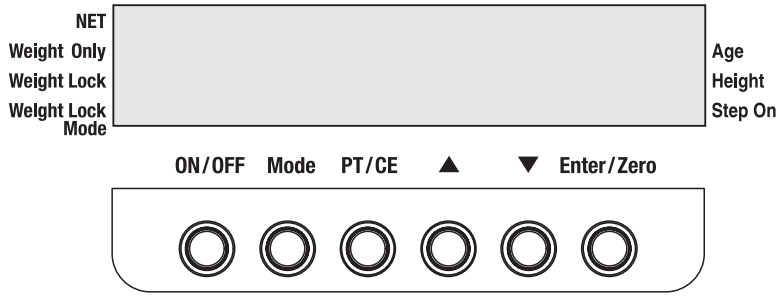
TANITA recomienda que cada instalación realice inspecciones periódicas de cada unidad.

1. Revise lo siguiente por lo menos diariamente:
   - Que la unidad esté sobre una superficie estable y nivelada
2. Inspeccione visualmente lo siguiente por lo menos semanalmente:
   - La pantalla, para detectar daños o contaminación
   - Todos los cables, cordones y extremos de los conectores, para detectar daños o contaminación
   - Todos los accesorios (sensores, electrodos, etc.), para detectar desgaste o daños
3. Inspeccione visualmente lo siguiente por lo menos mensualmente:
   - Los tornillos de montaje en la base

Actualice los ajustes, reemplace los ítems o llame al servicio técnico, según sea necesario, de acuerdo a los resultados de la inspección visual. No utilice la unidad si ve signos de daños. El equipo que está dañado debe ser inspeccionado por personal calificado para verificar su operación adecuada antes de usarlo nuevamente.

El equipo debe ser inspeccionado de acuerdo con la normativa de cada país.

Denominación y funciones de la pantalla y de las teclas operativas



ON/OFF **Botón ON / OFF** : encienda / apague el aparato

Mode **Tecla de selección de modo** : Selección de Analizador de composició`n corporal / Báscula de pesaje

PT/CE **PT / CE** : Fijar tara preestablecida / Eliminar valores de entrada

▲ **ARRIBA** : Incrementar valores numéricos

▼ **ABAJO** : Disminuir valores numéricos

Enter/Zero **Intro / Puesta a cero** : Introducir valor de entrada / Poner báscula a cero / Config. de modo

NET : Indica que se ha introducido el peso de la ropa

Weight Only : Indica el Modo Sólo pesaje (báscula)

Weight Lock : Indica el bloqueo del Peso

Weight Lock Mode : Indica que la función Bloqueo de peso está activada

Age : Indica que se ha introducido la edad

Height : Indica que se ha introducido la altura

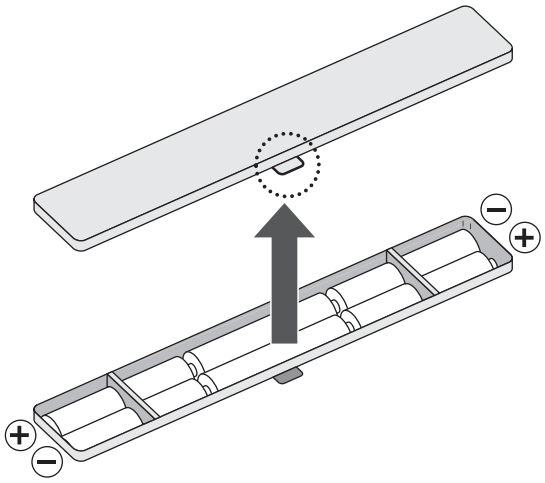
Step On : Indica el inicio de la medición

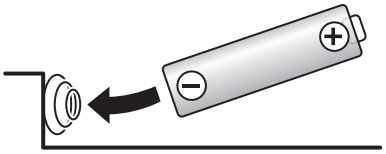
<Símbolos y sus significados>

P T	Tara preestablecida (Peso de la ropa)		Hombre		Mujer
	Modo atleta	⎓	Corriente continua		Entrada, salida
	Atención. Consulte la información adjunta	~	Corriente alterna		Polaridad negativa
⊕ LR6,15A,"AA" ⊖	⊕ de Corriente alterna				

Preparación (Suministro eléctrico)

<Uso del Adaptador de CA>

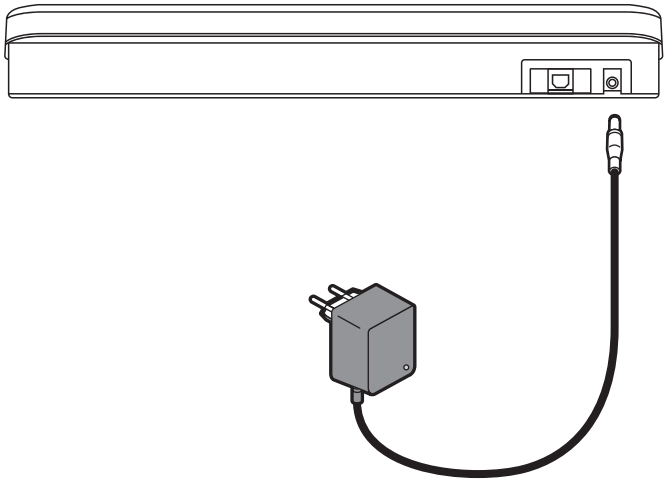




⚠
- Sustituya las pilas LR6 (AA) con cuidado, para evitar que caigan sobre sus pies.
- Asegúrese de que las pilas se insertan con la polaridad correcta ⊕/⊖. Si la polaridad es incorrecta, podrían producirse fugas en las pilas y dañar el aparato.
- Cuando no vaya a usar la unidad durante un período de tiempo prolongado, retire las pilas antes de guardar el aparato.

<Uso de las pilas>

(1) Inserte el conector del Adaptador de CA en la toma de CA del lateral derecho de la unidad principal.
(2) Conecte el Adaptador de CA en el enchufe de corriente.



⚠Precauciones

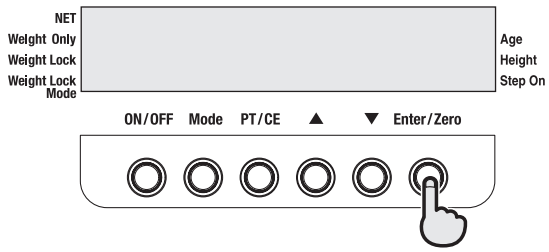
- Este aparato debe usarse con el adaptador de CA incluido.
- Siga las instrucciones siguientes para obtener una medición correcta.
  Puede que no sea posible medir en un entorno inestable.
  Durante una medición, no toque ningún cable de conexión "como el cable de adaptador de CA y el cable comunicación con el PC" para evitar la inestabilidad en la báscula.

Configuración Varios

Active el modo de configuración.

1 Pulse ON/OFF para encender la unidad.

2 Pulse Enter/Zero durante 1 segundo.

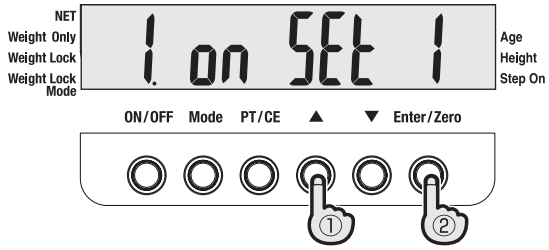


Aparece en pantalla SET 0.



3 Seleccione los elementos de configuración.

1) con ▲ o ▼,
2) y la tecla **Enter/Zero**.



SET1 Establecer ON / OFF de la señal sonora.
(0.off or 1.on)

SET2 Establecer ON / OFF de la selección de atleta.
(0.off or 1.on)

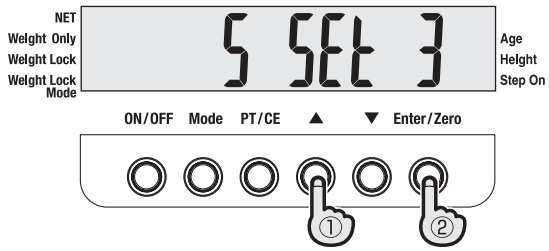
SET3 Establecer el c_lculo automático del tiempo durante la entrada.
(introduzca el rango de 0 - 9 segundos)
* Desactivar la función de cálculo automático “0”.

SET4 Establecer el tiempo de apagado automático.
(0, 5, 10, 30, 60 minutos, defecto:5 minutes)
* « 0 » fonction d’arrêt automatique désactivée.

SET5 Coloque la unidad.
(0kg o 1.lb, por defecto: 1.lb)

4 Introduzca el valor de configuración.

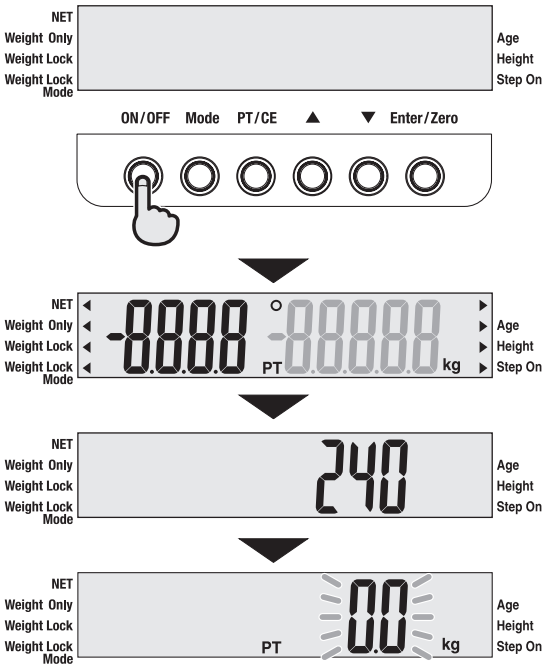
1) con ▲ o ▼,
2) y la tecla **Enter/Zero**.



5 Presione ON/OFF para apagar la unidad.

Modo de empleo (Selección de modo)

1 Pulse ON/OFF para encender la unidad.



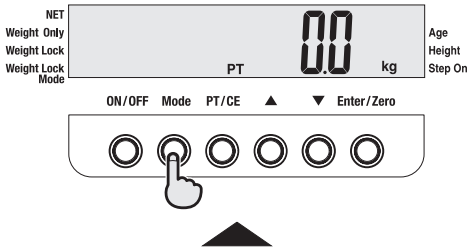
Se muestra el nombre del Modelo.

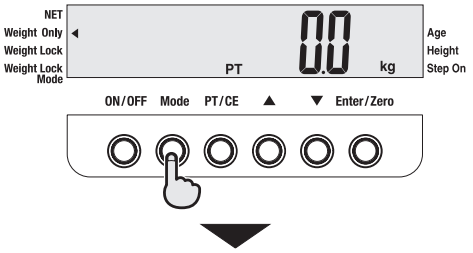
00 aparece en pantalla (Analizador de composición corporal).

El modo se selecciona con la **Mode** tecla.

Composición corporal (☞P.71)

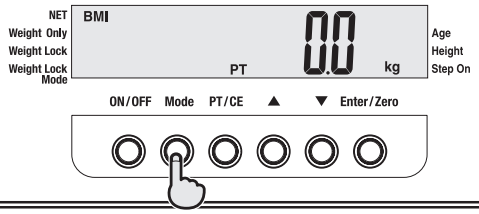
Báscula (☞P.74)

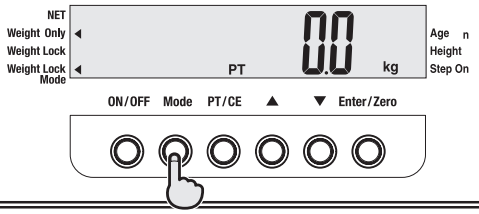




Báscula (Modo IMC) (☞P.76)

Báscula (Bloqueo de peso) (☞P.75)

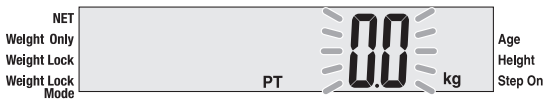




Modo de empleo (Analizador de composición corporal)

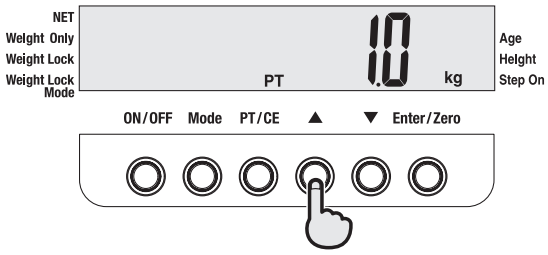
1 Pulse ON/OFF para encender la unidad.

2 Compruebe que está seleccionado el modode Analizador de composición corporal (☞P.70).



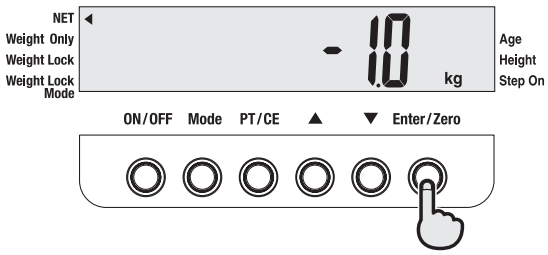
3 Introduzca el peso de la ropa.

1) con ▲ o ▼,



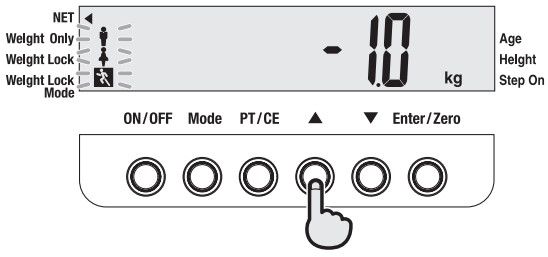
2) y la tecla **Enter/Zero**.

* **PT/CE** ➡ elimina los valores introducidos.



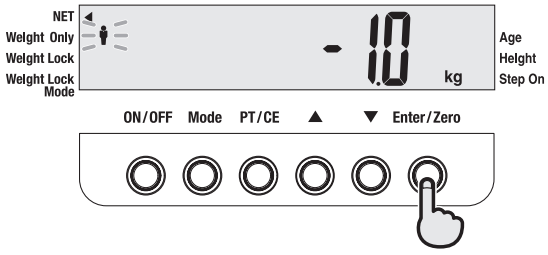
4 Seleccione el tipo de Cuerpo y el Sexo.

1) con ▲ o ▼,



2) y la tecla **Enter/Zero**.

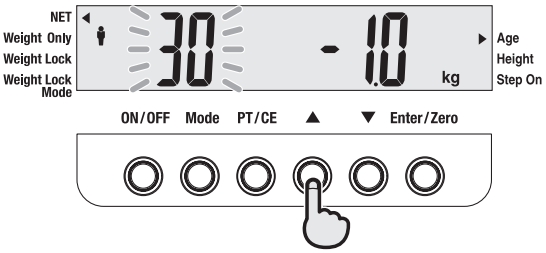
* **PT/CE** ➡ vuelve al estado anterior.



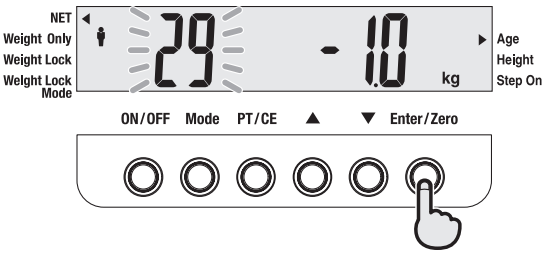
Modo de empleo (Analizador de composición corporal) (cont.)

5 Introduzca la edad

1) con ▲ o ▼,

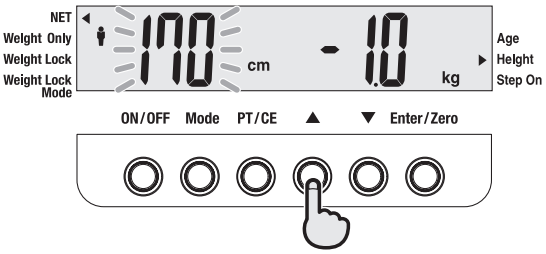


2) y la tecla **Enter/Zero**.
* **PT/CE ➡** vuelve al estado anterior.

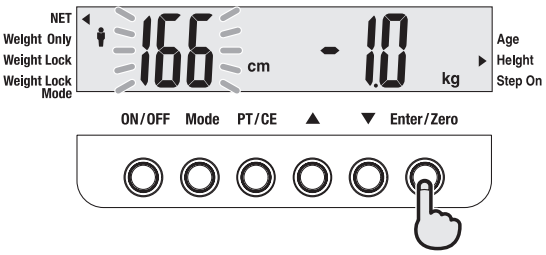


6 Introduzca el peso

1) con ▲ o ▼,



2) y la tecla **Enter/Zero**.
* **PT/CE ➡** vuelve al estado anterior.

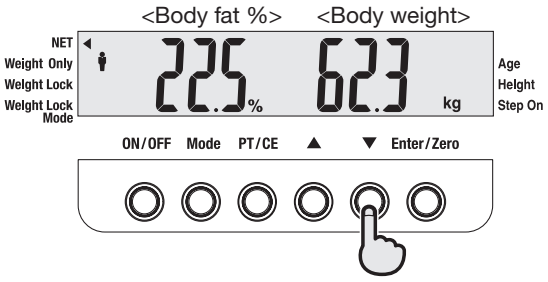


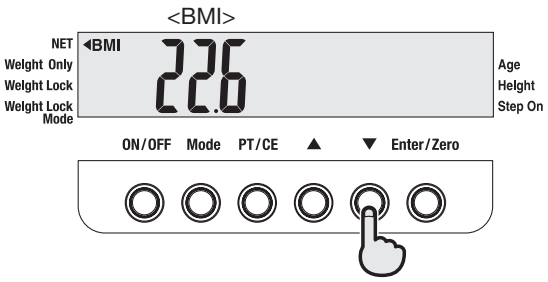
7 Súbase a la plataforma con los pies descalzos, después de que parpadee “Step On”.

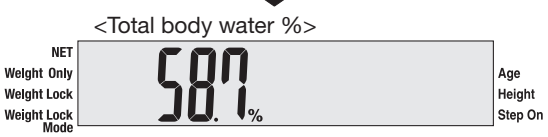




8 Finalización de la medición.





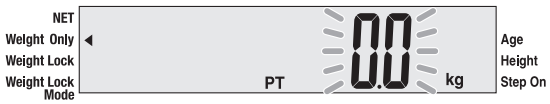


* **PT/CE**, **Enter/Zero** ➡ elimina el resultado en pantalla.

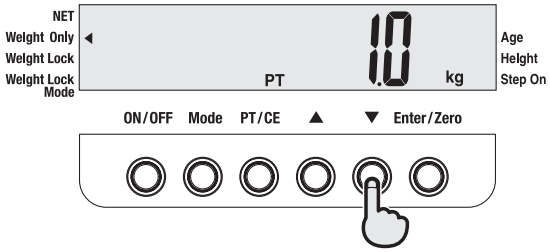
Modo de empleo (Báscula)

1 **Pulse ⊙/ȯ para encender la unidad.**

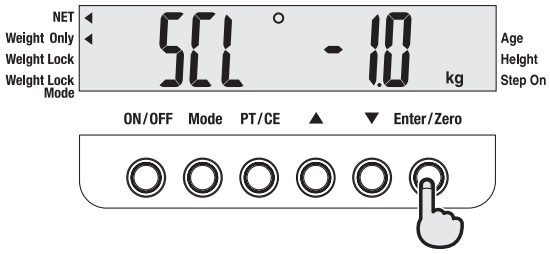
2 **Compruebe que está seleccionado el modo sólo Peso (☞P.70).**



3 **Introduzca el peso de la ropa.**
1) con ▲ o ▼,

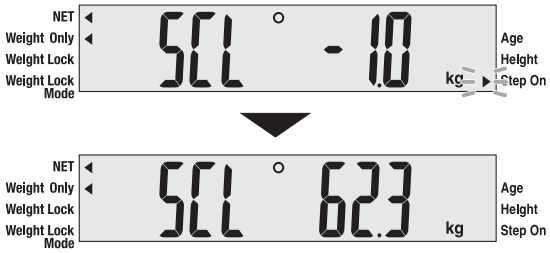


2) y la tecla **Enter/Zero**.
* **PT/CE** ➡ Borrar el valor introducido.



4 **Súbase a la plataforma con los pies descalzos, después de que parpadee "Step On".**

5 **Finalización de la medición.**

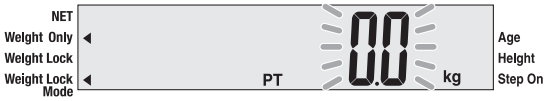


Modo de empleo (Báscula • Modo Bloqueo de peso)

Activaci_n de la función Bloqueo de peso.

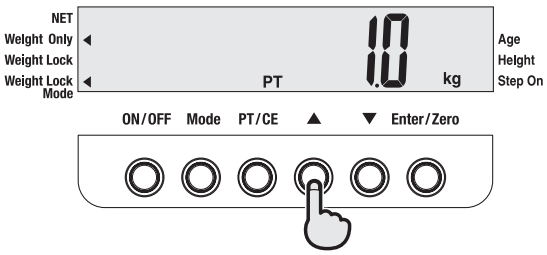
1 Pulse ON/OFF para encender la unidad.

2 Compruebe que está seleccionado (Modo bloqueo de peso) (☞P.70).



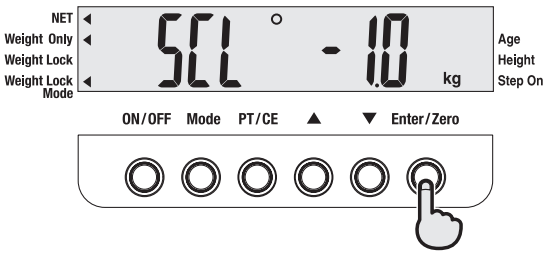
3 Introduzca el peso de la ropa.

1) con ▲ o ▼,

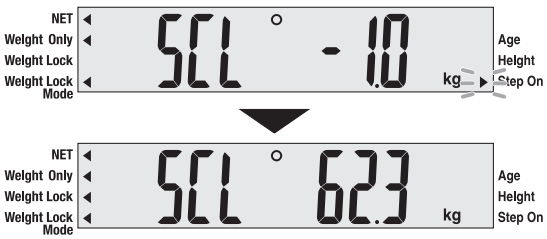


2) y la tecla **Enter/Zero**.

* **PT/CE** ➡ elimina los valores introducidos.



4 Súbase a la plataforma con los pies descalzos, después de que parpadee “Step On”.



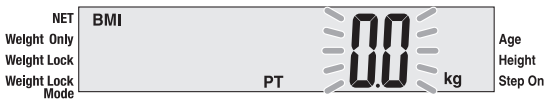
5 Finalización de la medición.

* **Enter/Zero** ➡ elimina el resultado en pantalla

Modo de empleo (Modo IMC)

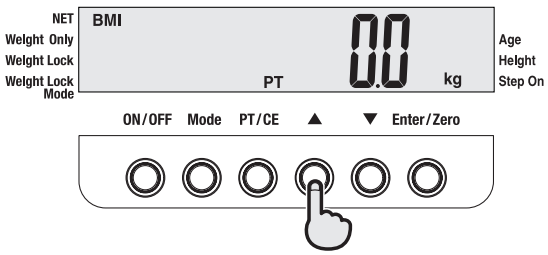
1 Pulse ON/OFF para encender la unidad.

2 Compruebe que el modo IMC está seleccionado (☞P.70).



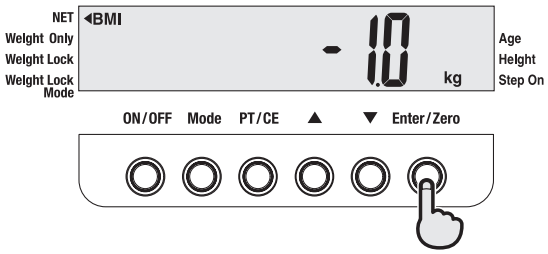
3 Introduzca el peso de la ropa.

1) con ▲ o ▼,



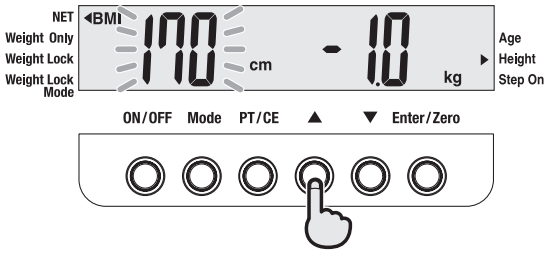
2) y la tecla **Enter/Zero**.

* **PT/CE** ➡ elimina los valores introducidos.



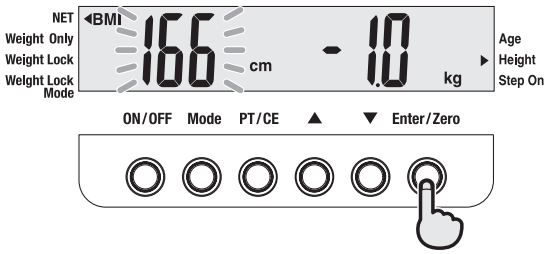
4 Introduzca la altura

1) con ▲ o ▼,



2) y la tecla **Enter/Zero**.

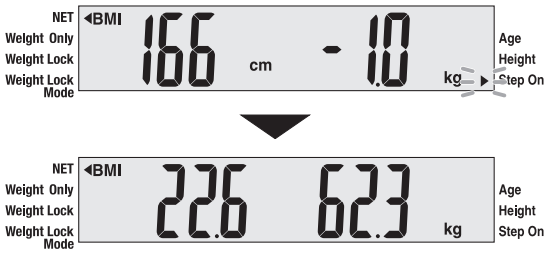
* **PT/CE** ➡ vuelve al estado anterior



5 Súbase a la plataforma con los pies descalzos, después de que parpadee "Step On".

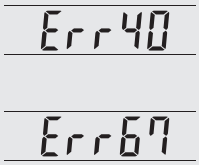
6 Finalización de la medición.

* **Enter/Zero** ➡ elimina el resultado en pantalla



Daño a la unidad

- Compruebe los siguientes puntos antes de solicitar reparaciones.

Síntoma		Comprobar
Cómo medir	**Error de medición de impedancia** 	• Efectúe la medición con los pies descalzos. • Si tiene las plantas de los pies secas, aplique aproximadamente 0,5 ml de agua con el cuentagotas suministrado en los electrodos antes de realizar la medición. • Compruebe la información introducida.
	Error de punto cero 	• Apague la unidad, retire los elementos de la plataforma y vuelva a encender la unidad; luego, vuelva a realizar la medición.
	El peso medido no es estable.	• ¿Está instalada la máquina en un lugar afectado por vibraciones? • ¿Está inclinada la plataforma? ⇨ Mantenga la plataforma en posición horizontal. • ¿Hay algún objeto atascado en los espacios de la plataforma? ⇨ Retire cualquier objeto que esté atascado en los espacios.
Sección de visualización	**No aparece ninguna indicación en la pantalla después de conectar la alimentación eléctrica.**	• Compruebe que la fuente de alimentación está conectada correctamente.
	 **s'affiche.**	• El peso que se desea medir excede el margen de medición.

Nota

• Si aparece un error distinto de los descritos anteriormente, apague la unidad y vuelva a realizar la medición.
Si aparece un mismo error repetidamente, póngase en contacto con nuestro centro de atención al cliente.

Diversos criterios

¿Que es el porcentaje de grasa corporal?

Porcentaje de grasa corporal es la cantidad de grasa corporal expresada como una proporción del peso corporal.

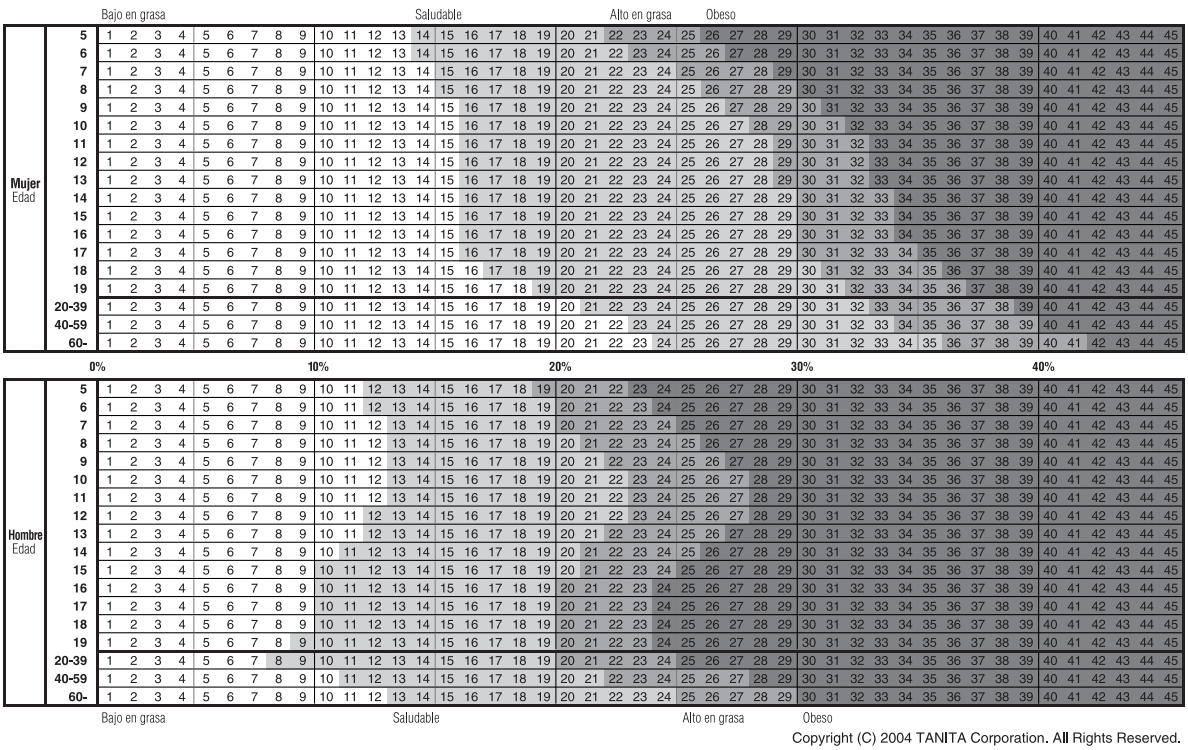
Se ha demostrado que la reducción de los niveles excesivos de grasa corporal disminuye el riesgo de ciertas enfermedades tales como la hipertensión arterial, las enfermedades cardiacas, la diabetes y el cáncer.

En el gráfico se muestran los niveles saludables de grasa corporal.

Ìndices de grasa corporal para niños medianos [1,2]
Margen de grasa corporal para adultos normales [3,4]

[1] *Susan Jebb et al. Obesity Research 2004;12;A156-157 "Nuevas curvas de referencia de grasa corporal para niños"*

[2] *Gallagher D et al. Am J Clin Nutr 2000,72:694-701. "Healthy percentage body fat ranges:an approach for developing guidelines based on body mass index."*



Copyright (C) 2004 TANITA Corporation. All Rights Reserved.

Bajo en grasa : por debajo del margen saludable de grasa corporal. Aumento del riesgo de problemas desalud.

Saludable : dentro del margen saludable de grasa corporal para su edad/sexo.

Alto en grasa : por encima del margen saludable. Aumento del riesgo de problemas de salud.

Obeso : muy por encima del margen saludable de grasa corporal. Aumento considerable del riesgo de problemas de salud relacionados con la obesidad.

¿QUÉ ES EL PORCENTAJE DE AGUA CORPORAL TOTAL?

Porcentaje de agua corporal total es la cantidad total de líquido que hay en el cuerpo de una persona, expresada como porcentaje de su peso total. lEl agua desempeña un papel vital en muchos de los procesos corporales, y se encuentra en todas las células, tejidos y órganos del cuerpo. El mantenimiento de un porcentaje adecuado de agua corporal total garantizará que el cuerpo funcione de manera eficiente, y reducirá el riesgo de aparición de los trastornos de salud asociados.

Los niveles de agua del cuerpo fluctúan naturalmente a lo largo del día. De hecho, el cuerpo tiende a deshidratarse después de una noche larga y se observan diferencias en la distribución de fluidos entre el día y la noche. Ingerir grandes cantidades de comida, beber alcohol, menstruar, enfermarse, hacer ejercicio y bañarse pueden provocar variaciones en los niveles de hidratación.

Su porcentaje de agua corporal debe servirle de guía, y no debe ser utilizado específicamente para determinar el porcentaje de agua corporal total absoluto recomendado para usted. Es importante tratar de lograr cambios a largo plazo en el porcentaje de agua corporal total y mantenerlo a un nivel saludable y constante.

Si bebe de golpe una gran cantidad de agua, su nivel de agua no cambiará inmediatamente. De hecho, aumentará la lectura de su grasa corporal debido al incremento de peso. Supervise periódicamente todas las lecturas para realizar un seguimiento del cambio relativo.over time to track the relative change.

El porcentaje varía de una persona a otra, pero como guía, los porcentajes de agua corporal total medios para un adulto saludable son:

Mujer :45 a 60%
Varón :50 a 65%
Fuente :Información basada en investigación interna de Tanita

Note: El porcentaje de agua corporal total tenderá a disminuir a medida que el porcentaje de grasa corporal aumente. Una persona que tenga un alto porcentaje de grasa corporal puede estar por debajo del porcentaje de agua corporal medio. A medida que pierda grasa corporal, el porcentaje de agua corporal total deberá acercarse gradualmente a los niveles típicos indicados anteriormente.

¿QUE ES EL NIVEL DE GRASA VISCERAL?

Esta función indica el nivel de grasa visceral de su cuerpo.
Grasa visceral es la grasa que se encuentra en el interior de la cavidad abdominal, rodeando los órganos vitales de la zona del tronco (zona abdominal). Las investigaciones han demostrado que aunque el peso y la grasa corporal se ma tengan constantes, a medida que se envejece varía la distribución de la grasa en el cuerpo, y que es mucho más probable que ésta se desplace a la zona del tronco, especialmente después de la menopausia. Asegurándose de tener los niveles sanos de grasa visceral reducirá el riesgo de contraer ciertas enfermedades tales como enfermedades cardiacas e hipertensión arterial, y retardar la aparición de la diabetes tipo 2.

El monitor de composición corporal Tanita le proporcionará una medición del nivel de grasa corporal en una escala que va del 1 al 59.

1 a 12
Indica que usted tiene un nivel saludable de grasa visceral. Continúe controlando su nivel de grasa visceral para garantizar que siempre mantenga el nivel adecuado.

13 a -59
Indica que usted tiene un nivel excesivo de grasa visceral. Piense en la introducción de algunos cambios en su forma de vida, posiblemente a través de un cambio en su dieta o haciendo más ejercicios.

Fuente : Información de la Universidad de Columbia (Nueva York) y del Instituto Tanita (Tokio)

Nota:
- Aunque usted tenga un índice de grasa corporal bajo, es posible que tenga un nivel de grasa visceral alto.
- Si desea un diagnóstico medico, consulte a un medico.

Diversos criterios (cont)

- ¿Que es el metabolismo basal (MB)?

¿QUÉ ES BMR?

El MB es el nivel mínimo de energía que su cuerpo necesita para funcionar eficientemente en reposo, incluyendo los órganos de los sistemas respiratorio y circulatorio, el sistema nervioso, el hígado, los riñones y otros órganos. Usted quema calorías independientemente de la actividad que esté realizando, incluso cuando duerme.

Aproximadamente un 70 % de las calorías que se consumen diariamente son utilizadas para el metabolismo basal. Además, cuando se realiza cualquier tipo de actividad se utiliza energía, sin embargo, cuanto más vigorosa sea esa actividad, mayor será la cantidad de calorías que se queme. Ello se debe a que el músculo estriado (que representa aproximadamente un 40% del peso corporal) funciona como un motor y utiliza una gran cantidad de energía. El metabolismo basal se ve afectado en gran medida por la cantidad de músculos que usted tenga; el aumento de la masa muscular ayuda al metabolismo basal.

Realizando estudios con individuos sanos, los científicos han observado que a medida que las personas envejecen, varía su metabolismo basal. El metabolismo basal aumenta a medida que el niño crece. Después de alcanzar un máximo, a la edad de 16 ó 17 años, el metabolismo basal comienza a disminuir como se muestra en el gráfico que aparece a continuación.

Tener un metabolismo basal más elevado aumentará la cantidad de calorías utilizadas y ayudará a reducir la cantidad de grasa corporal. Un metabolismo basal bajo hará que resulte más difícil perder grasa corporal y peso en general.

¿CÓMO CALCULA EL MONITOR DE COMPOSICIÓN CORPORAL TANITA EL MB?

El método básico para calcular el MB es una ecuación estándar que utiliza el peso y la edad. Tanita ha investigado exhaustivamente la relación entre el MB y la composición corporal, por lo que ofrece al usuario una medición mucho más exacta y personalizada, basada en la medición de la impedancia. Este método ha sido validado médicamente mediante la utilización de calorimetría indirecta (análisis de la composición del aliento)*.

* Reliability on equation for Basal Metabolic Rate: At: 2002 Nutrition Week: A Scientific and Clinical Forum and Exposition Title: International Comparison: Resting Energy Expenditure Prediction Models: The American Journal of CLINICAL NUTRITION (1Fiabilidad de la ecuación para el cálculo del metabolismo basal: Publicado en: Semana de nutrición del año 2002: Foro científico y clínico, y título de exposición: Comparación internacional: Modelos para la predicción del gasto de energía en estado de reposo: Revista Americana de NUTRICIÓN CLÍNICA).

- ¿Qué es la edad metabólica?

Esta función calcula el MB e indica la edad media asociada a ese tipo de metabolismo.

Si su edad metabólica es mayor que su edad real, ello es una señal de que necesita mejorar su metabolismo basal. Hacer más ejercicios ayudará a la creación de tejido muscular sano, lo que a su vez mejorará su edad metabólica.

Los valores de las mediciones que se visualizan en el display van de 12 a 50. Si el valor de la medición fuera menor de 12 aparecerá en el display como “12”, y si fuera mayor de 50 aparecerá como “50”.

¿Que es la masa muscular? (18 años de edad aplicable - 99)

El valor de masa muscular que aparece en el display incluye los músculos esqueléticos, los músculos lisos (tales como los del corazón y del aparato digestivo) así como el agua contenida en los mismos.
Los músculos desempeñan un papel importante ya que funcionan como un motor en cuanto a lo que a consumo de energía se refiere.
A medida que aumenta su masa muscular, aumenta el consumo su de energía, lo que le ayuda a reducir los niveles excesivos de grasa corporal y a perder peso de una manera saludable.

- ¿Qué se entiende por masa ósea? (18 años de edad aplicable - 99)

Esta función indica la cantidad de hueso (nivel mineral del hueso, calcio y otros minerales) en elcuerpo.
Los estudios realizados han demostrado que el ejercicio y el desarrollo de tejido muscular están relacionados con unos huesos más sanos y fuertes. Mientras que es muy probable que la estructura ósea no experimente cambios notables a corto plazo, es importante que tenga huesos sanos y los cuide a través de una dieta equilibrada y mucho ejercicio. Las personas que estén preocupadas por las enfermedades óseas deberían consultar a su médico de cabecera. Puede que la lectura de la masa ósea de personas que tengan osteoporosis o densidad baja del hueso, debido a una edad avanzada, o juvenil, embarazo, tratamientos hormonales u otras causas no sea del todo precisa.

A continuación, se incluye el resultado de la masa ósea estimada de las personas de 20 a 40 años _franja de edad en la que se supone que tenemos la mayor cantidad de masa ósea_ por peso. (Fuente: Tanita Body Weight Science Institute). Veuillez utiliser les tableaux ci-dessous à titre indicatif pour comparer vos relevés de masse corporelle.

Utilice los gráficos siguientes como referencia para cotejar la lectura de su masa ósea.

Mujeres : media de la masa ósea estimada

Peso (lb)		
Menos de 110 lb	110lb - 165 lb	165 lb o más
4,3 lb	5,3 lb	6,5 lb

Peso (kg)		
Menos de 50 kg	50 kg - 75 kg	75 kg o más
1,95 kg	2,40 kg	2,95 kg

Hommes : Moyenne de la masse osseuse estimée

Peso (lb)		
Menos de 143 lb	143 lb - 209 lb	209 lb o más
5,9 lb	7,3 lb	8,1 lb

Peso (kg)		
Menos de 65 kg	65 kg - 95 kg	95 kg o más
2,66 kg	3,29 kg	3,69 kg

Nota: Las personas descritas seguidamente pueden obtener lecturas distintas y deben considerar los valores facilitados únicamente como referencia.
- Personas ancianas
- Mujeres durante o después de la menopausia
- Personas que reciban terapia a base de hormonas

La "masa ósea estimada" es el valor calculado estadísticamente en función de su correlación con la cantidad libre de grasa (tejidos distintos al graso). Dicha masa no indica directamente la dureza o resistencia de los huesos, ni el riesgo a sufrir fracturas óseas. Si le preocupa el estado de sus huesos, le recomendamos encarecidamente que consulte a un especialista.

Conexión a un ordenador personal

La interfaz USB permite la entrada y salida de este equipo.

- Especificaciones

Normas de comunicación	USB
Método de comunicación	Método de comunicación asincrónica
Velocidad de la señal	9600 bps
Longitud de bits de datos	8 bits
Paridad	Ninguno
Bit de parada	1 bit
Control de flujo	Ninguno
Terminador	CR+LF

Nota

- En la parte trasera de la unidad, se encuentran ubicados un conector USB (hembra de 4 clavijas y tipo B).
- Los cables de conexión no viene incluidos, utilice los suyos según proceda.
  USB: (macho) de 4 clavijas y tipo A - (macho) de 4 clavijas y tipo B.
- Debe instalar el controlador necesario en su PC, descarga disponible de http://www.tanita.com o en el CD-Rom adjunto.

- Transmission de données

⚠MISE EN GRADE Les données sont transmises immédiatement après la pesée, quel que soit le réglage du périphérique de réception (PC, etc.). Il faudra donc que le périphérique soit prêt pour la réception des données avant la pesée.

(1) Format de données de sortie (en el caso a la unidad de kg)

Remarque

- Les données respectives sont séparées par des virgules (,).
- El terminador (fin de los datos) es CR (código ASCII 0DH), LF (código ASCII 0AH). Un 0 aquí corresponde a cero.
- Les données de contrôle pour les éléments 1 – 4 sont pour des extensions. Elles ne sont pas utilisées actuellement et le côté réception peut donc les ignorer.
- En raison de ses spécifications, le pèse-personne sortira un signal non pertinent approximativement 0,1 secondes après la sortie de données. Assurez-vous que ce signal est ignoré et ne l'importez pas.

Datos completos del cuerpo entero

Modelo		Número de serie		Tipo corporal		Sexo		Edad	
MO	"XXXXXX"	SN	"XXXXXXXX"	Bt	0 ou 2	GE	0 ou 2	AG	XX

Altura		Peso de la ropa		Peso		% grasa		Masa grasa	
Hm	XXX.X	Pt	XX.X	Wk	XXX.X	FW	XX.X	fW	XXX.X

Masa libre de grasa		Masa muscular		Puntuación de masa muscular del cuerpo entero		Masa ósea		Agua total en el cuerpo	
MW	XXX.X	mW	XXX.X	sW	XX	bW	XXX.X	wW	XXX.X

Índice de agua corporal		Índice masa corporal		Peso estándar		Obesidad		Índice de grasa visceral	
ww	XX.X	MI	XXX.X	Sw	XXX.X	OV	XXX.X	IF	XX

Índice de metabolismo basal (kJ)		Índice de metabolismo basal (kcal)		Análisis metabolismo basal		Edad metabólica		Impedancia (50kHz)	
rb	XXXXX	rB	XXXXX	rJ	XX	rA	XX	ZF	XXXX.X

Suma de comprobación	
CS	XX

Conexión a un ordenador personal (cont)

(2) Datos de salida

<modo kg / cm>

Elemento	Encabezado	Formato	modo kg / cm	Orden de salida				
				Monitor de composición corporal			escala	IMC
				Adulto	Atleta	Niño		
Datos de control	{0		Fijado a 2 bytes	1	1	1	1	1
Datos de control	~0		Fijado a 1 byte	2	2	2	2	2
Datos de control	~1		Fijado a 1 byte	3	3	3	3	3
Datos de control	~2		Fijado a 1 byte	4	4	4	4	4
Modelo	MO	"XXXXXX"	Fijado a 8 bytes ("SC-240")	5	5	5	5	5
Número de serie	SN	"XXXXXXXX"	Fijado a 10 bytes	6	6	6	6	6
Tipo corporal	Bt	0 o 2	Fijado a 1 byte (0:Estándar 2:Atleta)	7	7	7		
Sexo	GE	1 o 2	Fijado a 1 byte (1:Masculino 2:Femenino)	8	8	8		
Edad	AG	XX	Puede variar de 1 a 2 bytes	9	9	9		
Altura	Hm	XXX.X	Puede variar de 4 a 5 bytes (cm)	10	10	10		7
Peso de la ropa	Pt	XX.X	Puede variar de 3 a 4 bytes (unidades de 0,1kg)	11	11	11	7	8
Peso	Wk	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1kg)	12	12	12	8	9
% grasa	FW	XX.X	Puede variar de 3 a 4 bytes (unidades de 0,1%)	13	13	13		
Masa grasa	fW	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1kg)	14	14	14		
Masa libre de grasa	MW	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1kg)	15	15	15		
Masa muscular	mW	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1kg)	16	16			
Puntuación de masa muscular del cuerpo entero	sW	XX	Puede variar de 1 a 2 bytes (1 a 24)	17	17			
Masa ósea	bW	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1kg)	18	18			
Agua total en el cuerpo	wW	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1kg)	19	19			
Índice de agua corporal	ww	XX.X	Fijado a 4 bytes	20	20			
Índice masa corporal	MI	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1)	21	21	16		10
Peso estándar	Sw	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1kg)	22				
Obesidad	OV	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1%)	23				
Índice de grasa visceral	IF	XX	Puede variar de 1 a 2 bytes	24	22			
Índice de metabolismo basal (kJ)	rb	XXXXX	Puede variar de 1 a 5 bytes (unidades de 1kJ)	25	23			
Índice de metabolismo basal (kcal)	rB	XXXXX	Puede variar de 1 a 5 bytes (unidades de 1kcal)	26	24			
Análisis metabolismo basal	rJ	XX	Puede variar de 1 a 2 bytes (1 a 24)	27	25			
Edad metabólica	rA	XX	Fijado a 2 bytes	28	26			
Impedancia (50kHz)	ZF	XXXX.X	Puede variar de 1 a 2 (4-55)	29	27	17	9	
Suma de comprobación	CS	XX	Fijado a 2 bytes	30	28	18	10	11

Ejemplo de salida

Estándar, Masculino, 30 años de edad, Altura 170 cm

{0, 16, ~0, 1, ~1, 1, ~2, 1, MO, "SC-240", SN, "00000002", Bt, 0, GE, 1, AG, 30, Hm, 170, Pt, 0.0, Wk, 82.7, FW, 18.6, fW, 15.4, MW, 67.3, mW, 64.0, sW, 19, bW, 3.3, wW, 48.0, ww, 58.0, MI, 28.6, Sw, 63.6, OV, 30.0, IF, 6, rb, 8255, rB, 1973, rJ, 12, rA, 28, ZF, 369.4, CS, FD

modo lb / ft-in

Elemento	Encabezado	Formato	modo lb / ft-in	Orden de salida				
				Monitor de composición corporal			escala	IMC
				Adulto	Atleta	Niño		
Datos de control	{0		Fijado a 2 bytes	1	1	1	1	1
Datos de control	˜0		Fijado a 1 byte	2	2	2	2	2
Datos de control	˜1		Fijado a 1 byte	3	3	3	3	3
Datos de control	˜2		Fijado a 1 byte	4	4	4	4	4
Modelo	MO	“XXXXXX”	Fijado a 8 bytes (“SC-240”)	5	5	5	5	5
Número de serie	SN	“XXXXXXXX”	Fijado a 10 bytes	6	6	6	6	6
Tipo corporal	Bt	0 or 2	Fijado a 1 byte (0:Estándar 2:Atleta)	7	7	7		
Sexo	GE	1 or 2	Fijado a 1 byte (1:Masculino 2:Femenino)	8	8	8		
Edad	AG	XX	Puede variar de 1 a 2 bytes	9	9	9		
Altura	Hm	XXX.X	Fijado a 4 bytes (in)	10	10	10		7
Peso de la ropa	Pt	XX.X	Puede variar de 3 a 4 bytes (unidades de 0,2 lb)	11	11	11	7	8
Peso	Wk	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,2 lb)	12	12	12	8	9
% grasa	FW	XX.X	Puede variar de 3 a 4 bytes (unidades de 0,1%)	13	13	13		
Masa grasa	fW	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,2 lb)	14	14	14		
Masa libre de grasa	MW	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,2 lb)	15	15	15		
Masa muscular	mW	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,2 lb)	16	16			
Puntuación de masa muscular del cuerpo entero	sW	XX	Puede variar de 1 a 2 bytes (1 a 24)	17	17			
Masa ósea	bW	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,2 lb)	18	18			
Agua total en el cuerpo	wW	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,2 lb)	19	19			
Índice de agua corporal	ww	XX.X	Fijado a 4 bytes	20	20			
Índice masa corporal	MI	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1)	21	21	16		10
Peso estándar	Sw	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,2 lb)	22				
Obesidad	OV	XXX.X	Puede variar de 3 a 5 bytes (unidades de 0,1%)	23				
Índice de grasa visceral	IF	XX	Puede variar de 1 a 2 bytes	24	22			
Índice de metabolismo basal (kJ)	rb	XXXXX	Puede variar de 1 a 5 bytes (unidades de 1kJ)	25	23			
Índice de metabolismo basal (kcal)	rB	XXXXX	Puede variar de 1 a 5 bytes (unidades de 1kcal)	26	24			
Análisis metabolismo basal	rJ	XX	Puede variar de 1 a 2 bytes (1 a 24)	27	25			
Edad metabólica	rA	XX	Fijado a 2 bytes	28	26			
Impedancia (50kHz)	ZF	XXXX.X	Puede variar de 1 a 2 (4-55)	29	27	17	9	
Suma de comprobación	CS	XX	Fijado a 2 bytes	30	28	18	10	11

Ejemplo de salida

Estándar, Masculino, 30 años de edad, Altura 170 cm

{0, 16, ~0, 1, ~1, 1, ~2, 1, MO, “SC-240”, SN, “00000003”, Bt, 0, GE, 1, AG, 30, Hi, 67.0, Pt, 0.0, Wp, 182.2, FW, 18.7, fW, 34.0, MW, 148.2, mW, 140.8, sW, 19, bW, 7.4, wW, 105.6, ww, 58.0, MI, 28.5, Sw, 140.4, OV, 29.8, IF, 6, rb, 8247, rB, 1971 ,rJ, 12, rA, 29, ZF, 372.8, CS, 2A

Aspectos técnicos

Medición de la composición corporal mediante el método BIA.

Introducción

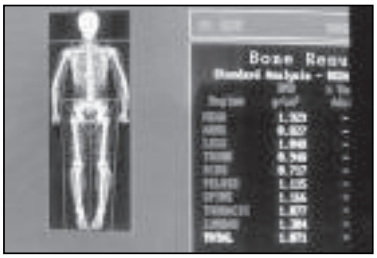
Este equipo proporciona valores estimados para cada valor medido de porcentaje de grasa corporal, masa de grasa, masa libre de grasa, masa muscular y masa ósea mediante el método DXA para Japón, así como un valor estimado para el valor medido de agua corporal total mediante el método de dilución que utiliza un análisis de impedancia bioeléctrica (método BIA).
Para realizar una medición, se debe seleccionar un modo según el tipo corporal.
1) Estándar (para 5 a 99 años de edad)
2) Atlético (para atletas que se ejercitan más que el común de las personas)
La fiabilidad de la medición de la composición corporal de atletas, etc., que tienen una composición distinta al común de las personas, puede mejorarse dividiendo el modo de medición según cada tipo corporal.

- Principios de medición de la composición de estructura corporal

AIB es un método para medir la composición corporal – masa grasa, masa muscular estimada, etc. – mediante la medición de la impedancia bioeléctrica en el cuerpo. La grasa que se encuentra en el cuerpo no es un buen conductor de electricidad, mientras que el agua, cuya mayor parte se encuentra en los músculos, es un conductor eficaz de la electricidad. El grado de dificultad con el que la electricidad se transmite a través de una sustancia se conoce como resistencia eléctrica y el porcentaje de grasa y otros componentes corporales puede inferirse a partir de la medición de esta resistencia. El Analizador de la Composición Corporal de Tanita mide la composición corporal utilizando una fuente de corriente continua que genera una corriente de alta frecuencia (50kHz, 90µA).

- ¿Qué es el método DXA?

La absorciometría radiológica dual (DXA) se diseñó en un principio para medir el contenido mineral de los huesos, pero en el modo de exploración mediante escáner del cuerpo entero el porcentaje de grasa corporal, la masa grasa y la masa libre de grasa de determinadas partes del cuerpo (brazos, piernas, tronco) también puede medirse. La imagen de abajo muestra un ejemplo de los resultados de la medición de la composición corporal obtenidos mediante la DXA.



Resultados de la medición de la composición corporal obtenidos mediante la DXA (Lunar Co., Ltd; DPX-L)

- ¿Qué es el método de dilución?

En el método de dilución se utiliza una cantidad conocida de una sustancia etiquetada y se mide la concentración en equilibrio que se diluye uniformemente para obtener la cantidad total de disolvente que diluye a la sustancia etiquetada.
Para medir el agua corporal total (ACT), generalmente se utiliza óxido de deuterio (D2O) como sustancia etiquetada. El óxido de deuterio utiliza el agua corporal total general como medio de dilución, lo que permite obtener el agua corporal total. Para obtener la cantidad de fluido extracelular se utiliza bromuro de sodio (NaBr) como sustancia etiquetada. Se dice que el bromuro (Br) no penetra al interior de las células y que utiliza el fluido extracelular como medio de dilución.

- ¿Qué es la grasa visceral?

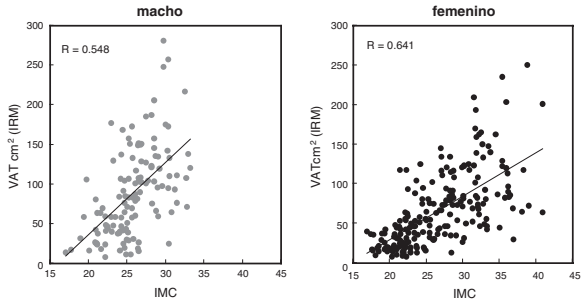
Visceral adipose tissue (VAT) is fat that accumulates in the abdominal cavity and around internal organs. VAT is said to be more likely to cause lifestyle-related diseases than subcutaneous adipose tissue (SCAT). Accordingly, knowing and periodically checking the VAT accumulation risk serves as an important guide in the prevention of lifestyle-related diseases.

Tanita has developed the technology for measuring the VAT accumulation risk through bioelectrical impedance analysis (BIA) in comparison with image analysis applied to magnetic resonance imaging (MRI), in addition to the established technology for measuring the percent of body fat. The VAT accumulation risk is calculated by estimating the VAT area by the BIA method on the basis of MRI image processing. This method has a higher correlation than the estimation of the VAT accumulation risk based on BMI or abdominal circumference (waist circumference), allowing estimation that corresponds more precisely to individuals.

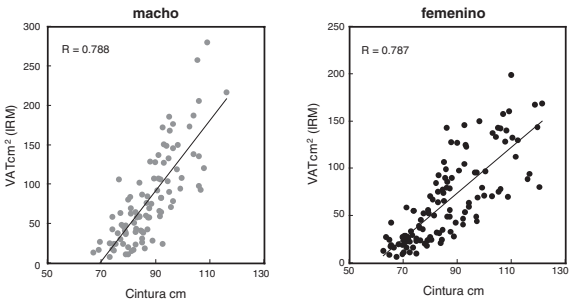
*The VAT area by MRI is calculated by carrying out an image processing of the cross section of the lumber vertebra L4-L5 regions.

(Fig. 1 - Fig. 3: Research results by N. Y. Columbia University and Jikei University Published by the North American Association for the Study of Obesity [NAASO] in 2004.)

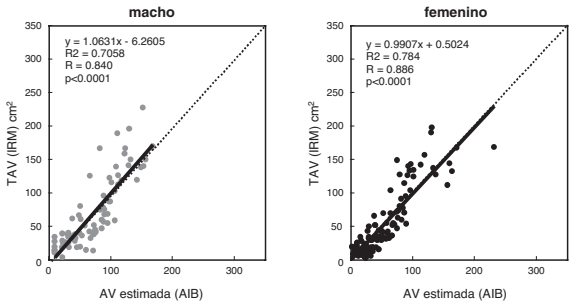
<Fig. 1> Relación entre el área del TAV y el IMC



<Fig. 2> Relación entre el área del TAV y la circunferencia de la cintura



<Fig. 3> Relación entre el área TAV MRI y se estima Zona TAV por AIB Tanita



Aspectos técnicos (cont)

- Facteurs menant à des erreurs de mesure

En el método BIA se mide la impedancia y se calcula la composición corporal a partir del valor obtenido. Se sabe que la impedancia cambia en una cantidad correspondiente al agua corporal total que ocupa aproximadamente el 60% del peso y que su distribución y temperatura cambian. Por esta razón, ya sea para fines de investigación para realizar mediciones que se repiten diariamente, las condiciones de medición deben mantenerse constantes. La adopción de la tecnología de reactancia permite obtener mediciones de una estabilidad nunca antes vista; sin embargo, los cambios de temperatura y distribución del agua corporal total o de volumen de flujo sanguíneo en las extremidades debido a ejercicios, baños, etc., afectan los resultados de las mediciones debido a que la resistencia eléctrica del cuerpo también cambia.

Por lo tanto, se recomienda efectuar las mediciones en las condiciones siguientes para obtener resultados estables.

1)Después de 3 horas de levantarse, habiendo realizado las actividades diarias normales de este período. (La impedancia se mantiene en un nivel alto si usted permanece sentado después de levantarse o si sólo se mueve en un coche, etc.)
2)Cuando hayan transcurrido 3 horas o más tiempo después de comer. (2 a 3 después de comer, la impedancia tiende a disminuir).
3)Cuando hayan transcurrido 12 horas o más tiempo después de hacer ejercicio. (Dependiendo del tipo e intensidad del ejercicio, la impedancia no tiende a cambiar de forma estable).
4)Vacíe la vejiga antes de realizar la medición.
5)En caso de mediciones repetidas, realice las mediciones a la misma hora si es posible. (Al mismo tiempo que se realiza la medición de peso, las mediciones pueden ser más estables si se realizan a la misma hora del día).

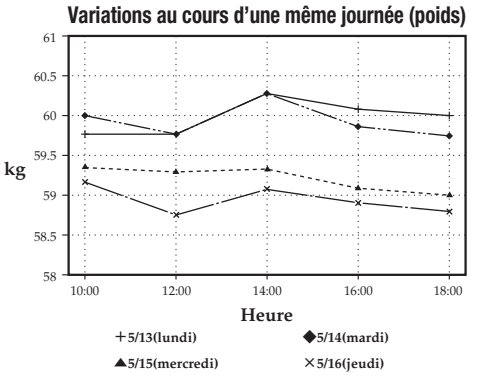
Se pueden obtener valores muy estables realizando las mediciones en las condiciones descritas anteriormente.

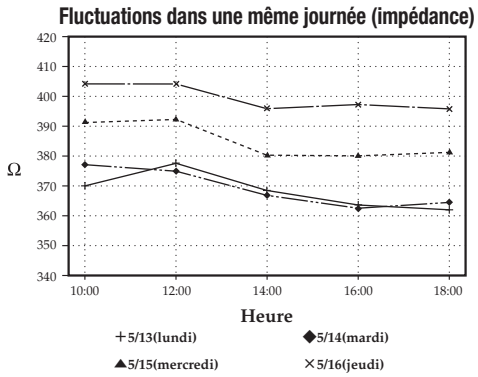
En el desarrollo de este equipo se establecieron 6 puntos como condiciones para la ecuación de regresión.

1)Prohibición de ingerir alcohol hasta 12 horas antes de la medición.
2)Prohibición de hacer ejercicio excesivo hasta 12 horas antes de la medición.
3)Prohibición de comer y beber en exceso en el día anterior a la medición
4)Prohibición de comer y beber hasta 3 horas antes de la medición.
5)Evitar realizar las mediciones durante el período menstrual (mujeres)

2) Variaciones interdiarias

Los diagramas que se muestran debajo incluyen ejemplos de mediciones reales sobre variaciones interdiarias. Se realizó un estudio para determinar el grado de variación de la impedancia entre los pies durante el estado de deshidratación. Los primeros dos días representan la rutina cotidiana normal del sujeto, mientras que en los dos días posteriores se indujo el estado de deshidratación mediante una sauna.





Durante la rutina cotidiana no se registraron variaciones interdiarias de importancia en cuanto al peso corporal, la impedancia entre los pies o el porcentaje de grasa corporal. Sin embargo, durante el estado de deshidratación se registró una disminución del peso corporal de 1kg y un aumento de la impedancia entre los pies de aproximadamente 15Ω, durante el primer día en el que se indujo la deshidratación, y de 30-35Ω el segundo día. Como consecuencia de ello, el porcentaje de grasa corporal
aumentó el 1% el primer día en el que se indujo la deshidratación y el 1,5-2% el segundo día.
Como se ha mencionado anteriormente, la impedancia aumenta cuando el peso corporal disminuye (por ejemplo, debido a la deshidratación) y disminuye cuando el peso corporal aumenta debido a excesos en el consumo de comida y bebida. La variación interdiaria de la impedancia es por lo tanto inversamente proporcional al cambio del peso corporal.
Estas variaciones interdiarias son causadas por factores como:

1)Aumentos temporales del peso corporal (agua corporal total) originados por comer o beber en exceso.
2)Deshidratación debida a sudoración abundante durante la realización de ejercicio intenso.
3)Deshidratación debida al consumo de alcohol o al uso de diuréticos.
4)Deshidratación debida a la sudoración abundante durante la toma de saunas, etc.

Por consiguiente, se recomienda proporcionar al sujeto instrucciones para ayudar a eliminar estas causas cuando se requieran mediciones precisas.

Especificaciones

Modelo		SC-240 / SC240IM	
Fuente de suministro eléctrico	**Adaptador AC**	Centro Negativo	
	Batería	LR6 (AA) x 6	
Consumo eléctricon		0,5 W	
Medición de impedancia	**Sistema de medición**	Análisis de impedancia bioeléctrica tetra polar	
	Frecuencia de medición	50 kHz	
	Corriente de medición	90 µA	
	Rango de medición	150-1200 Ω	
Medición de peso	**Sistema de medición**	Célula de carga indicadora de tensión	
	Capacidad máxima	440 lb	200 kg
	graduación mínima	0,2 lb	0,1 kg
Elementos de información de entrada	**Peso de la ropa**	0-44 lb / incrementos de 0,2 lb	0-10 kg / incrementos de 0,1 kg
	Sexo	Hombre / Mujer	
	Tipo de estructura corporal	Estándar / Atlético	
	Edad	5 - 99 año (Estándar) / 18 - 99 años (Atlético)	
	Altura	3 ft-7 ft 11,5 in / incrementos de 0,5 in	90-249 cm / incrementos de 1 cm
Elementos de información de salida	**Peso**	0-440 lb/incrementos de 0,2 lb	0-200,0 kg/incrementos de 0,1 kg
	% graisse corporelle visé	3-75% / incrementos de 0,1%	
	IMC	incrementos de 0,1	
	% Agua Total	15 - 85% / incrementos de 0,1%	
Conexiones de interfaz		USB	
Peso del equipo		10,0 lb	4,5 kg
Tamaño		13,4×17,2×2,1 in	341×437×54 mm

USA y Canada

Comisión Federal de Comunicaciones y Canadá CIEM comentario

Este equipo ha sido probado y cumple con los límites para un dispositivo digital de Clase B, según la Parte 15 de las normas FCC y canadienses ICES-003. Estos límites están diseñados para proporcionar una protección razonable contra las interferencias perjudiciales en una instalación residencial. Este equipo genera, utiliza y puede irradiar energía de radiofrecuencia y, si no se instala y utiliza de acuerdo con las instrucciones, puede causar interferencias perjudiciales en las comunicaciones de radio. Sin embargo, no hay garantía de que no se produzcan interferencias en una instalación en particular. Si este equipo causa interferencias perjudiciales en la interferencia de radio o televisión, lo que puede determinarse encendiéndolo y apagándolo, se recomienda al usuario que intente corregir la interferencia mediante una o más de las siguientes medidas:

• Cambiar la orientación o ubicación de la antena receptora.
• Aumentar la separación entre el equipo y el receptor.
• Conectar el equipo a un tomacorriente en un circuito diferente de aquel al que está conectado el receptor.
• Consultar con el distribuidor o con un radio o televisión con experiencia con experiencia.

Modificaciones

La FCC exige que el usuario sea notificado de que cualquier cambio realizado en este dispositivo que no sea aprobado expresamente por Tanita Corporation podría invalidar el usuario para utilizar el equipo.

<U.S.A. representative>

TANITA® Corporation of America, Inc.

2625 South Clearbrook Drive, Arlington Heights, Illinois 60005, U.S.A. TEL: 1-847-640-9241 FAX: 1-847-640-9261 http://www.tanita.com

<Manufacturer>

TANITA® Corporation

1-14-2, Maeno-cho, Itabashi-ku, Tokyo 174-8630 , Japan TEL: +81 (0) 3-3968-7048 FAX: +81 (0) 3-3967-3766 http://www.tanita.co.jp

TANITA Europe B.V.
Hoogoorddreef 56-E,
1101 BE Amsterdam, the Netherlands
TEL: +31-20-560-2970
FAX: +31-20-560-2988
http://www.tanita.eu

TANITA Health Equipment H.K.LTD.
Unit 301-303, Wing On Plaza, 3/F., 62 Mody Rord,
Tsimshatsui East, Kowloon, Hong Kong
TEL: +852-2834-3917
FAX: +852-2838-8667
www.tanita.asia

TANITA India Private Limited
A-502, Mittal Commercia, Off. M.V. Road(Andheri Kurla Road),
Marol, Andheri-East, Mumbai 400 059 INDIA
TEL: +91-22-3192-6107
FAX: +91-22-2859-9143
www.tanita.co.in

TANITA (Shanghai) Trading Co., Ltd.
Room 8005, 877 Huai Hai Zhong Lu, Shanghai,
The People's Republic of China
TEL: +86-21-6474-6803
FAX: +86-21-6474-7901
www.tanita.com.cn

Copyright © 2013 TANITA Corporation. All Rights Reserved.

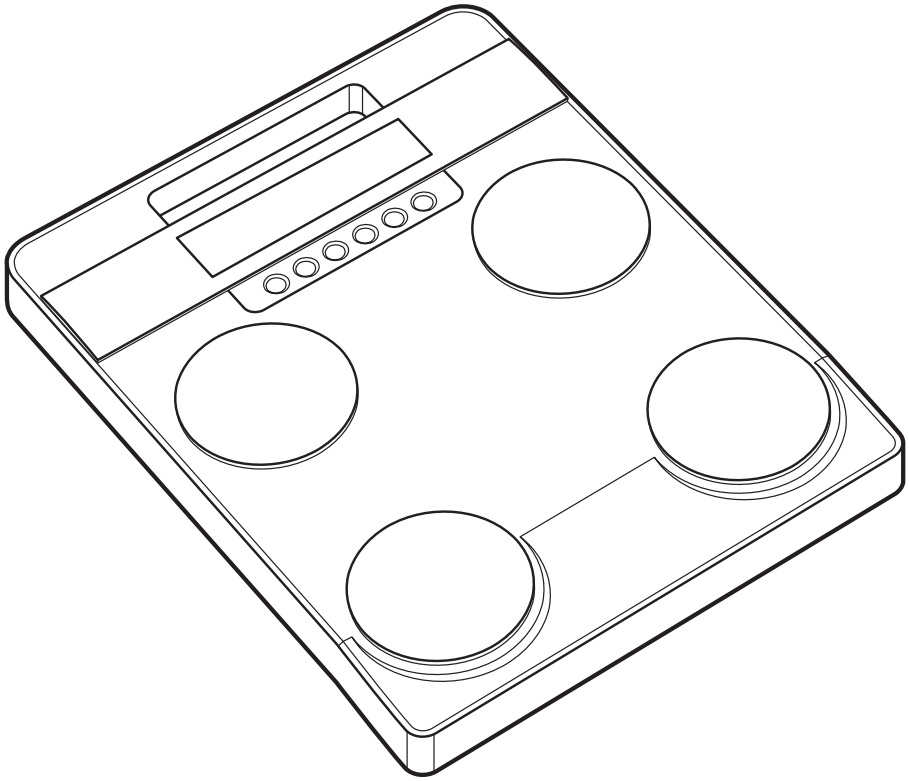
Feb 2013.TY.C.SC2407611(1)

TANITA®
Monitoring Your Health

ANALYSEUR DE LA COMPOSITION CORPORELLE

SC-240 / SC-240IM

Mode d'emploi



<Conditions d'utilisation>

Plage de température d'utilisation	: 0°C à 35°C (32F° à 95°F)
Humidité relative	: 30% à 80% (sans condensation)
Altitude maxi	: 2,000m ASL (6,500ft ASL)
Plage de pression de l'Environnement	: 86kPa à 106kPa

<Conditions de rangement>

Plage de température ambiante	: -10°C à 60°C (14°F à 140°F)
Plage d'humidité relative	: 10% à 90% (sans condensation)

Pour éviter tout mauvais fonctionnement, ne pas ranger l'appareil dans un endroit ensoleillé, ni dans on lieu soumis à des changements importants de température ou de condensation, ou encore dans un endroit très poussiéreux ou à proximité d'un feu, ou dans un endroit soumis à des vibrations ou à des chocs.

⚠ Veuillez lire attentivement ce mode d'emploi et le conserver à portée de la main pour consultation ultérieure.

Utilisation prévue

- Cet appareil est utilisé pour le dépistage de certaines maladies et de certains états de santé de l'adulte associés au poids et à la composition corporelle.
- Cet appareil est utilisé pour le suivi et la prévention de conditions causées par un dépôt excessif de tissus adipeux, tels que le diabète, l'hyperlipémie, la cholélithiase (calculs biliaires) et la stéatose hépatique.
- Cet appareil est utilisé dans le suivi des changements de la composition corporelle des personnes liés à la proportion de tissus adipeux par rapport aux tissus maigres.
- Cet appareil est utilisé pour évaluer l'efficacité des programmes nutritionnels et d'exercices pour la santé et la condition physique.
- L'analyseur de composition corporelle TANITA est indiqué pour l'utilisation aux mesures de poids et d'impédance, ainsi qu'à l'estimation de l'indice de masse corporelle (IMC), du pourcentage total de graisse corporelle, de la masse hydrique totale et de son pourcentage, de la masse musculaire (muscles squelettique et muscles lisses), de l'indice physique, de la masse osseuse, de l'indice de graisse viscérale avec plage de santé, du taux métabolique de base (TMB), et de l'âge métabolique, au moyen de l'analyse d'impédance bioélectrique (BIA).
  L'appareil est indiqué pour l'utilisation pour des enfants et des adolescents de 5 à 17 ans en bonne santé et des adultes en bonne santé à style de vie actif, modérément actif, ou inactif.

Efficacité

1. Ce produit est simple à utiliser, ne nécessite pas d'installations spéciales et aucune expertise n'est requise pour prendre les mesures.
2. Les mesures peuvent être prises rapidement et facilement, ne causant qu'un désagrément minimal pour le patient.



Table des matières

Avant l'utilisation

Mesures de sécurité.....33
Noms des pièces et accessoires.....36
Noms et fonctions du panneau d'affichage et de fonctionnement Touches.....37
Préparatifs (Alimentation).....38
Réglages divers.....39

Comment l'utiliser

Comment l'utiliser (mode de sélection).....40
Comment l'utiliser (l'analyse de composition corporelle).....41
Comment l'utiliser (Pèse-personne).....44
Comment l'utiliser (Pèse-personne / Mode de verrouillage du poids).....45
Comment l'utiliser (Mode IMC).....46

Si nécessaire

Est-il cassé?.....47
Différents critères.....48
Connexion à un micro-ordinateur.....52
Notices techniques.....56
Spécifications.....60

F

Pour votre sécurité

Cette section explique les mesures de précaution à prendre pour éviter tout risque de blessures des utilisateurs de l'appareil et des autres personnes, ainsi que tout dommage à la propriété. Veuillez vous familiariser avec ces informations, afin de vous assurer d'un fonctionnement sans danger de cet appareil.

⚠Avertissement	**Le fait de ne pas respecter les instructions distinguées par ce symbol-epeut entraîner de graves blessures corporelles ou même la mort.**
⚠Prudence	**Le fait de ne pas respecter les instructions distinguées par ce symbole peut entraîner de graves blessures ou des dommages à la propriété.**
⊘	**Ce symbole indique quelles actions sont interdites.**
❗	**Ce symbole indique quelles instructions doivent toujours être suivies.**

⚠ Avertissement

⊘ Interdit

Cet appareil ne doit pas être utilisé sur des sujets portant un pacemaker ou tout autre implant mécanique.

Cet appareil laisse passer à travers votre corps un courant électrique extrêmement faible qui pourrait causer des interférences avec des implants médicaux électriques et provoquer leur mauvais fonctionnement, entraînant un préjudice grave.



Ne pas manipuler la prise avec les mains mouillées.

Ceci pourrait résulter en un choc électrique, un incendie ou une fuite.

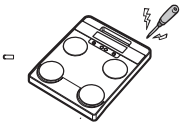


Garder cet apparei l loin de tout gaz inf lammable et de tous environnements riches en oxygène.



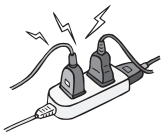
Ne modifier cet appareil en aucun cas.

Ceci pourrait causer un choc électrique ou une blessure, ou affecter la précision de l'analyse.



Ne pas utiliser un adaptateur multiprise.

Ceci pourrait provoquer un incendie.



❗ Toujours…

Utilisez toujours une prise correctement câblée.

Seuls des câbles et des équipements d'origine sont autorisés.

⚠Prudence

Interdit

Garder loin de l'eau.

Éviter d'utiliser sur des sujets allergiques aux métaux.
L'acier inoxydable utilisé dans les électrodes de cet appareil peuvent causer des réactions allergiques.

Ne pas sauter sur l'appareil.

Ne pas prendre appui sur l'appareil.
Ne pas utiliser cet appareil près d'autres produits qui émettent des radiations électromagnétiques.

Ne pas insérer les doigts dans les ouvertures.

Ne pas appliquer de force sur l'écran.
Le panneau de l'écran pourrait se briser et causer une blessure.

Aider les personnes handicapées.
Les personnes handicapées qui ne peuvent prendre elles-mêmes les mesures doivent obtenir l'aide d'une autre personne.

Toujours…

S'assurer de la propreté de la plate-forme de la balance, en utilisant un désinfectant appr prié, après chaque utilisation.

S'écarter du sujet au cours de la prise de mesure, afin d'éviter des chocs électrique ou d'assurer la précision de la mesure.

Surveiller continuellement le sujet et l'appareil pour détecter toute anomalie.
En cas de découverte d'une anomalie sur le sujet ou l'appareil, prendre les mesures appropriées, comme par exemple, arrêter l'appareil, tout en s'assurant de la sécurité du sujet.

Débranchez l'appareil de la prise électrique lorsqu'il n'est pas utilisé pendant de longues périodes de temps.

L'interprétation des résultats d'analyse (par ex. l'évaluation des mesures et la formulation des programmes d'exercice basées sur les résultats) doit être effectuée par un professionnel.
Les mesures pour perdre du poids et les programmes d'exercices basés sur une auto-analyse peuvent être dangereuses pour la santé. Suivre toujours les conseils d'un professionnel compètent.

Cet appareil est conçu comme étant un appareil de Classes B IT (principalement pour les systèmes destinés à être utilisés dans des environnements domestiques) et est certifié CE (EMC), mais il peut affecter les appareils sensibles aux ondes électromagnétiques.
Lors du branchement d'un ordinateur ou d'appareils périphériques à cet appareil, veuillez utiliser des appareils conformes à IEC60601-1 (EN60601-1). L'alimentation électrique doit provenir d'un transformateur d'isolation médical pour les appareils IEC60950 (EN60950). Pendant le fonctionnement, conserver une distance de 1,5 m entre les appareils. Un manquement à cette instruction pourrait causer des chocs électriques pour le sujet ou un mauvais fonctionnement.Cet appareil est conçu comme étant un appareil de Classes B IT (principalement pour les systèmes destinés à être utilisés dans des environnements domestiques) et est certifié CE (EMC), mais il peut affecter les appareils sensibles aux ondes électromagnétiques.

Pour votre sécurité

Pour des mesures précises

Interdit

Éviter de prendre les mesures après un exercice intense.

Ceci pourrait produire des mesures inexactes. Veuillez prendre les mesures après un repos suffisant.



Éviter de prendre les mesures après avoir absorbé trop de nourriture ou de liquides ou en cas de déshydratation.

Ceci pourrait produire des mesures inexactes. Pour une plus grande précision, éviter d'utiliser l'appareil au réveil. Utiliser celui-ci toujours à la même heure ou à la même occasion, au moins trois heure après avoir pris un repas.



Ne pas prendre de mesure tout en utilisant un appareil de transmission, tel qu'un téléphone portable, ce qui pourrait affecter la lecture des résultats.

Toujours…

Pour un suivi précis des modifications, autant que faire ce peu, utiliser l'appareil dans les mêmes conditions et dans la même position.

Les lectures sont très affectées par le niveau d'hydratation et la position du corps.Veuillez utiliser l'appareil chaque fois au même moment de la journée, dans les mêmes conditions et avec le corps dans la même position.



Éviter de prendre les mesures dans différents endroits, avec des températures très différentes.

Ceci pourrait causer des mesures inexactes. Si l'appareil est déplacé dans un nouvel endroit, avec une différence de température de 20°C (36°F) ou plus, laisser l'appareil au repos pendant au moins 2 heures avant de l'utiliser.



Les pieds nus doivent être placés correctement sur la plate-forme à électrodes.

S'assurer que la semelle des chaussures du sujet ne porte pas d'excès de terre, car cela pourrait bloquer le courant électrique faible.

Utiliser une surface stable.

Si l'appareil n'est pas utilisé sur une surface stable, des erreurs de mesure peuvent se produire.

Planning de maintenance

Always…

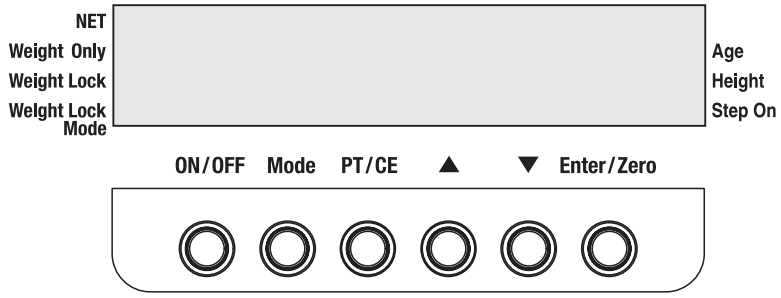
TANITA recommande que chaque site effectue périodiquement des contrôles de chaque appareil.

1. Au moins une fois par jour, vérifier:
   - que l'appareil se trouve sur une surface stable et plane
2. Au moins une fois par semaine, inspecter visuellement:
   - l'écran, pour tout endommagement ou toute contamination
   - tous les câbles, les cordons et les extrémités des connecteurs pour tout dommage ou toute contamination
   - tous les accessoires (capteurs, électrodes, etc.), pour usure ou dommages
3. Au moins chaque mois, inspecter visuellement:
   - Les vis de montage du pied

Selon les résultats obtenus au cours des inspections visuelles, mettre à jour les réglages, remplacer les objets ou appeler pour une réparation. Si tout signe d'endommagement est remarqué, ne pas utiliser l'appareil. Le matériel qui a été endommagé doit être vérifié pour garantir un fonctionnement correct, par un personnel compétent, avant d'être réutilisé.

L'équipement doit être inspecté conformément aux règlements de chaque pays.

Nomenclature et fonctions de l'écran d'affichage et des touches d'opération



ON/OFF Touche MARCHE / ARRÎT : pour allumer et éteindre l'unité

Mode Touche de sélection de mode **:** Sélectionne Analyse de composition corporelle / Pèse-personne

PT/CE **PT / CE** : Tare prédéfinie / Efface les valeurs entrées

▲ **HAUT** **:** Augmente les valeurs numériques

▼ **BAS** **:** Diminue les valeurs numériques

Enter/Zero **Entrer / Remise à zéro :** Entrer valeur d'entrée / Remettre la balance à zéro / Réglage du mode

NET **:** Indique que le poids des vêtements a été entré

Weight Only : Indique que le mode Poids uniquement est activé (pèse-personne)

Weight Lock : Indique que le poids est en cours de verrouillage

Weight Lock Mode : Indique que la fonction de verrouillage du poids est activée

Age : Indique que l'âge est entré

Height **:** Indique que la taille est entrée

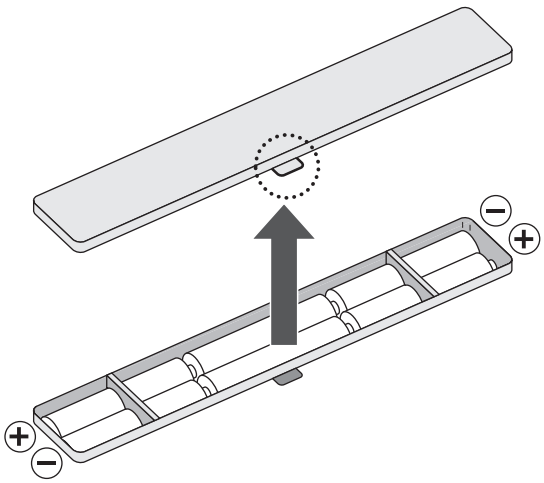
Step On **:** Indique le début de la mesure

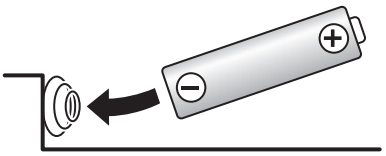
<Symboles et leur signification>

P T	Tare prédéfinie (Poids des vêtements)		Mâle		Femelle
	Athletic mode		Courant direct		Entrée, sortie
	Avertissement. Veuillez consulter les renseignements ci-joints		Courant alternatif		Polarité négative
⊕ LR6,15A,"AA" ⊖	⊕ pour la polarité positive				

Préparation (alimentation)

<Utiliser des piles>

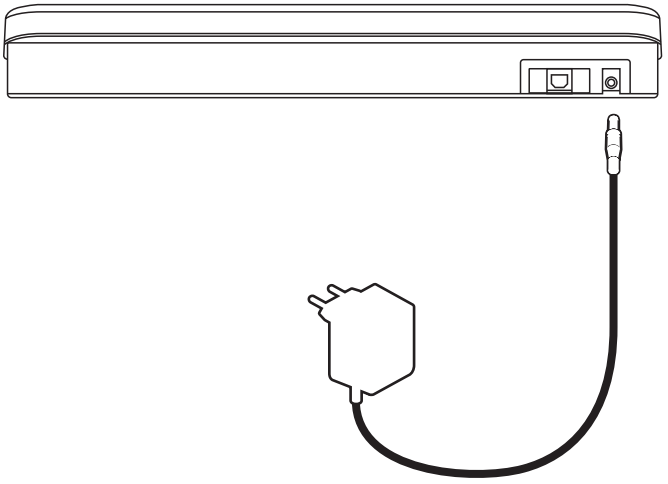




⚠
- Faites attention en changeant les piles LR6 (AA) pour éviter qu'elles ne tombent sur vos pieds.
- Vérifiez si vous avez bien inséré les piles dans le bon sens ⊕ / ⊖. Si la polarité est incorrecte, les piles risquent de fuir et d'endommager l'appareil.
- Lorsque l'appareil n'est pas utilisé pendant une période prolongée, retirez les piles avant de le ranger.

<Utiliser l'adaptateur AC>

(1) Insérer le jack de l'adaptateur AC dans l'entrée AC située sur le côté droit de l'unité principale.
(2) Brancher l'adaptateur AC dans la prise de courant.



⚠Attention

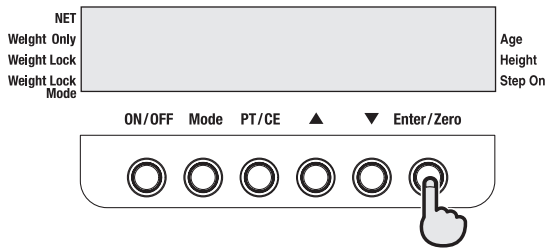
- Cet appareil doit étre utilisé avec l' adaptateur AC fourni.
- Veuillez respecter les instructions suivantes pour obtenir une mesure exacte.
  La mesure peut ne pas être possible sur un emplacement instable.
  Au cours de la mesure du poids, ne touchez aucun câble de connexion, tel que le câble de l'adaptateur AC et le câble de communication relié au PC afin d'éviter toute installation instable.

Réglages divers

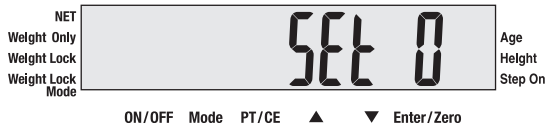
Lancer le mode de réglage.

1 Appuyez sur ON/OFF pour activer le pouvoir.

2 Appuyez sur Enter/Zero pour 1 seconde.

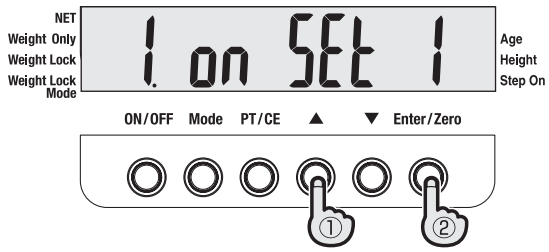


SET 0 s'affiche.



3 Selectionner les éléments du réglage.

1) par un ▲ ou ▼,
2) **Enter/Zero** et clé.



SET1 Réglage de la tonalite sur MARCHE / ARRÊT.
(0.marche ou 1.arrêt)

SET2 Réglage de la sélection athlète sur MARCHE / ARRÉT.
(0.marche ou 1.arrêt)

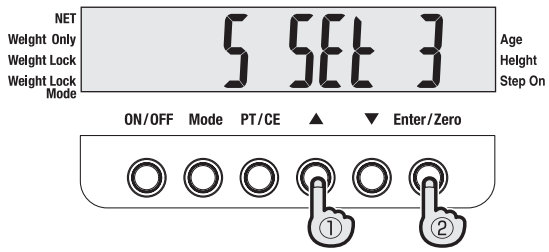
SET3 Réglage du temps de détermination automatique lors de l'entrée des données.
(plage d'entrée de 0 à 9 secondes)
* « 0 » fonction de détermination automatique désactivée.

SET4 Réglage du temps de mise à l'arrêt automatique.
(0, 5, 10, 30, 60 minutes, défaut:5 minutes)
* « 0 » fonction d'arrêt automatique désactivée.

SET5 régler l'appareil
(0kg ou 1,lb, default:1.lb)

4 Entrez la valeur du réglage.

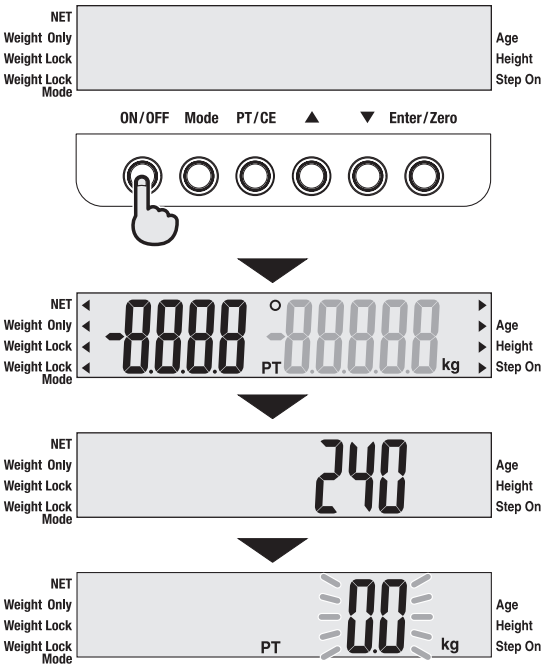
1) par un ▲ ou ▼,
2) et **Enter/Zero** et clé.



5 Appuyez sur ON/OFF pour l'éteindre.

Comment utiliser (mode de sélection)

1 Appuyez sur ON/OFF pour activer le pouvoir.

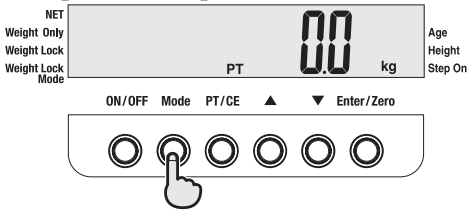


Le nom du modèle est affiché.

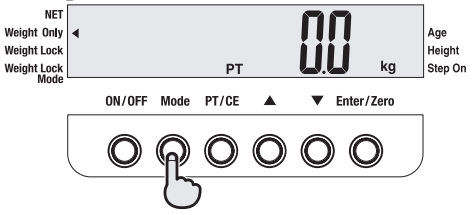
est affiché (Analyse de composition corporelle).

Le mode est sélectionné par la touche **Mode**.

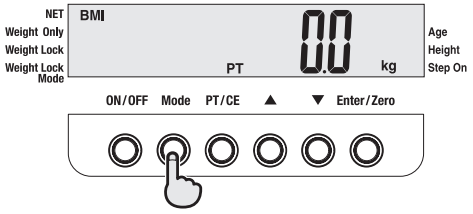
Composition corporelle (☞P.41)



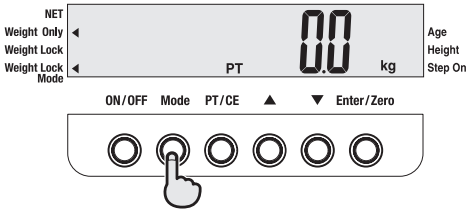
Pèse-personne (☞P.44)



Pèse-personne (Mode IMC) (☞P.46)



Pèse-personne (Verrouillage du poids) (☞P.45)



Comment utiliser (l'analyse de composition corporelle)

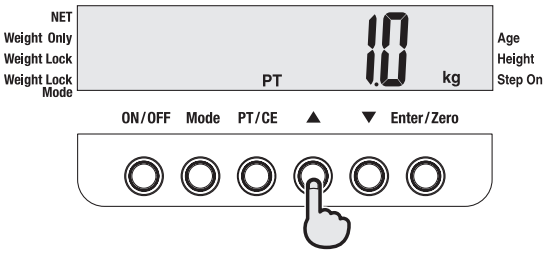
1 Appuyez sur ON/OFF pour activer le pouvoir.

2 Vérifiez que le mode d'analyse de (la composition corporelle est sélectionné (☞P.40).



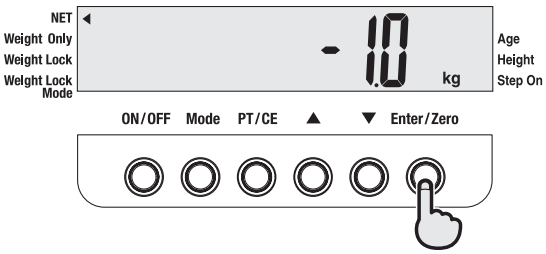
3 Entrez le poids des vêtements.

1) par un ▲ ou ▼,



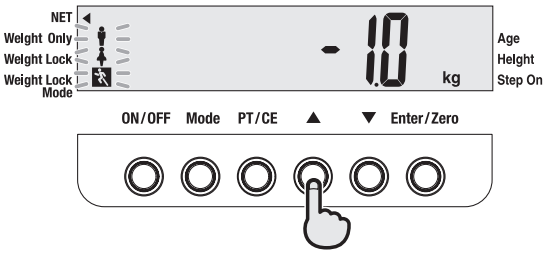
2) **Enter/Zero** et clé.

* **PT/CE** ➡ efface votre entrée.



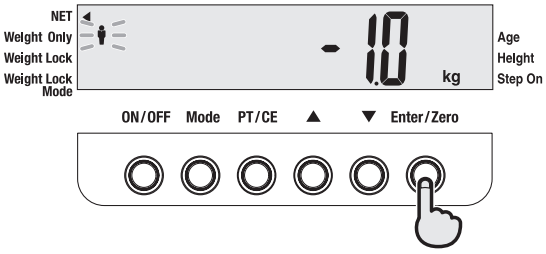
4 Selectionnez le type de corpulence et le sexe.

1) by ▲ or ▼,



2) **Enter/Zero** et clé.

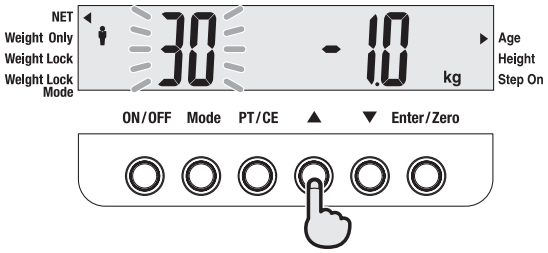
* **PT/CE** ➡ retour à l'état précédent.



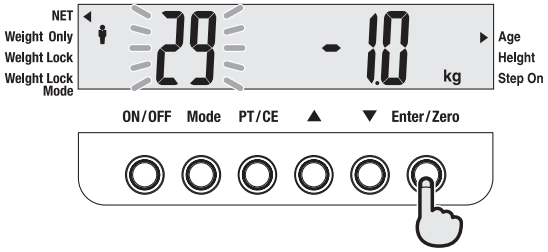
Comment utiliser (l'analyse de composition corporelle) (suite)

5 Entrez votre âge

1) par un ▲ ou▼,

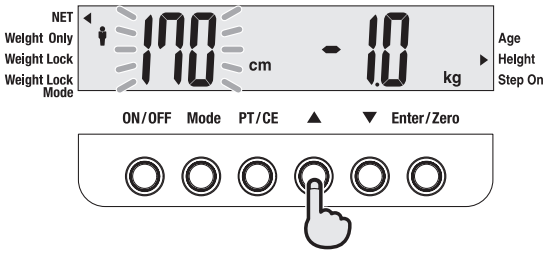


2) **Enter/Zero** et clé.
* **PT/CE** ➡ retour â l'état précédent.

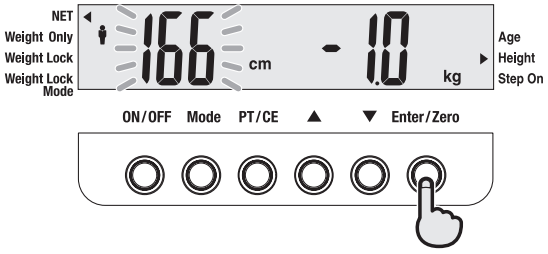


6 Entrez votre taille

1) par un ▲ ou▼,

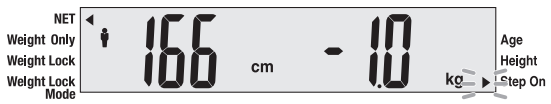


2) **Enter/Zero** et clé.
* **PT/CE** ➡ retour â l'état précédent.



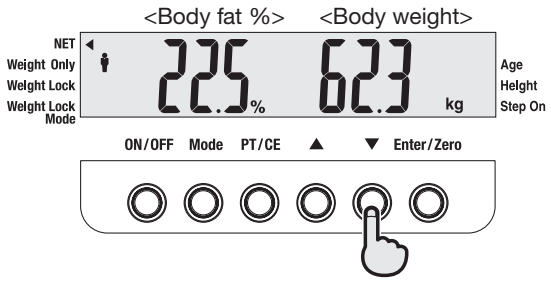
Comment utiliser (l'analyse de composition corporelle) (suite)

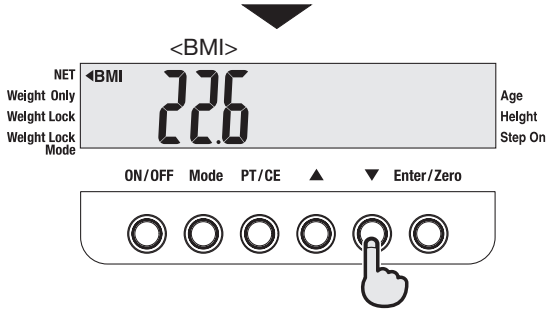
7 **Montez sur la plate-forme pieds nus, lorsque « Step on » clignote.**

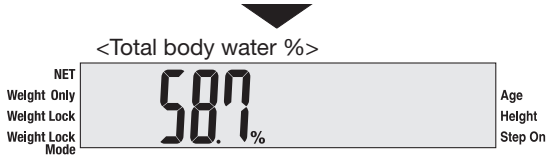




8 **Mesure terminée.**







* **PT/CE**, **Enter/Zero** ➡Efface les résultats affichés

F

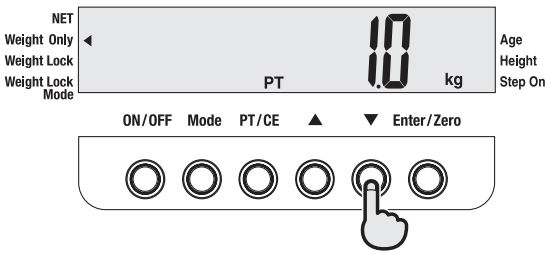
Comment utiliser (Pèse-personne)

1 **Appuyez sur ON/OFF pour activer le pouvoir.**

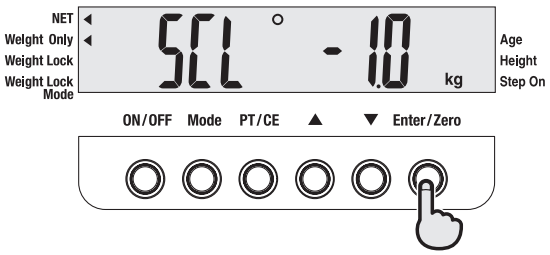
2 **Verifiez que le mode Poids uniquement est sélectionné (☞P.40).**



3 **Entrez le poids des vêtements.**
1) par un ▲ ou ▼,

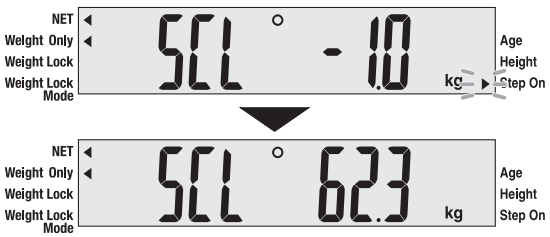


2) **Enter/Zero** et clé.
* **PT/CE** ➡ retour â l'état précédent.



4 **Montez sur la plate-forme, lorsque « Step on » clignote.**

5 **Mesure terminée.**

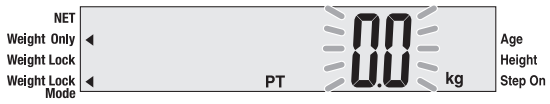


Comment utiliser (Pèse-personne / Mode de verrouillage du poids)

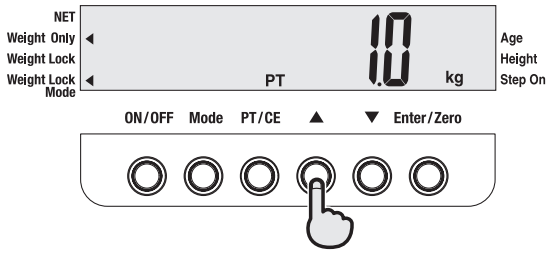
Activation de la fonction de verrouillage du poids.

1 **Appuyez sur ON/OFF pour activer le pouvoir.**

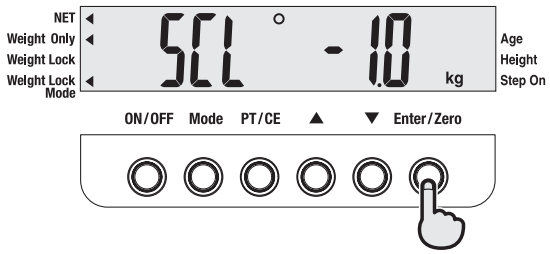
2 **Verifiez que le mode Poids uniquement (Mode de verrouillage du poids) est sélectionn (☞P.40).**



3 **Entrez le poids des vêtements.**
1) par un ▲ ou ▼,

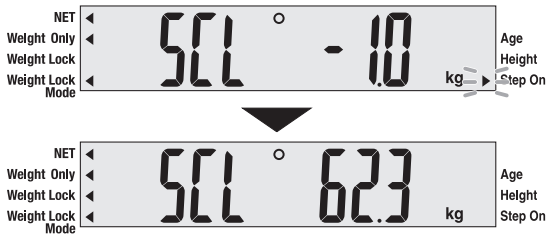


2) **Enter/Zero** et clé.
* **PT/CE** ➡ retour â l'état précédent.



4 **Montez sur la plate-forme, lorsque « Step on » clignote.**

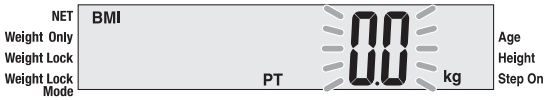
5 **Mesure terminée.**
* **Enter/Zero** ➡ Efface les résultats affichés



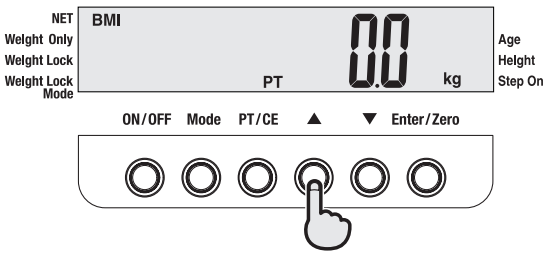
Comment utiliser (Mode IMC)

1 **Appuyez sur ON/OFF pour activer le pouvoir.**

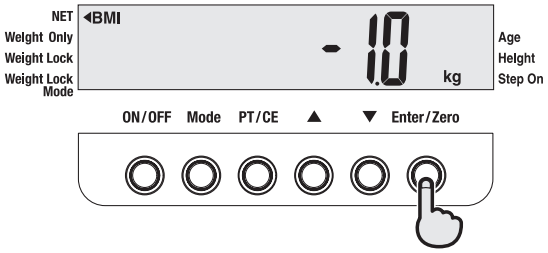
2 **Verifiez que le mode IMC est sélectionné (☞P.40).**



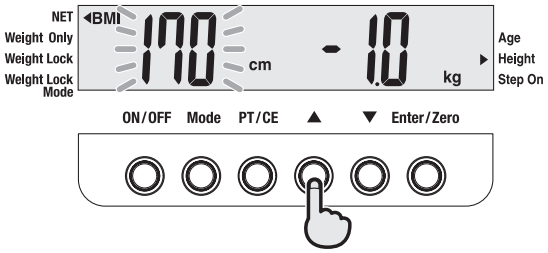
3 **Entrez le poids des vêtements.**
1) par un ▲ ou ▼,



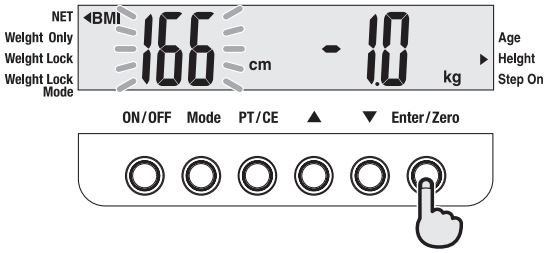
2) **Enter/Zero** et clé.
* **PT/CE** ➡ retour â l'état précédent.



4 **Entrez votre taille**
1) par un ▲ ou ▼,

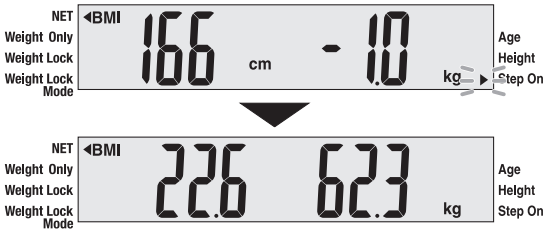


2) **Enter/Zero** et clé.
* **PT/CE** ➡ retour â l'état précédent.



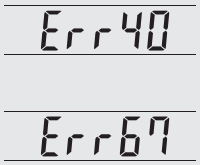
5 **Montez sur la plate-forme, lorsque « Step on » clignote.**

6 **Mesure terminée.**
* **PT/CE**, **Enter/Zero** ➡ Efface les résultats affichés



Est-il cassé?

- Vérifier les points suivants avant de faire appel au réparateur.

Symptôme		Vérifier
Comment mesurer	**Erreur de mesure d'impédance** 	• Veiller à être pieds nus. • Lorsque les plantes de vos pieds sont sèches, verser environ 0.5 ml d'eau sur les électrodes à l'aide du compte-gouttes fourni avant de procéder à la mesure. • Vérifier les données saisies.
	Erreur du point zéro 	• Eteindre l'appareil, retirer les éléments du plateau et rallumer l'appareil, puis recommencer la mesure.
	Le poids mesuré n'est pas stable.	• Est-il installé dans un endroit soumis à des vibrations? • Le plateau est-il incliné? ⇨ Maintenir le plateau en position horizontale. • Un objet est-il coincé dans les trous du plateau? ⇨ Retirer tout objet coincé dans les trous.
Section d'affichage	**Rien n'est affiché même lorsque l'appareil est allumé.**	• Vérifier si l'alimentation est connectée correctement
	 **s'affiche.**	• Le poids à mesurer dépasse la plage des valeurs possibles.

Remarque

- Si une erreur autre que celle citée ci-dessus est affichée, éteindre l'appareil une fois, puis recommencer la mesure.
  Si la même erreur s'affiche plusieurs fois, prendre contact avec notre centre de service client.

Critères divers

Critères basés sur le pourcentage de graisse corporelle

Le taux de graisse corporelle est le rapport entre votre masse graisseuse et votre masse totale.
Il a été prouvé que la réduction de l'excès de graisse corporelle réduit le risque de certaines maladies telles que l'hypertension artérielle, les maladies cardiaques, le diabète et le cancer.
Le tableau ci-dessous vous montre les plages saines du taux de graisse corporelle.

Eventails de données de graisse corporelle pour enfants moyens[1]
Normes du taux de graisse corporelle (valeurs pour des adultes standards)[2]

[1] *Susan Jebb et al. Obesity Research 2004;12;A156-157 « Nouvelles courbes de référence des réserves adipeuses de l'organisme pour les enfants »*

[2] *Gallagher D. et al. Am J. Clin Nutr, 2000, 72 : pp. 694-701. "Eventails de données en pourcentage de graisse corporelle pour une bonne santé : une approche pour développer les directives, basées sur l'index de graisse corporelle."*

| | | Maigreur | | | | | | | | | Valeurs saines | | | | | | | | | | | | | | | | | | | | | Surpoids | | | | | | | | | | Obésité | | | | | | | | | | | | | | | | | | |

QU'EST-CE QUE LE TAUX DE MASSE HYDRIQUE?

Le taux de masse hydrique (TBW) est la quantité totale d'eau contenue dans le corps d'une personne et exprimée en pourcentage de son poids total. l'eau joue un rôle essentiel dans de nombreux processus du corps humain et se retrouve dans toutes les cellules, tissus et organes. En maintenant un taux de masse hydrique sain, vous assurez le fonctionnement efficace de votre corps, et vous réduisez le risque de problème de santé associés.

Les niveaux d'eau de votre corps fluctuent naturellement durant la journée. Votre corps a tendance à se déshydrater après une longue nuit et il existe des différences de distribution des fluides entre le jour et la nuit. Le fait de faire de grands repas, boire de l'afalcool, être menstruée, être malade, faire de l'exercice ainsi que se baigner peuvent faire varier vos niveaux d'hydratation.

Votre relevé de taux de masse hydrique fait office de référence et ne devrait pas être utilisé pour déterminer de façon spécifique votre taux absolu de masse hydrique recommandé.
Il importe d'observer les changements à long terme du taux de masse hydrique et de maintenir un taux sain et régulier.

L'absorption d'une grande quantité d'efeau en une seule fois ne changera pas instantanément votre niveau d'eau. En fait, elle augmentera votre mesure du taux de graisse corporelle du fait du gain de poids supplémentaire. Surveillez toutes les lectures régulièrement afin de détecter tout changement relatif.

Chaque individu diffère, voici les taux moyens de masse hydrique pour un adulte en bonne santé, pour référence :

Femme :45 à 60%
Homme:50 à 65%
Source :Based on Tanita's Internal Research

Remarque: Le taux de masse hydrique a tendance à diminuer alors que le taux de graisse corporelle augmente. Il se peut qu'ufun individu ayant un taux de graisse corporelle élevé soit en dessous du taux de la masse hydrique moyenne. Lorsque vous perdez de la masse grasse, votre taux de masse hydrique devrait se rapprocher progressivement de la plage représentative indiquée ci-dessus.

QU'EST-CE QUE LE POURCENTAGE DE GRAISSE VISCERALE ?

Cette fonction indique la pourcentage de graisse viscérale dans votre corps.
La graisse viscérale est la graisse qui se trouve dans la cavité abdominale interne, autour des organes vitaux du tronc (abdomen). Les recherches montrent que même si votre poids et votre graisse corporelle restent constants, la répartition de graisse change au fur et à mesure que vous vieillissez et il est vraisemblable qu'elle soit transférée au tronc, surtout après la ménopause. Vous pouvez réduire le risque de certaines maladies, comme les maladies cardiaques, la surtension artérielle et le déclenchement de diabète de type 2 en maintenant des niveaux de graisse viscérale sains.

Le contrôleur de composition corporelle Tanita vous fournit une plage de graisse viscérale de 1 à 59.

Classement de 1 à 12
Indique que vous avez un niveau de graisse viscérale sain. Continuez de contrôler ce taux pour veiller à ce qu'il reste conforme à la plage normale.

Classement de 13 à 59
Indique que vous avez un niveau excessif de graisse viscérale. Réfléchissez à la possibilité de changer votre mode de vie, peut-être par des changements diététiques ou en augmentant vos activités physiques.

Source : Données de l'université de Columbia (New York) et de l'institut Tanita (Tokyo)

Note:
•Même si vous avez un faible taux de graisse corporelle, il se peut que vous ayez un taux élevé de graisse viscérale.
•Pour un diagnostic médical, veuillez consulter votre médecin.

Critères divers (suite)

- Qu'est - ce que le taux de metabolisme debase (BMR) ?

QU'EST-CE QUE LE BMR ?

Votre MB représente le niveau minimum d'énergie dont votre corps a besoin au repos pour exercer ses fonctions normales, telles que la respiration, la circulation sanguine, le système nerveux, le foie, les reins et les autres organes. Quoi que vous fassiez, vous brûlez des calories, même en dormant.

Environ 70% des calories que vous consommez chaque jour sont utilisées pour votre métabolisme basal. De plus, vous dépensez de l'énergie dans n'importe quelle activité de la journée. Cependant, plus l'activité est vigoureuse, plus vous brûlez de calories. Ceci est dû au fait que les muscles de votre squelette (qui représentent environ 40 % du poids de votre corps) agissent comme un moteur et consomment beaucoup d'énergie. Votre métabolisme basal est considérablement affecté par la quantité de muscles que vous avez ; augmentez votre masse musculaire et vous aidez votre métabolisme basal.

En étudiant des individus en bonne santé, les chercheurs ont découvert qu'en vieillissant, le métabolisme de base des humains change. Le métabolisme basal augmente à la maturation d'un enfant. Après une pointe à l'âge de 16 ou 17 ans, le taux commence à se réduire progressivement, comme illustré ci-dessous.

Le fait de posséder un métabolisme basal plus élevé augmente le nombre de calories consommées et aide à réduire le taux de graisse corporelle. Un faible taux de métabolisme basal rend la perte de graisse corporelle et de poids plus difficile.

CALCUL DU BMR PAR UN ANALYSEUR DE COMPOSITION CORPORELLE TANITA

Le MB se calcule très simplement par une équation standard utilisant le poids et l'âge. Tanita a mené des recherches approfondies sur la relation existante entre le TMB et la composition corporelle, ce qui a permis une lecture des mesures d'impédance, beaucoup plus précise et personnalisée pour l'utilisateur. Cette méthode a été validée sur le plan médical en utilisant la calorimétrie indirecte (mesure de la composition respiratoire).*

* Fiabilité de l'équation sur le Taux Métabolique Basal : À : 2002 Nutrition Week : A Scientific and Clinical Forum and Exposition Title: International Comparison: Resting Energy Expenditure Prediction Models: The American Journal of CLINICAL NUTRITION (Semaine de la nutrition 2002, forum scientifique et clinique sur les modèles de prévision de consommation d'énergie au repos).

- Qu'est - ce que l'âge métaboliue?

Cette fonction calcule votre MB et indique l'âge moyen associé à ce type de métabolisme. Si votre BMR est supérieur à votre âge réel, cela signifie que vous avez besoin d'améliorer votre taux de métabolisme. Davantage d'exercices vous permet de produire des tissus musculaires sains, ce qui améliorera votre âge métabolique.

Les résultats s'échelonnent de 12 à 50. Toute valeur inférieure à 12 s'affiche comme "12" et toute valeur supérieure à 50 s'affiche comme "50".

- Qu'est - Ce que la masse Mmusclaire? (Applicable 18 ans - 99)

Cette fonction indique le poids des muscles de votre corps. La masse musculaire affichée inclut les muscles squelettiques (comme les muscles cardiaques et digestifs) et l'eau contenue dans ces muscles. Les muscles jouent un rôle important car ils agissent comme moteur au niveau de la consommation d'énergie. Au fur et à mesure que votre masse musculaire augmente, votre consommation d'énergie augmente, ce qui vous aide donc à réduire les niveaux de graisse corporelle superflus et à perdre du poids de manière saine.

- Qu'est - Ce que la masse osseuse? (Applicable 18 ans - 99)

Cette fonction indique la quantité d'os (niveau minéral osseux, calcium ou autres minéraux) dans le corps.

Les recherches ont montré que l'exercice et le développement de tissus musculaires produisent les os les plus forts et les plus sains. Même s'il est peu vraisemblable que la structure osseuse subisse des changements visibles en une courte période de temps, il est important que vous développiez et maintenez des os sains en ayant un régime alimentaire équilibré et en faisant beaucoup d'exercice. Les gens qui s'inquiètent des maladies osseuses devraient consulter leur médecin. Les gens qui souffrent d'ostéoporose ou de faible densité osseuse en raison de leur âge avancé, de leur jeune âge, d'une grossesse, d'un traitement hormonal ou d'autres causes, risquent de ne pas obtenir d'évaluations précises de leur masse osseuse.

Vous trouverez ci-dessous les résultats des évaluations de la masse osseuse pour les personnes âgées de 20 à 40 ans qui sont considérées comme ayant la quantité la plus importante de masse osseuse, par tranche de poids. (Source : Institut des sciences sur le poids corporel Tanita).

Veuillez utiliser les tableaux ci-dessous à titre indicatif pour comparer vos relevés de masse corporelle.

Femmes : Moyenne de la masse osseuse estimée

Poids (lb)		
Moins de 110 lb	110lb - 165 lb	165 lb et plus
4,3 lb	5,3 lb	6,5 lb

Poids (kg)		
Moins de 50 kg	50 kg - 75 kg	75 kg et plus
1,95 kg	2,40 kg	2,95 kg

Hommes : Moyenne de la masse osseuse estimée

Poids (lb)		
Moins de 143 lb	143 lb - 209 lb	209 lb et plus
5,9 lb	7,3 lb	8,1 lb

Poids (kg)		
Moins de 65 kg	65 kg - 95 kg	95 kg et plus
2,66 kg	3,29 kg	3,69 kg

Note: Les personnes décrites ci-dessous peuvent obtenir divers résultats et doivent uniquement utiliser les valeurs indiquées à titre indicatif.

- Les personnes âgées
- Femmes pendant ou après la ménopause
- Les personnes qui reçoivent une thérapie hormonale

" Estimated bone mass " (la masse osseuse estimée) est une valeur estimée de manière statistique sur la base de sa corrélation avec les quantités libres de graisse (tissus autres que la graisse). " Estimated bone mass " (la masse osseuse estimée) ne donne pas un jugement direct de la dureté ou de la résistance des os ou des risques de fractures osseuses. Si vous vous inquiétez au sujet de vos os, nous vous recommandons de consulter un spécialiste.

Branchement sur un ordinateur

L'interface USB permet l'entrée et la sortie de cet appareil.

- Spécifications

Norme de communication	USB
Méthode de communication	Transaction asynchrone
Vitesse du signal	9600 baud
Longueur des bits utiles	8 bits
Parité	Aucune
Bit d'arrêt	1 bit
Contrôle de débit	Aucun
Terminateur	CR+LF

Notes

- Un connecteur USB (type B, 4 broches, femelle) se trouvent à l'arrière de l'unité principale.
- Veuillez fournir vos propres câbles, si nécessaire, car aucun n'est inclus.
  USB : type A, 4 broches (mâle) – type B, 4 broches, (mâle)
- Vous devez installer le pilote nécessaire sur votre PC, téléchargez disponibles à partir http://www.tanita.com ou sur le CD-ROM fourni.

- Transmission de données

⚠MISE EN GRADE Les données sont transmises immédiatement après la pesée, quel que soit le réglage du périphérique de réception (PC, etc.). Il faudra donc que le périphérique soit prêt pour la réception des données avant la pesée.

(1) Format de données de sortie (dans le cas de l'unité de kg)

Remarque

- Les données sont divisées par des virgules (,) pour chaque type de données.
- Le terminateur (la fin des données) est CR (Code ASCII 0DH), LF (Code ASCII 0AH). 0 représente un zéro.
- Les données de commande pour les éléments 1 - 4 sont pour l'expansion. Ils ne sont pas utilisés actuellement pour le côté réception peut les ignorer.
- En raison de ses caractéristiques, l'échelle va émettre un signal pertinent environ 0,1 seconde après la sortie de données. Assurez-vous que vous ignorez ce signal et ne pas l'importer.

Données du corps entier

Modèle		N d'identification		Statut		Genre		Age	
MO	"XXXXXX"	SN	"XXXXXXXX"	Bt	0 ou 2	GE	0 ou 2	AG	XX

Taille		Poids des vêtements (PT)		Poids		% graisse		Masse graisseuse	
Hm	XXX.X	Pt	XX.X	Wk	XXX.X	FW	XX.X	fW	XXX.X

FFM		Masse musculaire		Score de masse musculaire du corps entier		Masse osseuse		Teneur en eau du corps entier (TBW)	
MW	XXX.X	mW	XXX.X	sW	XX	bW	XXX.X	wW	XXX.X

Pourcentage d'eau dans le corps		BMI		Score de masse musculaire du corps entier		Obésité		Taux de graisse viscérale	
ww	XX.X	MI	XXX.X	Sw	XXX.X	OV	XXX.X	IF	XX

BMR (kJ)		BMR (kcal)		Analyse du métabolisme de base		Âge métabolique		Impédance (50kHz)	
rb	XXXXX	rB	XXXXX	rJ	XX	rA	XX	ZF	XXXX.X

Somme de contrôle	
CS	XX

Branchement sur un ordinateur (suite)

(2) Eléments de données de sortie

<mode kg / cm>

Elément	En-tête	Format	mode kg / cm	Ordre de sortie				
				Moniteur de composition corporelle			Échelle	BMI
				Adulte	Athlète	Enfant		
Données de contrôle	{0		2 octets fixes	1	1	1	1	1
Données de contrôle	~0		1 octet fixe	2	2	2	2	2
Données de contrôle	~1		1 octet fixe	3	3	3	3	3
Données de contrôle	~2		1 octet fixe	4	4	4	4	4
Modèle	MO	"XXXXXX"	8 octets fixes ("SC-240")	5	5	5	5	5
Numéro de série	SN	"XXXXXXXX"	10 octets fixes	6	6	6	6	6
Morphologie	Bt	0 or 2	1 octet fixe (0:Standard 2:Athlète)	7	7	7		
Sexe	GE	1 or 2	1 octet fixe (1:homme 2:femme)	8	8	8		
Age	AG	XX	1-2 octets variables	9	9	9		
Taille	Hm	XXX.X	4-5 octets variables (cm)	10	10	10		7
Poids des vêtementst	Pt	XX.X	3-4 octets variables (interchangeable entre 0,1 kg)	11	11	11	7	8
Poids	Wk	XXX.X	3-5 octets variables (interchangeable entre 0,1 kg)	12	12	12	8	9
% de graisse	FW	XX.X	3-4 octets variables (interchangeable entre 0,1%)	13	13	13		
Masse de graisse	fW	XXX.X	3-5 octets variables (interchangeable entre 0,1 kg)	14	14	14		
FFM	MW	XXX.X	3-5 octets variables (interchangeable entre 0,1 kg)	15	15	15		
Masse musculaire	mW	XXX.X	3-5 octets variables (interchangeable entre 0,1 kg)	16	16			
Score de masse musculaire du corps entier	sW	XX	1-2 octets variables (1-24)	17	17			
Masse osseuse	bW	XXX.X	3-5 octets variables (interchangeable entre 0,1 kg)	18	18			
TBW (Teneur en eau du corps entier)	wW	XXX.X	3-5 octets variables (interchangeable entre 0,1 kg)	19	19			
Pourcentage d'eau dans le corps	ww	XX.X	4 octets variables (interchangeable entre 0,1%)	20	20			
BMI	MI	XXX.X	3-5 octets variables (interchangeable entre 0,1)	21	21	16		10
Poids standard	Sw	XXX.X	3-5 octets variables (interchangeable entre 0,1 kg)	22				
Obésité	OV	XXX.X	3-5 octets variables (interchangeable entre 0,1%)	23				
Taux de graisse viscérale	IF	XX	1-2 octets variables	24	22			
BMR (kJ)	rb	XXXXX	1-5 octets variables (interchangeable entre 1 kJ)	25	23			
BMR (kcal)	rB	XXXXX	1-5 octets variables (interchangeable entre 1 kcal)	26	24			
Analyse du métabolisme de base	rJ	XX	1-2 octets variables (1-24)	27	25			
Âge métabolique	rA	XX	2 octets variables	28	26			
Impédance (50 kHz)	ZF	XXXX.X	1-2 octets variables (4-55)	29	27	17	9	
Somme de contrôle	CS	XX	2 octets fixes	30	28	18	10	11

Exemple de sortie

Standard, Homme, 30 ans, Taille 170 cm

{0, 16, ~0, 1, ~1, 1, ~2, 1, MO, "SC-240", SN, "00000002", Bt, 0, GE, 1, AG, 30, Hm, 170, Pt, 0.0, Wk, 82.7, FW, 18.6, fW, 15.4, MW, 67.3, mW, 64.0, sW, 19, bW, 3.3, wW, 48.0, ww, 58.0, MI, 28.6, Sw, 63.6, OV, 30.0, IF, 6, rb, 8255, rB, 1973, rJ, 12, rA, 28, ZF, 369.4, CS, FD

mode lb / ft-in

Elément	En-tête	Format	mode lb / ft-in	Ordre de sortie				
				Moniteur de composition corporelle			Échelle	BMI
				Adulte	Athlète	Enfant		
Données de contrôle	{0		2 octets fixes	1	1	1	1	1
Données de contrôle	~0		1 octet fixe	2	2	2	2	2
Données de contrôle	~1		1 octet fixe	3	3	3	3	3
Données de contrôle	~2		1 octet fixe	4	4	4	4	4
Modèle	MO	"XXXXXX"	8 octets fixes ("SC-240")	5	5	5	5	5
Numéro de série	SN	"XXXXXXXX"	10 octets fixes	6	6	6	6	6
Morphologie	Bt	0 or 2	1 octet fixe (0:Standard 2:Athlète)	7	7	7		
Sexe	GE	1 or 2	1 octet fixe (1:homme 2:femme)	8	8	8		
Age	AG	XX	1-2 octets variables	9	9	9		
Taille	Hm	XXX.X	4 octets fixes (in)	10	10	10		7
Poids des vêtementst	Pt	XX.X	3-4 octets variables (interchangeable entre 0,2 lb)	11	11	11	7	8
Poids	Wk	XXX.X	3-5 octets variables (interchangeable entre 0,2 lb)	12	12	12	8	9
% de graisse	FW	XX.X	3-4 octets variables (interchangeable entre 0,1%)	13	13	13		
Masse de graisse	fW	XXX.X	3-5 octets variables (interchangeable entre 0,2 lb)	14	14	14		
FFM	MW	XXX.X	3-5 octets variables (interchangeable entre 0,2 lb)	15	15	15		
Masse musculaire	mW	XXX.X	3-5 octets variables (interchangeable entre 0,2 lb)	16	16			
Score de masse musculaire du corps entier	sW	XX	1-2 octets variables (1-24)	17	17			
Masse osseuse	bW	XXX.X	3-5 octets variables (interchangeable entre 0,2 lb)	18	18			
TBW (Teneur en eau du corps entier)	wW	XXX.X	3-5 octets variables (interchangeable entre 0,2 lb)	19	19			
Pourcentage d'eau dans le corps	ww	XX.X	4 octets variables (interchangeable entre 0,1%)	20	20			
BMI	MI	XXX.X	3-5 octets variables (interchangeable entre 0,1)	21	21	16		10
Poids standard	Sw	XXX.X	3-5 octets variables (interchangeable entre 0,2 lb)	22				
Obésité	OV	XXX.X	3-5 octets variables (interchangeable entre 0,1%)	23				
Taux de graisse viscérale	IF	XX	1-2 octets variables	24	22			
BMR (kJ)	rb	XXXXX	1-5 octets variables (interchangeable entre 1 kJ)	25	23			
BMR (kcal)	rB	XXXXX	1-5 octets variables (interchangeable entre 1 kcal)	26	24			
Analyse du métabolisme de base	rJ	XX	1-2 octets variables (1-24)	27	25			
Âge métabolique	rA	XX	2 octets variables	28	26			
Impédance (50 kHz)	ZF	XXXX.X	5-6 octets variables (interchangeable entre 0,1)	29	27	17	9	
Somme de contrôle	CS	XX	2 octets fixes	30	28	18	10	11

Exemple de sortie

Standard, Homme, 30 ans, Taille 67,0 in

{0, 16, ~0, 1, ~1, 1, ~2, 1, MO, "SC-240", SN, "00000003", Bt, 0, GE, 1, AG, 30, Hi, 67.0, Pt, 0.0, Wp, 182.2, FW, 18.7, fW, 34.0, MW, 148.2, mW, 140.8, sW, 19, bW, 7.4, wW, 105.6, ww, 58.0, MI, 28.5, Sw, 140.4, OV, 29.8, IF, 6, rb, 8247, rB, 1971 ,rJ, 12, rA, 29, ZF, 372.8, CS, 2A

Notices techniques

Mesure de la composition corporelle par la méthode BIA.

Introduction

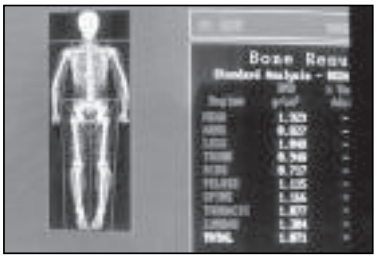
Cet équipement fournit des valeurs estimées pour chaque valeur mesurée du pourcentage de graisse corporelle, de la masse grasse, la masse maigre, la masse musculaire et la masse osseuse par la méthode DXA pour les japonais et la valeur estimée pour la teneur en eau du corps par la méthode de dilution utilisant l'analyse d'impédance bio-électrique (méthode BIA).
Pour la mesure, un mode doit être sélectionné selon type de forme corporelle.
1) Standard (pour individus de 5 à 99 ans)
2) Athlète (pour les athlètes pratiquant plus d'activités physiques que les autres)
La fiabilité de la mesure des compositions corporelles des athlètes, etc., dont la composition diffère de celle des autres,est accrue en divisant le mode de mesure basé sur chaque type de forme corporelle.

- Principe de mesure de la composition corporelle

La BIA permet d'analyser les constituants du corps (masse grasse, masse musculaire estimée, etc.) en mesurant l'impédance bioélectrique du corps. Les graisses contenues dans le corps ne laissent pratiquement pas passer l'électricité, à l'inverse d'un autre constituant corporel, à savoir l'eau, qu'on retrouve en grande quantité dans les muscles. Le degré de difficulté de conduction de l'électricité est appelé résistance électrique. A l'aide d'une alimentation électrique constante à haute fréquence (50 kHz, 90µA), cette résistance permet d'évaluer le taux de graisse ainsi que d'autres constituants du corps.

- Qu'est-ce que la méthode DXA ?

Conçue, à l'origine, pour calculer la teneur minérale des os, le DXA peut également mesurer le taux de graisse, la masse grasse et la masse maigre, pour chaque partie du corps (bras, jambes, torse), par scintigraphie du corps entier. L'image ci-dessous présente un exemple de calculs de composition corporelle par DXA.



Résultats de mesures de composition corporelle par DXA (Lunar Co., Ltd ; DPX-L)

- Qu'est-ce que la méthode de dilution ?

Dans la méthode de dilution, une substance étiquetée d'une quantité connue est donnée et la concentration en équilibre diffusée de façon uniforme est mesurée afin d'obtenir le montant total de solvant qui dilue la substance marquée.
Pour mesurer la teneur en eau du corps (TBW), l'oxyde de deutérium (D2O) est utilisé en règle générale comme substance étiquetée. L'oxyde de deutérium utilise la teneur en eau du corps comme espace de dilution de manière à obtenir la teneur en eau du corps. Pour obtenir la quantité de liquide extracellulaire, du bromure de sodium (NaBr) est utilisé comme substance étiquetée. Le brome (Br) est sensé ne pas pénétrer à l'intérieur des cellules, et utilise le liquide extracellulaire comme espace de dilution.

- Qu'est-ce que la graisse viscérale ?

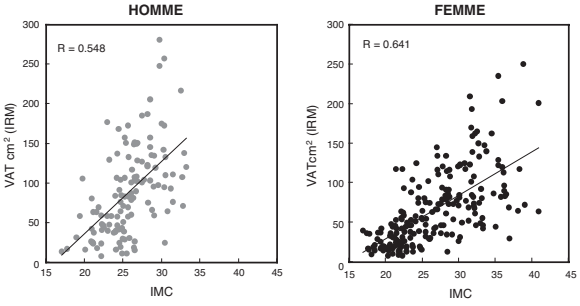
Les tissus adipeux viscéraux (TAV) sont de la graisse qui s'accumule dans la cavité abdominale et autour des organes internes. On considère que les TAV sont plus susceptibles d'engendrer des maladies liées au mode de vie que les tissus adipeux sous-cutanés (TASC).

Ainsi, le fait de connaître et de vérifier de façon périodique le risque d'accumulation de TAV peut servir de guide utile pour prévenir les maladies liées au mode de vie. Tanita a développé la technologie permettant de mesurer le risque d'accumulation de TAV par analyse d'impédance bioélectrique (BIA) en comparaison à une analyse d'image appliquée à l'imagerie par résonance magnétique (IRM), en plus des technologies établies pour mesurer le pourcentage de graisse corporelle. Le risque d'accumulation de TAV est calculé par estimation de la zone de TAV à l'aide de la méthode BIA, en se basant sur le traitement d'image IRM. Cette méthode fournit une corrélation plus élevée que l'estimation du risque d'accumulation de TAV basée sur l'IMC ou la circonférence abdominale (tour de taille), permettant ainsi des estimations correspondant plus précisément aux individus.

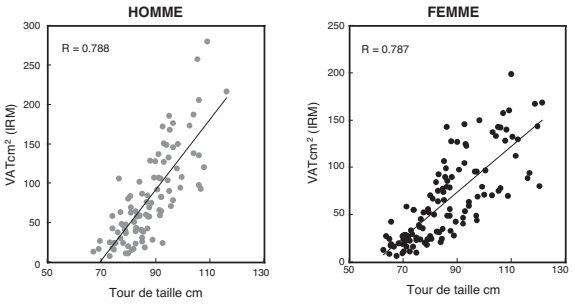
*La zone de TAV par IRM est calculée en effectuant un traitement d'image numérique d'une section transversale au niveau de la 4ème et de la 5ème vertèbre lombaire.

(Fig. 1 - Fig. 3 : Résultats des travaux de recherche de la N. Y. Columbia University et la Jikei University, publiés en 2004 par la North American Association for the Study of Obesity [NAASO].)

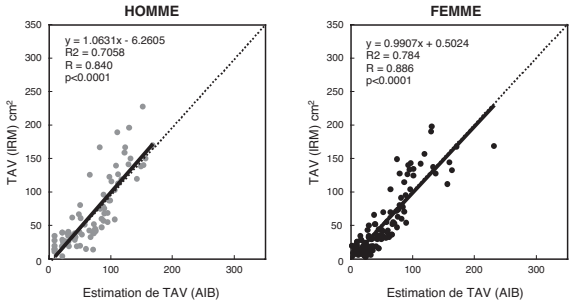
<Fig. 1> Relation entre la zone de TAV et l'IMC



<Fig. 2> Relation entre la zone TAV et le tour de taille



<Fig. 3> Relation entre la zone de TAV par IRM et l'estimation de TAV Zone par AIB de Tanita



Technical notes (suite)

- Facteurs menant à des erreurs de mesure

Dans la méthode BIA, l'impédance est mesurée et la composition corporelle est calculée sur la base de la valeur. On sait que l'impédance varie selon la quantité totale d'eau dans le corps, qui représente environ 60 % du poids, et les changements au niveau de la répartition et de la température. Pour cette raison, dans un objectif de recherche ou pour effectuer des mesures répétitives quotidiennes, les conditions de mesure doivent être maintenues constantes. Et en adoptant la technologie de réactance, il est désormais possible d'obtenir des mesures plus stables que jamais. Toutefois, les mesures effectuées dans des conditions variables de de température et de distribution de la teneur en eau du corps ou du volume de débit sanguin des extrémités (suite à des activités physiques, un bain , etc.), affectent les résultats obtenus étant donné que la résistance électrique varie également dans le corps.
Par conséquent, il est conseillé d'effectuer les mesures dans les conditions suivantes pour obtenir une mesure stable.

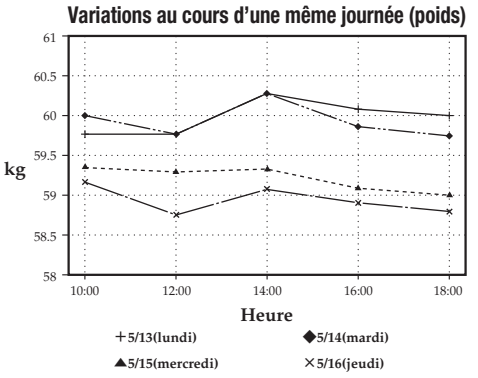
1)3 Heures se sont écoulées après le réveil et des activités normales sont pratiquées pendant cette période. (Les transits d'impédance restent à un niveau élevé si on reste assis après le réveil ou si l'on se déplace uniquement en voiture, etc.)
2)3 heures ou plus se sont écoulées après le repas. (Pendant 2 – 3 heures après le repas, l'impédance a tendance à diminuer.)
3)12 heures ou plus se sont écoulées après une activité physique intense. (La tendance à des changements d'impédance n'est pas stable selon le type et la rigueur de l'activité physique.)
4)La vessie doit être vide avant de prendre les mesures.
5)Pour des mesures répétitives, mesurer à la même heure autant que possible. (Au moment de la pesée, les mesures peuvent être stabilisées en effectuant la pesée à la même heure de la journée)

Des valeurs mesurées très stables peuvent être obtenues en respectant les conditions de mesure suivantes.
Et lors de la conception de cet équipement, les 6 éléments suivants ont été définis comme conditions de l'équation de régression.

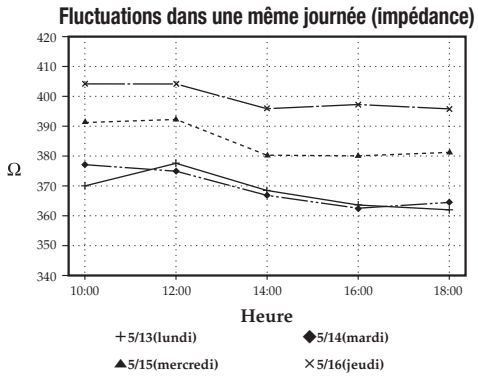
1)Interdiction de consommer de l' alcool 12 heures avant la mesure
2)Interdiction de pratiquer des activités physiques excessives 12 heures avant la mesure.
3)Interdiction de manger et de boire excessivement la veille de la mesure
4)Interdiction de manger et de boire 3 heures avant la mesure
5)Eviter la période menstruelle (femmes)

2) Changements au cours d'une même journée

Les diagrammes ci-dessous présentent des exemples d'analyse des variations enregistrées au cours d'une même journée. Une étude a été réalisée pour déterminer le degré de changement d'impédance, entre les pieds, en période de déshydratation. Les deux premiers jours correspondent à un régime quotidien normal, tandis que les deux suivants ont été marqués par un état de déshydratation provoqué par des séances de sauna.



Aucun changement important n'a été noté dans la mesure du poids, de l'impédance entre les pieds ou du pourcentage de graisse dans le corps en régime quotidien normal. En situation de déshydratation, toutefois, on a relevé une perte de poids de 1 kg, avec augmentation de l'impédance entre les pieds d'environ 15 Ω le premier jour et de 30 Ω - 35 Ω le second. De fait, le taux adipeux est monté de 1 %, le premier jour et de 1,5 Ω 2 %, le deuxième jour de déshydratation.



Comme déjà évoqué, l'impédance augmente quand le poids diminue (comme en déshydratation) et se réduit lorsque le poids s'élève après consommation de nourriture et boissons. La variation d'impédance d'un jour à l'autre est donc inversement proportionnelle à la fluctuation du poids. Ces changements d'un jour à l'autre ont, notamment, pour origine :

1)Un accroissement passager du poids (teneur hydrique total du corps) à cause d'une consommation excessive d'aliments et de liquides ;
2)Une déshydratation causée par une sudation importante au cours d'exercices physiques intenses ;
3)Une déshydratation provoquée par l'absorption d'alcool ou l'utilisation de diurétiques ;
4)Une déshydratation due à une forte sudation en sauna, etc.

C'est pourquoi, il est recommandé de remettre ces instructions au sujet pour l'aider à éliminer tous ces facteurs susceptibles de fausser les calculs.

Spécifications

Modèle		SC-240 / SC240IM	
Source d'alimentation	**Adaptateur courant alternatif**	Center Minus	
	Batterie	LR6 (AA) x 6	
Consommation		0.5 W	
Impédance Mesure	**Système de mesure**	Analyse d'impédance bioélectrique tétrapolaire	
	Fréquence de mesure	50 kHz	
	Courant de mesure	90 µA	
	Gamme de mesure	150-1200 Ω	
Poids Mesure	**Système de mesure**	Cellule de mesure de jauge d'effort	
	Capacité Maximum	440 lb	200 kg
	Graduation Minimum	0,2 lb	0,1 kg
Input Items	**Poids des habits**	0-44 lb / 0,2 lb increments	0-10 kg / 0,1 kg increments
	Sexe	Homme / Femme	
	Type corporel	Standard / Athlète	
	Age	5-99 ans (Standard) / 18-99 ans (Athlète)	
	Taille	3 ft-7 ft 11,5 in / incréments de 0,5 in	90-249 cm / incréments de 1 cm
Output Items (Affichage)	**Poids**	0-440 lb/incréments de 0,2 lb	0-200,0 kg/incréments de 0,1 kg
	% graisse corporelle visé	3-75% / incréments de 0,1%	
	IMC	Incréments de 0,1	
	% de masse grasse	15 - 85% / Incréments de 0,1%	
Interface Données de sortie		USB	
Poids de l'équipement		10,0 lb	4,5 kg
Taille		13,4×17,2×2,1 in	341×437×54 mm

USA et Canada

Federal Communications Commission et canadienne ICES avis

Cet équipement a été testé et s'est avéré conforme aux limites pour un appareil numérique de classe B, conformément à la Partie 15 des règlements de la FCC et canadienne ICES-003. Ces limites sont conçues pour fournir une protection raisonnable contre les interférences nuisibles dans une installation résidentielle. Cet équipement génère, utilise et peut émettre des fréquences radio et, s'il n'est pas installé et utilisé conformément aux instructions, il peut causer des interférences nuisibles pour les communications radio. Cependant, il n'existe aucune garantie que des interférences ne se produiront pas dans une installation particulière. Si cet équipement provoque des interférences nuisibles à la réception radio ou de télévision, ce qui peut être déterminé en l'éteignant et rallumant, l'utilisateur est encouragé à essayer de corriger l'interférence par une ou plusieurs des mesures suivantes:

• Réorienter ou déplacer l'antenne de réception.
• Augmentez la distance entre l'équipement et le récepteur.
• Connecter l'équipement à une sortie sur un circuit différent de celui sur lequel est branché le récepteur.
• Consulter le revendeur ou un technicien de radio ou télévision expérimenté.

Modifications

La FCC exige que l'utilisateur soit averti que toute modification apportée à cet appareil qui ne sont pas expressément approuvés par Tanita Corporation peuvent annuler le droit de l'utilisateur à utiliser l'équipement.

<U.S.A. representative>

TANITA® Corporation of America, Inc.

2625 South Clearbrook Drive, Arlington Heights, Illinois 60005, U.S.A. TEL: 1-847-640-9241 FAX: 1-847-640-9261 http://www.tanita.com

<Manufacturer>

TANITA® Corporation

1-14-2, Maeno-cho, Itabashi-ku, Tokyo 174-8630 , Japan TEL: +81 (0) 3-3968-7048 FAX: +81 (0) 3-3967-3766 http://www.tanita.co.jp

TANITA Europe B.V.
Hoogoorddreef 56-E,
1101 BE Amsterdam, the Netherlands
TEL: +31-20-560-2970
FAX: +31-20-560-2988
http://www.tanita.eu

TANITA Health Equipment H.K.LTD.
Unit 301-303, Wing On Plaza, 3/F., 62 Mody Rord,
Tsimshatsui East, Kowloon, Hong Kong
TEL: +852-2834-3917
FAX: +852-2838-8667
www.tanita.asia

TANITA India Private Limited
A-502, Mittal Commercia, Off. M.V. Road(Andheri Kurla Road),
Marol, Andheri-East, Mumbai 400 059 INDIA
TEL: +91-22-3192-6107
FAX: +91-22-2859-9143
www.tanita.co.in

TANITA (Shanghai) Trading Co., Ltd.
Room 8005, 877 Huai Hai Zhong Lu, Shanghai,
The People's Republic of China
TEL: +86-21-6474-6803
FAX: +86-21-6474-7901
www.tanita.com.cn

Copyright © 2013 TANITA Corporation. All Rights Reserved.

Feb 2013.TY.C.SC2407611(1)

Chapter 38. Vital Sign Measures: Temperature, Respiratory Rate, Oximetry, Blood Pressure, and Pulse

38.1 Introduction

The many extraneous factors influencing the vital signs are controlled by standardizing the measurement technique and the environment in which the measurement is made.

38.2 Preparation for Measure of Vital Signs

Participants should abstain from caffeine, smoking, and exercise at least one-half hour prior to and until completion of all vital signs measurements. Vital signs should take place in a separate, quiet room where no other activity is taking place, and where temperature fluctuations are minimal. Scheduling procedures should try to establish consistent appointment times to minimize as much as possible the impact of daily variations in pulse, temperature, respiratory rate and blood pressure.

Equipment (including Form 120-Vital Signs, digital oral thermometer, oximeter, sphygmomanometer, appropriate-sized cuffs, etc.) should be checked and waiting for the participant.

38.3 Temperature Measure

PVDOMICS requires oral measurements to be made at all sites. Oral temperatures are influenced by drinking, chewing, smoking, and breathing with the mouth open. For the oral temperature measures in PVDOMICS to be accurate, the participant must not have eaten, drunk, or smoked anything in the last 30 minutes, as the temperature of food, drink, or smoke can dramatically affect readings. Wearing overly warm outer garments can also affect temperatures. All participants should be sitting in a comfortable room temperature area without bulky jackets or heavy coats for at least 15 minutes prior to measure.

The manufacturer of the temperature device you use will provide information on how to use it. Be sure to read and follow the instructions to obtain an accurate temperature.

38.4 Respiratory Rate Measure

The respiratory rate is the number of breaths that a participant takes each minute. The rate should be taken when the participant is at rest in a quiet room for at least 15 minutes, and it is assessed by counting the number of times the chest rises in one minute.

38.5 Pulse and Oxygen Saturation Measure

The manufacturer of the oximetry device you use will provide information on how to use it. Be sure to read and follow the instructions to obtain an accurate oxygen saturation measurement.

In order for the pulse oximeter to function, the probe must be placed where a pulse can be detected. Temperature will affect the ability to detect a signal. Be sure the room and patient are comfortably warm.

Probes are designed for use on the finger, ear lobe or forehead. An ear lobe or forehead probe should be used in patients with a history of scleroderma, Raynaud's phenomenon or in those cases when oximetry cannot be performed using the digits. The type of probe used will be recorded on Form 120.

1. Turn the pulse oximeter on: it will go through internal calibration and checks.
2. Select the appropriate probe with particular attention to correct sizing and where it will go (2nd or 3rd finger, ear or forehead). Make sure the site is clean. Remove any nail varnish if the finger is used.
3. Connect the probe to the pulse oximeter.
4. Position the probe carefully; make sure it fits easily without being too loose or too tight.
5. Do not use a finger on the arm being used for blood pressure monitoring as cuff inflation will interrupt the pulse oximeter signal.
6. Allow several seconds for the pulse oximeter to detect the pulse and calculate the oxygen saturation.
7. Look for the displayed pulse indicator that shows that the machine has detected a pulse. Without a pulse signal, any readings are meaningless.
8. Once the unit has detected a good pulse, the oxygen saturation and pulse rate will be displayed. Allow at least 1 minute prior to recording the saturation number.
9. Oximeters may occasionally give a false reading - if in doubt, function of the oximeter probe can be checked by placing it on your own finger. If no signal is obtained after the probe has been placed on a finger, and you have checked that the probe functions on yourself, then try another finger on the same hand. If there is still no pulse detectable, the other hand may be tried after measure of BP and the cuff has been removed from the arm. Ultimately if the digits still cannot provide pulse and oximetry (such as in participants with scleroderma) oximetry and pulse can be obtained from the earlobe or forehead.

38.6 Blood Pressure Measure

An appropriate size cuff should be used. This is defined as a blood pressure cuff containing a bladder, which covers at least 2/3 of the distance from the acromion to the olecranon. If there is any doubt about cuff size, then a larger rather than an inappropriately small cuff should be used. In overweight adults, it may be necessary to use a large adult or thigh cuff to obtain an accurate measurement.

1. The participant should be seated with arm extended at **heart level** for approximately 15 minutes prior to making the measurement. The participant should be relaxed, seated with back supported with legs uncrossed and feet comfortably flat on the floor and not dangling..
2. The right arm is to be used consistently for measurement of blood pressure. If this is not possible, use the left arm. Indicate which arm is used to measure pulse and blood pressure on the case report form.
3. Fold the cuff bladder in half mating each corner of the bladder to find and mark the midpoint on the cuff cover. Do not use a permanent marking on the bladder because it may become dislocated and off-center.
4. The brachial artery is located by palpation. Place the appropriately sized cuff around the upper right arm so that the midpoint of the length of the bladder lies over the brachial artery and the mid-height of the cuff is at heart level.
5. The lower edge of the cuff, with its tubing connections, should be placed about 1 inch above the natural crease across the inner aspect of the elbow.
6. The cuff is wrapped snugly around the bare arm, with the palm of the participant's hand turned upward.
7. Blood pressure can be measured using standard auscultatory methods or using an oscillometric device such as the Dinamapp. The manufacturer of the blood pressure device you use will provide information on how to use it. Be sure to read and follow the instructions to obtain an accurate blood pressure measure.
8. Try to use the same method throughout the study. The method of measuring blood pressure should be recorded in the CRF.

38.7 Pulse Measure

This measurement serves two purposes: (1) to document the resting heart rate at the time of examination, and (2) to permit detection of gross irregularities of heart rhythm which may affect the interpretation of the blood pressure readings.

1. The measurement of pulse is performed only after the participant has been seated quietly, with feet flat on the floor, in an erect but comfortable posture, for at least fifteen minutes.
2. The right arm is to be used consistently for measurement of the pulse. If this is not possible, use the left arm.
3. Pulse can be measured by palpation of the radial artery at the wrist. This is done for 30 seconds. Alternatively, an oscillometric device such as the *Dinamapp* may be used. The manufacturer of the device you use will provide information on how to use it. Be sure to read and follow the instructions to obtain an accurate pulse.
4. Try to use the same method throughout the study.
5. Any marked irregularity observed during this period should be called to the attention of the Principal Investigator.

Chapter 39. Six Minute Walk Test (6MWT)

39.1 Introduction

This MOP chapter is designed to guide the performance of the 6-minute walk test (6MWT) using standardized procedures and techniques in order to provide accurate test results in a safe testing environment for participants enrolled in the PVDOMICS study. The 6MWT is a practical simple test to perform that does not require exercise equipment. The 6MWT measures the distance that a participant can walk quickly on a flat hard surface in a period of 6 minutes (the 6MWD).

The 6MWT evaluates the global and integrated responses of all body systems involved during exercise. It does not provide specific information on the function of each of the different organs and systems involved as is possible with the cardiopulmonary exercise test. Most participants do not achieve maximal exercise capacity during the 6MWT, and instead, choose their own level of intensity.

The primary measurement of the procedure is distance walked in 6 minutes. Use of supplemental oxygen is documented and heart rate and oxygen saturation by pulse oximetry (SpO2) is recorded and may be useful information. No attempt is to be made during the test to determine the optimal level of supplemental oxygen with exertion; rather, supplemental oxygen is used to insure adequate oxygenation during the procedure. Changes in 6MWT distance are a standard accepted measure of function and/or drug efficacy in pulmonary arterial hypertension.

Only one 6-minute walk test is performed for the PVDOMICS Study. No historical data is accepted. Participants will have only one attempt to complete the test. If the participant is unable to complete the test, record available information on Form 133-6MWT and enter the data into the database.

On 06/18/2018, the DCC provided each center with one Masimo oximeter, lanyard, and forehead probe that must be used prospectively. Each clinical center is responsible for replacing any lost and/or damaged piece(s) of equipment. Clinical centers may opt to purchase an additional set of equipment. Contact the Jose Ramos at the PFT Core (pvd-lungcore@bio.ri.ccf.org) for supplier contact information.

39.1 Technologist/Coordinator Training and Experience

It is not mandatory for the person conducting the 6MWT for the PVDOMICS Study to be a pulmonary function technologist (see also section 39.3.1). In some cases, it may be the study coordinator. Regardless, the individual who conducts the 6MWTs will be trained using this standard protocol, and should be supervised for several tests before performing them alone.

39.2 Participant Preparation

Table 1: Pre-Test Instructions
• **Wear loose-fitting, comfortable clothing and shoes suitable for exercise**
• Participant should use their usual waking aid(s) during the test (cane, walker, rollator etc.)
• A light meal is acceptable before early morning or early afternoon tests.
• Medication holds are not specifically required for 6MWT

The participant should rest ten minutes prior to start of test and have not done vigorous exercise within 2 hours prior to test. It is recommended that 6MWT be performed BEFORE CPET.

39.3 Contraindications and Safety

Table 2: Contraindications for Performing the Test	
Absolute contraindications	Unstable angina in the previous month
	Myocardial infarction in the previous month
Relative contraindications	Severe untreated arterial hypertension at rest (180 mmHg systolic, 100 mmHg diastolic)
	Resting pulse rate > 120/minute
	See below for Sp02 requirements (pre-test procedure -Section 39.4)

1. Stable exertional angina is not an absolute contraindication for the 6MWT, but participants with this disorder should perform the test with their anti-angina medication at the ready.

2. Medications to treat asthma and angina will be available, including supplemental O_2 and albuterol (metered dose inhaler or solution for nebulizer). Sublingual nitroglycerin should be available. A telephone or other means will be readily available to enable a call for help, and the medical director of the PFT laboratory will establish the appropriate location for the crash cart.

Table 3 Reasons for Immediately Stopping the Test - Do Not Restart
Chest pain
Intolerable dyspnea
Leg cramps, staggering
Diaphoresis, pale or ashen appearance
Near syncope, syncope, dizziness, light-headedness or feeling faint
Oxygen saturation drops ≤80% while walking

If a test is stopped for any of the reasons listed above, the participant should sit or lie supine as appropriate. The following should be obtained based on the judgment of the assessor: blood pressure, pulse rate, SpO2 and a physician evaluation. Oxygen should be administered as appropriate.

DO NOT RESTART THE TEST IF IT IS STOPPED FOR ANY REASON NOTED IN TABLE #3.

39.3.1 Test Supervision

a. Physicians are not required to be present during all tests. The physician ordering the test, supervising laboratory physician or the laboratory's standard operating procedure should define whether physician attendance at a specific test is required. Call the physician PI for approval if you are unable to reach a resting pre-test O2 saturation ≥ 92%, or if other contraindications are present.
b. Technologists must be trained in at least Basic Life Support by attending an American Heart Association accredited program. Advanced cardiac life support training is desirable.
c. The person(s) conducting the 6MWT must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of the above reasons, the participant should sit or lie supine as appropriate depending on the severity of the event and the test giver's assessment of the severity of the event. Activation of the institution's emergency response system may be required. The following should be obtained based on the judgment of the test giver: blood pressure, pulse rate, and a physician evaluation. Oxygen should be administered as appropriate.
d. Pulse oximetry **should be monitored continuously** during the walk.

39.4 6MWT Testing Procedures

Pre-Test Procedure	
Appropriate order	Check for a complete physician's order
Demographics	Identify the participant using two separate identifiers and record demographic information
Discuss test with participant	Briefly explain the purpose of the test in a manner that is understood by the participant.
Participant preparation	Measure blood pressure.
	Check for contraindications to testing
	Have the participant stand
	Place the provided Masimo pulse oximeter probe on **finger or forehead** (**See note 1 on page 39.4);** and record resting SpO2 and pulse rate. Ensure participant is on Room Air for 5 min, if possible, before checking SpO2. If the participant is prescribed > 4L O2 at rest please GET APPROVAL FROM PI PRIOR TO REMOVING 02. Measure and record resting room air SpO2, and record resting SpO2 and O2 delivery method/cannula type while on O2 (If needed) (See below regarding 02 use during walk).
	Explain and record the Borg scale: see Appendix 1
	The technologist should be trained in pulse oximetry applications, quality assurance and limitations.

-Continued from previous page	If supplemental oxygen is to be used, ensure that the participant is familiar with pulling an E cylinder trolley (rather than pushing it). An alternative method that may be used is to adapt a rollator to accommodate an oxygen cylinder trolley, in which case it can be pushed like a walker. The participant should not carry their oxygen. **Please convert participant from their own oxygen system to an E cylinder to** be pulled or pushed using a rollator. Oxygen should be administered as a continuous flow, as opposed to "on demand (pulse)". The test administrator should not pull the oxygen cylinder for the participant. IF THE ROOM AIR REST PRE-TEST 02 SATURATION IS ≤ 88%, THEN TITRATE THE 02 SATURATION TO ≥ 92% BEFORE WALKING THE PARTICIPANT (SEE NOTE BELOW). IF ROOM AIR REST 02 SATURATION IS ≥89%, THEN WALK PARTICIPANT ON CURENT 02 REQUIREMENT (PRESCRIBED OR USED DURING PRIOR 6MWT). Record baseline heart rate and SpO2 at rest after 5 minutes or when the SpO2 has been stable for 2 minutes, whichever comes first. Record the oxygen device, liter flow and the use of a walking aid.

Note 1: Use the provided Masimo oximeter and strap (lanyard) in all participants. In participants with peripheral vascular compromise including Scleroderma, Raynaud's, etc., use the provided forehead probe and secure the probe with self-adhesive gauze (e.g., Coban) or headband (not provided by DCC). It is recommended that the device be positioned in such a manner that the participant cannot read the O2 saturation and heart rate values (i.e., hip or back) **(SEE PAGE 39.5).** The device should be positioned in such a manner that the technician can read the O2 saturation continuously at a minimum of two times for each lap **(SEE PAGE 39.5).**

Unless participant is staggering or a fall risk, the technician SHOULD NOT walk with the participant. Participants with congenital PH and associated hypoxemia can perform 6MWT if pre-test O2 saturation is ≤ 89% and test may continue if Sp02 falls to ≤ 80%, at the discretion of the physician PI. If the participant has congenital PH and associated hypoxemia, and if unable to titrate up Sp02 to ≥ 92%, it is recommended to perform 6MWT on 02 level that has been prescribed or used on previous 6MWT. There is no upper limit of O2 administration mandated for the 6MWT. If any concern arises in the pre-test 6MWT period, contact PI.

Placement of Masimo Oximeter and Strap (lanyard)

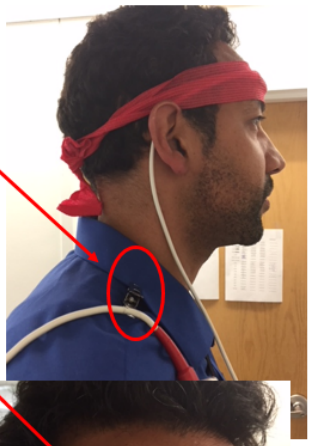


Positioning of the Masimo forehead probe and lanyard

1. The lanyard should be placed across the patients body with the oximeter readout on the back of the patient which will remove it from their view

2. The cord coming from the oximeter to patients forehead should be clipped to the patients shirt/blouse (as shown Pic. 2) to avoid the cord from dragging or becoming a tripping hazard.

3. The cord should run behind the patients ear and should be positioned between the hairline and the eyebrow (may have to slightly move to improve signal strength).





6MWT Protocol continues on next page

6MWT Procedure	
Before Starting	Complete the first part of the worksheet/report
	Set the lap counter to zero and timer to 6 minutes
	Take the participant to the starting point of the walk. This may be the end of the walk track or it may be a point in the hallway marked with the distance to the end of the hallway the participant will be walking toward when the test starts. If the latter is the case, record that distance (starting residual). Make sure that the oxygen probe (**finger or forehead)** is giving a steady pulse oximetry reading and that the participant cannot see the O2 saturation/heart rate values.
	Instruct the participant by **reading the instructions** as follows (hearing impaired participants may benefit from written as well as verbal instructions): *"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway between the markers, as many times as you can in 6 minutes.* *I will let you know as each minute goes past, and then at 6 minutes I will ask you to stop where you are.* *Six minutes is a long time to walk, so you will be exerting yourself. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but please resume walking as soon as you are able.* *Remember that the objective is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.* *Do you have any questions?"* If the participant is unfamiliar with the test, it is a good idea to demonstrate how you would like the participant to walk around the cones/markers as it is important that they do not cut the lap distance short by turning before or at the markers.
	While standing at the starting point, tell the participant: *"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. When the 6 minutes are up I will tell you to stop. I want you to stop right where you are and I will come to you. Start now, or whenever you are ready."*
Testing	Position the participant at the starting point.

	As soon as the participant starts to walk, start the timer. Do not walk with the participant. Pulse oximetry should be measured continuously.
	During the walk, do not talk to anyone else except the participant. Use an even tone of voice when using the standard phrases of encouragement. Watch the participant and do not get distracted. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Directly observe the 02 saturation/heart rate value twice per lap. **IMMEDIATELY STOP THE TEST IF O2 SATURATION FALLS TO ≤ 80%.**
	Standard phrases of encouragement: After the first minute, tell the participant: *"One minute has passed. You have 5 minutes to go"* When the timer shows 4 minutes remaining, tell the participant: *"Two minutes have passed. You have four minutes to go."* When the timer shows 3 minutes remaining, tell the participant: *"Three minutes have passed. You are halfway done."* When the timer shows 2 minutes remaining, tell the participant: *"Four minutes have passed. You have only 2 minutes left."* When the timer shows only 1 minute remaining, tell the participant: *"Five minutes have passed. You have only 1 minute to go."* When the timer is 15 seconds from completion, say: *"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."*
	Walk the participant (if able) to the room where you started. When the participant sits down start the elapsed timer.
	Take a post-walk blood pressure, but be sure to notice the HR shown on the oximeter when the elapsed timer indicates the first minute has passed. Record the post-walk heart rate.
	Record the post-walk dyspnea score using the Borg scale. See Appendix 1
	During post walk recovery, record the heart rates and SpO2 at 1 and 2 minutes.
	Record the number of laps from the counter (or tick marks on the worksheet) and the additional distance covered (the number of feet in the first (if walk was started from any point on the 6m walk track other than the starting point) and final partial lap) using incremental markers on the wall or floor as distance guides.
	Calculate and record the total distance walked.
	Congratulate the participant on good effort, and offer a drink of water.

	Note: If the participant stops during the test, and needs to rest, say, "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the participant stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue, or if O2 SATURATION ≤ 80%., take a chair over the participant to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and reason for stopping prematurely.

39.5 Procedure Notes

1. Sources of variability
   There are many sources of variability in this test including height, age, weight, disease, and musculoskeletal disorders. Procedural sources of variability will be controlled as much as possible.
2. Practice walks
   Practice walks are not utilized for PVDOMICS. The technician can demonstrate if required.
3. Instructions and encouragement
   The script provided in this document will be used to explain the test and instruct the participant. Standardized phrases of encouragement will be limited to declaring the elapsed time and the time remaining each minute during the test.
4. Supplemental O2
   See above section 39.4 for guidelines of oxygen administration. The type of O_2 delivery device/cannula will also be noted on the report. The participant should be transitioned to an E cylinder from their own oxygen system.

39.6 Equipment, Supplies and Location:

The 6MWT will be performed indoors, along a flat, long, straight, corridor with a hard surface with little traffic. Ideally, the walking course should be approximately 30 meters (100 feet) in length. Track lengths as low as 50 feet have been found to be acceptable.

The course will be marked with visible markers (e.g., traffic cones or marks on the floor). A starting line, which marks the beginning and end of each lap, will be marked on the floor. Incremental markers of distance on the floor or wall (e.g., every 10 feet) help to measure the distance walked. Record length of track utilized for testing.

The following equipment is used for the 6MWT:

1. Stopwatch
2. Mechanical counter or other method to count laps
3. Markers to identify the course
4. Borg Dyspnea Scale (appended to end of Form 133-6MWT)
5. Chair or wheelchair
6. Form 133-6MWT data form on a clipboard
7. Masimo pulse oximeter, lanyard and forehead probe (one set provided by DCC)
8. Self-adhesive gauze (e.g., Coban) or headband (not provided by DCC)
9. Sphygmomanometer and appropriate sized cuffs

10. Access to an automatic electronic defibrillator
11. Telephone

39.7 Test Data Reporting

Test results will be recorded on Form 133-6 Minute Walk and entered into the DCC database. The following items should be recorded on Form 133.

- PVDOMICS Study ID, alpha code and date of test
- Resting variables
- Blood pressure, heart rate, Borg scale, and room air SpO_2, Oximeter probe site (finger, forehead)
- Exercise variables
    - Total distance walked
    - Oxygen usage if applicable
        - Liter flow (continuous or pulsed)
        - Delivery device (nasal cannula, other)
        - Mode of transport (pulled tank or pushed tank using rollator)
    - Borg Dyspnea scale obtained immediately after walk
    - Reason for early termination, if applicable.
    - Cumulative time spent resting (breaks during walk), in seconds.
    - Heart rate and SpO2 obtained at 1 and2 minutes after termination of the walk. Timer to begin when the participant is seated in a chair after the walk is terminated.

39.8 Reference:

1. Task Force Report, ATS/ERS Technical Standard. An official European Respiratory Society/American Thoracic Society. Technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014; 44: 1428-1446.

Appendix 39.1 Modified Borg Rating Scale for Perceived Dyspnea

0	Nothing at all
0.5	Very, very slight shortness of breath
1	Very mild shortness of breath
2	Mild shortness of breath
3	Moderate shortness of breath or breathing difficulty
4	Somewhat severe
5	Strong or hard breathing
6	-
7	Severe shortness of breath or very hard breathing
8	-
9	Extremely severe
10	Shortness of breath so severe you need to stop

MOP Chapter 39: PVDOMICs Six Minute Walk (6MWT)

Summary Sheet for Recent Changes to MOP Chapter 39 and Form 133-6MWT

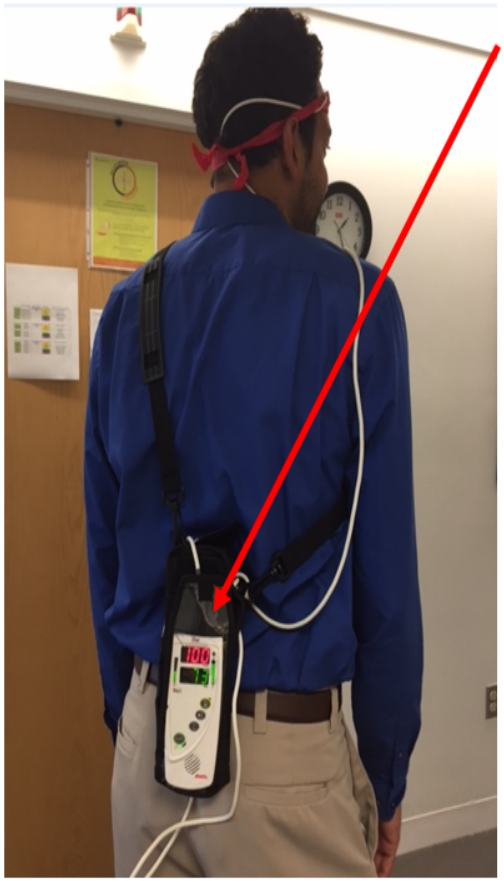
1. Has the participant avoided rigorous exercise for 2 hours? (non-invasive CPET should be done afterwards if scheduled for the same day). If yes, reschedule the test.
2. Ensure that participant is not wheelchair bound, no medical conditions restricts walking, and is safe to perform six minute walk.
3. Is the participant using 4 liters or more of oxygen at rest? If so, ask supervising provider if the participant is safe to do a room air saturation. If not, then mark under Q4 on Form 133 PI feels performing 6MWT would jeopardize safety and do not perform 6MWT.
4. Start 10 minute rest period (if using oxygen, remove oxygen after 5 minutes-need oxygen off for 5 minutes to do room air saturation).
5. Check blood pressure, Borg dyspnea score and check room air saturation after ten minutes of rest. Make sure to mark the type of oximeter used (finger, ear or forehead). If any circulatory disorders (i.e. scleroderma) a forehead or ear probe must be used.
6. Pre–test oxygen saturation: To be performed during 10 min pre-test rest period
    a. If oxygen saturation on room air or home O2 flow is 88% or less at rest, then add additional supplemental O2 to achieve a resting O2 saturation of 92% or greater (unless participant has congenital heart disease), then proceed with 6MWT as per MOP Chap 39.
    b. If room air oxygen saturation is 89% or greater at rest, than perform 6MWT on room air or home O2 flow rate as prescribed, or O2 flow level as administered on prior 6MWT.
    c. If unable to achieve a resting O2 saturation of 89% or greater with supplemental oxygen then contact physician provider for approval to perform 6MWT safely.
    d. After making change in O2 administration wait for a minimum of 2 minutes after change to ensure O2 saturation is stabilized.
7. Record baseline Pre-test Sp02 Q12 on Form 133 (this is completed only if your participant is using oxygen for the 6MWT).
8. If using oxygen, you must convert participant to an E cylinder that can be pushed or pulled using a rollator.
9. **A continuous pulse oximetry reading is needed for all 6 MWT**. The pulse ox used should be less than 2 lbs in weight and transported by the participant using a lanyard, fanny pack or other carrying device. The participant should not be able to see the pulse ox readings. The person administering the 6WMT should be able to see the readings easily. Again, if the participant has circulatory issues a forehead or ear probe must be used.
10. Proceed with the test as per MOP Chapter 39. If the participant has chest pain, intolerable dyspnea, leg cramps, diaphoresis, is ashen, near syncope, syncope, falls or oxygen saturation drops to 80% or below, **STOP THE WALK IMMEDIATELY**. The supervising physician should be notified and emergency care provided as directed. Record the reason for test termination on Q22 on Form 133.

MOP Chapter 39: PVDOMICS Six Minute Walk (6MWT) Addendum

Summary Sheet for Recent Changes to MOP Chapter 39 and Form 133-6MWT

1. Check if participant avoided rigorous exercise for 2 hours. Non-invasive CPET should be done afterwards if scheduled for the same day. If yes to exercise, try to reschedule the test.
2. Ensure that participant is not wheelchair bound, no medical conditions restricts walking, and is safe to perform 6MW.
3. Is the participant using 4 liters or more of oxygen at rest? If so, ask supervising provider if the participant is safe to do a room air saturation. If not, then mark under Q4 on Form 133 PI feels performing 6MWT would jeopardize safety and do not perform 6MWT.
4. Start 10 minute rest period (if using oxygen, remove oxygen after 5 minutes-need oxygen off for 5 minutes to do room air saturation).
5. Check blood pressure, Borg dyspnea score and check room air saturation after ten minutes of rest. Identify type of oximeter probe used: forehead [is preferred], finger, ear or forehead). If any circulatory disorders (i.e. scleroderma) a forehead or ear probe must be used.
6. Pre–test oxygen saturation: Performed during 10 min pre-test rest period
    a. If oxygen saturation on room air or home O2 flow is 88% or less at rest, then add additional supplemental O2 to achieve a resting O2 saturation of 92% or greater (unless participant has congenital heart disease), then proceed with 6MWT as per MOP Chap 39.
    b. If room air oxygen saturation is 89% or greater at rest, then perform 6MWT on room air or home O2 flow rate as prescribed, or O2 flow level as administered on prior 6MWT.
    c. If unable to achieve a resting O2 saturation of 89% or greater with supplemental oxygen contact physician provider for approval to perform 6MWT safely.
    d. After making change in O2 administration wait for a minimum of 2 minutes after change to ensure O2 saturation is stabilized.
7. Record baseline Pre-test Sp02 Q12 on Form 133 (completed only if participant is using oxygen for the 6MWT).
8. If using oxygen, convert participant to an E cylinder that can be pushed or pulled using a rollator.
9. **Use continuous pulse oximetry for all 6 MWT**. Use study-provided Masimo pulse oximeter, lanyard and forehead probe (preferred). Participant should not see the pulse ox readings. The person administering the 6WMT should be able to see the readings easily. Refer to MOP Chapter 39 for placement. Try not to use an ear probe, if possible due to greater chance of motion, however, persons with circulatory issues may need to have the ear probe used.
10. Proceed with the test as per MOP Chapter 39. If the participant has chest pain, intolerable dyspnea, leg cramps, diaphoresis, is ashen, near syncope, syncope, falls or oxygen saturation drops to 80% or below, **STOP THE WALK IMMEDIATELY**. The supervising physician should be notified and emergency care provided as directed. Record the reason for test termination on Q22 on Form 133.

Correct Placement of Masimo Oximeter and Strap (lanyard)



Positioning of the Masimo forehead probe and lanyard

1. The lanyard should be placed across the patients body with the oximeter readout on the back of the patient which will remove it from their view

2. The cord coming from the oximeter to patients forehead should be clipped to the patients shirt/blouse (as shown Pic. 2) to avoid the cord from dragging or becoming a tripping hazard.

3. The cord should run behind the patients ear and should be positioned between the hairline and the eyebrow (may have to slightly move to improve signal strength).





Chapter 40. Electrocardiogram (ECG)

This manual chapter is intended to serve as both a training and a reference document for persons who perform the ECG for the PVDOMICS study using standardized procedures and techniques. This will aid in obtaining accurate test results and a safe testing environment.

The Cardiovascular Physiology Core (CPC) will review all PVDOMICS participants' ECG reports submitted to the core laboratory. The CPC is located at the Cleveland Clinic in Cleveland, Ohio and is under the direction of W. H. Wilson Tang, M.D.

40.1 Overview

An electrocardiogram is a routinely used, non-invasive procedure that allows physicians to monitor and assess the electrical activity in the heart. It is recognized as the gold standard for detecting heart arrhythmias and conduction delays[1].

All study participants will receive an ECG. The ECG must be done for the PVDOMICS study. Results from a prior ECG, even if recent, cannot be used.

40.2 Site and Technician Certification

Before ECG studies may be performed on subjects, each site will be required to complete the following list of requirements:

1. Establish two or three primary contact persons at their site who will be responsible for communication with and transmission of ECG data to the Study Coordinator. The Study Coordinator will be responsible for transferring ECGs to the Data Coordinating Center (DCC) through the secure portal.
    1.1. Each of these individuals must provide the PVDOMICS Study Coordinator with contact information for the PVDOMICS Cardiovascular Physiology Core (CPC) via a completed Form 10-Study Personnel. The Study Coordinator will be responsible for entering this information into the study database.
2. Review and become familiar with this MOP chapter and study procedures.
    2.1. Ensure that this chapter of the Manual of Operations (Chapter 40) and Form 245 (Center Electrocardiogram Data Transmittal Form) are available and easily accessible to all individuals who will perform an ECG for the PVDOMICS study.
    2.2. Each individual who will perform an ECG for the PVDOMICS study should review the ECG Study Training Webinar video and slides available on the PVDOMICS website.

3. Provide the name of the manufacturer(s) of the ECG cart(s) that will be used for PVDOMICS. This information must be added to Form 20 (Equipment for PVDOMICS Testing Registration Form) and entered into the database.

    3.1. Any change of equipment must be reported to the study coordinator so that they can update the database to reflect the most current information.

4. Submit two ECG printouts from a healthy adult subject as per the transfer protocol found below (Section 40.9). The two ECGs must be from different subjects on different days.

    4.1. Sites will be evaluated based on their ability to: (1) follow a site qualification protocol, (2) generate reproducible ECG data, and (3) transmit data to the CPC.

    4.2. Test results will be compared to data available on normal individuals from the CPC laboratory and the published literature.

    4.3. It is suggested that each local site limit the number of ECG technicians who will be performing ECGs for the PVDOMICS study. This will diminish variability in testing.

5. Receive approval from the CPC to proceed with testing of subjects.

    5.1. Sites should await feedback from the CPC laboratory confirming that their site has qualified prior to scheduling study patients for testing.

40.3 Participant Contraindications and Safety

ECG is a non-invasive procedure with little to no risk. If there is any question as to the suitability of the participant to receive an ECG, the site PI should be contacted.

Personnel performing the ECG for the PVDOMICS study should be trained in the appropriate placement of the electrode leads, competent at using the necessary equipment, and familiar with this MOP. They must also be certified in basic cardiac life support and able to recognize abnormal rhythms and ST segment changes indicative of acute myocardial infarction (MI) on an ECG.

40.4 Equipment and Supplies:

1. ECG system

    1.1. Instrumentation should meet the specifications set by the American Heart Association (AHA) [1-4], including a continuous display of a minimum of three leads.

    1.2. Instrumentation must have the capacity to print a copy of a 12-lead ECG.

1.3. System settings should be as follows for the 12-lead ECG:

Report Sequence	Standard
Rhythm Leads	I
Gain	10
Report Format	4x2.5R1
Number of copies	1
Delete ECG after transmission	NO
Autosave ECG	YES
Interpretation	YES
Print Interpretation	YES

2. Resuscitation cart [4]
    2.1. Airway management equipment
    2.2. Defibrillator
    2.3. Airway suction apparatus, tubing and disposable ends
    2.4. Emergency medications (e.g., epinephrine, lidocaine, nitroglycerine)

40.5 Equipment Quality Control

The ECG machine should be regularly checked for quality control and maintained as per the manufacturer's recommendations.

40.6 Participant Preparation (Pre-Test Instructions):

1. Identify participant using two separate identifiers.
2. Briefly explain the procedure and answer the participant's questions before the test.
    2.1. Explain that the test requires access to the chest wall as this may be uncomfortable for some participants.
3. Obtain informed consent (if applicable in your institution) by personnel who can accurately describe the test and potential risks.
4. Skin preparation is essential to reduce surface resistance and ensure a good ECG signal.[2,3,4] The following steps may be used at the discretion of the personnel performing the ECG.
    4.1. Use alcohol wipes to remove surface oils.

4.2. Shave hair, when applicable.

4.3. Abrade skin with fine emery cloth, 240 grit sandpaper or other appropriate mechanical skin preparation device.

40.7 ECG electrode placement:

1. Instruct the participant to lie flat on their back for the duration of the procedure.

1.1. If the participant cannot lie flat because of orthopnea or other physical limitation, have the participant lay as flat as possible while still maintaining participant comfort.

2. Use a drape across the chest for participant comfort, both for modesty and to prevent the participant from becoming chilled during the test.

3. The standard 10-electrode configuration will be used for electrode placement when obtaining a 12-lead ECG.

3.1. When placing electrodes on the chest of female participants, always place electrodes under the breast tissue rather than on the breast. This consideration supersedes other placement criteria. Take care to maintain participant comfort and avoiding "cupping" the breast tissue during electrode placement.

3.2. The right arm (RA) and left arm (LA) electrodes should be placed on the ventral side of the arm, 2 to 3 inches above the wrist.

3.3. The right leg (RL) and left leg (LL) electrodes should be placed on the anterior side of the leg, 2 to 3 inches above the ankle.

3.4. The precordial leads (V1-V6) are placed as below (see Figure 40.7.1):

V1: 4th intercostal space at the right sternal border

V2: 4th intercostal space at the left sternal border

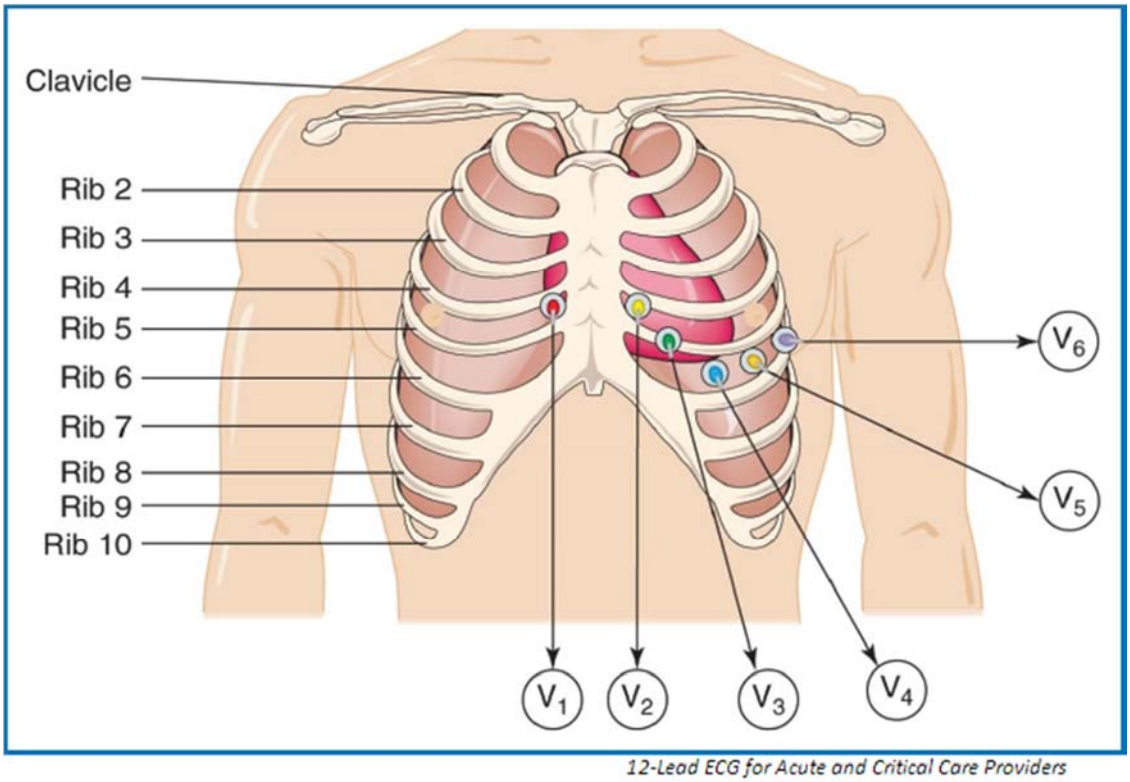
V3: midway between V2 and V4

V4: 5th intercostal space at the midclavicular line

V5: 5th intercostal space, midway between V4 and V6

V6: 5th intercostal space at the midaxillary line

Figure 40.7.1: Precordial Lead Placement for 12-lead ECG



12-Lead ECG for Acute and Critical Care Providers
2006, Pearson Education, Inc. Upper Saddle River, NJ

40.8 Procedure:

1. Enter participant data into the ECG machine as per the table below. If your specific machine does not list one of these fields, skip over it. If your specific machine has a field not listed below, leave it blank. DO NOT include any of the following in any field: first or last name, initials, medical record number, social security number or date of birth.

Field Listed on ECG Machine	**Information Entered by the ECG Technician**
New Patient?	YES
Last Name	PVDOMICS
First Name*	Enter 2 digit alphacode assigned to this participant. *(Obtain this ID from local site study coordinator.)*
Participant ID*	Enter 6 digit Identification Number assigned to this participant. *(Obtain this ID from local site study coordinator.)*
Secondary ID	Enter 2 digit alphacode assigned to this participant. *(Obtain this ID from local site study coordinator.)*
Pacemaker	Select YES or NO as appropriate
Gender	Select MALE or FEMALE as appropriate
Height	Enter Height in centimeters, rounded to the nearest whole number. *Note: if height measurement is recorded on Form 120 Study Visit Vital Signs (taken on day one), record that height rounded to the nearest whole number.*
Weight	Enter Weight in kilograms, rounded to the nearest whole number. *Note: if weight measurement is recorded on Form 120 Study Visit Vital Signs (taken on day one), record that weight rounded to the nearest whole number.*
Race	Select the appropriate predefined race category (as *self-reported* by the participant).
Age	Enter participant's age as a whole number.
Referring Physician	Enter the local site PVDOMICS Study PI.
Reason for Test	RESEARCH
Technician*	Select or enter the technician's PVDOMICS username or other ID.**
Location	Leave blank if system allows, or leave the default setting in place.

*Required fields

** If the technician has a PVDOMICS username, that should be used. If not, their normal identification should be selected. Be sure that the technician's name selected matches the technician actually performing the test and the technician name listed on Form 245.

2. Instruct participant to breathe normally but not to move their extremities.
3. Ensure that a good quality signal is being recorded.
4. Press the "Start/Stop" key on the ECG machine to initiate data collection. The machine will automatically print a copy of the ECG and store the data if another copy needs to be printed later.
5. Record extraneous movement or tremors, extreme obesity and any medications the participant is currently taking that may cause bradycardia on Form 245 (Center Electrocardiogram Data Transmittal Form) as these circumstances may explain abnormal results.

    5.1. Extreme obesity will be judged on a case-by-case basis by the local site PI or the technician performing the procedure and should be noted if the participant's weight or excess body tissue may have interfered with the results of the test.

40.9 ECG Transmission to the Cardiovascular Physiology Core (CPC):

De-identified ECG reports will be sent to the CPC. The only identifiers on the ECGs submitted to the CPC will be the participant's PVDOMICS ID and alphacode. Each report will be scanned/converted into Portable Document Format (PDF) and sent securely to the CPC.

1. Verify that the participant's 6-digit PVDOMICS ID number, their 2-digit alphacode and the date of testing are included on the ECG printout.

    1.1. If one of these three components are missing, use a black pen to write the missing component on the ECG printout before converting it into a PDF file.

2. Verify that no other identifiers are included on the ECG printout.

    2.1. If any other identifiers exist (e.g. participant's date of birth or medical record number), obscure that identifier using a black marker or other means before converting the ECG printout into a PDF file.

3. Send one PDF copy of the ECG printout to the CPC.

    3.1. Scan ECG printout into a secure computer and save as a PDF file.

    3.2. Name the PDF file according to the convention: **ECG_######_ac_mmddyyyy.pdf** Where "######" is the participant's unique 6-digit PVDOMICS ID#, "ac" is the participant's unique alpha code, and "mmddyyy" is the test date. Do not use any special characters in the file name.

        For example: ECG_987654_AC_12102016.pdf

    3.3. Send PDF file to the DCC as outlined in Manual of Operations Chapter 6-Appendix 1: Securely Transferring Documents to PVDOMICS DCC Server

4. Complete and enter Form 245 Center Electrocardiogram (ECG) Data Transmittal Form into the PVDOMICS Study database or provide the local site study coordinator with the completed form for data entry.

    4.1. Form 245 must be entered into the database before the CPC can enter any results so it is important to get this form entered as soon as possible.

5. File paper copies of participant's ECG and completed Form 245 in their study record.

40.10 References

1. Kadish AH, Buxton AE, Kennedy HL, et al. ACC/AHA clinical competence statement on electrocardiography and ambulatory electrocardiography: A report of the ACC/AHA/ACP-ASIM task force on clinical competence (ACC/AHA Committee to develop a clinical competence statement on electrocardiography and ambulatory electrocardiography) endorsed by the International Society for Holter and noninvasive electrocardiography. Circulation 2001;104:3169-78.
2. Committee on Electrocardiography, American Heart Association. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography: Circulation 1967;35:583-602.
3. Bailey JJ, Berson AS, Garson A Jr, Horan LG, Mcfarlane PW, Mortara DW, Zywietz C. Recommendations for standardization and specifications in automated electrocardiography: bandwidth and digital signal processing. A report for health professionals by an ad hoc writing group of the Committee on Electrocardiography and Cardiac Electrophysiology of the Council on Clinical Cardiology, American Heart Association. Circulation 1990;81:730-739.
4. Kligfield P, Gettes LS, Bailey JJ, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: The electrocardiogram and its technology: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation 2007:115;1306-24.
5. Fletcher GF, Balady G, Froelicher VF, et al. Exercise Standards: A Statement for Healthcare Professionals From the American Heart Association. Circulation 1995;91:580-615.

Chapter 41 PVDOMICS Clinical Center Sleep Study Monitoring MOP

41.1 Purpose and Background:

The relationships of sleep disordered breathing and pulmonary hypertension have been described albeit data which have amassed thus far have been limited from the standpoints of small numbers of participants, limited study design and lack of inclusion and consideration of objective pulmonary hemodynamic parameters. The PVDOMICS study provides an ideal platform to more accurately and comprehensively characterize the relationships of sleep disordered breathing and pulmonary hypertension in a prospective manner. The collection of rich phenotypic data in the setting of pulmonary hypertension as proposed provides a unique opportunity to examine the sleep-pulmonary hypertension inter- relationships on a more granular level.

Abbreviations and acronyms are located at the end of this chapter.

41.2 Logistics for Sleep Reading Core

The Sleep Reading Core under the direction of Dr. Reena Mehra (email: mehrar@ccf.org), is part of the Data Coordinating Center at the Cleveland Clinic, Cleveland, Ohio. Additional contact information can be found in the PVDOMICS Address Directory. All sleep study files will be transmitted to the DCC Sleep Core for scoring of the data and assessment of quality grade.

41.3 Overview

This manual provides standard operating procedures for the management of Overnight Sleep Study Monitoring for the PVDOMICS Study. This manual will address the acquisition, processing, scoring, archiving, and transfer of data; as well as the certification of Clinical Centers. If the participant has had a sleep study within the last year of study enrollment, then it is at the discretion of the Clinical Center as to whether a research sleep study should be performed.

41.3.1 Sleep Study for PVDOMICS Study

Overnight sleep monitoring will be performed routinely in all enrollees to acquire standardized baseline information on sleep disordered breathing and to quantify overnight oxygen saturation patterns. Participants already receiving oxygen supplementation and/or positive airway pressure therapy on a regular, nightly basis will be studied during use of these. A portable home monitoring system (Nox T3, Carefusion) will be used, with recordings of nasal airflow, chest wall and abdominal motion as well as pulse oximetry, heart rate, and position. Each center will purchase the equipment necessary to perform these studies, and study personnel will be trained in the proper application of the devices.

41.3.2 Historical Sleep Study

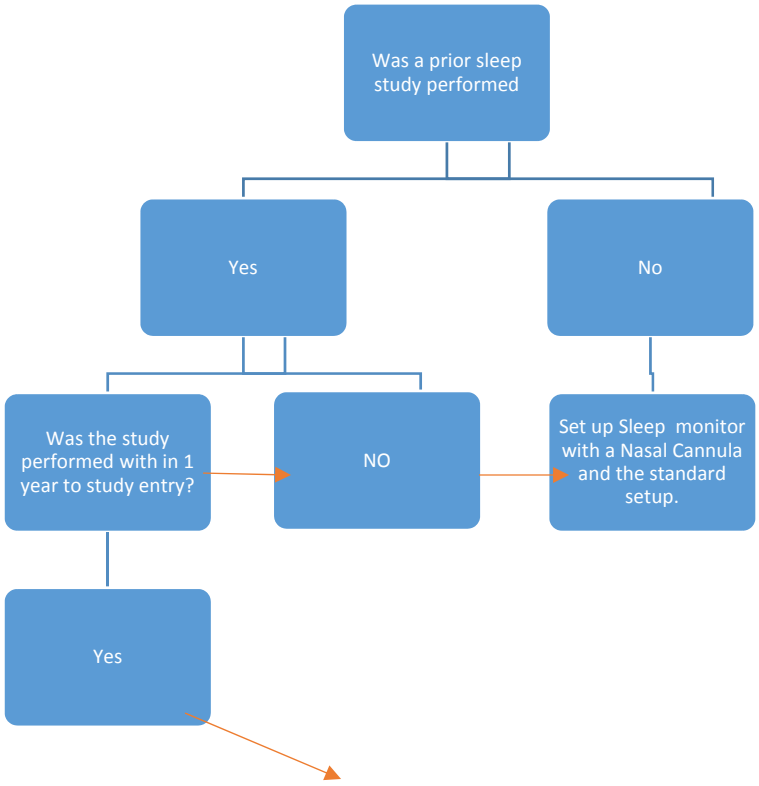
If the participant has had a sleep study within the last year of study enrollment, then it is at the discretion of the Center PI as to whether a research sleep study should be performed. The results of prior sleep studies as well as any additional testing or interventions obtained as a consequence of the portable monitoring will be recorded. The historical sleep study data must meet the PVDOMICS inclusion criteria. Sleep studies will be scored using standardized methods for home sleep apnea testing and will conform to American Academy of Sleep Medicine guidelines. The summary report will be electronically transmitted to the DCC for integration into the database and for statistical analysis. If this information is available on a clinical basis within 1 year prior to study entry and with no change in nighttime oxygen or sleep disorder therapy, and in the opinion of the investigator, no change in participant condition that would impact results, then the clinically available data may be considered adequate for inclusion in the case report form – if available, a copy of that study be

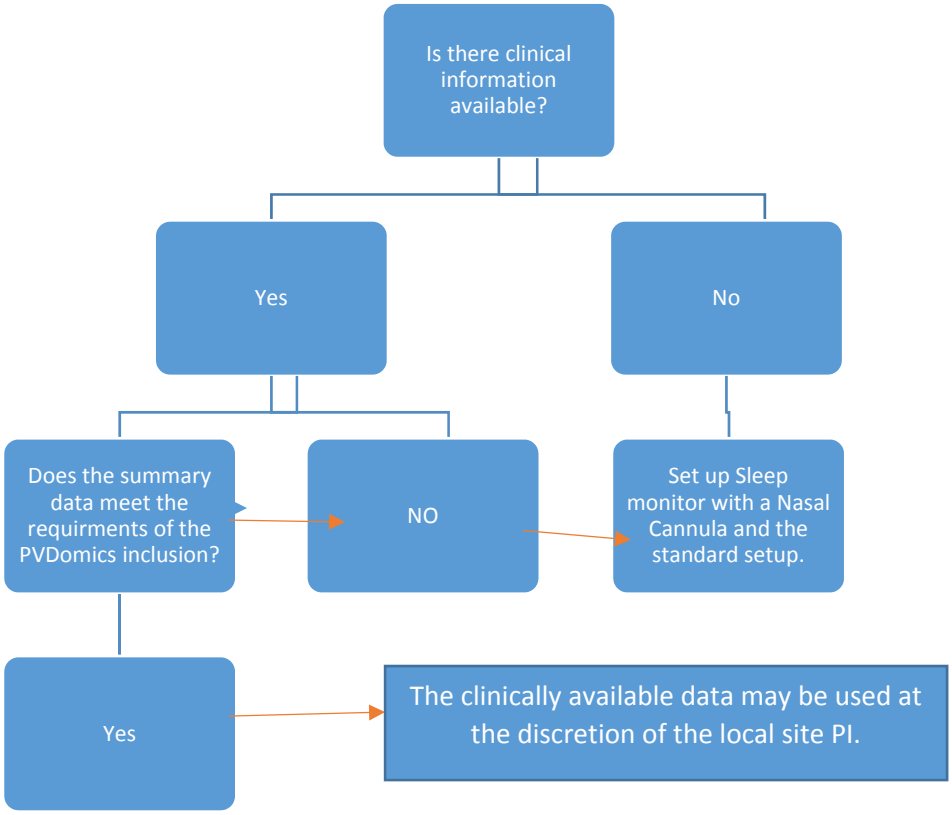
acquired for central review, quality assessment and scoring. Changes in participant conditions that would impact the results include a recent stroke, heart attack, congestive heart failure, and any new diagnosed arrhythmia within 1 year prior to study entry.

PVDomics Historical Sleep Data Summary

Recording Information	**Respiration Overview**	**Saturation**
Recording Date	AHI	Desaturation Index
Recording Duration	ODI	Lowest SpO2
Bed time Start	**Respiratory Indices**	Average SpO2
Bed time Ends	Apnea Index	Desaturation < 90%
Total Time in bed	Hypopnea Index	Desaturation <85%
		SpO2 time <90%
Pulse	**Respiratory Count**	SpO2 time <85 %
Average Pulse	Obstructive Apnea	
Highest Pulse	Central	
Lowest Pulse	Hypopneas	

***See PVDOMICS Historical Sleep Data Form (Form 155)**





See PVDOMICS protocol section 4.2.8 for more information

41.4 Sleep Study Monitoring

All sleep monitoring devices and kits should be labeled with the site's contact information.

* All equipment must be tested and labeled before given to a participant for home use.



Each unit should be labeled with the Center ID and a chronological number. Each unit and unit packaging container should be labeled with the Center address and a contact phone number.

Each participant will be taught how to self-apply the sensors for the portable sleep testing to take place in their own homes. Application of sensors will be demonstrated by PVDOMICS Study-trained certified staff. Staff must be able to follow procedures in this manual in order to produce technically acceptable overnight sleep recordings.

- Participants will be asked to demonstrate their understanding of sensor placement and will be provided with simple pictorial and written instructions.
- Participants will be asked to apply the sensors before bedtime and remove them upon awakening.
- Participants will be asked to bring with them their Positive Airway Pressure device with them to the visit if it's known that they are currently on treatment.
- Participants are to return monitor and kit to the clinical center using local site funds (by mail, courier or direct drop-off)

At the Clinical Center:

- Units are cleaned prior to data processing.
- Data are downloaded to local computers.
- Downloaded study data are reviewed by the local center coordinator to ensure data integrity
- Data file is transmitted electronically to the Sleep Study Core via secure file transfer protocol.

At the Sleep Study Core:

- Sleep Core staff will review data file to determine study quality.
- Each sleep study is scored using approaches that comply with AASM guidelines for standard hypopnea and apnea definitions.
- If Sleep Core staff determines that a study that does not meet minimal quality grades (3 hours of score-able data) the center will be informed and coached, as needed, to help future participants collect quality sleep data.
- Note: a repeat sleep test for the PVDOMICS Study will **NOT** be completed for research purposes.

Certification is essential to ensure that the equipment, software, and recording used in this study are standardized and consistent. All PVDOMICS clinical centers will convert the data file to EDF and transfer the file into the SSH home directory for PVDOMICS on the DCC server.

41.5 Center and Technician PVDOMICS Study Certification

The Sleep Core requires at least one (1) Staff member at each collection Center to be certified to collect for the PVDOMICS study. This certified research staff will be responsible for protocol adherence by any study personnel performing data collection at that Center. Certification must be accomplished prior to the Center performing actual data collection.

Sleep monitoring data collection certification is provided upon demonstration that the staff member has:

- Basic understanding of sleep-specific study objectives and protocol for PVDOMICS.
- Understanding of equipment and application of specific sensors to be used for the sleep monitoring data acquisition.

- Demonstrated compliance with the study protocol for sleep monitoring data collection and data transmittal to the Sleep Core including removal of identifier information and correct re-identification with participant ID and study date.
- Submission of two acceptable overnight pilot studies (non-participant) recordings. Pilot studies on non-participant are conducted to assure that all staff are familiar with the equipment and protocol.

These data file submissions must be correctly de-identified, re-identified with a standard convention, successfully converted to EDF format and placed on DCC server using SSH. This serves both as part of the research staff certification process and as practical experience in using the equipment in the study environment. Certification studies also allow for verification that all sensors and equipment are functioning properly before being used on a study participant, and that post-acquisition treatment and transfer of data is consistent with study protocol. The certifying research staff does need not to actually perform every required task, but will be responsible for the acceptable completion of each task.

To be considered acceptable, the recordings submitted for certification must:

- Have adequate quality signal on each channel (i.e. all electrodes must work) and signals must be relatively free from artifact.
- Reflect sleep monitoring protocol and procedure including placement of electrodes and sensors.
- Have correct study identification as a certification recording using the following format when naming (or re-naming) the recording: {Sleep] [CR][staffusername]_[complete date of study].
  An example of this format would be:

  Sleep_CRsmiths_10292016
- The electronic recording file must be accompanied with paperwork that matches this naming convention and additionally includes the technician identification and equipment ID.
- Include Form 152-Download and File Transmission.

41.6 Equipment and Supplies

After written informed consent is obtained, participants will be instructed in the use of the Nox T3 portable monitor. This battery-operated device can store data at 200 Hz, with 1 GB of storage capacity allowing storage of data from up to 1-24 hours of recording. The local center should contact their Research Administrator for information on insurance coverage for the Nox T3 device to cover any loss, stolen, or damaged devices. Any device insurance policy must be covered using local Center funds. The sleep monitor service agreement will need to be in good standing, if expired the agreement will need to be renewed using local Center funding.

The following supplies need to be purchased using local Center funds:

Nox-T3 portable sleep monitor- The sleep monitoring device and accessories should be stored in a clean, dry space. The device is not waterproof. Each device will be tested for a minimum of 4 hours during normal work hours to assure all signals are working accurately before sleep data collection begins.



- **<u>Nox Cannulas/ Filter Tube connectors</u>**- for measurement of flow for apnea detections.
  If a filter is not directly attached to the cannula then the connecter will need to be purchased.
  The cannula will be disposed of after each single participant use. A <u>new cannula</u> will be sent home with each participant.
  Part Number: 69594 40 Nox Cannula with Filter – Adult

- **<u>ECG leads and electrodes</u>**- Single use electrodes will be snapped on three wire leads to allow the recording of ECG activity on two channels. One electrode shall be placed approximately 3 – 5 cm. (2 finger breadths) below the midpoint of the right clavicle and one below the midpoint of the left clavicle. One electrode shall be placed approximately on the lower left abdomen within the rib cage frame (intercostalspace) 3 – 5 cm. The ECG data are collected at a sampling rate of 200Hz. (.ie Kendall™ Foam electrodes). The snap leads may be purchased at any medical supply chain (ie. MVAP).





- **<u>NOX RIP belts</u>** = Respiratory Efforts are monitored utilizing respiratory inductance plethysmography (RIP), secured around the thorax and abdomen. The sensors are snapped into the designated areas on the portable sleep monitor. Measure the circumference around the participant

chest (belt circumference will be centered under the armpit) and abdomen (belt circumference will be centered over the belly button) to determine what size belt is needed.

Part Number: 69590 Nox RIP Belts, Disposable - Small (belt size 50-85 cm (20-34 in)
Part Number: 69591 Nox RIP Belts, Disposable - Medium (belt size 75-125 cm (30-49 in)
Part Number: 69592 Nox RIP Belts, Disposable - Large (belt size 100-170 cm (39-67 in)
Part Number: 27641-001 14 Nox RIP Belts, Disposable - Extra Large (belt size 125- 210 cm (49-82 in)

- **Nonin and Wrist Ox**= Pulse oximetry is measured through a DC channel and is designated SaO2 on the montage via a reusable fingertip probe. The sensor is placed on the index finger (preferably on the non-dominant hand). The sensor is plugged into the designated area on the wrist device.
  Part Number: 69466 1 WristOx2TM, Model 3150

- **Mask pressure tubing and a CPAP adapter** = For participants using **Positive Airway Pressure (PAP) Flow** in the study, flow should be measured from the output signal from the PAP device, which interfaces with a port on the PAP mask and tubing that connects to the Nox T3 device.
  Part Number: 22990-001 50 CPAP Mask Tubing and TRP-740 adapter

- **Batteries**= AA (Nox sleep monitor) and AAA (Nonin pulse oximeter) batteries (alkaline and Lithium)

- **Scanpor** = Paper tape that will be used to help secure leads.



- **Sandwich bags** = Bags will be used to separate wires for easy home application.

41.7 Participant Contradictions and Safety

Sleep monitoring is a non-invasive procedure with little to no risks. If there is any question as to the competency of the participant to receive and take home a NOX-T3 portable sleep monitor, the Center PI should be contacted.

Personnel instructing/performing the sleep monitor setup for the PVDOMICS study should be trained in the appropriate placement of the electrode and leads, competent at using the necessary equipment, and familiar with this MOP.

Sleep Monitor Initialization starts on next page

41.8 Sleep Monitor Initialization

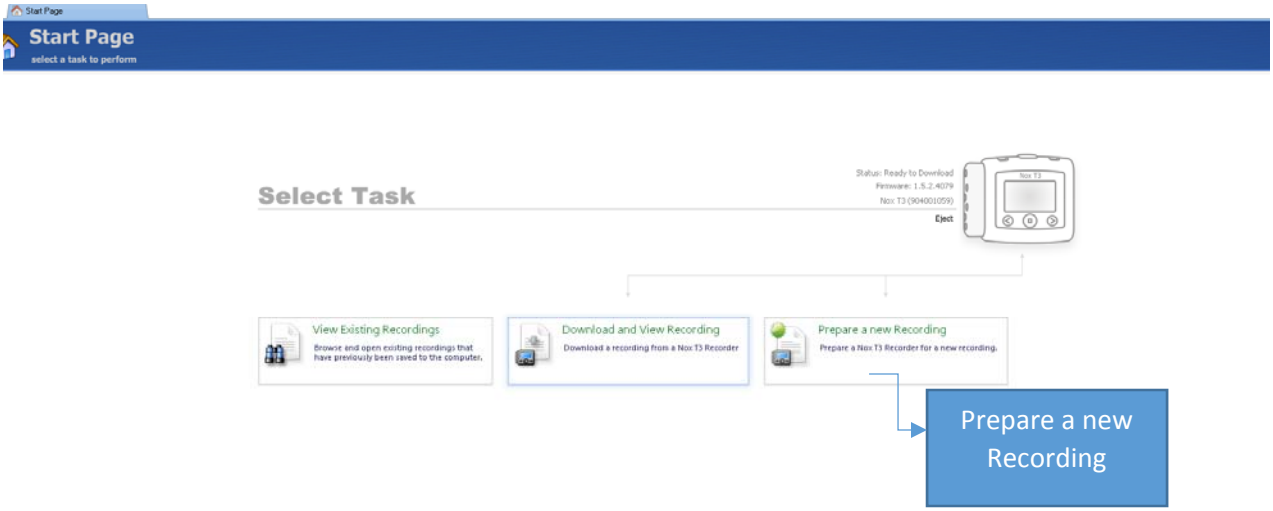
The Noxturnal® software interacts with the NOX-T3 device. Software version **4.4.214926** will need to be installed before proceeding. Review the system requirements and contact your administrator if installation privileges are needed.

41.8.1 Preparing a Study Using the Noxturnal® Software: To run the Noxturnal® application, double-click on the desktop icon or click on the application icon in the Windows start menu. To close the application either click on the **X** in the top right corner, or on the File menu choose **Exit**.



41.8.2 Preparing a Recording: The **Start Page** sheet in which the user interfaces with the T3 devices and the recorded data. This sheet also guides the user through the most common tasks to perform in the application.

41.8.3 Prepare a new Recording: To start a new recording, select this option. A configuration wizard will guide the user through the configuration process.



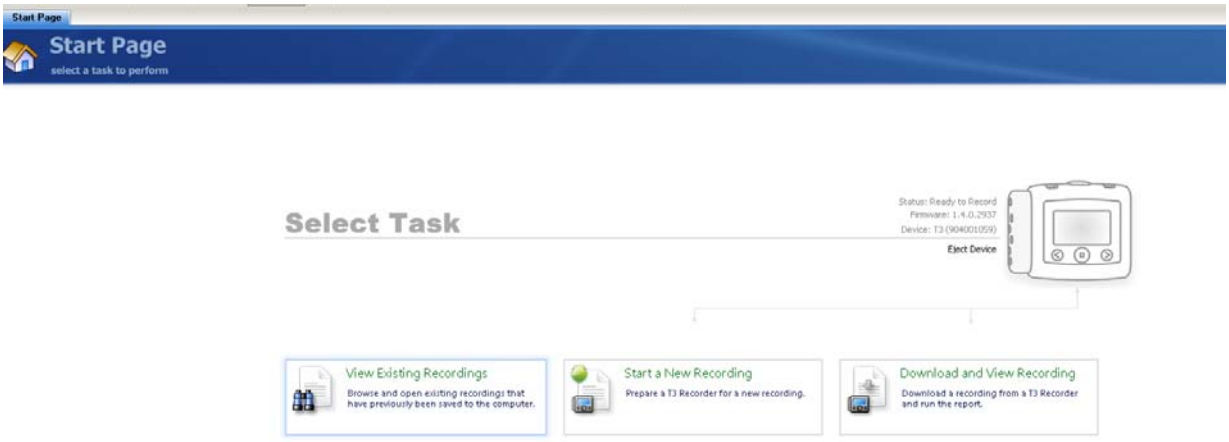
41.8.4 Connecting the T3 device: Start by connecting a T3 device to a USB cable to the computer. The USB connector is placed under the battery lid. To open the battery lid, press with a pen or similar tool on the battery lid pin and slide the battery lid downward.

Refer to Preparing the NOX-T3 for new recordings:

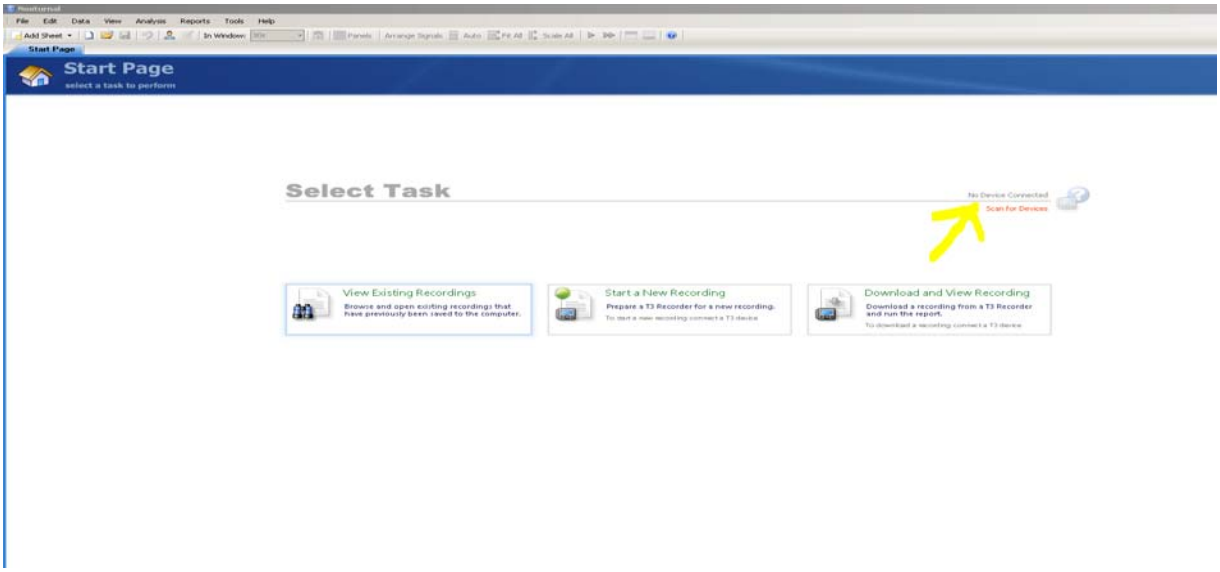
http://www.carefusion.com/our-company/video-gallery?video=4770674290001



41.8.5 Noxturnal® automatically detects the device and shows information about the device in the top right corner of the **Start Page**. Detection can take 2-4 seconds.

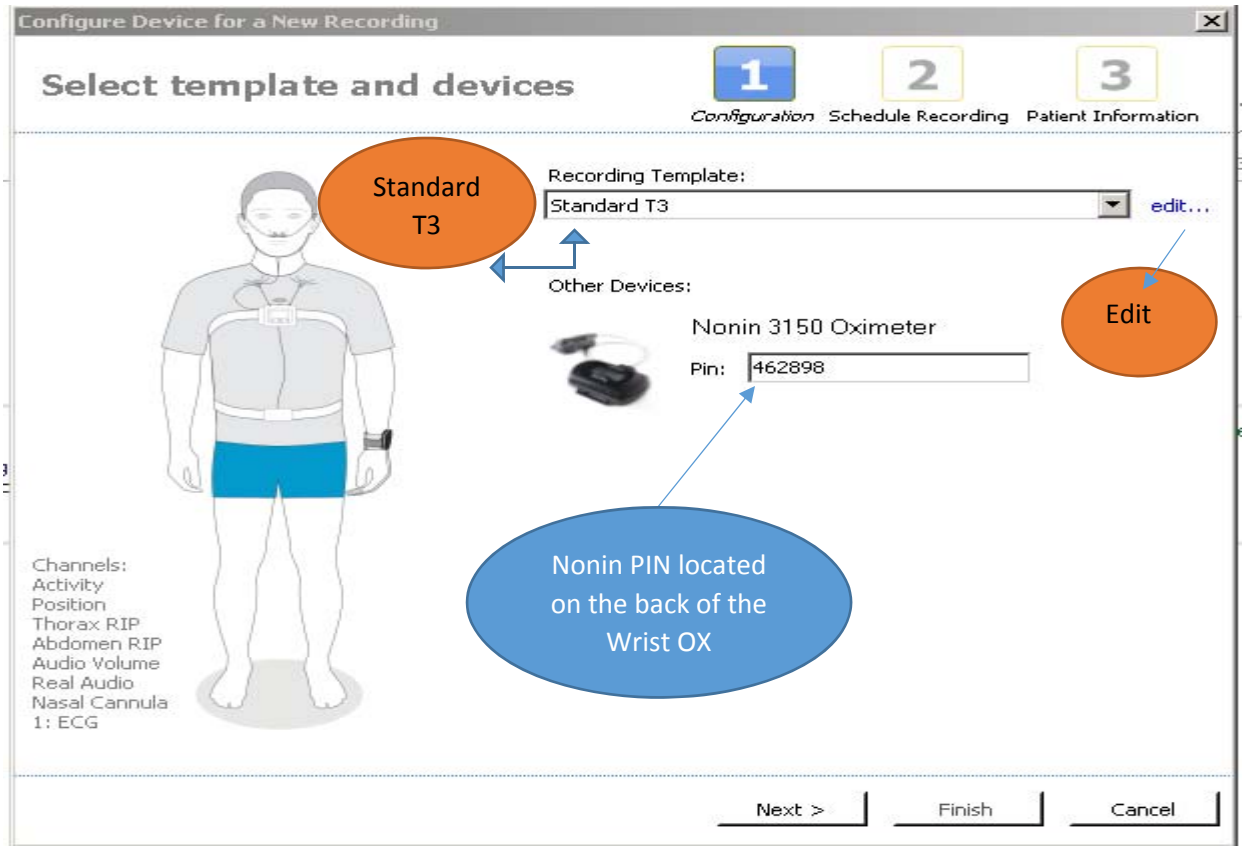


If the device is not detected, click the **Scan for Devices** link located on the start page of the **Noxturnal® Software**.

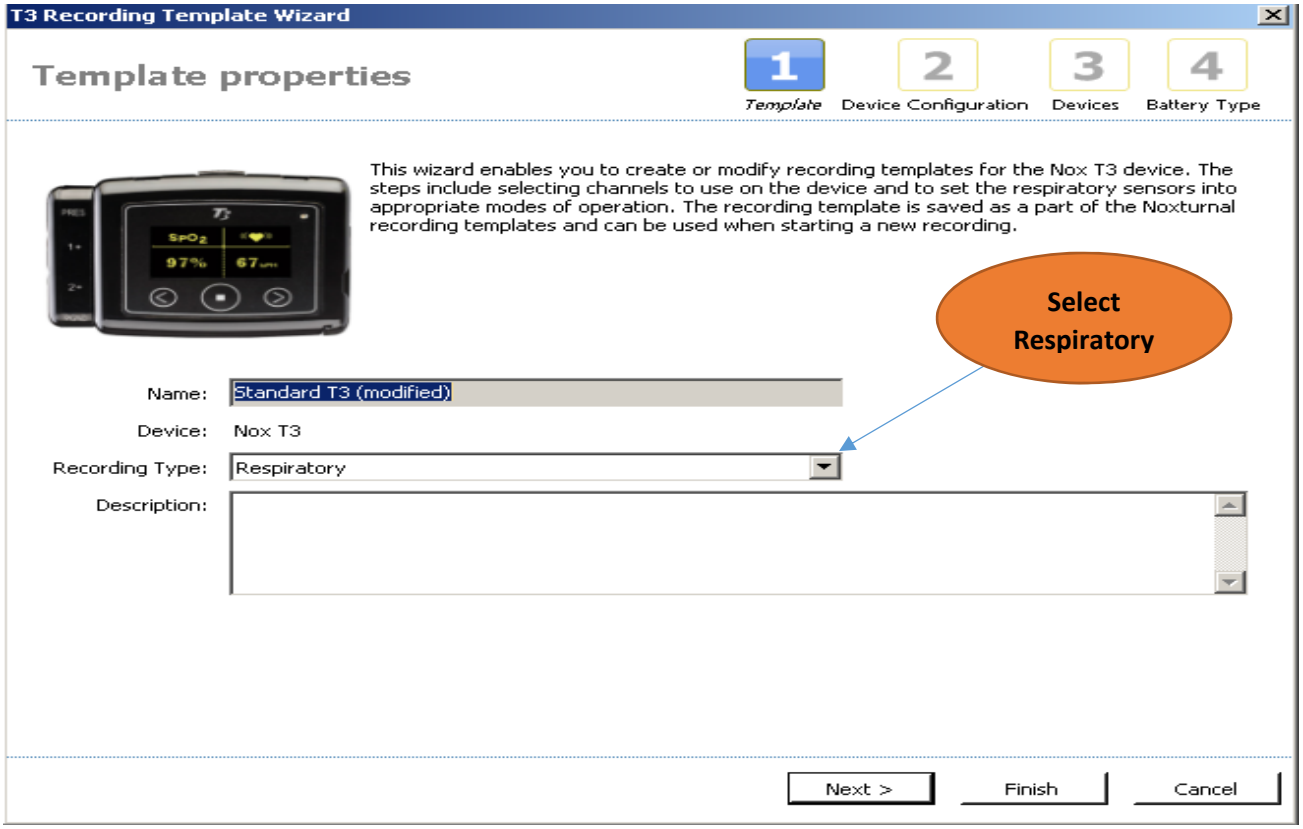


41.8.6 Click **Prepare a New Recording** to configure the device for a new recording. A wizard opens up which will guide you through configuring the T3 device.

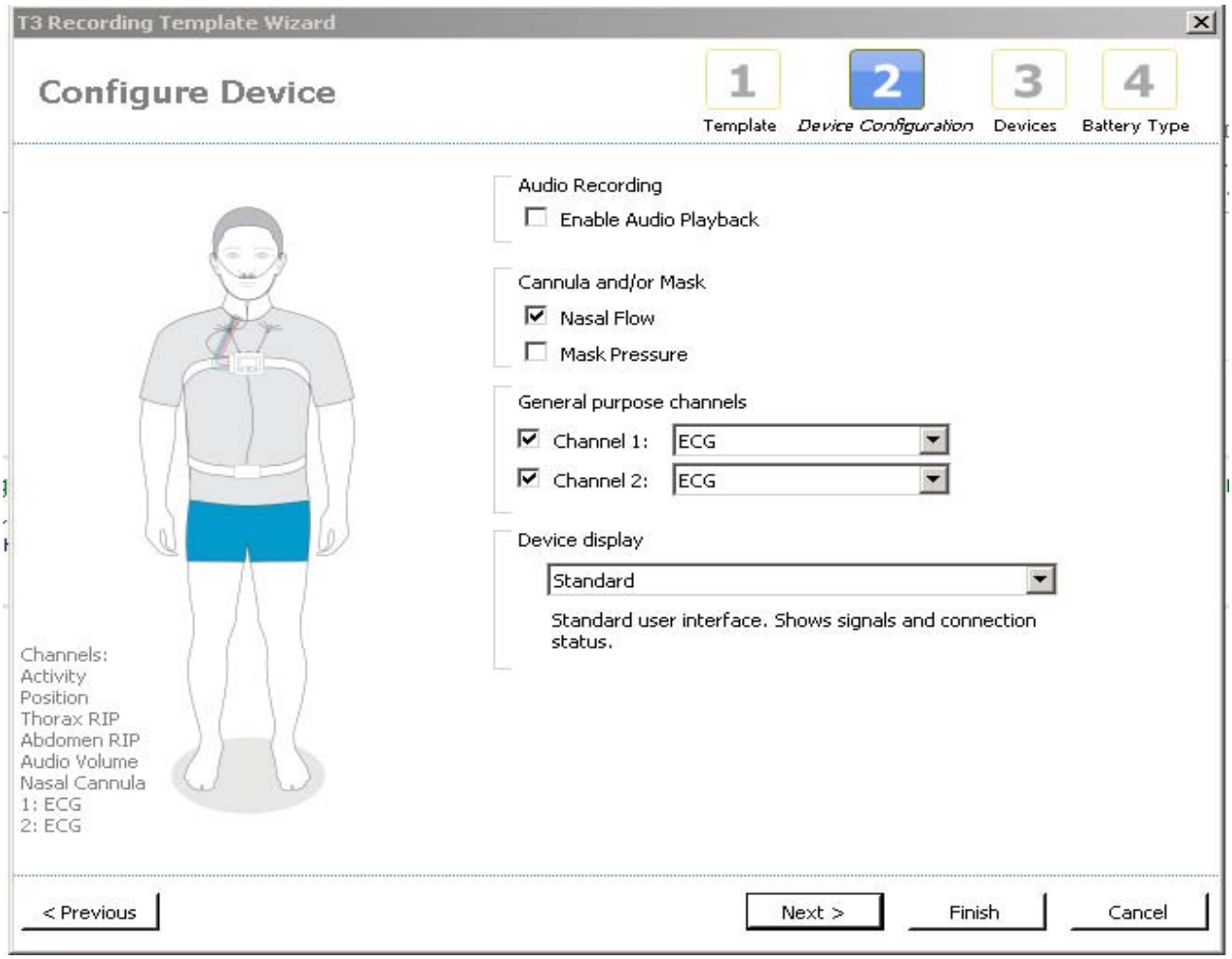
41.8.7 Select the recording Template, as **Standard T3,** and enter the **PIN** located at the back of the Wrist Ox and then select **edit** to modify the channels.



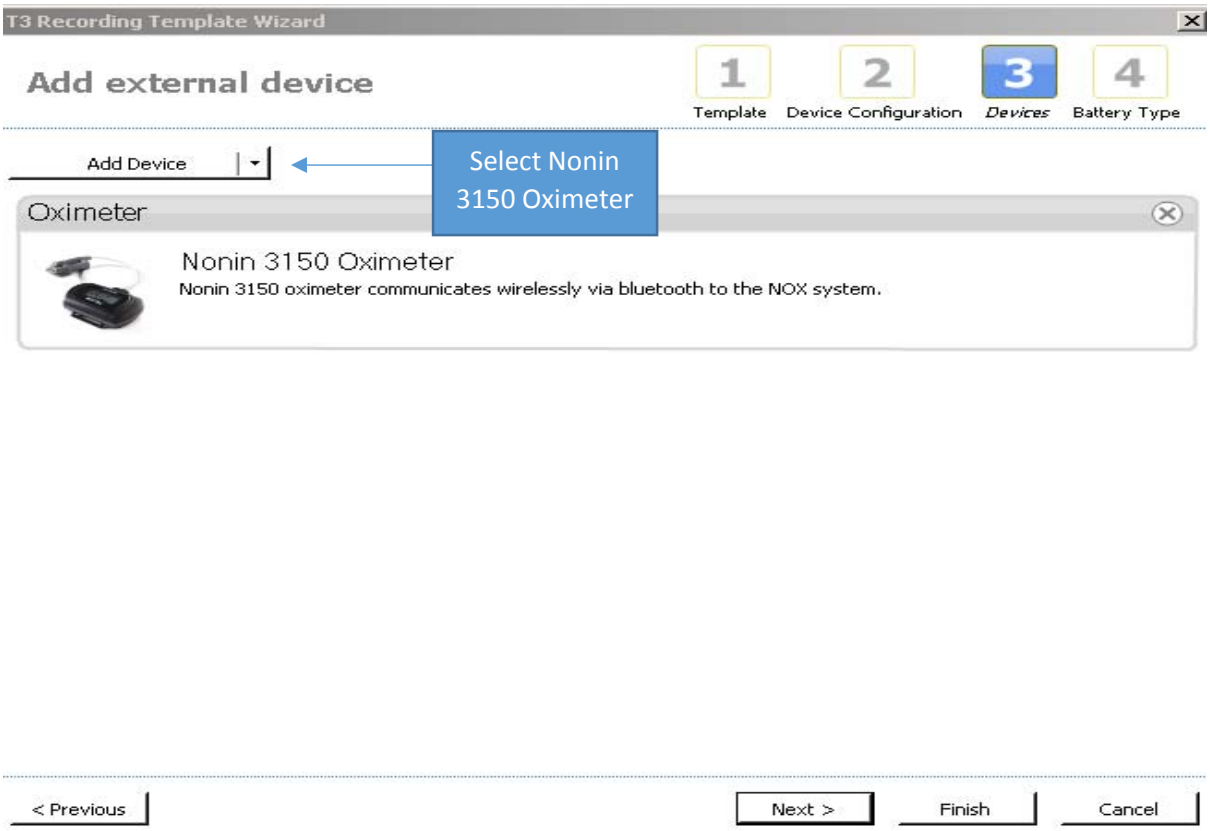
41.8.8 Select Recording type as **Respiratory** from the drop down. Then select **Next**.



41.8.9 Configure Device with Nasal Flow: Select Nasal Flow, Channel 1 ECG and Channel 2 ECG and uncheck Audio Recording, and **Standard** for Device display.

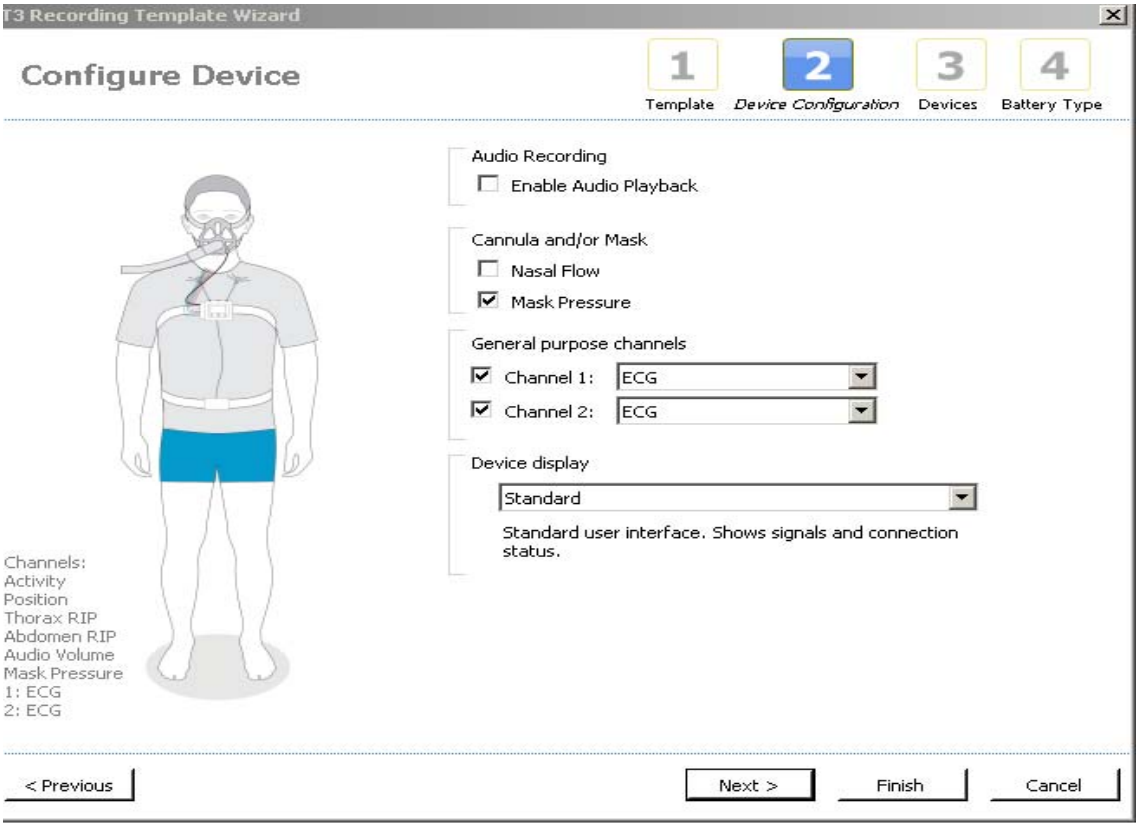


41.8.10 Add external Device: Select from the drop down the type of Nonin oximeter device that will be used. **Once the oximeter has been paired to the device, the device and oximeter will only interact with each other.**



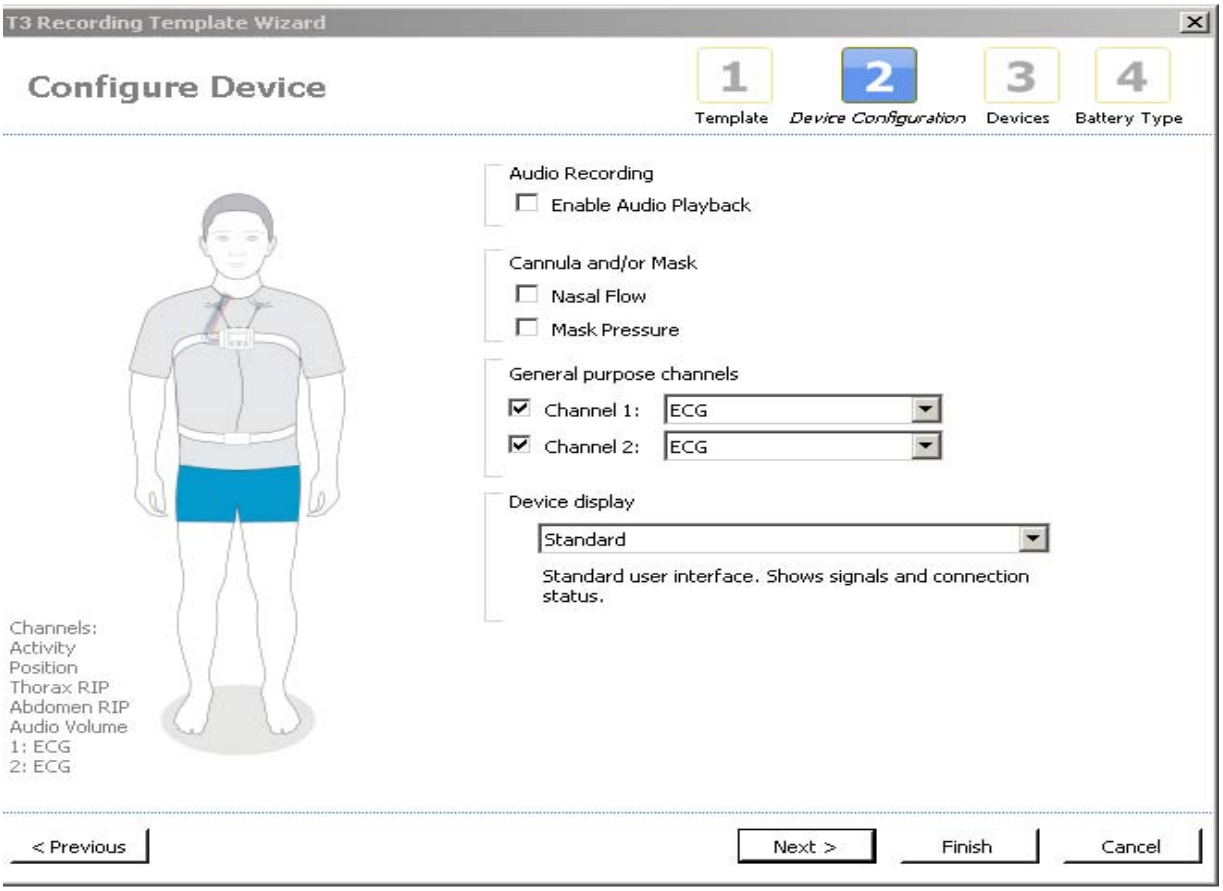
See next page for 'New Recording for a Participant with PAP Use

41.9 New Configuration for a Participant with PAP Use: In step 1**,** Select **T3 with ECG and CPAP** and **edit** the signals. In step 2 of the Set up Wizard, select √ "Mask Pressure instead of "Nasal Pressure", Channel 1 ECG and Channel 2 ECG, and the **Standard** Device display.

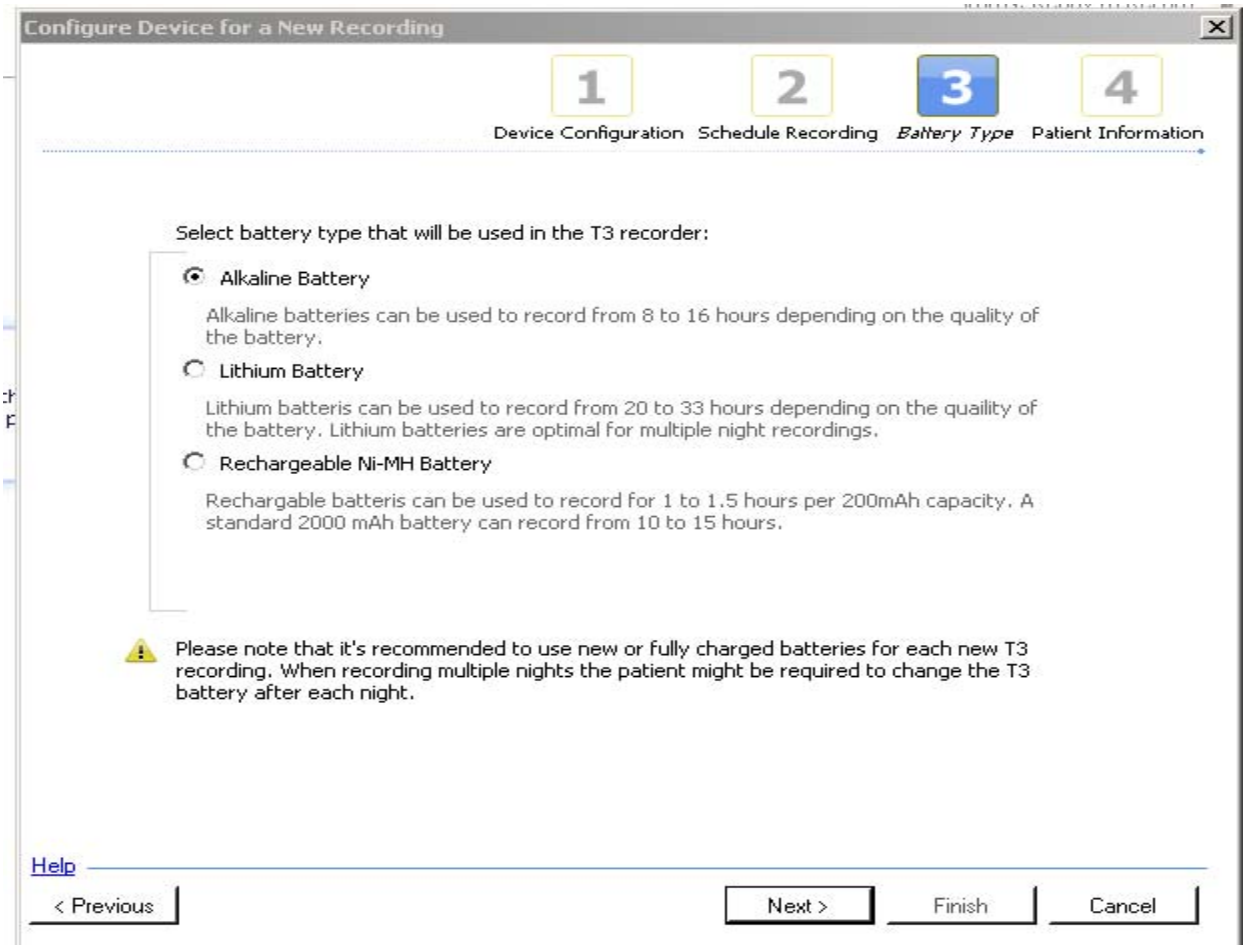


See next page for 'New Recording for a Participant with Supplemental Oxygen Use

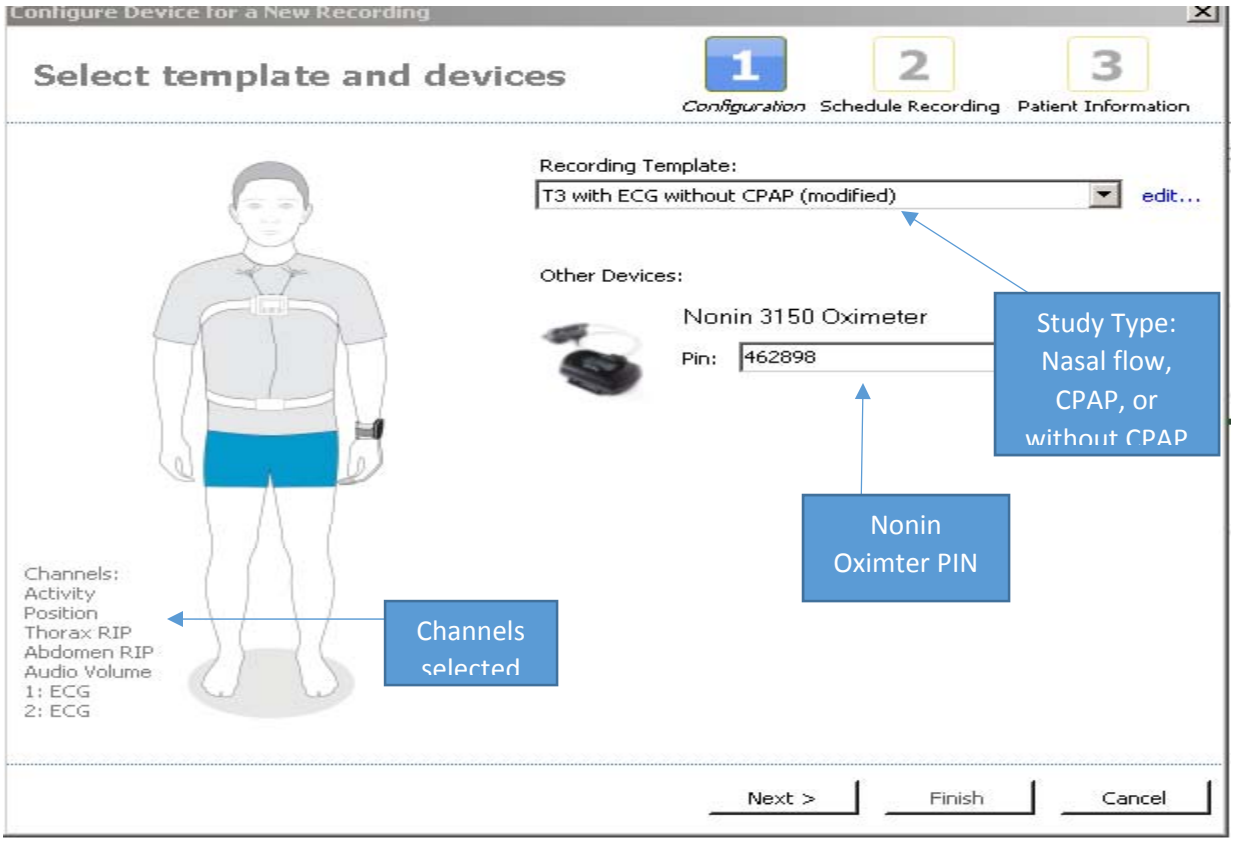
41.9.1 Preparing a Record for a participant with Supplemental Oxygen use: In step 1 of the Set up Wizard, select **T3 with ECG without CPAP** and **edit** the signals, in step 2 un-check nasal flow and mask pressure, and place a√ by Channel 1 ECG and Channel 2 ECG, and the **Standard** device display.



41.9.2 Click the **Next** button to continue to the battery type selection page. On this page select which battery type is used with the Nox-T3 device. A new fully charged battery must be used with each new T3 recording.

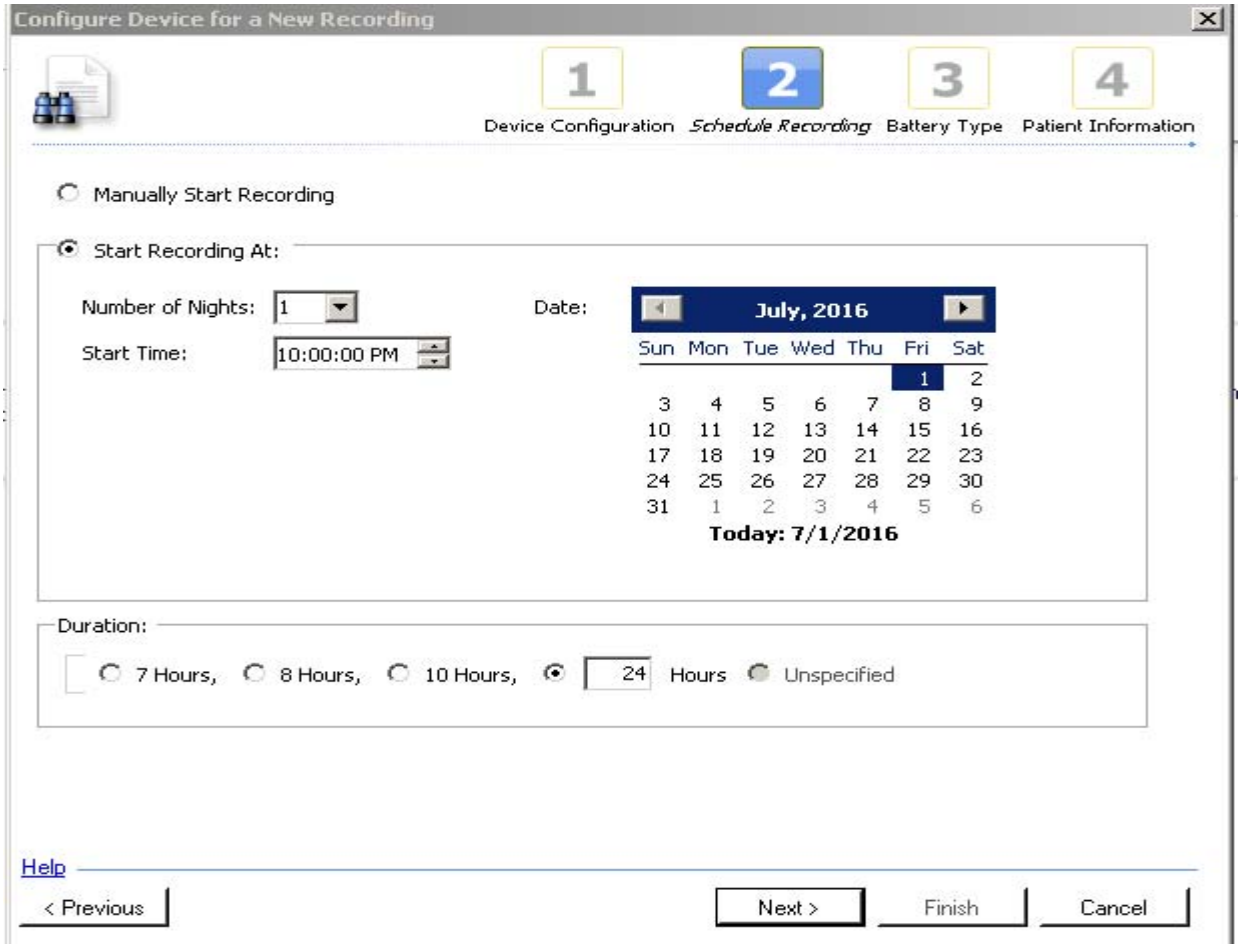


41.9.3 Click the **finish** button. The screen will return to the first step of the configuration setup. On the configuration page, channels selected will be displayed on the lower left corner.

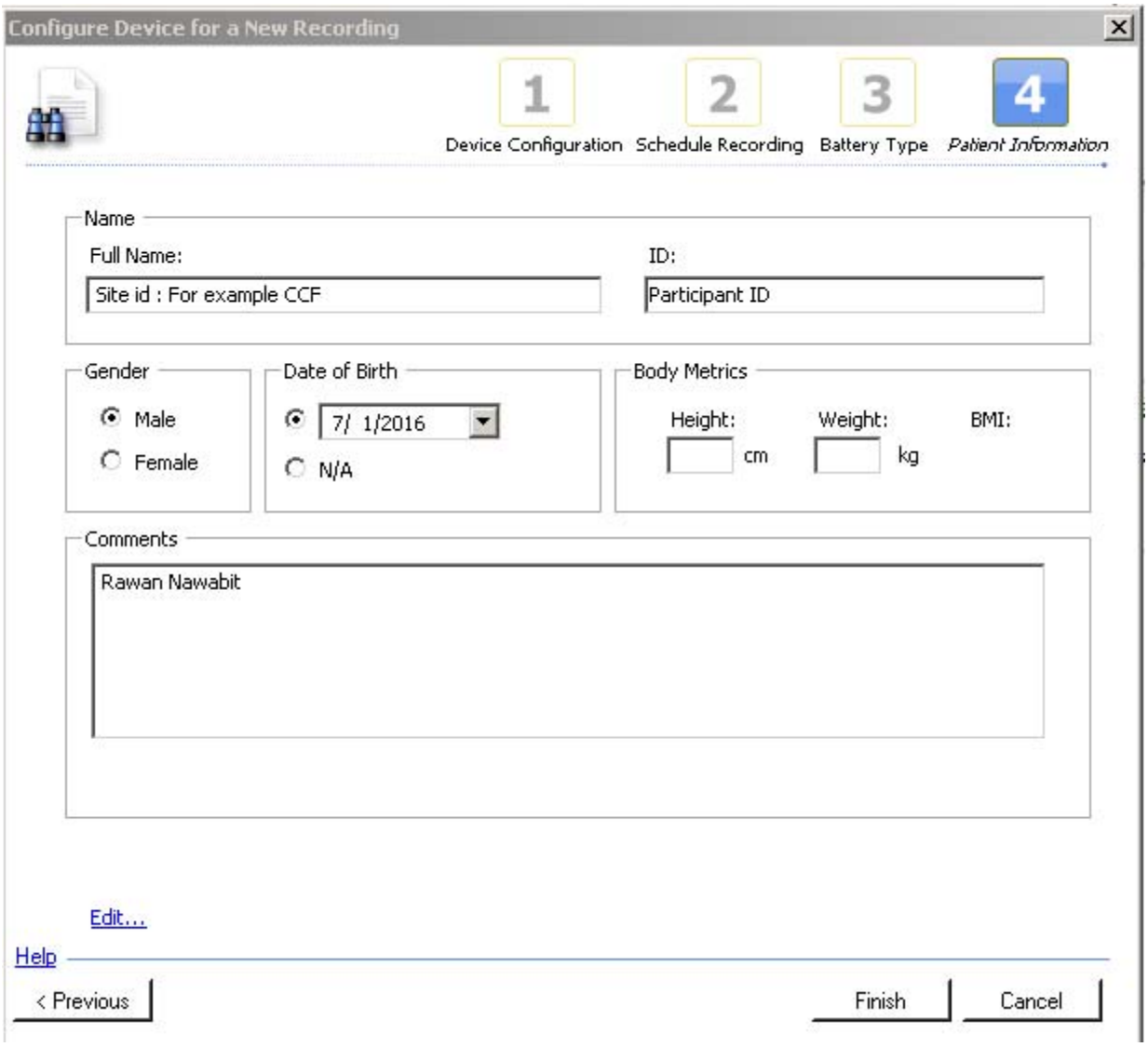


41.9.4 After selecting the appropriate template, select **next** to schedule the recording time. **Start recording option** to schedule a specific recording time. The device will turn itself on and automatically start recording at the specified time.

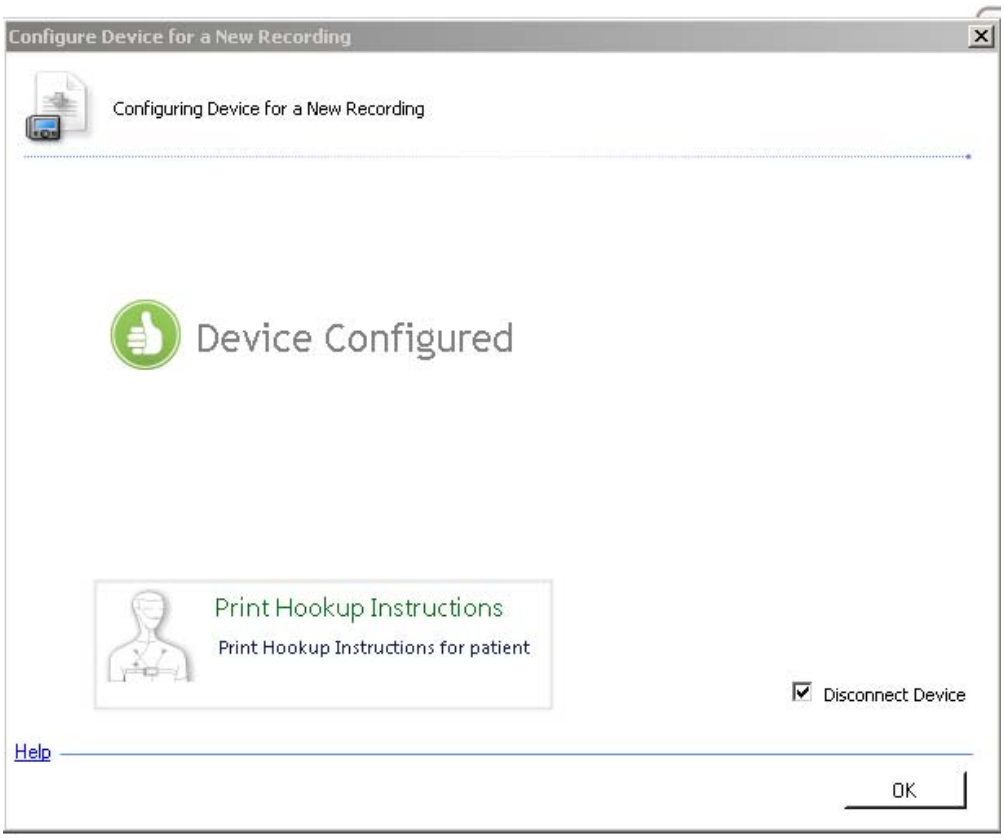
41.9.5 Start the device 30 minutes before the participant's anticipated scheduled time to bed and select the box (fourth option) for **24 Hours** duration. If another number appears in the option. Highlight and delete the pre-filled number and enter **24**.



41.9.6 Click the **Next** button to continue to the participant information page and enter the participants' information including Study ID. Full Name will be the Center ID, ID will be the participant study ID and Date of Birth will be the date the device is initialized/set up, and the comments section will contain the study personnel name who set up the device.



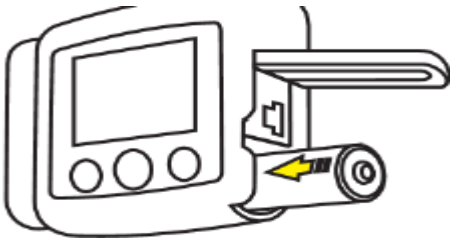
41.9.7 After entering the information, click the **Finish** button to send the configuration to the T3 device. Finally a confirmation page appears confirming the T3 device has been configured. Once you have completed the setup check the box at the lower left corner to disconnect the device. The hook up instructions will **not be** printed from the software, use the instructions located in the manual. This action will allow safe removal of the device from the computer.



41.10 Insert Battery into the Device:

Before you pack up the device for the participant:

***** It is very important place a new battery into the device prior to each deployment. ******

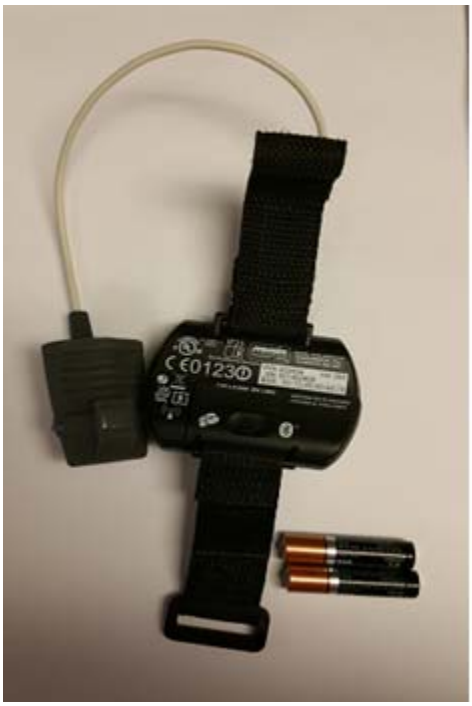


41.10.1 Open the battery compartment by pressing down the battery lid pin with a pen or similar tool and slide the lid towards the bottom of the device.

41.10. 2 Place one AA battery in the compartment aligning the battery poles as illustrated on the back of the device (the positive (+) pole is towards the battery lid).

41.10. 3 Close the battery compartment by pressing the lid back towards the device without causing any strain, then slide

41.11 Nonin Pulse Oximeter: **Insert** two AAA batteries in the back of the device. The oximeter will only turn on once it has sensed a finger has been inserted into the sensor.





41.12 Participant Assessment and Participant Preparation

41.12.1 Identify participant using two separate identifiers. Explain to the participant the rationale behind conducting the sleep study. (For example: *'The PVDOMICS study provides a platform to better understand the relationship of sleep apnea and pulmonary hypertension.'*)

41.12.2 Briefly explain the procedure and answer the participant's questions before the setup.

41.12.2.1 Explain that the sleep monitor requires access to the chest and chest wall, abdomen, head, and wrist and finger of the non-dominant hand.

41.12.2.2 Explain that wearing the device may be a little uncomfortable for some.

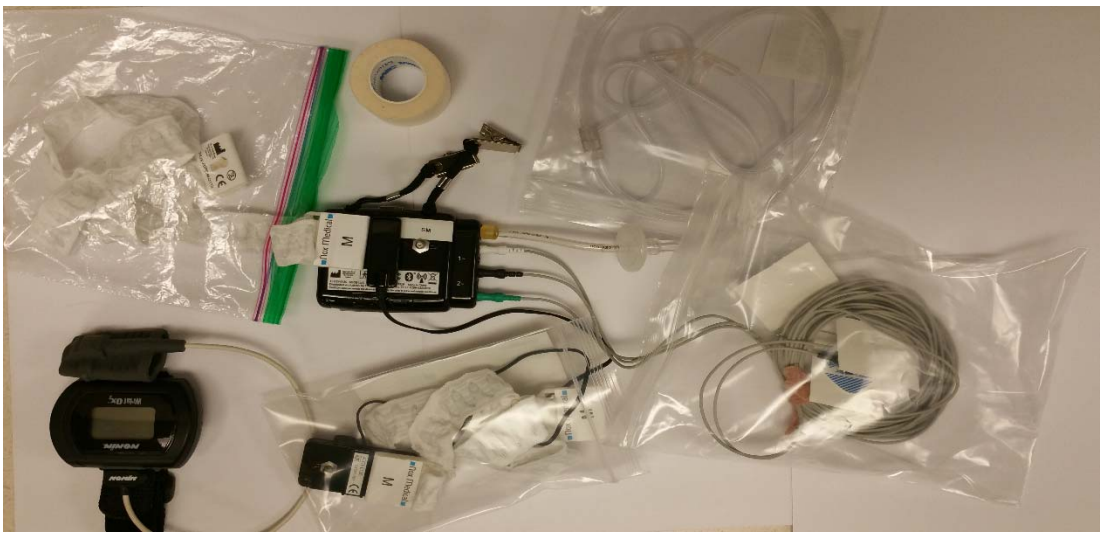
41.12.2.3 Explain that skin redness from the removal of the adhesive and temporary depigmentation under the area of ECG attachment may occur but it's rare.

41.12.3 Explain importance of completing and returning Form 151-Participant Sleep Study Questionnaire with the participant.

41.12.4 Instruct the participant on how to wear the device and allow the participant time to demonstrate applying the sensors before they leave the visit. The following video will aid in the demonstration, click on the link: https://www.youtube.com/watch?v=CteI_GhyP9g

A Carefusion 24-hour hotline is available for any technical support: **1-800-231-2466**, dial 1 at the prompt, and then 3 for sleep support.

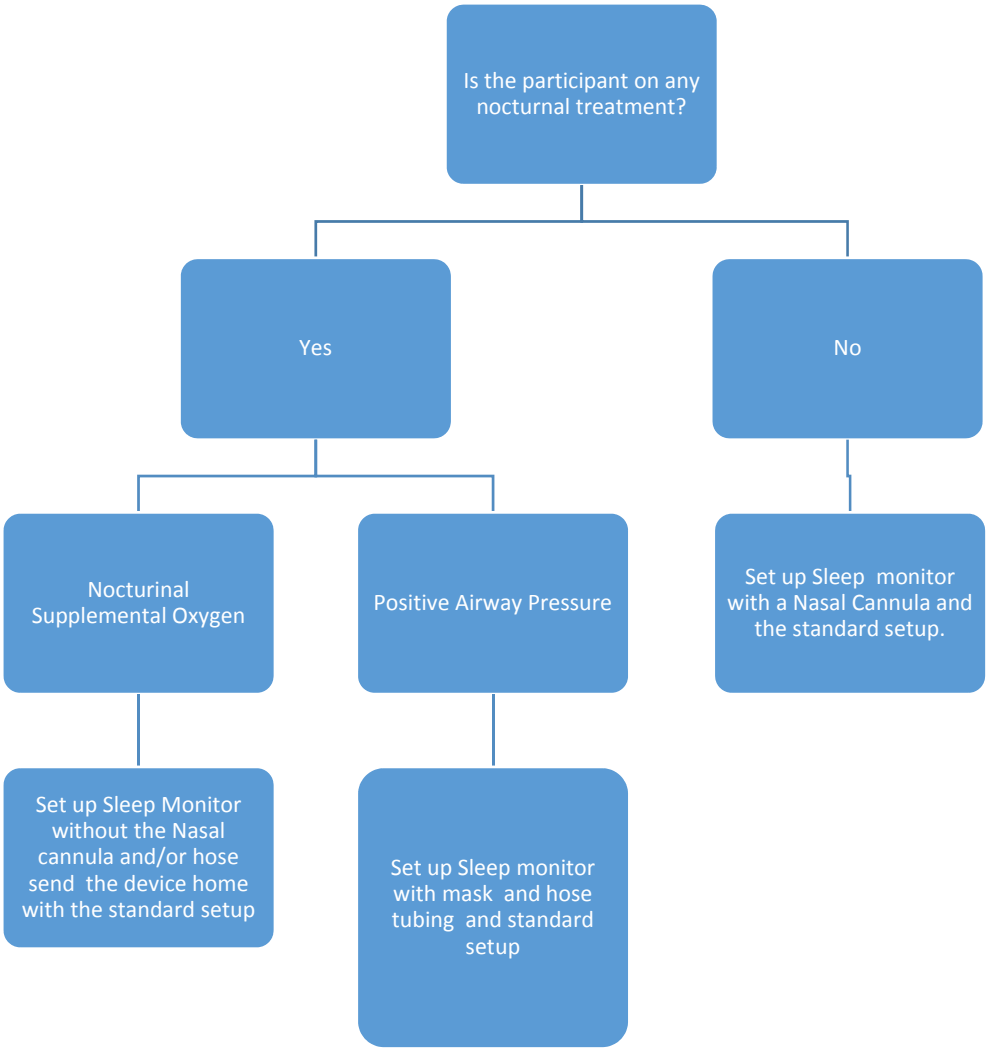
41.12.5 Place all items in the bag, and individually separate the wires in a zip lock bag while still attached to the device for easy application at home.



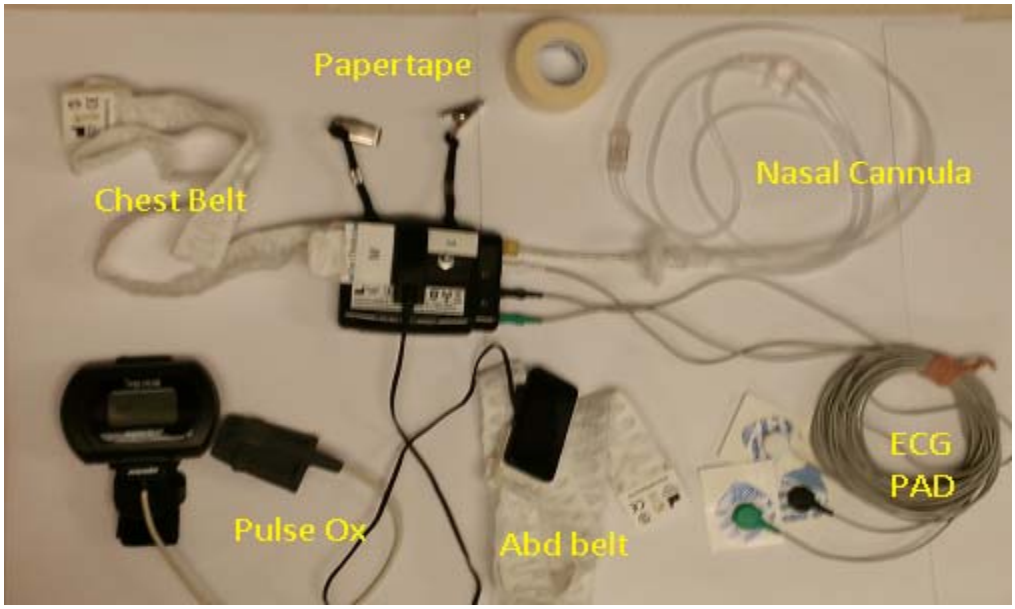
41.12.6 Place instructions, contact information, and the Sleep Questionnaire in the bag and instruct the participant to return everything with the equipment.

41.12.7 Units are returned to the clinic site using local center funds (by mail, courier or direct drop-off).

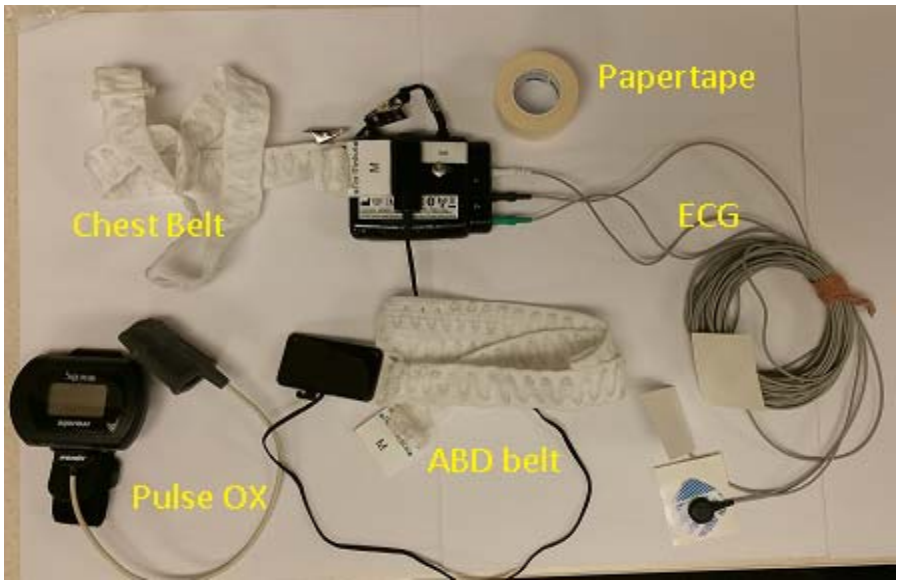
41.13 Setting Up Monitor to Send Home with Participant:



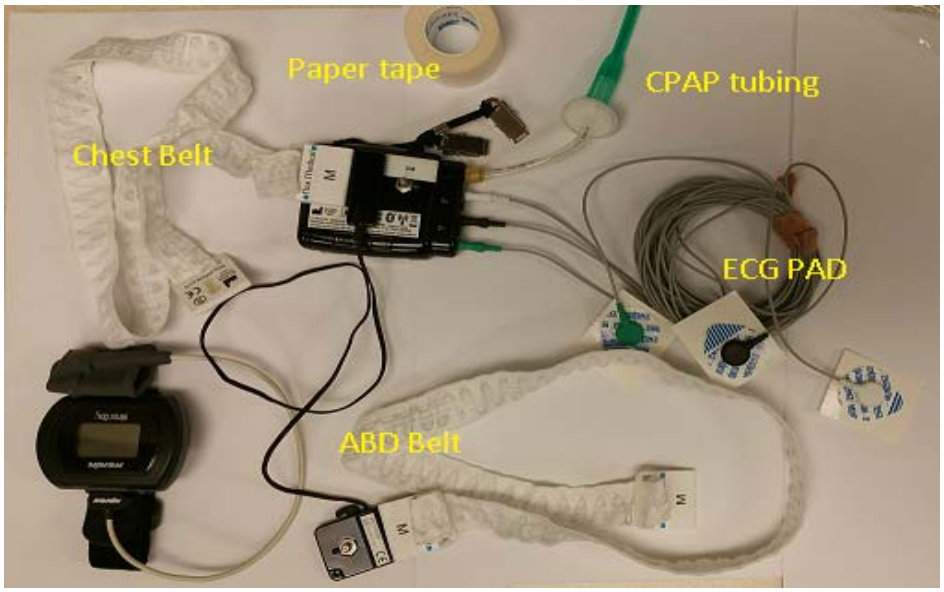
41.13.1 Standard set up for participant **without** nocturnal supplemental oxygen or positive airway pressure (PAP) treatment: Plug the snap wire leads into the ports labeled **1**+, **2+**, and **PGND**. Snap the **ECG Pads** at the end of the snap wire leads. Attach the Nasal Cannula into the **PRES** port. Snap one end of the **chest** belt into back of the device and snap one end of the **abdominal** belt into the external wire.

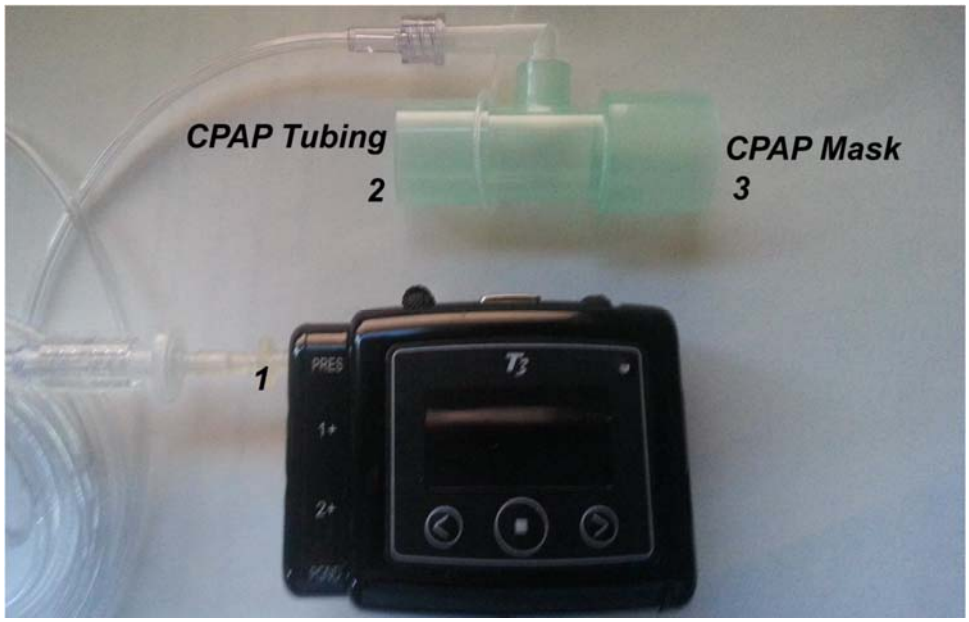


41.13.2 Standard setup for participant using supplemental **nocturnal oxygen**: Plug the snap wire leads into the ports labeled **1**+, **2+**, and **PGND**. Snap the **ECG Pads** at the end of the snap wire leads. Snap one end of the **chest** belt into back of the device and snap one end of the **abdominal** belt into the external wire



41.13.3 Standard setup for participant using nocturnal PAP**:** Plug the snap wire leads into the ports labeled **1**+, **2+**, and **PGND**. Snap the **ECG Pads** at the end of the snap wire leads. Attach the **CPAP tubing** in to the **PRES** port. Snap one end of the **chest** belt into back of the device and snap one end of the **abdominal** belt into the external wire.





41.14 Returned Equipment Care Prior to Data Download

Clean the sleep monitoring device before downloading data. Use a soft cloth dampened with hospital grade cleaner that is not corrosive to the plastic or metal (for example: Cavicide). Wipes can also be used (for example: CaviWipes or Sani Cloth).

The sleep monitoring device and accessories should be stored in a clean, dry space. The device is not waterproof. Each device will be tested for a minimum of 2 hours during normal work hours to assure all signals are working accurately before sleep data collection begins. All reusable components should be cleaned between participant uses. Do not pour or spray any liquids directly on the device.



41.14.1 Lay a protective pad on a flat surface. (For example: a CHUX pad). Place gloves on and open the package containing the monitor and accompanying paperwork. Remove the paperwork and set aside. Remove the batteries from the unit.

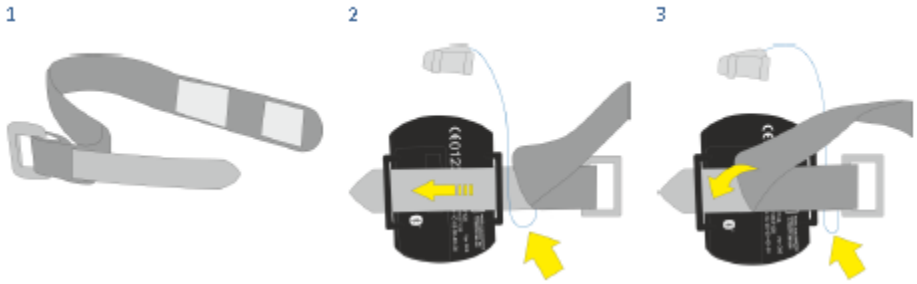
41.14.2 Remove the plastic bag containing the nasal cannula and discard the tubing. Inspect the monitor for signs of damage in case the corresponding sleep study has poor quality signals.

41.14.3 Unsnap and discard the abdominal and thoracic belts.

41.14.4 Disinfect the monitor, ECG wires, and the oximeter with a disinfecting wipe. During this cleaning, turn the disinfecting towelette frequently. Do not allow any liquids to enter any openings on the device. After the unit has been disinfected, allow it to air dry.

41.14.5 Wipe down and disinfect the accompanying case that the unit arrived in.

41.14.6 The wristband of the oximeter is reusable and is not designed for single-participant use. It needs to be cleaned after every use, by hand washing it with a mild detergent. The band is removed, disinfected and air dried. Once it has air dried, replace the band back into the device.



41.14.7 Remove gloves, placing them with the dirty items on the protector, gather or roll it up to enclose all the dirty disposable items. Discard into the appropriate trash receptacle. Wash your hands before conducting the download of the data.

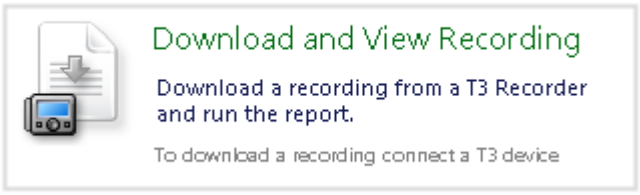
41.14.8 Discard and/or replace any broken wires.

41.15 Sleep Monitor Data Download

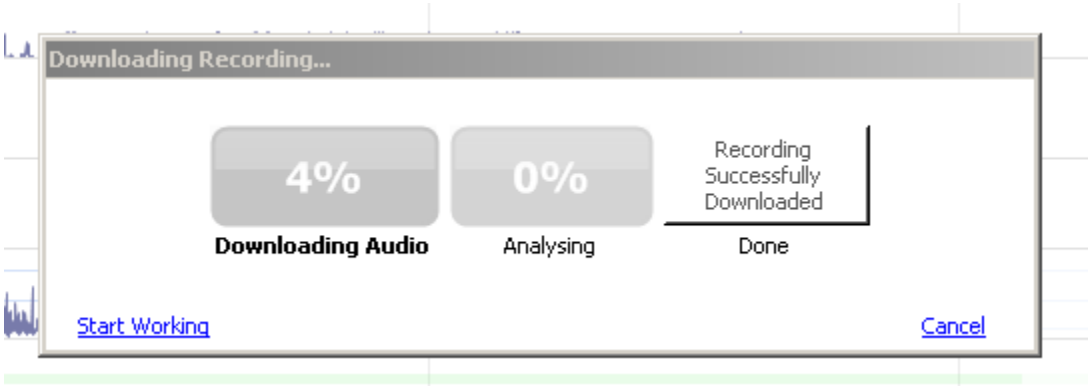
Downloading the recording:

After device and equipment are cleaned**,** download the recorded data from a T3 device to the computer connect the device to the USB port on the computer. Noxturnal® software automatically detects the device and displays information on the **Start Page**. Detection can take 2-4 seconds. If the T3 device is not detected, click the **Scan for Devices** link.

41.15.1 Click the **Download and View Recoding button** on the start page.



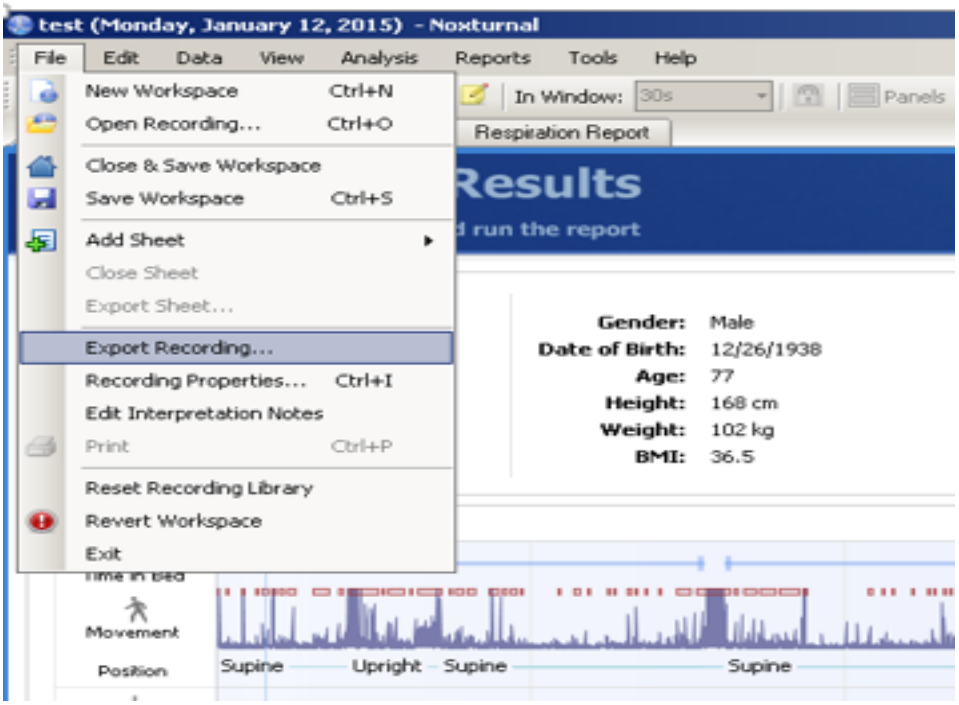
41.15.2 A download progress dialog will appear that breaks down the progress while downloading.



41.15.3 After download is completed, the recordings are automatically added to the recording library.

41.16 Converting a file to EDF format:

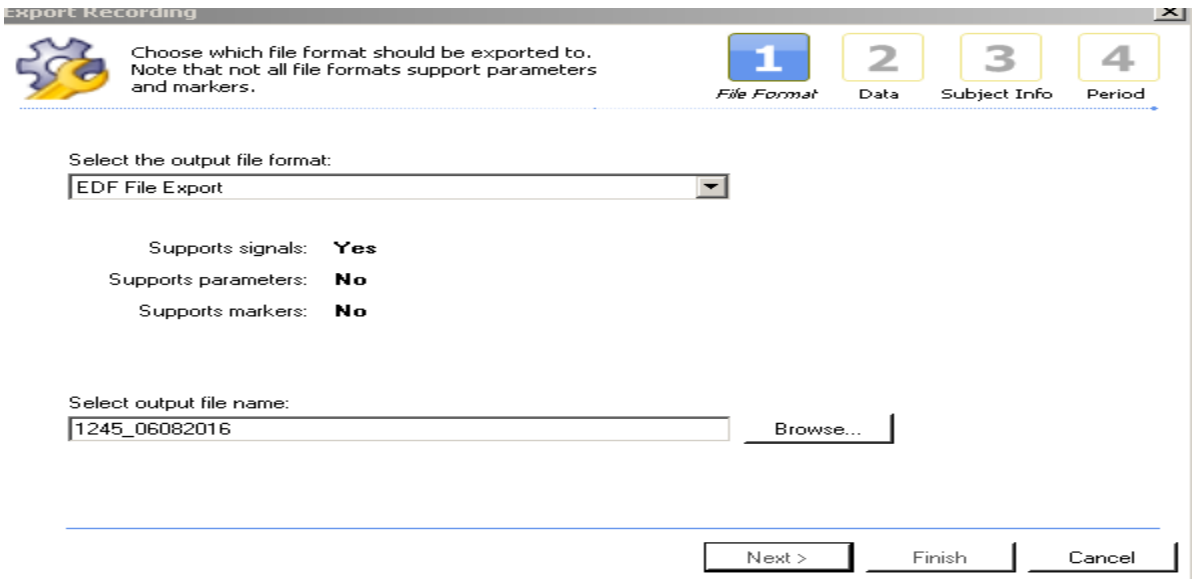
To convert the data file to EDF, the data file must be opened. If the data file is not opened, locate the data file by moving the mouse to the top left corner and select **Open Recording**. Move the mouse to the top left corner and select **File.** From the drop down menu select, **Export Recording**



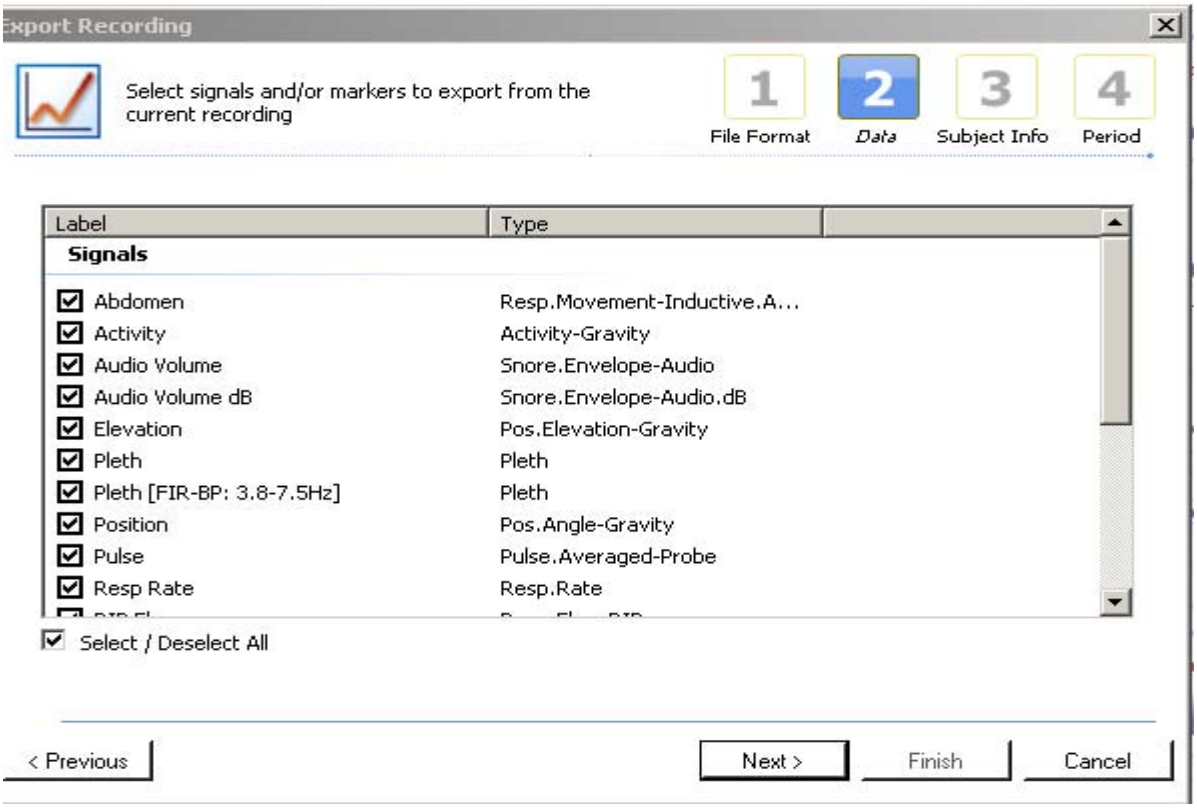
41.16.1 A wizard will appear, select EDF File Export, and click on **browse** to select the location of where you would like to place the EDF file. Enter the participant's ID with the date of recording night and then save. The data file name will be in the format:

Filename Format Sleep_XXXXXX_mmddyyyy.edf

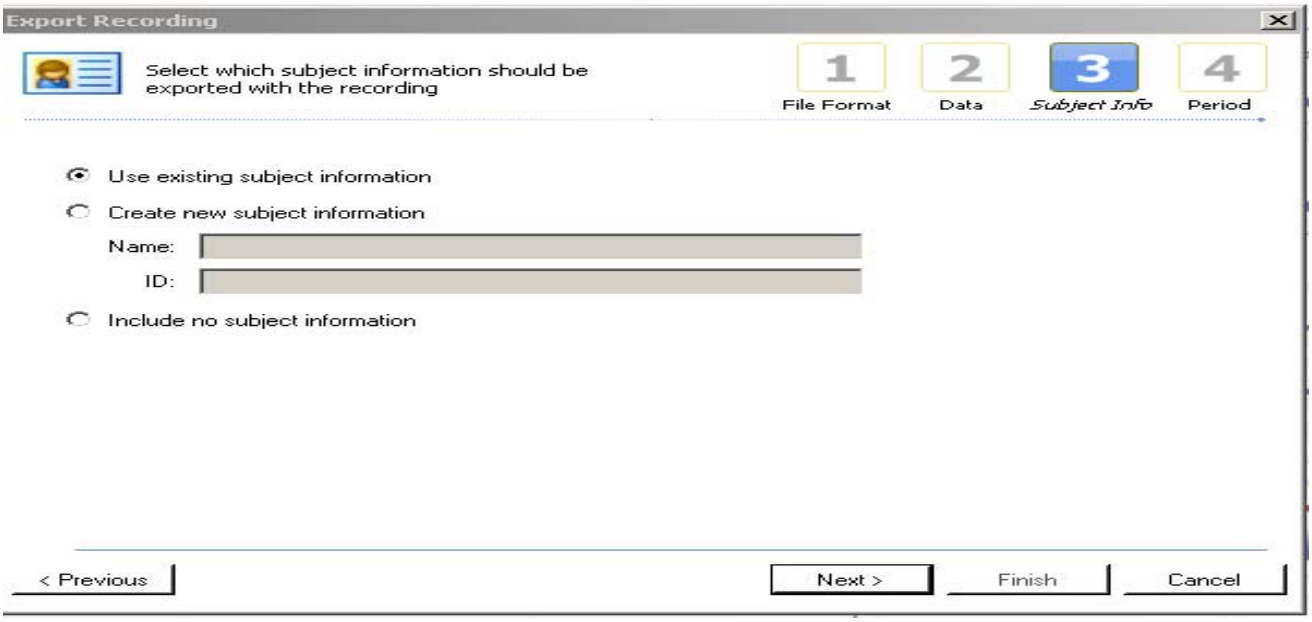
File content | PVDOMICS ID | Date of test | file type



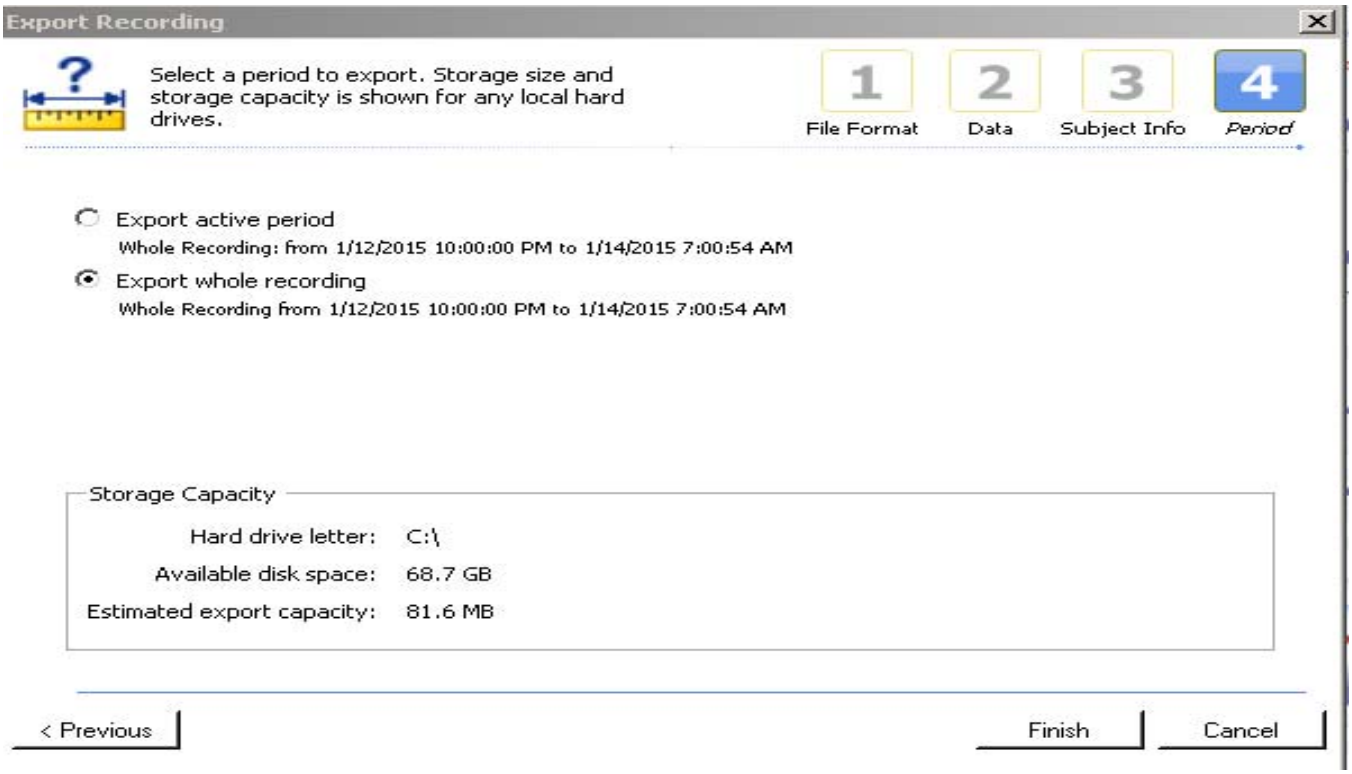
41.16.2 Click on **next.** Place a √ mark in the select/deselect All option. All signals should have a **√ mark** next to them**.**



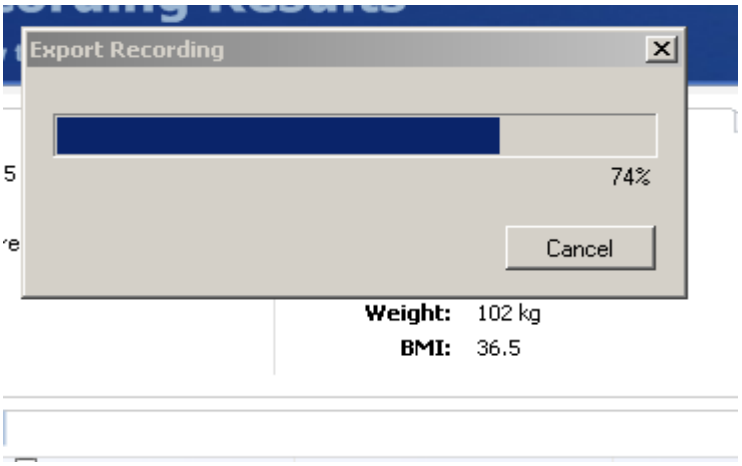
41.16.3 If the participant information is correct, select "**Use existing subject information"**. If not, select "**Create new subject"** and send an email to inform Rawan Nawabit nawabir@ccf.org of the discrepancy with the participant file. Then select **Next.**



41.16.4 Selecting a period to export: **Export whole recording** will be selected. Then select **Finish**



41.16.5 A progress bar of the recording will appear.
Once this has been completed, the study will be in the destination selected in step 6.21.1



41.17 Right click on the folder to create a zip file and use the same naming scheme as above and log in to SSH with previously assigned account name and password. Drag and drop file into SSH home directory for PVDOMICS on DCC server.

41.17.1 Sleep Monitor Data Transmission

Clinical Centers will transmit the home sleep monitor data to **SSH home directory**.

All electronic data transmitted to the DCC must be stripped of all participant identifying information and saved with the unique Study ID.

Log into SSH home directory and drop files into the PVDOMICS DCC server.

If difficulties connecting or uploading are experienced, contact pvd-systems@bio.ri.ccf.org.

41.18 Retention of Data

The Clinical Center must retain original versions of the sleep recording data files that have been created by the download of the overnight study. It is preferred that the Center also retain copies of the EDF output files. However, if the EDF file is sent electronically, this is not required. One CD-ROM disk containing a copy of the original sleep recording and a copy of the converted EDF files always must be retained at the Center in a secure location. These files are source documents and shall serve as “back up” files only.

41.19 Abbreviations and Acronyms

AASM	American Academy of Sleep Medicine
AHI	Apnea Hypopnea index
ASV	Adaptive- Servo Ventilation
BIPAP	Bilevel Positive Airway Pressure
CPAP	Continuous Positive Airway Pressure
EDF	European Data Format
HR	Heart rate
PAP	Positive Airway Pressure
PI	Principal Investigator

PM	Portable Monitor
TST	Total Sleep Time

PVDOMICS Study General Participant Instructions

Thank you for participating in the PVDOMICS Study. You have received a portable sleep monitoring unit with setup supplies. The instructions were reviewed with you at your visit and below is the instruction sheet to provide additional help. Additionally, you received a questionnaire to complete the following morning after you wear the monitor during your sleep.

Give yourself at least 30 minutes before bedtime
to put on the sleep monitor.

Here is a link for additional assistance:

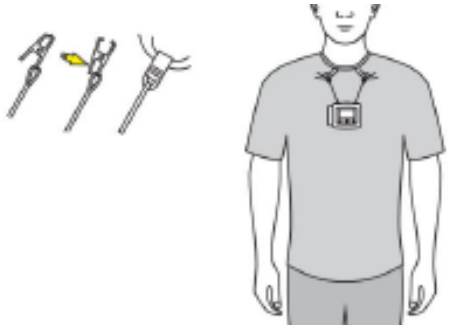
https://www.youtube.com/watch?v=CteI_GhyP9g

If you have any questions, please contact:

Name:_____ Phone Number: _____

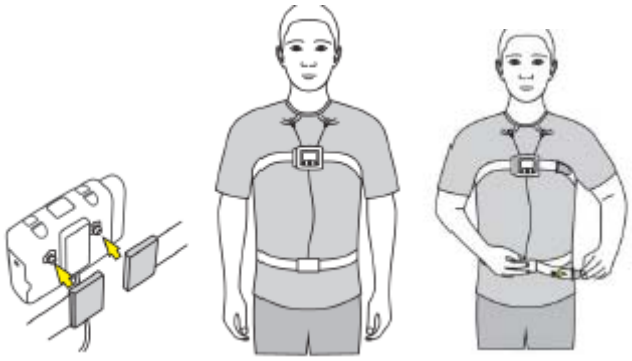
Putting the Sleep Monitor on Before Going to Sleep

1. Attach the device: The device should be worn over clothing. Snap the clips that are attached to the device to your shirt.



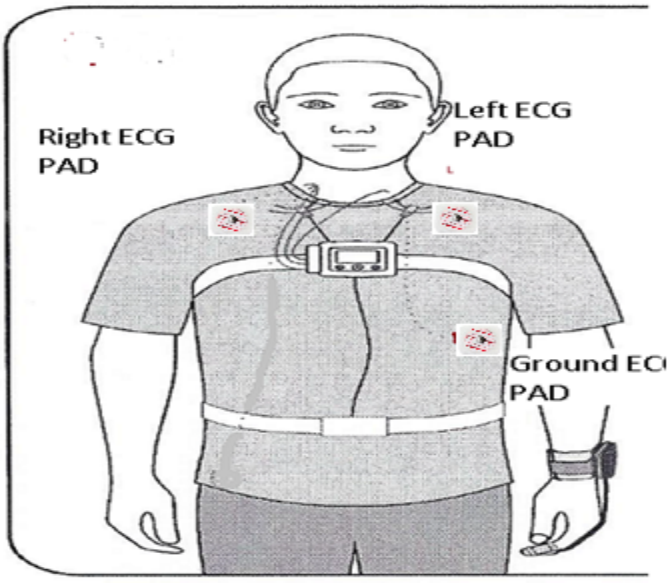
2. Write the time you started putting on the device on Form 151- Participant Sleep Study Questionnaire.
3. Wrap the <u>chest</u> belt and adjust the cable length if needed and snap in place. Wrap the <u>abdominal belt</u> and adjust the cable the length if needed and snap in place.

The belts should be worn snug and not tight. If the belts feel loose, use the sliders to adjust the belt length.



4. Placement of the ECG sticky pads: Using an alcohol prep pad clean your skin in the following spots:
    - below the front of your right and left shoulder under your collar bone
    - on the left side below the rib cage with rubbing alcohol.

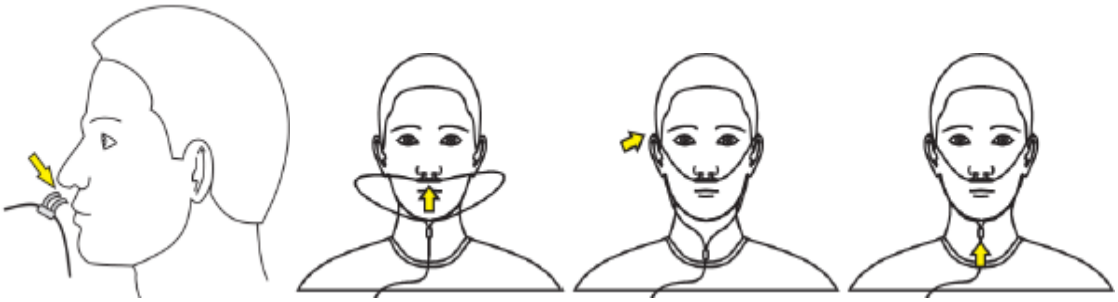
    Shave the area if needed to help secure leads. Remove the backing of the sticky pad and place the wire labeled **1+** ECG electrode under the right side of your collar bone, and the wire labeled **2+** under the left side of your collar bone and the wire labeled **PGND** on the left side below the rib cage.



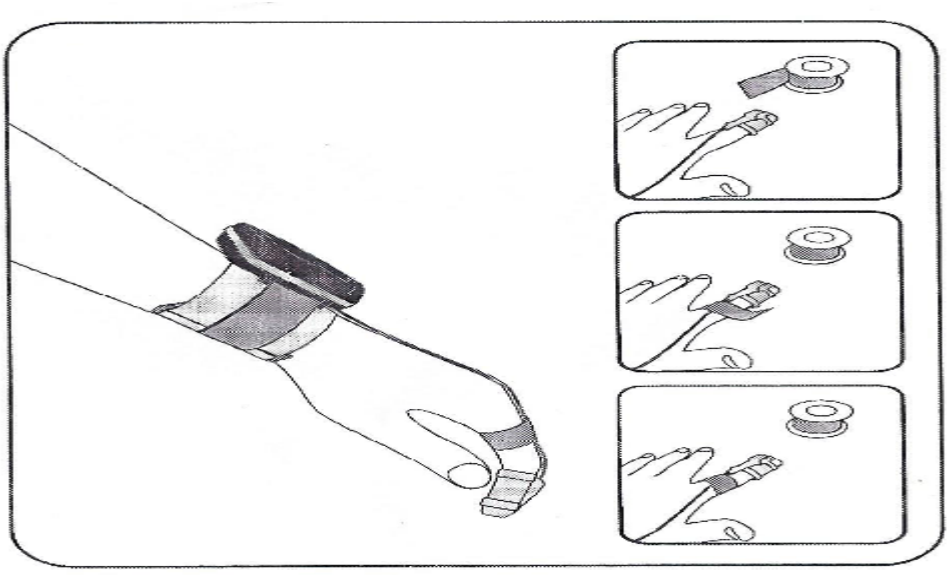


Sticky PAD

5. Place the prongs gently in the nostrils. The prongs should point downward inside the nostrils. Pull the cannula over your ears and then position the tubing under your chin. Slide the fastener snugly under the chin. **** If you are on home supplemental Oxygen you will skip this step and wear your oxygen therapy as you would normally. ** PAP therapy see PAP set up handout and this step will be skipped.



6. Put the probe of the oximeter on your finger and attach the strap with the wrist device on your non-dominate hand. Place a piece of tape around your finger over the white cable to keep this from falling off. The device will automatically start reading.



7. The indicator light on the device blinks green when the recording is in progress and functioning normally. When there are any device warnings the light blinks orange.

1. On the top right corner is a battery bar which shows the battery status. The battery bar is full when the device has fresh batteries.
2. In the bottom left corner is a number indicating how many recordings are stored on the device. The device can contain as many recordings as the internal 1GB memory allows.



Morning after Sleeping with the Monitor

1. Keep everything attached and do not unhook any of the wires from the unit.
2. Remove the wrist device and oximeter off your hand.
3. Remove the nasal cannula tubing from your face and place it in the resealable bag provided. Seal the bag as much as possible.
4. Unsnap the ECG wires attached to the sticky pads. Remove the sticky pads from your skin and throw them away. *(If needed, use baby oil, olive oil, or mineral oil on a cotton ball. Pour a little on the cotton ball. Rub it over the adhesive areas on your skin, and let it sit. Then use a wet wash cloth to remove it.)*
5. Unhook the belts and leave them attached to the unit.
6. After you have removed everything, place the unit, belts, connectors and tubing in the case with the equipment unit still attached.
7. **Complete Form 151- Participant Sleep Study Questionnaire**.

Returning the Device

- Check to see that the device, belts, tubing, wrist device and wiring are in the carry case provided by your coordinator.
- Place the device bag, the completed Form 151-Sleep Study Questionnaire, and any other forms that you need to return to **PVODOMICS** study personnel. You will return these items to **PVDOMICS** staff in the manner agreed upon during your visit.

If you have any questions, please contact

Name:_____ Phone Number: _____

Thank You for Participating!

Appendix 2: PVDOMICS Study Instructions for Participant Using Positive Airway Pressure (PAP) Device

Thank you for participating in the PVDOMICS Study. You have received a portable sleep monitoring unit with setup supplies. The instructions were reviewed with you at your visit and below is the instruction sheet to provide additional help. Additionally, you received a questionnaire to complete the following morning after you wear the monitor during your sleep.

Give yourself at least 30 minutes before bedtime
to put on the sleep monitor.

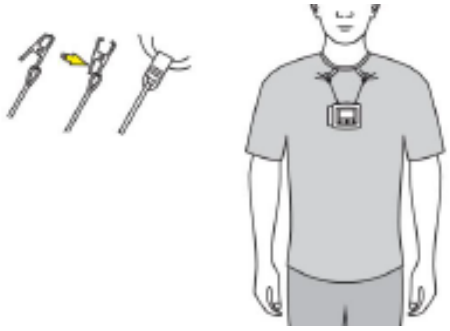
Here is a link for additional assistance:
https://www.youtube.com/watch?v=CteI_GhyP9g

If you have any questions, please contact:

Name:_____ Phone Number: _____

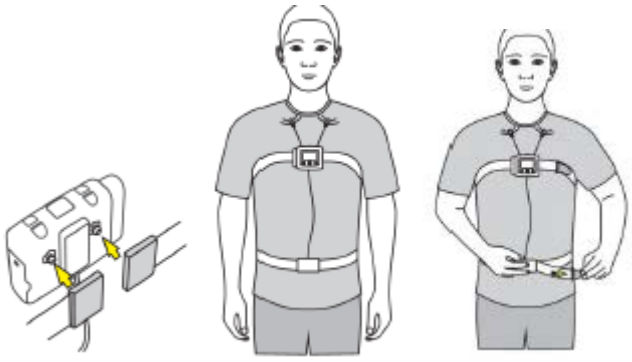
Putting the Sleep Monitor on Before Going to sleep

1. Attach the device: The device should be worn over clothing. Snap the clips that are attached to the device to your shirt.



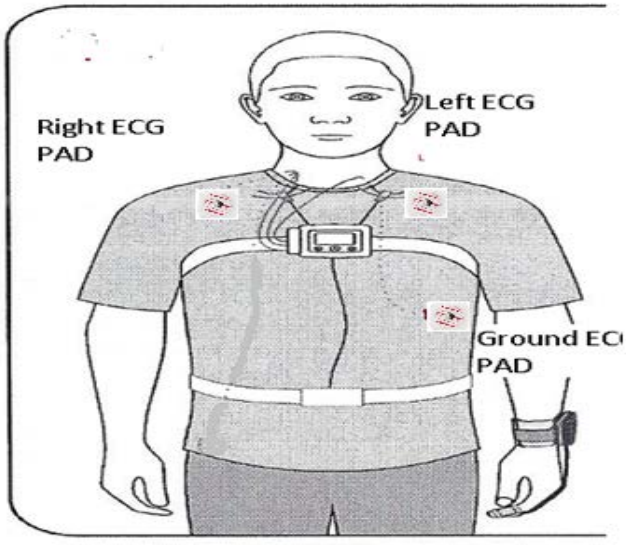
2. Write the time you started putting on the device on Form 151- Participant Sleep Study Questionnaire.

3. Wrap the chest belt and adjust the cable length if needed and snap in place. Wrap the abdominal belt and adjust the cable the length if needed and snap in place. The belts should be worn snug and not tight. If the belts feel loose, use the sliders to adjust the belt length.



4. Placement of the ECG sticky pads: Using an alcohol prep pad, clean your skin in the following spots:
    - below the front of your right and left shoulder under your collar bone
    - on the left side below the rib cage with rubbing alcohol.

   Shave the area if needed to help secure leads. Remove the backing of the sticky pad and place the wire labeled **1+** ECG electrode under the right side of your collar bone, and the wire labeled **2+** under the left side of your collar bone and the wire labeled **PGND** on the left side below the rib cage.

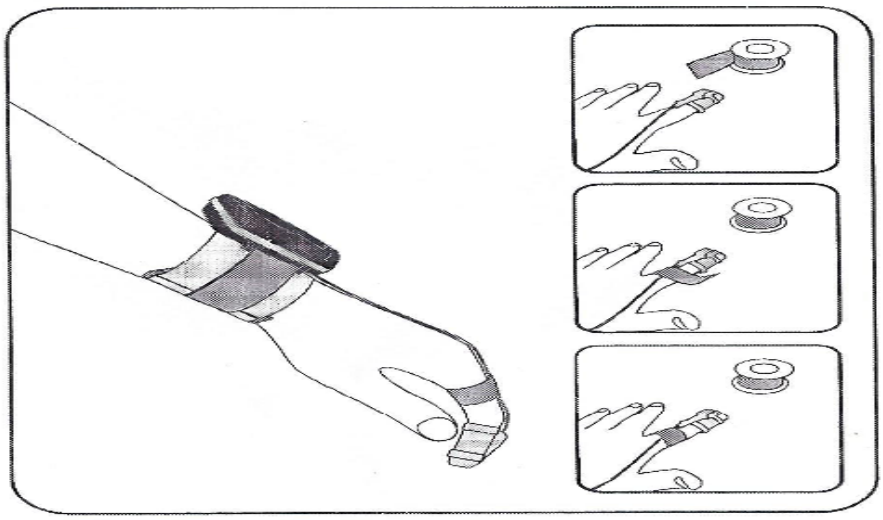




Sticky PAD

5. Plug the plastic tubing into your mask and PAP machine. See Participant PAP adapter sheet (*see end of this document).*

6. Put the probe of the oximeter on your finger and attach the strap with the wrist device on your non-dominate hand. Place a piece of tape around your finger over the white cable to keep this from falling off. The device will automatically start reading.



7. The indicator light on the device blinks green when the recording is in progress and functioning normally. When there are any device warnings the light blinks orange.

1. On the top right corner is a battery bar which shows the battery status. The battery bar is full when the device has fresh batteries.
2. In the bottom left corner is a number indicating how many recordings are stored on the device. The device can contain as many recordings as the internal 1GB memory allows.



Morning after Sleeping with the Monitor

1. Keep everything attached and do not unhook any of the wires from the unit.
2. Remove the wrist device and oximeter off your hand.
3. Remove the nasal cannula tubing from your face and place it in the resealable bag provided. Seal the bag as much as possible.
4. Unsnap the ECG wires attached to the sticky pads. Remove the sticky pads from your skin and throw them away. *(If needed, use baby oil, olive oil, or mineral oil on a cotton ball. Pour a little on the cotton ball. Rub it over the sticky areas on your skin, and let it sit. Then use a wet wash cloth to remove it.)*
5. Unhook the belts and leave them attached to the unit.
6. After you have removed everything, place the unit, belts, connectors and tubing in the case with the equipment unit still attached.
7. **Complete Form 151- Participant Sleep Study Questionnaire**.

Returning the Device

- Check to see that the device, belts, tubing, wrist device and wiring are in the carry case provided by your coordinator.
- Place the device bag, the completed Form 151-Sleep Study Questionnaire, and any other forms that you need to return to **PVODOMICS** study personnel. You will return these items to **PVDOMICS** staff in the manner agreed upon during your visit.

If you have any questions, please contact

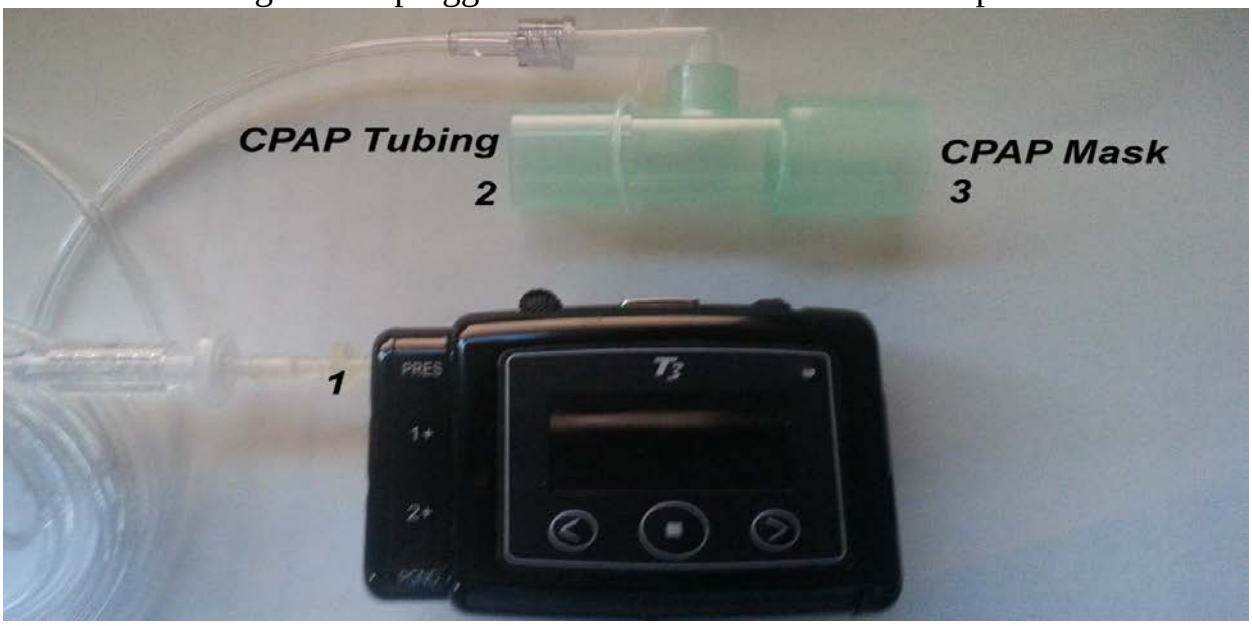
Name:_____ Phone Number: _____

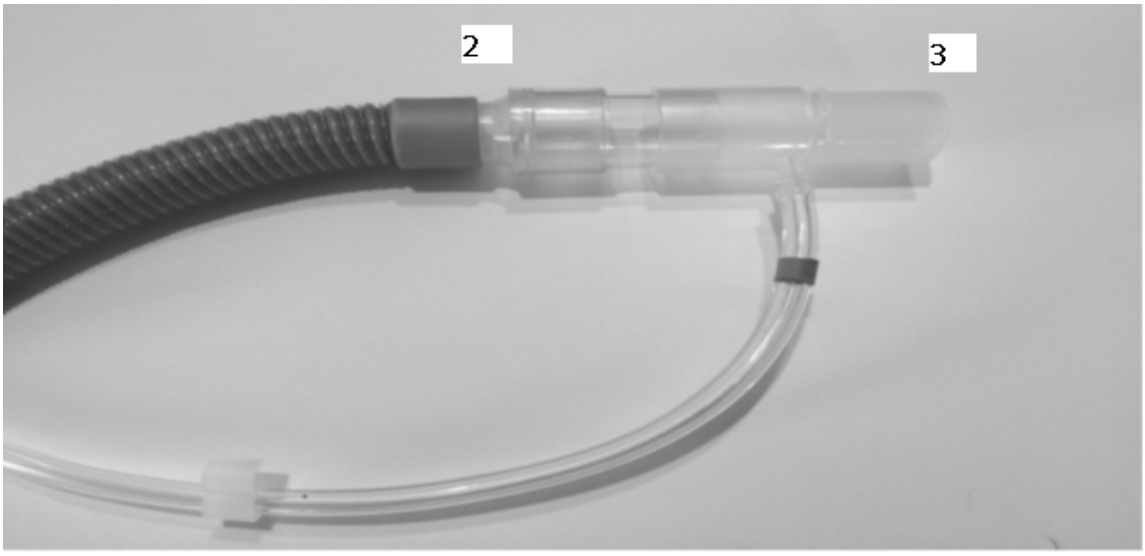
Thank You for Participating!

Participant Positive Airway Pressure Adapter Instruction Sheet

Instructions to monitor CPAP pressure and flow using the Sleep Monitor.

1. Plug the small adapter Marked **1** into the side of the sleep Monitor where the cannula normally is plugged.
2. Plug the small end of the adapter marked **2** into the CPAP tubing.
3. Plug the large end of the adapter into the CPAP mask marked **3**.
4. The mask's elbow will be plugged into the larger end of the adapter and the hose/tubing will be plugged into the smaller end of the adapter.





Appendix 3: PVDOMICS Study Instructions for Participant Using Supplemental Oxygen

Thank you for participating in the PVDOMICS Study. You have received a portable sleep monitoring unit with setup supplies. The instructions were reviewed with you at your visit and below is the instruction sheet to provide additional help. Additionally, you received a questionnaire to complete the following morning after you wear the monitor during your sleep.

Give yourself at least 30 minutes before bedtime
to put on the sleep monitor.

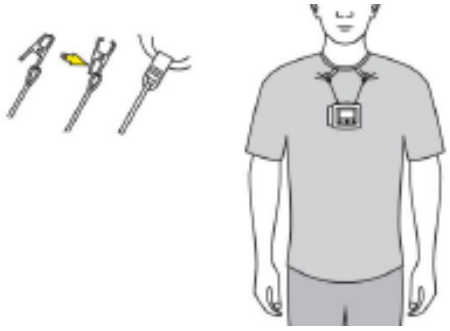
Here is a link for additional assistance:
https://www.youtube.com/watch?v=CteI_GhyP9g

If you have any questions, please contact:

Name:_____ Phone Number: _____

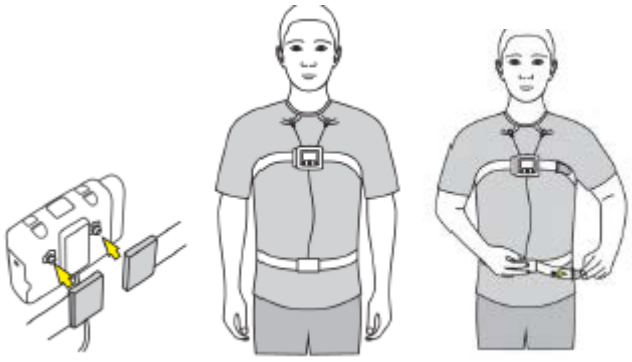
Putting the Sleep Monitor on Before Going to sleep

1. Attach the device: The device should be worn over clothing. Snap the clips that are attached to the device to your shirt.



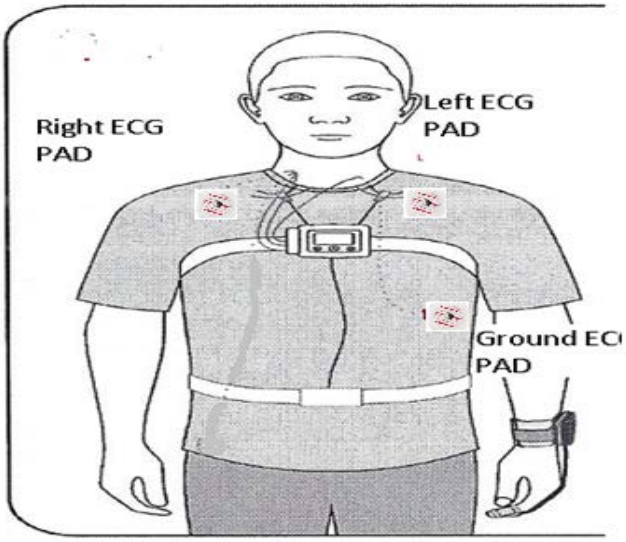
2. Write the time you started putting on the device on Form 151- Participant Sleep Study Questionnaire.

3. Wrap the chest belt and adjust the cable length if needed and snap in place. Wrap the abdominal belt and adjust the cable the length if needed and snap in place. The belts should be worn snug and not tight. If the belts feel loose, use the sliders to adjust the belt length.



4. Placement of the ECG sticky pads: Using an alcohol prep pad, clean your skin in the following spots:
    - below the front of your right and left shoulder under your collar bone
    - on the left side below the rib cage with rubbing alcohol.

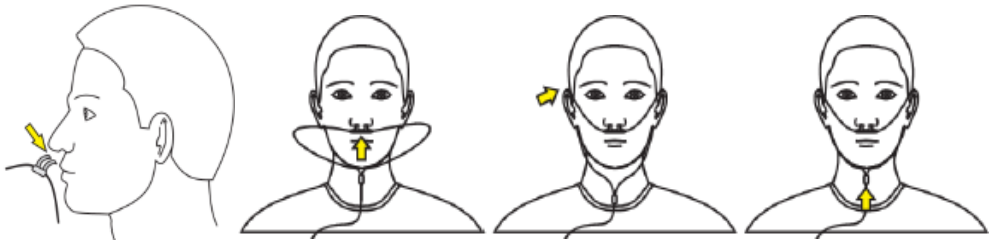
   Shave the area if needed to help secure leads. Remove the backing of the sticky pad and place the wire labeled **1+** ECG electrode under the right side of your collar bone, and the wire labeled **2+** under the left side of your collar bone and the wire labeled **PGND** on the left side below the rib cage.



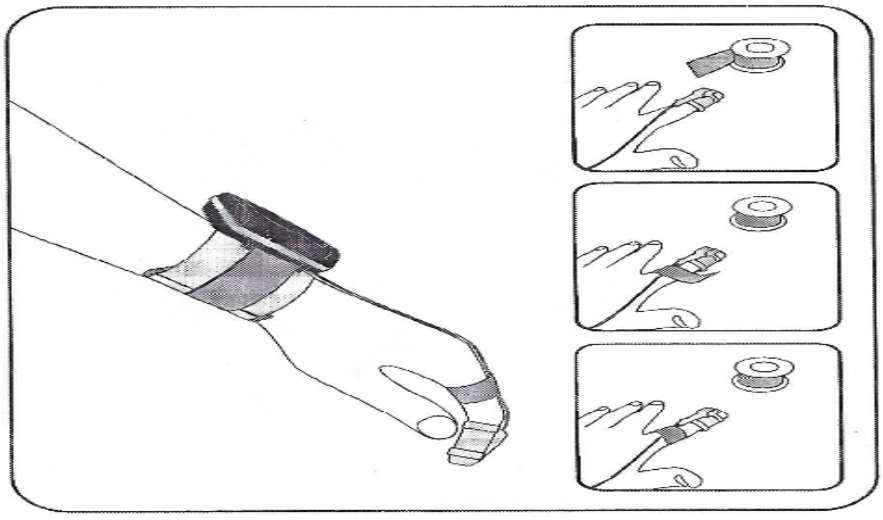


Sticky PAD

5. Place the prongs gently in the nostrils. The prongs should point downward inside the nostrils. Pull the cannula over your ears and then position the tubing under your chin. Slide the fastener snugly under the chin.
   **** If you are on home supplemental oxygen you will skip this step and wear your oxygen therapy as you would normally.
   **** PAP therapy see PAP set-up handout and this step will be skipped.



6. Put the probe of the oximeter on your finger and attach the strap with the wrist device on your non-dominate hand. Place a piece of tape around your finger over the white cable to keep this from falling off. The device will automatically start reading.



7. The indicator light on the device blinks green when the recording is in progress and functioning normally. When there are any device warnings the light blinks orange.

1. On the top right corner is a battery bar which shows the battery status. The battery bar is full when the device has fresh batteries.
2. In the bottom left corner is a number indicating how many recordings are stored on the device. The device can contain as many recordings as the internal 1GB memory allows.



Morning after Sleeping with the Monitor

1. Keep everything attached and do not unhook any of the wires from the unit.
2. Remove the wrist device and oximeter off your hand.
3. Remove the nasal cannula tubing from your face and place it in the resealable bag provided. Seal the bag as much as possible.
4. Unsnap the ECG wires attached to the sticky pads. Remove the sticky pads from your skin and throw them away. *(If needed, use baby oil, olive oil, or mineral oil on a cotton ball. Pour a little on the cotton ball. Rub it over the adhesive areas on your skin, and let it sit. Then use a wet wash cloth to remove it.)*
5. Unhook the belts and leave them attached to the unit.
6. After you have removed everything, place the unit, belts, connectors and tubing in the case with the equipment unit still attached.
7. **Complete Form 151- Participant Sleep Study Questionnaire**.

Returning the Device

- Check to see that the device, belts, tubing, wrist device and wiring are in the carry case provided by your coordinator.
- Place the device bag, the completed Form 151-Sleep Study Questionnaire, and any other forms that you need to return to **PVODOMICS** study personnel. You will return these items to **PVDOMICS** staff in the manner agreed upon during your visit.

If you have any questions, please contact

Name:_____ Phone Number: _____

Thank You for Participating!

PVDOMICs Nox T3 Ordering Supplies

Call 1-800-231-2466 for Vyaire/Carefusion Customer Service

Reference Quote # 2016-34912

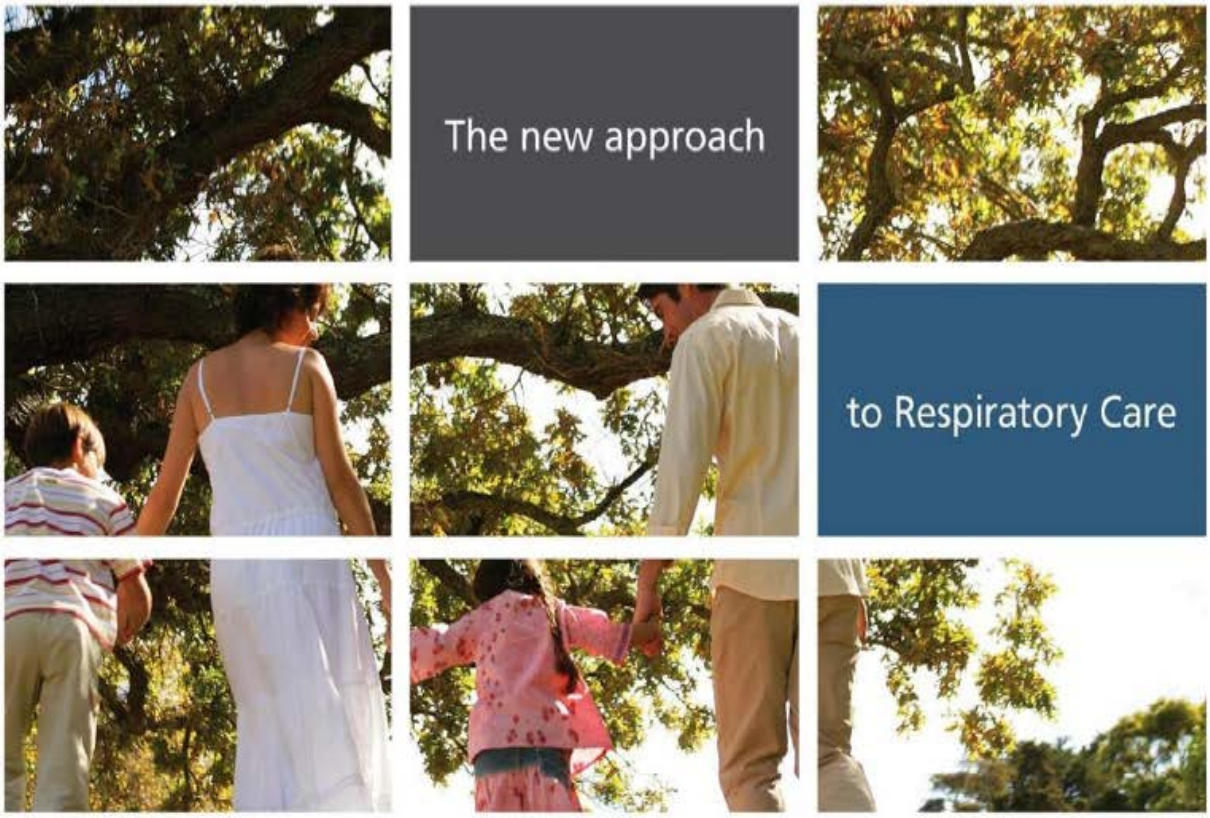
- **Have account number ready.**
- **They may ask for a copy of the attached quote for proof.**
- **There is a minimum of $75 per order. Mention that this is needed "NOW" Minimum order will be waived.**
- **Supplies may be purchased from any preferred vendor.**

If you have any questions please feel free to contact Rawan Nawabit (nawabir@ccf.org or 216-445-1593)

Or

Your local rep which is located at the end of this document.

Respiratory Products Proposal



Quote 2016-34912

Prepared for: Rawan Nawabit
Cleveland Clinic
Cleveland Clinic, Ohio
216-445-1593
nawabir@ccf.org

Prepared by:
Scott Minnich
CareFusion Respiratory Technologies
(724) 316-4979
scott.minnich@carefusion.com

CareFusion
has joined BD

CareFusion
has joined BD

Price Quotation

Customer: Cleveland Clinic

Quotation Number: 2016-34912

11203 Stokes Blvd
Cleveland
Clinic, Ohio 44104

Quote Date: 11/28/2016
Quote Expiration: 1/27/2017

Attn: Rawan Nawabit

Product	Description	Qty	List Price Each	Unit Price	Extended Price
T3					
69594	NOX NASAL CANNULA W/FILTER,BX/40	1	$120.00	$120.00	$120.00
69452	PRO-FLOW NASAL/ORAL	1	$5.00	$5.00	$5.00
69590	NOX DISPOSABLE RIP BELT,SMALL,BX/20	1	$140.00	$140.00	$140.00
69591	NOX DISPOSABLE RIP BELT,MED,BX/20	1	$140.00	$140.00	$140.00
69592	NOX DISPOSABLE RIP BELT,LARGE,BX/20	1	$140.00	$140.00	$140.00
27641-001	NOX DISPOSABLE RIP BELT X-LG BX/14	1	$160.00	$160.00	$160.00
69447	T3 FILTER TUBE CONN - 50PK	1	$115.00	$115.00	$115.00
22989-001	3150 WRIST BAND	1	$7.50	$7.50	$7.50
21817-001	NOX ABDOMEN CABLE	1	$50.00	$50.00	$50.00
21818-001	NOX-T3 CARRY CASE	1	$40.00	$40.00	$40.00
69446	T3 SERVICE KIT	1	$70.00	$70.00	$70.00
27781-001	NOX-T3 HOOK-UP GUIDE, PKG 25 Nox-T3 portable sleep monitor patient hook-up guide	1	$12.50	$12.50	$12.50
Additional					
22990-001	NOX T3 CPAP MASK ADAPTER	1	$6.50	$6.50	$6.50
Additional					
464719	ELECTD LDS W/SFTY CONN 1.5M PK5 Leads. Electrodes with Safety Connector 5/PK	1	$50.00	$50.00	$50.00
Additional					
464720	ELECTRODE LEADS,NICOLET,GOLD,1.5M,12 PK	1	$125.00	$125.00	$125.00
Additional					
464721	ELCTD GOLD CUP 10MM 1MM LEAD PK12	1	$120.00	$120.00	$120.00
Additional					
466631	ELECTRODES BLUE SENSOR DISP WET GEL	1	$19.00	$19.00	$19.00
Additional					
466632	ELECTRODE LEADS,NICOLET,DOME,3.0M,5 PK	1	$44.00	$44.00	$44.00

Total List Price: $1,364.50

CPAP titration parts

MVAP Medical Supplies

1415 Lawrence Drive Newbury Park, CA 91320

Toll Free: 1-877-735-6827 (MVAP) Toll Free Fax: 1-877-735-7213



Item #: 2002G
Category: Cannulas

Price: $0.50

Order Options:

Qty: 1

Add to Cart

Add to Wish List



TRP-740

Oxygen Enrichment Attachment

More Info

$2.95

1

Add to Cart

Add to Wish List

Adapter for use with Gas Sampling tubing:



51302

CPAP In Line Adapter

More Info

$2.50

1

Add to Cart

Add to Wish List

Local Center Vyaire Rep

Brigham – Kevin.LeKites@Vyaire.com

Cornell and Columbia – Jill.Lynch@Vyaire.com

Hopkins – Barry.Peoples@Vyaire.com

Arizona – Charity.Schneider@Vyaire.com

Mayo – Corey.Eckhoff@Vyaire.com

Vanderbilt – Drew.Lackner@Vyaire.com Regional Manager

Chapter 42: Core Sleep Study Monitoring Core MOP

Revision 12/29/2016

42.1 Purpose and Background:

The relationships of sleep disordered breathing and pulmonary hypertension have been described albeit data which have amassed thus far have been limited from the standpoints of small numbers of participants, limited study design and lack of inclusion and consideration of objective pulmonary hemodynamic parameters. The PVDomics study provides an ideal platform to more accurately and comprehensively characterize the relationships of sleep disordered breathing and pulmonary hypertension in a prospective manner. The collection of rich phenotypic data in the setting of pulmonary hypertension as proposed provides a unique opportunity to examine the sleep-pulmonary hypertension inter-relationships on a more granular level.

42.2 Logistics for Sleep Reading Core

The Sleep Reading Core under the supervision of Dr. Reena Mehra (email: mehrar@ccf.org), is part of the Data Coordinating Center at the Cleveland Clinic, Cleveland, Ohio. Additional contact information can be found in the PVDOMICS Address Directory. All sleep study files will be transmitted to the DCC Sleep Core for scoring of the data and assessment of quality grade.

42.3 Overview

This manual provides standard operating procedures for Readying Core management of Overnight Sleep Study Monitoring. This manual will address the scoring, archiving, and transfer of data; as well as the certification of Clinical Centers.

42.3.1 Sleep Study for PVDOMICS Study

Overnight sleep monitoring will be performed routinely in all enrollees to acquire standardized baseline information on sleep disordered breathing and to quantify overnight oxygen saturation patterns. Participants already receiving oxygen supplementation and/or positive airway pressure therapy on a regular, nightly basis will be studied during use of these. A portable home monitoring system (Nox T3, Carefusion) will be used, with recordings of nasal airflow, chest wall and abdominal motion as well as pulse oximetry, heart rate, and position. Each center will purchase the equipment necessary to perform these studies, and study personnel will be trained in the proper application of the devices.

42.3.2 Historical Sleep Study

If the participant has had a sleep study within the last year of study enrollment, then it is at the discretion of the Center PI as to whether a research sleep study should be performed. The results of prior sleep studies as well as any additional testing or interventions obtained as a consequence of the portable monitoring will be recorded. The historical sleep study data must meet the PVDomics inclusion criteria. Sleep studies will be scored using standardized methods for home sleep apnea testing and will conform to American Academy of Sleep Medicine guidelines. The summary data will be electronically transmitted to the DCC for integration into the database and for statistical analysis If this information is available on a clinical basis within 1 year prior to study entry and with no change in nighttime oxygen or sleep disorder therapy, and in the opinion of the investigator, no change in patient condition that would impact results, then the clinically available data may be considered adequate for inclusion in the case report form – if available, a copy of that study be acquired for Reading Core review, quality assessment and scoring.

42.4 Center and Equipment Study Certification

The Sleep Core requires at least one (1) Staff member at each Clinical Center to be certified to collect for the PVDOMICS study, two persons are preferred. This certified research staff will be responsible for protocol adherence by any study personnel performing data collection at that Center. Certification must be accomplished prior to the Center performing actual data collection. Sleep monitoring data collection certification is provided upon demonstration that the staff member has:

- Basic understanding of sleep-specific study objectives and protocol for PVDOMICS.
- Understanding of equipment and application of specific sensors to be used for the sleep monitoring data acquisition.
- Demonstrated compliance with the study protocol for sleep monitoring data collection and data transmittal via secure file transfer to Sleep Core including removal of identifier information and correct re-identification with participant ID.

In order to obtain sleep monitoring data collection certification, the following items must be met by the individual to be certified:

- Submission of two acceptable overnight pilot studies (non-participant) recordings. Pilot studies on volunteers are conducted to assure that all staff are familiar with the equipment and protocol.

These submissions must be correctly de-identified, re-identified with a standard convention, successfully converted to EDF format and upload to the secure server. This serves both as part of the research staff certification process and as practical experience in using the equipment in the study environment. Certification studies also allow for verification that all sensors and equipment are functioning properly before being used on a study participant, and that post-acquisition treatment and transfer of data is consistent with study protocol. The certifying research staff does need not to actually perform every required task, but will be responsible for the acceptable completion of each task.

To be considered acceptable, the recordings submitted for certification must:

- Have adequate quality signal on each channel (i.e. all electrodes must work) and signals must be relatively free from artifact.
- Reflect sleep monitoring protocol and procedure including placement of electrodes and sensors.
- Have correct study identification as a certification recording using the following format when naming (or re-naming) the recording: [CR] [staffID]_[date of study]. An example of this format would be CRstaffID_102916. The electronic recording file must be accompanied with paperwork that matches this naming convention and additionally includes the technician identification and equipment ID.
- Include the following:
    - Form 150- Clinical Center Participant Sleepy Study Initialization, Demonstration and Placement
    - Form 152- Clinical Center Sleep Study Download and File Transmission

Data Management at the Reading Core

42.5 Study Receipt

Upon receipt of studies at the Sleep Core, the study data will be checked for quality. The receipt information includes: Subject ID, Study Date, date received via FTP, unit ID, and Staff ID. If there is a discrepancy between the data contained on the Sleep study evaluation Form and Sleep Study recorded file or any missing data on the forms an e-mail will be sent to the Site Coordinator requesting clarification.

A copy of Form 150 and 152 is sent to the Reading Core regardless of the quality or length of the recording. If at time of download of the Sleep monitor unit there is no data, the Form 150 and 152 must be sent. A note should be made on the forms that there was no data at the time of download. Short studies or problem studies that do not meet the criteria to be "passed" for scoring at preliminary review, should still be sent to the Sleep Core with any notes as to what troubleshooting was done, and if the reason for the short study can be determined. The Sleep Core tracks all problems relating to lost sleep studies and must receive this paperwork on a regular basis. The problem studies are monitored and if any systemic pattern is observed study-wide, we will work to resolve the problem. These forms can be placed on the secure server.

42.6 Preliminary Review and Scoring

The Noxturnal ® Offline Analysis program will be run at the Sleep Core prior to review of studies by the Polysomnologist for accurate visualization of signals and graphic screens. After offline analysis of the record, the study will be reviewed to determine any signal quality issues, possible monitor/electrode malfunctions, pass/fail status and possible Urgent Alert status indicating need for priority scoring.

To be classified as “reliable sleep data”, the record must contain at least 3 hours of scorable/ reliable oximetry accompanied by one scorable respiratory channel (either nasal cannula, thoracic, or abdomen inductance plethysmography) after reported bedtime. Studies containing less than the minimal requirements will not be processed for scoring and the site coordinator will be notified via e-mail to request a repeat study from the participant.

The following categories of discrete breathing events will be identified during scoring: obstructive apneas, central apneas, and hypopneas. If flow from the nasal mask has been collected then obstructive events will be scored.

42.7 Reliability

A registered polysomnologist will be assigned to score all PVDomics sleep studies. A sample of studies will be re-circulated after relabeling their identifying information to assess intrascorer reliability.

42.8 Archiving

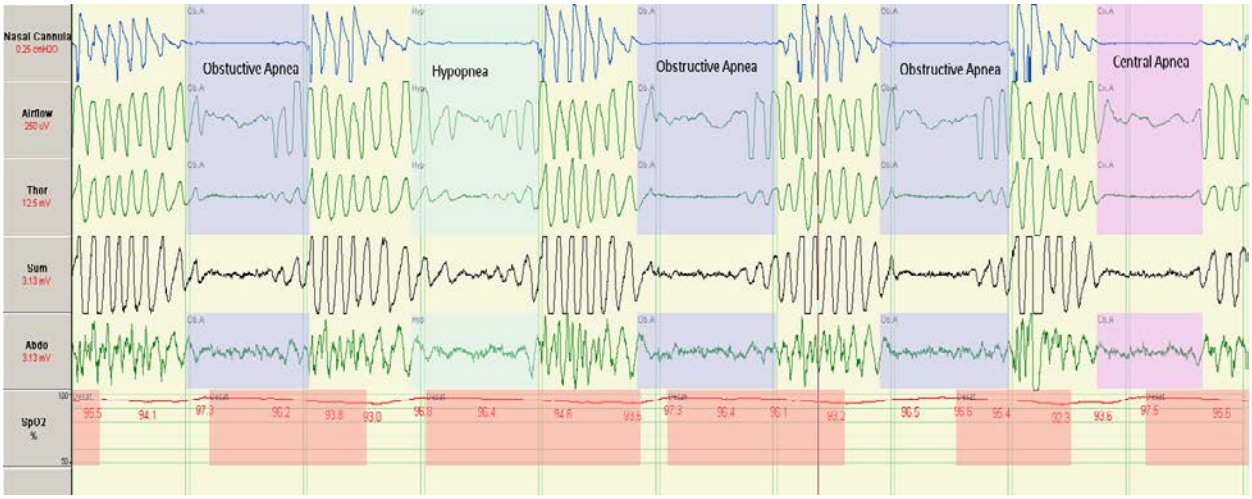
The clinical center must retain original versions of the sleep recording data files that have been created by the download of the overnight study. It is preferred that the site also retain copies of the EDF output files. However, if the EDF file is sent electronically, this is not

required. One CD-ROM disk containing a copy of the original sleep recording and a copy of the converted EDF files always must be retained at the local center in a secure location. These files are source documents and shall serve as “back up” files only.

42.9 Scoring Rules and Event Definitions

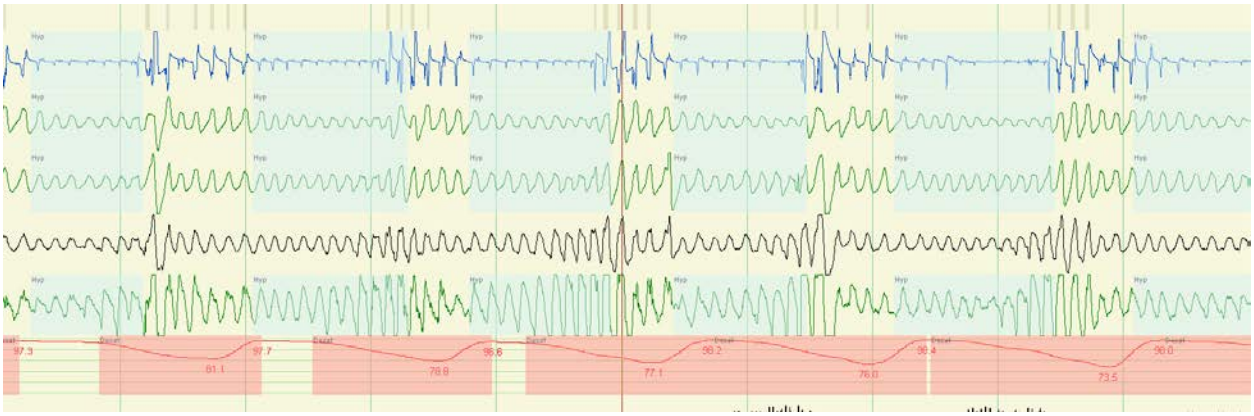
42.9.1 Apneic Events

An apnea occurs when there is a drop in the peak signal excursion by >90% of pre-event baseline using a nasal transducer and the duration of the drop is >10 seconds.



42.9.2 Hypopneic Events

A hypopneic event occurs when there is a peak signal excursion drop by >30% of pre-event baseline using nasal pressure or an acceptable alternative signal (e.g. RIP sum) lasting >10 seconds. The event must have a $\geq$3% oxygen desaturation.

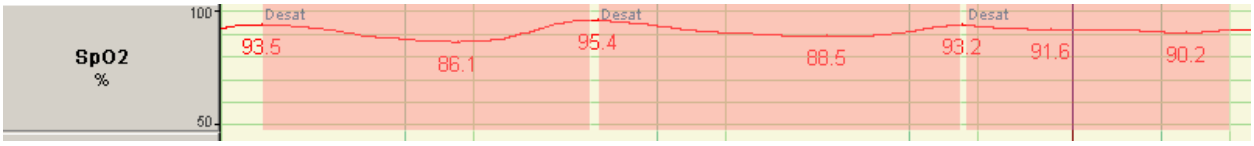


42.9.3 Duration of Apneic and Hypopneic Events

The beginning of an apneic or hypopneic event is defined as the first point at which cessation of airflow via nasal pressure transducer (for hypopneic events) is clearly evident on the tracing of nasal or mask. The end of an apneic or hypopneic event is defined as the last point at which cessation of airflow (for apneic events) or reduction of airflow (for hypopneic events) is clearly evident on the tracing of nasal or mask prior to an increase in airflow.

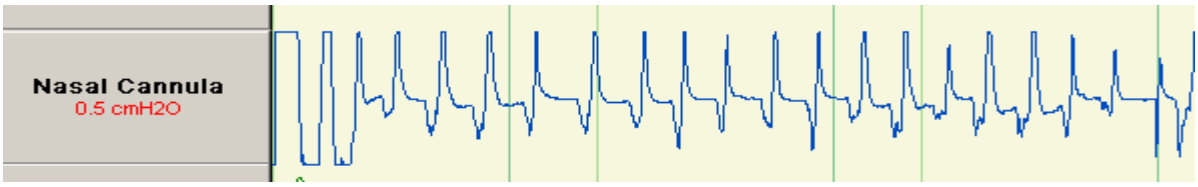
42.9.4 Oxygen Desaturation of ≥3%

A 3% oxygen desaturation refers to the change in saturation from a preceding stable level (immediately prior to the hypopnea) to the nadir level that follows the termination of the event (usually within 30seconds of the event). Saturation values that appear increased due to arousal and hyperventilation are not considered to represent the baseline value.



42.9.5 Nasal Flow Limitation

Nasal flow limitation is derived from the nasal cannula signal. A normal flow signal will present a regular sinus rhythm and curve. Flow limitation may occur with increase upper airway resistance, not sufficient enough to cause discrete apneas and hypopneas. A regular sinus curve will transform into a signal that resembles a lower case 'h'.



42.10 Medical Alerts

Studies identified as potential urgent alerts will be triaged for immediate scoring (within 48 hours of assignment to the scorer). Once fully scored and determined to meet criteria for Urgent Alerts, a physician investigator will be asked to review the study. Although not a medical alert, we will notify sites for those studies with an AHI≥15 suggestive of the diagnosis of moderate to severe obstructive sleep apnea so that this information can be shared with the participant.

- Urgent Alert criteria include: AHI ≥ 50; O2sat <85% for >10% of TST.

- Unusual HR/ECG (Pertains to the following arrhythmias:

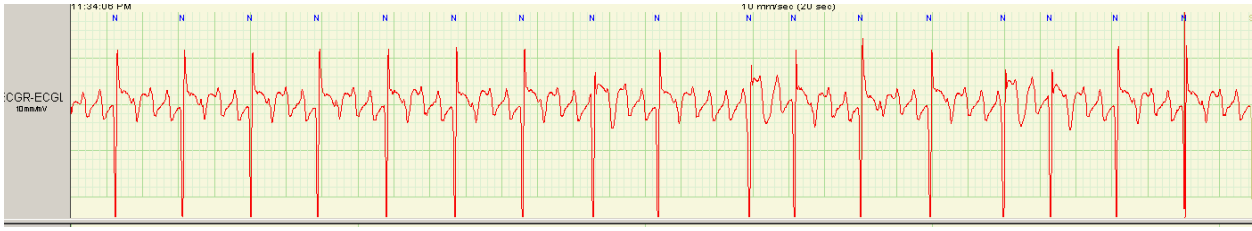
- Atrial Fibrillation/Atrial Flutter with rate< 50bpm or >150bpm



- Paroxysmal Atrial Fibrillation



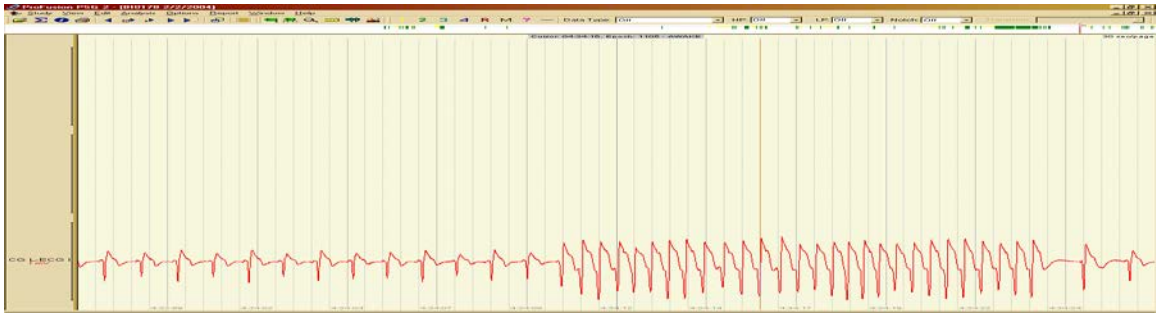
- Atrial Flutter



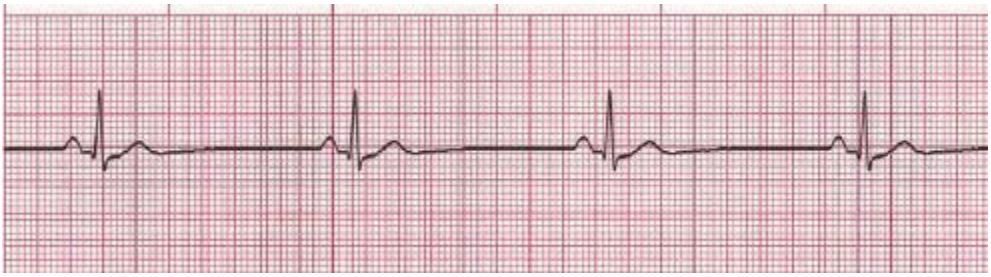
- Supraventricular Tachycardia sustained for 30 seconds or greater with heart rate >150 bpm



- Wide QRS Tachycardia (>4 beats with rate >100bpm)



- Marked bradycardia (<30bpm for 6 seconds or greater)



- Second degree AV block Mobitz Type II

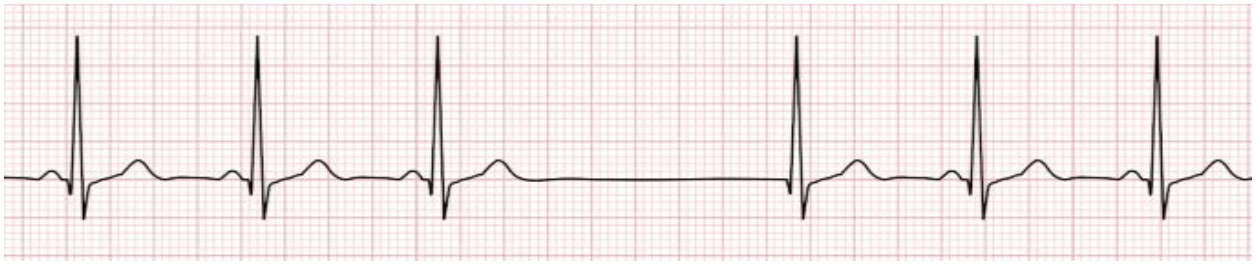




- Third degree AV block



- Sinus Pauses >3 seconds



42.11 Abbreviations and Acronyms

AASM	American Academy of Sleep Medicine
AHI	Apnea Hypopnea index
ASV	Adaptive- Servo Ventilation
BIPAP	Bilevel Positive Airway Pressure
CPAP	Continuous Positive Airway Pressure
EDF	European Data Format
HR	Heart rate
PAP	Positive Airway Pressure
PI	Principal Investigator
PM	Portable Monitor
TST	Total Sleep Time

42.12 References:

Berry RB[1], Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL,Tangredi MM; American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012 Oct 15;8(5):597-619.

Chapter 50. Pulmonary Function Testing Overview

50.1 General Overview

Pulmonary Function Testing (PFT) testing is one of several tests required for the PVDOMICS Study. This Manual of Operations (MOP) chapter provides an overview to additional PFT chapters which constitute a 'complete set' of PFTs and include the following components:

- Spirometry: MOP Chapter 51
- Lung Volumes by Body Plethysmography: MOP Chapter 52
- Single-Breath Carbon Monoxide Diffusing Capacity (DLCO): MOP Chapter 53

PFTs performed for the purposes of the PVDOMICS study are ideal. However, there are exceptions including when PFTs are performed for clinical care and/or historical data are available. Specific data items needed are discussed in the corresponding chapters for each of the PFT components identified above.

50. 2 Logistics

The PFT Core is a subsection of the Lung Physiology Core which is under the direction of Dr. Mitchell Olman and is part of the PVDOMICS Study Data Coordinating Center at the Cleveland Clinic, Cleveland, Ohio. Kevin McCarthy, RPPT, former manager of the Cleveland Clinic Pulmonary Function Lab and PVDOMICS Study consultant, provides technical direction and quality review of pulmonary function data submitted by the clinical centers. Additional contact information can be found in the PVDOMICS Address Directory.

All PFT tracings and study files will be transmitted to the DCC Core for assessment of quality. Parameters for assessing quality of PFTs review procedures are provided in MOP Chapter 55.

50.3 General Philosophy on Standardization

1. Equipment, procedures, and personnel qualifications are based on the commendations of the American Thoracic Society (ATS)
2. Spirometry procedures and systems at all sites must meet or exceed ATS-ERS standards.

50.4 System and Personnel Requirements

50.4.1 Local Center provides:

- Dedicated testing room
- PFT Equipment – type of machine is not dictated by PVDOMICS Study but PFT Core should be notified if equipment changes
- Names and contact information of PVDOMICS PFT personnel who are considered primary contacts at clinical center PFT Labs
- PVDOMICS data collection form(s), pens
- PVDOMICS Study ID and Alphacode (provided by the Study Coordinator)

50.4.2 PFT Core Provides:

- Instructions for standardized participant testing
- Webinar and individual training for:
  - PFT testing guidelines for PFTs completed for PVDOMICS Study
  - Instructions for transferring tracings to DCC/PFT Core

50.4.3 Clinical Center Personnel Requirements

All technicians should be certified pulmonary function technologists (National Board of Respiratory Care) or meet the recommendations for personnel qualifications issued by the ATS.

The PFT Core will provide training for PFT Lab, techs and coordinators as follows:

- Review of completed PFT Lab Exam form
- Initial PVDOMICS Study central training
- Webinar
- Data transfer
- Review of data and provide feedback to local center on transfer of first 5 cases per PFT tech and QC review
- Individual guidance by PFT Core personnel

50.5 Participant Exclusion from Pulmonary Function Testing

50.5.1 As previously stated, PFTs completed for clinical care will be accepted and must be within 1 year from date of PVDOMICS Form 100-Initial Enrollment.

50.5.2 Excluded from PFT Testing for PVDOMICS Study
Clinical Center PI or other Physician should determine whether undergoing a PFT for the purposes of the PVDOMICS Study will be harmful to the participant and should not be completed.

50.6 Participant Preparation

Participant preparation is described in detail for each component of the measurements. See Chapter 51 for spirometry, Chapter 52 for lung volumes, 53 for DLCO.

50.7 Equipment Quality Control

Table 1. ATS-ERS Recommended Spirometer Quality Control Procedures

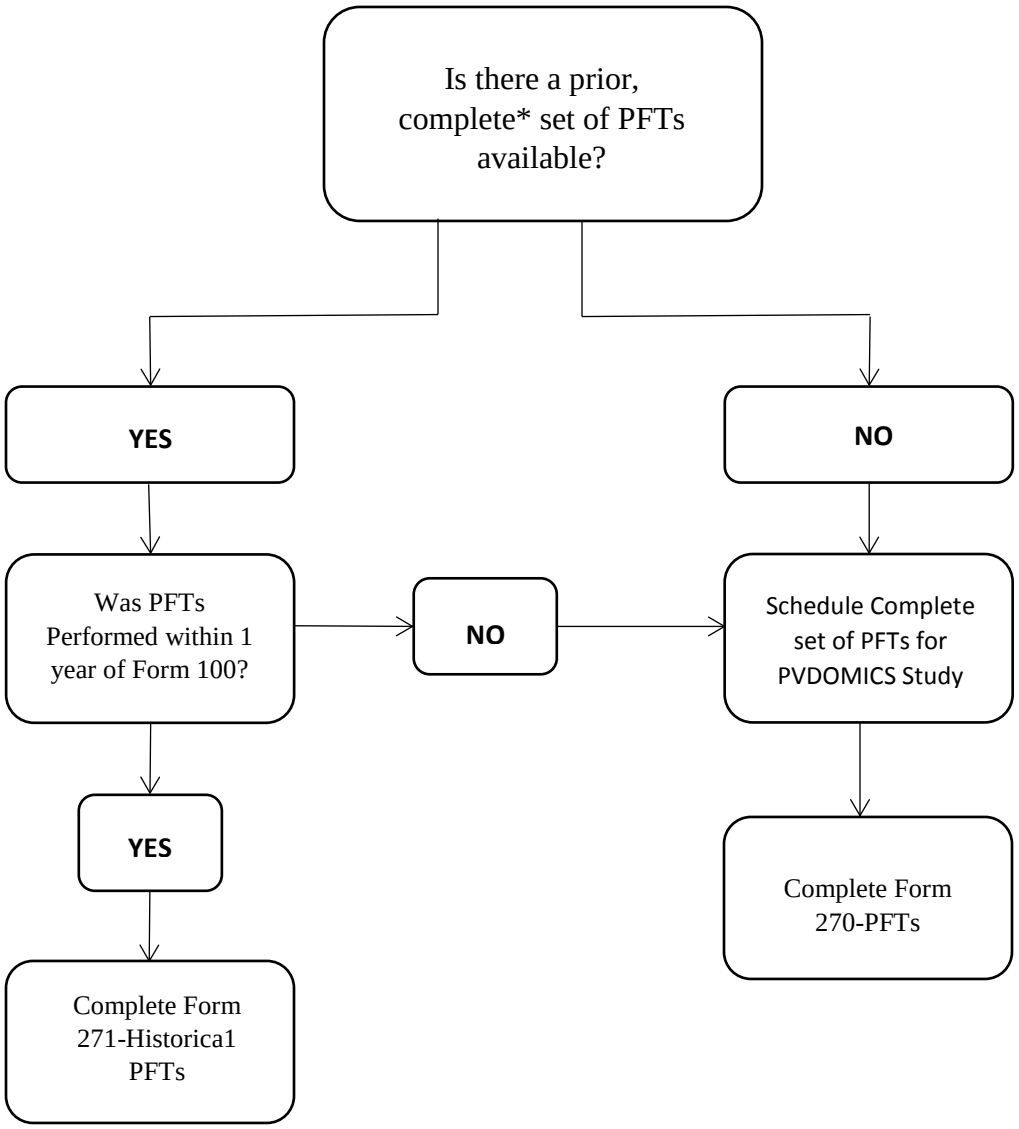
Test	Minimum Interval	Action
Volume	Daily	Calibration check with a 3-liter syringe
Software	2x/month	Perform test using "known biological control" subject, send to DCC

50.8 Data Submission

Specific data submission requirements for each test are documented in the three individual chapters (Chapters 51-53).

It is important for the technician to provide comments summarizing the technical acceptability of the testing session including any problems encountered.

Clinical Care/Historical PFTs



*Complete set of PFT's includes:
Spirometry, Lung Volumes, DLCO

Chapter 51. Spirometry

51.1 Introduction

Spirometry will be used to determine pulmonary functional impairment for PVDOMICS study. Results will be used to aid in classification of participants with pulmonary arterial hypertension.

51.2 Participant Preparation

1. Participant must be seated during test.
2. Nose clip must be worn during testing.
3. Participant should loosen any restrictive clothing.
4. If participant has dentures that are tight fitting they should remain in place. If dentures are loose they should be removed and the technician should ensure that the participant can form a tight seal around the mouthpiece.
5. In the event the participant is unable for any reason (i.e., scleroderma) to develop a tight seal around the mouthpiece, then an alternative mouthpiece can be used and, if necessary, held in place. If so, document non-standard mouthpiece on Form # 270 and document quality of seal on PFT report form.

51.3 Forced Vital Capacity (FVC)

1. Instruct participant, including a demonstration. Emphasize the necessity for a deep, full inspiration, a hard and forceful "blast," and a complete expiration for at least 6 seconds.
2. Perform at least three acceptable and reproducible FVC maneuvers as described below.

51.4 PVDOMICS Acceptability and Repeatability Criteria

Within Maneuver Criteria ("acceptability"):

1. Maneuver is free from artifacts
   a) cough during the first second of exhalation
   b) glottis closure that influences the measurement c) early termination or cutoff
   d) effort that is not maximal throughout the first second
   e) leak
   f) obstructed mouthpiece
2. Maneuver has good start
   a) back-extrapolated volume less than 5% of FVC or 0.15 L, whichever is greater
   b) time to peak expiratory flow is less than or equal to 0.12s
3. Maneuver has satisfactory end of test.
   a) duration of at least six seconds and a plateau ($\geq$ 1s) on the volume-time curve unless the participant cannot or should not continue to exhale for medical reasons (e.g., syncope)

51.5 Between Maneuver Criteria ("repeatability")

1. After three acceptable spirograms have been obtained, apply the following tests:
   a) the two largest FVCs must be within 0.150 L of each other
   b) the two largest FEV_1s must be within 0.150 L of each other
2. If both of these criteria are met, the test session may be concluded.
3. If both of these criteria are not met, continue testing until:
   a) both of the criteria are met with analysis of additional acceptable spirograms
   OR
   b) a total of eight tests have been performed (optional)
   OR
   c) the participant/participant cannot or should not continue
4. Save, as a minimum, three reproducible maneuvers**.**

51.6 Post-bronchodilator Testing

After the initial measurements of forced expiratory maneuvers, the test is repeated after an inhaled bronchodilator. Albuterol is the bronchodilator selected for use in the PVDOMICS study. Post-bronchodilator testing allows the investigators to determine how much the participant's lung function can be quickly reversed or returned toward normal.

Administer two puffs of albuterol using an aerosol spacer:

1. Shake the metered-dose inhaler (MDI) several times. Prime the MDI per the instructions on the package insert and attach it to an aerosol spacer.. Hand the MDI to the participant. The technician should observe the inhalation for proper administration and technique. The technician may administer the albuterol if this is lab policy.
2. The participant should exhale.
3. The spacer mouthpiece should be inserted fully into the mouth with the participant's lips closed around it—the MDI should be in its upright position in the spacer.
4. As the participant begins to inhale very slowly, the MDI should be triggered.
5. The participant should continue to inhale slowly and deeply to maximal inhalation (total lung capacity or TLC).
6. The breath should be held for at least 5 seconds at the end of a full inspiration.
7. Instruct the participant to shake the MDI and repeat steps 2–6 for a total of 4 puffs.

Although there may be a small benefit to waiting 5 minutes between inhalations of a bronchodilator, it is more practical and satisfactory to administer the second inhalation (1puff) about 30–60 seconds after the first. After administration of albuterol, maximum bronchodilation may take 30 minutes, but sufficient bronchodilation occurs within 15 minutes. Wait 15 minutes before performing post-bronchodilator spirometry.

51.7 Spirometry Data Submission Requirements:

1. Volume-time tracing for each effort.
2. Flow-volume curve for each effort.
3. Data table showing FVC, FEV1, FEV1/FVC ratio, FET (forced expiratory time), Vbe (back-extrapolated volume in liters, Vbe% (back-extrapolated volume, as % of FVC), TPEF (time to peak expiratory flow rate), PEFR, PIFR, FEF50, FIF50 for each effort.

A screen shot after completion of each effort is the most expedient method for obtaining all of the above.

Chapter 52. Lung Volumes by Body Plethysmography

52.1 Introduction

Body plethysmography will be used in the PVDOMICS study to determine lung function including functional residual capacity, residual volume, total lung capacity, and slow vital capacity. During the procedure the participant is seated in an enclosed chamber that measures changes in pressure, flow, or volume. Plethysmographic measurements of lung volumes can help differentiate restrictive and obstructive disease processes such as pulmonary fibrosis or COPD/asthma.

This document describes the specific procedures to be used for PVDOMICS study measurements. The procedures conform fully with the current ATS/ERS standards.

52.2 Definitions

- Thoracic Gas Volume (TGV) – the volume of gas measured at the time of shutter closure. May be slightly more or less than FRCpleth. Switch-in error, switch-in correction – the difference between FRC and TGV. Used to correct TGV to FRCpleth
- Functional Residual Capacity (FRC) – the volume of gas present in the lungs at end-expiration during tidal breathing. This may be determined by observing a volume-time tracing showing resting, non-coached tidal respiration. When a stable end-expiratory level is achieved (usually 3-10 breaths; no less than 3), the shutter is activated (closed) and remains closed for 2-3 seconds. The participant is instructed to perform a series of gentle (~+10cmH2O) 'pants' at a coached frequency between 0.5 and 1.0 Hz (30-60 cycles per minute).
- Residual Volume (RV) – the volume of gas remaining in the lung after maximal exhalation
- Expiratory Reserve Volume (ERV) – the volume of gas that can be maximally exhaled from the FRC
- Inspiratory Capacity (IC) – the maximum volume of gas that can be inspired from FRC
- Total Lung Capacity (TLC) – the volume of gas in the lungs after maximal inspiration
- Vital Capacity (VC) – the maximum volume of air that can be exhaled from full lung (TLC) to empty lung (RV) or the maximum volume that can be inhaled from empty lung to full lung (inspiratory vital capacity (IVC).

52.3 Participant Preparation

Pre-Testing: Plethysmography should not be attempted if the participant is unable to sit upright in the chamber, unable to perform the panting maneuver, or unable to perform maximal inspiratory and expiratory efforts. If the participant has severe claustrophobia that would preclude sitting in a phone booth-like structure with the door closed for 1-2 minutes at a time, it may not be possible to obtain plethysmographic measurements. If the participant has a known

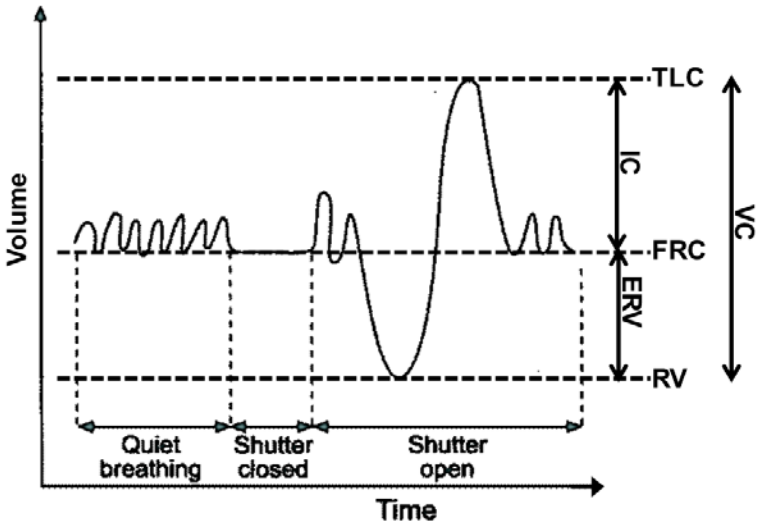
perforated tympanic membrane, a snug-fitting earplug may be used to prevent gas leaks during the panting maneuver. Supplemental oxygen flow must be discontinued during efforts.

Medication hold times are as per spirometry MOP. Spirometry should be delayed or rescheduled, if feasible, in the event that a study participant used a medication within the restricted time period. If the study participant is unable to hold bronchodilator mediations due to severe respiratory disease it is acceptable to proceed with testing. However, the medications, doses and times of administration of all bronchodilators taken within the past 24 hrs should be recorded,

Testing Procedures: All measured lung volumes should be linked. TGV and lung subdivision measurement must occur without the participant coming off of the mouthpiece. The participant should be instructed about the maneuvers involved in each step of the procedure, the importance of exerting maximal expiratory and inspiratory efforts during the RV and TLC phases of the maneuver, and how to pant during the shutter closure to obtain 0.5-1.0 Hz (30-60 cycles/minute) frequency and airway opening pressure changes of about ±10 cmH2O. Airways resistance measurements should not be done at the same time as plethysmographic lung volumes due to specific panting maneuvers used and their influence on end-expiratory lung volume. Nose clips should be in place throughout the maneuvers, and cheeks should be supported with both hands at least during the panting maneuver. After closing the door and allowing an appropriate period of time for thermal equilibration (no less than 20s), the participant should breathe through the mouthpiece in a relaxed manner until the end-expiratory volume is constant for at least 3 breaths before activating the shutter closure.

The preferred sequence of maneuvers after the shutter closure is maximal exhalation to RV (to obtain ERV), followed by maximal inhalation to TLC (to obtain VC). A series of 3-5 technically satisfactory panting maneuvers, followed by coupled ERV maneuvers, should be recorded. The participant may take a tidal breath or two after the shutter closure if dyspnea precludes an immediate ERV maneuver. Dyspnea is sometimes lessened by allowing a slightly larger than average tidal breath before exhalation to residual volume. If the thoracic gas volume measured during the shutter closure is displaced from the average end-expiratory volume prior to the shutter closure, the FRC volume marker should be adjusted manually (if not automatically adjusted by the software) to the end-expiratory volume. If the TGV is adjusted to FRCpleth automatically, visual verification of this correction is indicated. Three FRC values within 5% of one another should be averaged, and the average value reported as FRC. The technically satisfactory ERV values that are coupled to the selected FRC measurements are averaged, and subtracted from the average FRC value to obtain RV. The single largest technically acceptable VC value is added to the RV to obtain TLC.

See diagram on next page



If the participant is unable to perform the maneuvers in the preferred sequence, an acceptable alternative is to perform linked IC maneuvers after the shutter closure, followed by a slow expiratory VC maneuver. For this sequence the average of technically acceptable linked ICs is added to the mean FRC to obtain TLC, and the largest slow expiratory VC is subtracted from TLC to obtain RV. It also is acceptable to obtain measurements of VC (either inspiratory VC or slow expiratory VC) separately from the linked FRC-IC maneuvers or the linked FRC-ERV maneuvers if the participant is unable to perform the entire sequence with good efforts. If this is case, indicate the unlinked status of the vital capacity used to calculate TLC or RV in the COMMENTS section of your PFT report.

52.4 Data Submission

Please submit the following documentation. This will allow the quality of the measurements to be assessed and assigned in the database. As the information required to rate each testing session requires assessment of the individual efforts, we recommend a screenshot at the time of completion of each effort be taken and submitted.

a) Volume-time tracing showing tidal breathing before shutter closure, shutter closure and lung subdivisions measured after shutter opening. This allows assessment of stability of the assigned FRC level, patency of the shutter during the maneuver and the linking of all components of the lung volumes. This should be clearly labeled with effort number.

b) TGV loops scaled to allow the entire loop to be visualized, clearly labeled with effort number.

c) Data table showing TGV, FRCpleth, ERV, IC, VC, RV and TLC, clearly labeled with effort number.

Technician comments should summarize the technical acceptability of the testing session including any problems encountered.

Chapter 53: Clinical Center Single-Breath Carbon Monoxide Diffusing Capacity (DLCO) MOP

53.1 Introduction

The DLCO will determine the degree of pulmonary impairment in participants enrolled in the PVDOMICS Study. The purpose of this chapter is to ensure that the DLCO test is performed using standardized procedures and techniques in order to provide accurate test results and a safe testing environment for the participants enrolled in the PVDOMICS Study.

The diffusing capacity of the lung for carbon monoxide (DLCO) is used to evaluate the transfer of gas from the distal air spaces into the pulmonary capillaries. It can be measured when known and very low concentrations of carbon monoxide (CO) are inspired. The rate of CO disappearance is calculated from the ratio of the CO concentrations of the estimated alveolar and expired gas and then expressed as a function of the driving pressure (mLCO/min/mmHg).

53.2 Participant Preparation (Pre-Test Instructions):

- The participant should refrain from smoking or other CO exposures on the day of the test. The time of the last cigarette smoked should be recorded and noted in interpretation. Measure participant's height in centimeters (cm) to nearest cm, or in inches (in) to nearest ½ in, while he/she is standing erect, without shoes.
- The participant's weight should be measured using an accurate scale: weight is not required for reference values for DLCO, but may be useful for interpretive purposes.
- The participant's age should be recorded as age on their last birthday.
- The DLCO test should be done in the sitting position, with the participant sitting quietly for at least 5 minutes before testing and remaining seated throughout the procedure.
- The participant should refrain from exercise for at least 1 hour before the test and a large meal for at least 2 hours before the test.
- The participant should refrain from drinking alcohol for at least 4 hours before testing.
- If clinically acceptable, supplemental O_2 should be discontinued for 10 minutes before beginning the test. If this is done, monitor SpO_2 and resume oxygen therapy if the SpO_2 falls below 80%. Note the time off of supplemental oxygen and the SpO_2.
- If the participant cannot be off supplemental oxygen for a full 10 minutes plus 2 minutes for the DLCO test without the SpO_2 falling below 80%, the interval of time off O_2 should be adjusted appropriately and recorded so that the results can be interpreted accordingly.

53.3 Assessment of Participants:

- Assess each participant for physical and developmental status to determine ability to perform the diagnostic test and if special arrangements are required. If there is a language barrier, an interpreter will be used.
- Participants should be asked if they have complied with the preparation criteria including:
    - If they have recently smoked, and if so, what was the time?
    - If they have consumed alcohol within 4 hours of test starting time.

- If they have eaten within 2 hours of test starting time.
- If they have exercised within an hour of test starting time.

- Postponement may be necessary if the participant has not complied with the preparation criteria. The ordering physician is to be contacted to determine if rescheduling is necessary.

In order to properly interpret the test results, relevant clinical information should be provided in writing by the ordering physician (i.e., diagnosis and type of treatment).). Additionally, a measurement of hemoglobin concentration within two (2) weeks of the PFT needs to be obtained in order for accurate interpretation of DLCO.

-

53.4 Special Safety Precautions

The following may pose a relative danger to the participant and/or affect the validity of the test:

- More than five maneuvers will likely increase the COHb level by approximately 3.5%, which in turn will likely decrease the DLCO value by approximately 3-3.5%, and is not recommended.
- A large meal or vigorous exercise immediately before the test
- Mental confusion or poor muscular coordination that prevents the participant from adequately performing the maneuver or the inability to adequately seal their lips on the instrument mouthpiece.

53.5 Equipment Preparation

- Ensure CO_2 and H_2O absorbers (if applicable) are replaced at a frequency recommended by the manufacturer, when saturated (as indicated by color change), or sooner. Additionally, they should be placed in the proper order (i.e., the CO_2 absorber should precede H_2O absorber). If selectively permeable tubing is used, ensure it has been replaced at appropriate intervals as recommended by the manufacturer.
- Turn on the equipment to ensure adequate warm-up time, usually at least 30 minutes.
- Ensure the system is leak-free each day of use.
- Check inspiratory flow from the demand valve (if applicable, the maximal inspiratory pressure required for a 6 L/s inspiratory flow should be less than 10 cmH_20).
- Ensure gas chromatograph columns, or elements of the gas measuring system with limited life span are replaced at the frequency recommended by the manufacturer.

53.6 Calibration Check (Verification)

- Volume calibration check (verification) with a validated known-volume syringe (e.g., 3.00 L) should be performed each day the test is performed. The accuracy validation limit for recovered volume is ±3.5%. For large surveys or high participant loads the volume calibration check should be done more frequently.
- Two-point (zero and full scale) calibration of the gas analyzer(s) should be done each day. The gas used to calibrate the DLCO tracer gas and carbon monoxide analyzers should be certified to the hundredth of a percent for the tracer gas (helium or methane) and the nearest thousandth of a percent for carbon monoxide with an analytical accuracy of two percent.

53.7 DLCO Testing Procedures

Pre-Test Procedure	
Check participant identification	Identify the participant using an institutionally approved process.
Orders	Check for a complete physician's order.
Demographics	Collect and record demographic information.
Test explanation and participant training	Explain and demonstrate test maneuver, including a tight mouth seal.
	A complete deep breath with rapid inspiration is required after a complete slow exhalation.
	The breath hold should not consist of expiratory effort against the closed airway (Valsalva maneuver), and/or no inspiratory effort against a closed airway (Mueller maneuver).

Test Procedure	
Procedure	Instruct the participant to put mouthpiece in mouth and nose clip on nose and breathe quietly.
	Begin by measuring tidal breathing.
	After at least three breaths, instruct participant to exhale slowly to residual volume (RV).
	When at or near RV, activate the valves and instruct participant to inhale to total lung capacity (TLC) so that VI is inspired in less than 4 seconds. The inspired volume to test gas (VI should be at least 85% of the largest vital capacity measured that day.
	Coach the participant to hold his/her breath with the lungs held full for approximately 10 seconds.
	Instruct the participant to exhale at a moderate speed.
	After an appropriate washout volume (0.75-1.0L may be reduced to 0.5L if the VC is less than 2.0L)has been expired, collect a gas sample (alveolar sample) of 0.5 – 1.0L should be collected or measure the mean exhaled gas concentration over a comparable volume change
	Instruct the participant to come off the mouthpiece, but remain seated.
	Perform at least two acceptable maneuvers that agree within the largest of 10% of the mean value, or within 3 traditional DLCO units (1 SI unit) of each other. At least 4 minutes should be allowed between each test trial.

53.8 Review of Test Results:

- Individual test maneuvers are acceptable if:
  - Properly quality controlled instrumentation was used.
  - Inspire volume of test gas was at least 85% of largest VC in less than 3 seconds.
- A stable calculated breath-hold time of 10 ±2 seconds (8 to 12 seconds).
  - No evidence of leaks or Valsalva or Mueller maneuvers during the breath hold.
  - Expiration after breath hold in less than 4 seconds with appropriate clearance of dead space before sampling the alveolar gas. Note: tests outside these limits may still have clinical utility, but deviations from the standard acceptability criteria should be

noted and possible impact considered.

- Assure that the washout volume of anatomical and mechanical dead space before the alveolar sample is collected is 0.75 to 1.0 L. If a participant's VC is less than 2.0 L, the washout volume may need to be reduced to 0.5 L.
- Using a rapid gas analyzer with visual display, these washout and sample volumes can be adjusted in participants with low vital capacities to assure an appropriate sample for analysis. Settings should remain as indicated above (#2) for participant's whose vital capacity allows those volumes to be met easily.
- Assure that there were at least 4 minutes between maneuvers.
- Assure that at least two acceptable maneuvers have been performed that agree within the larger of 5% of the mean value, or 3 traditional DLCO units (1 SI unit) of each other.

Assure that the Jones-Mead method of calculating breath hold time was used. See Figure 1

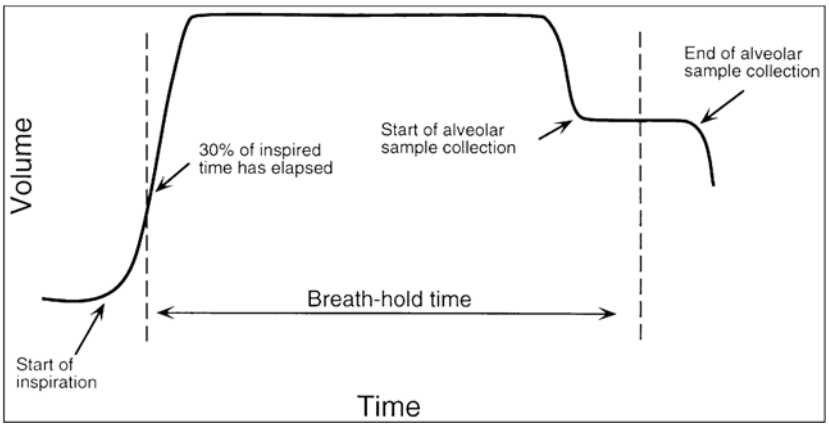


Figure 1: Graphic illustration of the Jones-Meade method for calculating the breath-hold time during the DLCO maneuver. The breath-hold time starts after 30% of the time it takes to inspire the test gas has elapsed, and ends halfway into the alveolar sample collection. The beginning of inspiration is determined using the back extrapolation technique, although it has been recently reported that there are no significant differences between the visual and extrapolation approaches.

- Assure between maneuver repeatability criteria has been met.

53. 9 Reporting of Test Results:

- The average of at least two acceptable maneuvers that meet the repeatability requirement should be reported (i.e., outliers need to be excluded).
- The report should always include:
  - Measured uncorrected DLCO
  - DLCO/VA, also known as KCO (VA is reported as BTPS)
- Any adjustments (e.g., Hb, COHb, PO_2) should also be reported separately along with the data used to make the adjustment.
- The average VA (BTPS) should be reported along with the predicted VA (the predicted TLC minus predicted dead space) and % predicted VA.
- The average VI at BTPS should be reported.

53.10 Data Submission requirements

- Screen shot showing volume-time tracing with mouth pressure for each effort.
- Screen shot showing gas analysis curve for each effort.
- Data table showing uncorrected DLCO, DL/VA, VA, Vin (IVC), VCmax, discard volume, sample volume, Tin (inspiratory time), Tex (expiratory time), BHT, FIHe(or FICH3), FAHe(or FACH3), FICO, FACO, Hb (if available), COHb (if available) for each effort and altitude (Pbar)

53.11 Procedure Notes:

- Various miscellaneous factors may affect this test.
    - A diurnal variation (1.2% fall/h from 9:30 AM to 5:30 PM) has been reported. However, this fall can be explained by increasing COHb and decreasing Hb concentrations.
    - A 13% change during menstrual cycle has been reported The highest DLCO value was observed just before the menses and the lowest DLCO value on the third day of menses.
    - A 15% reduction 90 minutes after ingesting ethanol has been reported.
    - Cigarette smoking or other causes of elevated COHb
    - Increased altitude. This will be adjusted for by the DCC.
- When test specifications are not met, such data should be reported with the warning that the data are suboptimal by providing technician comments detailing the procedural shortcoming.
- Small increases in COHb (about 0.7% per inhalation of test gas) occur when CO is inspired during the DLCO test.
- An adjustment for Hb concentration will be performed by the DCC. Measurements of Hb are acceptable within 2 weeks (in clinically stable participants without a suspicion for blood loss) of the DLCO measurement; the date and source of the Hb should be documented in the COMMENTS section of the report.

53.12 Equipment and Supplies:

- System description (e.g., manufacturer, model, type, accessories, additional features, and software version). The system should meet or exceed recommendations made in the latest ATS standardization document on DLCO.
- Cylinder of test gas appropriate for the testing system.
- Mouthpiece, nose clip, carbon dioxide (CO_2) and water absorbers, and other miscellaneous supplies needed (e.g., tissues, chart paper).
- Infection control supplies: disposable in-line filters (if used), gloves, gowns, masks, and protective eye wear (if applicable).
- Computer/recorder supplies.

Chapter 55. Quality Control of Pulmonary Function Tests

Prepared by Kevin McCarthy, RPFT
Cleveland Clinic Pulmonary Function Core

55.1 Introduction

Characterization of pulmonary function at or time of entry into the PVDOMICS study is an important aspect of the project. Clinical Centers will forward pulmonary function data (spirometry, lung volumes, diffusing capacity to PVDOMICS as PDF files of the screen shots taken during testing and reports generated upon completion of the test as well as completed PVDOMICS forms: Form 270 (Pulmonary Function Testing Form). Historical PFT data will be submitted in the same fashion using Form 271 (Historical Pulmonary Function Testing Form).

The forms and PDF files will be reviewed for adherence to ATS/ERS Guidelines by the Pulmonary Function Core using a spreadsheet designed to log the evaluation of every effort. A final data quality designation will be assigned to each pulmonary function test. The data will be rated as Acceptable, Usable, Unacceptable or Unable to Rate.

Data Evaluation:

55.2 Forced Spirometry Measurement Quality Grades
Quality Control Grades

1. Acceptable Forced Spirometry Measurement Received
   A forced spirometry measurement that was transferred to the PVDOMICS database that meets the ATS/ERS Guidelines for acceptability and repeatability with the current Best effort of Acceptable quality as outlined below.
2. Borderline Acceptable Forced Spirometry Measurement Received
   A forced spirometry measurement that was transferred to the PVDOMICS database meets the ATS/ERS Guidelines and the study specific criteria for acceptability but not repeatability or meets the ATS/ERS Guidelines and the study specific criteria for usable data with the current Best effort of Acceptable quality as outlined below.
3. Unacceptable Forced Spirometry Measurement Received A forced spirometry measurement that was transferred to the PVDOMICS database where the Current Best effort does not meet the ATS/ERS Guidelines and the study specific criteria for usable measurement as outlined below.
4. Unable to Rate
   A forced spirometry measurement that was transferred to the PVDOMICS database without sufficient information or documentation to evaluate the adherence to the ATS/ERS Guidelines and the study-specific criteria.

Acceptability and Repeatability Criteria

When reviewing individual efforts to determine their quality, the PVDOMICS PFT Overreader will be guided by the following criteria for acceptability and repeatability from the ATS/ERS document in accordance with their best clinical judgment:

- Criteria for Acceptability:
  - Start of test criteria:
    - Back extrapolated Volume within acceptable limits

- Back extrapolated volume < 5% of FVC or 150 ml whichever is greater.
- Or Back extrapolated volume < 5% of FVC > 100 ml whichever is greater when FVC is ≤ 1 L.

▪ Time to Peak Expiratory Flow is < 120 ms.

▪ Absence of artifact or cough within the 1st second.

o End of Effort Criteria

▪ Exhalation ≥ 6 seconds (no abrupt termination of flow) or 1 second plateau.

o Lack of Technical problems during effort (e.g., baseline drift)

o Criteria for Repeatability
▪ Will be based on the Best effort (highest) compared to next Best effort (second highest) based upon FVC and FEV1 values to be
- ± 150 ml or
- ± 100 ml when FVC <1L.

- **Forced Spirometry Overall Statements**

The following section lists the specific statements that will be generated by the Overreader during the QC process as explained below.

o **Forced Spirometry All Efforts**
▪ Measurement doesn't meet ATS/ERS standards; however Technician's note acceptably explains why measurement does not meet ATS/ERS criteria.
- QC Report statement: "Measurement does not meet ATS/ERS 2005 standards; however technician provided an adequate explanation why." This will be commented only if there is a technician's note explaining why the measurement does not meet ATS/ERS/study specific criteria and the OverReader determines this is an adequate reason for the measurement to be non ATS/ERS/study specific.

▪ Pneumotach reversed.
- QC Report statement: "All Efforts: Subject breathing on wrong side of pneumotach."
- Comment made if on all efforts the subject is breathing on the wrong side of the pneumotach (Upside down loops).

▪ Baseline drift.
- Report statement: "All Efforts: Baseline drift."
- Comment made if on all efforts there is significant baseline drift that in the judgment of the Overreader could affect the measurement.

▪ Poor subject effort on all efforts.
- QC Report statement: "All Efforts: Poor subject effort."
- Comment made if in the judgment of the Overreader all of the efforts represent a poor subject effort when no other statement could be used to describe the measurements

▪ Late time to peak flow
- QC Report statement: "All Efforts: Poor start of effort, late time to peak flow (≥ 120 ms)".
- Comment made if on all efforts the time to peak flow is ≥ 120 ms.

▪ Hesitation during start of forced exhalation, back extrapolated volume is greater than

- 5% of the total FVC or >150 ml whichever is greater. Or > 100 ml when FVC is < 1 L.
- QC Report statement: “All Efforts: Hesitation during start of forced exhalation,

▪ Back extrapolated volume is out of acceptable range.”
- Comment made if on all efforts the back extrapolated volume is greater than 5% of the total FVC or >150 ml whichever is greater or >100 ml when FVC is < 1 L.

▪ Only two acceptable efforts performed.
- QC Report statement: “All Efforts: Only two acceptable efforts performed.”
- Comment made if the “Best” effort for FEV1 and FVC are from the
- effort that meets the acceptability criteria and there is another effort that meets the acceptability criteria or the “Best” FEV1 and FVC come from 2 separate efforts and both efforts meet the acceptability criteria

▪ Only one acceptable effort performed.
- QC Report statement: “All efforts: Only one acceptable effort performed”.
- Comment made if the “Best” effort for FEV1 and FVC come from the
- same effort and that effort that meets the acceptability criteria

▪ Artifact/Cough during all efforts.
- QC Report statement: “All Efforts: Artifact/Cough during all efforts.”
- Comment if there is Artifact/Cough before FEV1 on all efforts or there is Artifact/Cough on all efforts that in the clinical judgment of the OverReader affect the measurement.

▪ No efforts available for analysis
- QC Report Statement: “All Efforts: No efforts available for analysis.”
- Comment made when there no efforts or values visible for analysis for a measurement.

▪ Unable to rate test
- QC Report Statement: “All Efforts: insufficient data forwarded to rate the quality of the test.”
- Comment made when there is insufficient data available to rate the quality of the test.

- **Forced Spirometry Best FEV1**
  - Pneumotach reversed.
    - QC Report statement: “Best FEV1: Subject breathing on wrong side of pneumotach, effort should have been deselected.”
    - Comment made if the Best FEV1 effort has the pneumotach reversed (upside down loop) and there is another effort that meets the acceptability criteria with the subject breathing on thePVDOMICS correct side of the pneumotach.
    - QC Report statement: “Best FEV1: Subject breathing on wrong side of pneumotach with no other acceptable efforts performed.”
    - Comment made if the Best FEV1 effort has the pneumotach reversed (upside down loop) and there are no other efforts that meets the acceptability criteria with the subject breathing on the correct side of the pneumotach.
  - Baseline drift.
    - QC Report statement: “Best FEV1: Baseline drift, effort should have been deselected.
    - Comment made if the Best FEV1 effort has a baseline drift and there is another effort that meets the acceptability criteria

without the baseline drift.
    - QC Report statement: “Best FEV1: Baseline drift with no other acceptable efforts performed.”
    - Comment made if the Best FEV1 effort has a baseline drift and there are no other efforts that meets the acceptability criteria
- Poor subject effort on effort with “Best FEV1”.
    - QC Report statement: “Best FEV1: Poor subject effort, effort should have been deselected.”
    - Comment made if the Best FEV1 is poor subject effort and there is another effort that meets the acceptability criteria when no other statement could be used to describe the measurement.
      This should be made based on ATS/ERS criteria and the judgment of the PVDOMICS Overreader.
    - QC Report statement: “Best FEV1: Poor subject effort with no other acceptable efforts performed”.
    - Comment made if the Best FEV1 is poor subject effort and there are no other efforts that meet the acceptability criteria when no other statement could be used to describe the measurement.
      This should be made based on ATS/ERS criteria and the judgment of the PVDOMICS Overreader.
- Late time to Peak
    - QC Report statement: “Best FEV1: Poor start of effort, late time to peak flow (≥ 120 ms), effort should have been deselected.”
    - Comment made if the Best effort for FEV1 has a time to peak ≥ 120 ms and there is another effort that meets the acceptability criteria in section 8.1.2.
    - QC Report statement: “Best FEV1: Poor start of effort, late time to peak flow (≥ 120 ms) with no other acceptable efforts performed.
    - Comment made if the Best effort for FEV1 has a time to peak ≥ 120 ms and there are no other efforts that meet the acceptability criteria in section 8.1.2.
- Hesitation during start of forced exhalation on the effort chosen as Best, back extrapolated volume is greater than 5% of the total FVC or >150 ml whichever is greater (or > 100 ml when FVC < 1 L).
    - QC Report statement: “Best FEV1: Hesitation during start of forced exhalation, back extrapolated volume is out of acceptable range, effort should have been deselected.”
    - Comment made if the Best effort for FEV1 has a back extrapolated volume that is greater than 5% of the total FVC or >150 ml whichever is greater (or > 100 ml when FVC < 1) and there is another effort that meets the acceptability criteria.
    - QC Report statement: “Best FEV1: Hesitation during start of forced exhalation, back extrapolated volume is out of acceptable range with no other acceptable efforts performed.”
    - Comment made if the Best effort for FEV1 has a back extrapolated volume that is greater than 5% of the total FVC or >150 ml whichever is greater (or > 100 ml when FVC < 1) and there are no other efforts that meet the acceptability criteria
- Artifact/Cough during measurement that was used as best: effort should have been deselected.
    - QC Report statement: “Best FEV1: Artifact/Cough during effort; effort should have been deselected.”
    - Comment made if the Best effort for FEV1 has an Artifact/Cough prior

to FEV1 and there is another effort that meets the acceptability criteria.
        - QC Report statement: "Best FEV1: Cough during effort with no other acceptable efforts performed."
        - Comment made if the Best effort for FEV1 has an Artifact/Cough prior to FEV1) and there are no other efforts that meet the acceptability criteria.
    - Best two FEV1s not repeatable: not within 150 ml.
        - QC Report statement: "Best two FEV1s not repeatable: not within 150 ml."
        - Comment made if the two highest FEV1 are not within 150 ml and the Best FEV1 effort meets the acceptability criteria.
    - Best FEV1: Abrupt end of exhalation.
        - QC Report statement: "Abrupt end of exhalation at or around 1second."
        -

- **Forced Spirometry Best FVC**

If the errors listed below in this section are found for the effort marked as, "Best FVC" within a measurement then the "QC Report Statement" listed under the error will be generated.

    - Pneumotach reversed.
        - QC Report statement: "Best FVC: Subject breathing on wrong side of pneumotach, effort should have been deselected.
        - Comment made if the Best FVC effort is separate from the Best FEV1 and has the pneumotach reversed (upside down loop) and there is another effort that meets the acceptability with the subject breathing on the correct side of the pneumotach.
        - QC Report statement: "Best FVC: Subject breathing on wrong side of pneumotach with no other acceptable FVC performed."
        - Comment made if the Best FVC effort separate from the Best FEV1 and has the pneumotach reversed (upside down loop) and there are no other efforts that meets the acceptability criteria with the subject breathing on the correct side of the pneumotach.
    - Baseline drift.
        - QC Report statement: "Best FVC: Baseline drift, effort should be deselected."
        - Comment made if the Best FVC effort is separate from the Best FEV1, has a baseline drift and there is another effort that meets the acceptability criteria without the baseline drift.
        - QC Report statement: "Best FVC: Baseline drift with no other acceptable FVC performed."
        - Comment made if the Best FVC effort separate from the Best FEV1 and has a baseline drift and there are no other efforts that meets the acceptability criteria.
    - Poor subject effort on effort with Best FVC.
        - QC Report statement: "Best FVC: Poor subject effort, effort should have been deselected."
        - Comment made if the "Best FVC effort is separate from the Best FEV1 effort, shows poor subject effort and there is another effort that meets the acceptability criteria when no other statement could be used to describe the measurement.
        - This should be made based on ATS/ERS criteria and the judgment of the PVDOMICS Overreader.
        - QC Report statement: "Best FVC: Poor subject effort with no other acceptable FVC performed."
        - Comment made if the "Best FVC effort is separate from the Best FEV1, is poor subject effort and there are no other efforts that meet the acceptability criteria when no other statement

could be used to describe the measurement.
        - This should be made based on ATS/ERS criteria and the judgment of the PVDOMICS Overreader.
    - Artifact/Cough during measurement that was used as Best, effort should have been deselected.
        - QC Report statement: "Best FVC: Artifact/Cough during effort, effort should have been deselected."
        - Comment made if the Best effort for FVC is separate from the Best FEV1, has an Artifact/Cough that in the clinical judgment of the PVDOMICS Overreader affects the FVC values and there is another effort that meets the acceptability criteria.
        - QC Report statement: "Best FVC: Artifact/Cough during effort with no other acceptable FVC performed."
        - Comment made if the Best effort for FVC is separate from the Best FEV1 and has an Artifact/Cough that in the clinical judgment of the PVDOMICS Overreader affects the FVC values and there are no other better efforts or FEV1 and FVC are coming from the same effort with an Artifact/Cough that in the clinical judgment of the PVDOMICS Overreader affects the FVC values.
    - Subject did not reach plateau at end exhalation, FVC may be underestimated.
        - QC Report statement: "Best FVC: Subject did not reach plateau at end exhalation, FVC may be underestimated."
        - Comment made only if in the opinion of the PVDOMICS Overreader, the "no plateau" has had a significant effect on the FVC.
    - Subject did not exhale for longer than 6 seconds.
        - QC Report statement: "Best FVC: Subject did not exhale for longer than 6 seconds FVC may be underestimated."
        - Comment made if the expiratory time is <6 seconds on the Best FVC effort and there is no plateau of the end expiratory arm regardless if the FVC and FEV come from the same effort.
          If the expiratory time <6 seconds and there is a plateau on the end expiratory arm this comment will not be generated.
    - Best two FVC not repeatable: not within 150 ml.
        - QC Report statement: "Best two FVC not repeatable: not within 150 ml."
        - Comment made if the two highest FVC are not within 150 ml and the Best FVC effort meets the acceptability criteria .
    - Best FVC: Abrupt end of exhalation.
        - QC Report statement: "Abrupt end of exhalation; FVC likely to be understated."
        - Comment made when on the Best FVC effort there is significant drop in the flow rate at the end of the exhalation with a very sharp angle on the volume time curve.

- **Forced Spirometry QC Grade**

After the QC statements are generated a grade will then be assigned based on Quality Control Statements generated during the Quality Control of the measurement. These grades will be:

- Acceptable.
- Borderline Acceptable.
- Unacceptable.

- The following is a list of statements generated and the QC grade that would be assigned to a measurement after the QC statements have been generated.

    - **Acceptable Forced Spirometry measurement received.**
        - No QC statement indicating less than optimal quality

        - ≥3 efforts including the current best that meets the acceptability outlined above.
    - **Borderline Acceptable Forced Spirometry measurement received.**
        - Data does not meet ATS/ERS 2005 standards; however technician provided
            - an adequate explanation why.
        - All Efforts: Only one acceptable effort performed.
            - With no QC error code generated and the current "Best" meets the acceptability criteria outlined above.
        - All Efforts: Only two acceptable efforts performed.
            - With no other error code generated and the current "Best" meets the acceptability criteria outlined above.
        - Best FEV1: Best two FEV1 not repeatable: not within 150 ml
            - With 2 or more loops including the current best that meets the acceptability criteria outlined above.
        - Best FVC: Best two FVC not repeatable: not within 150 ml.
            - With 2 or more loops including the current best that meets the acceptability criteria.
        - Best FVC: Subject did not reach plateau at end exhalation, FVC may be underestimated.
            - With no other error code generated and the current best meets the acceptability criteria outlined above.
        - Best FVC: Subject did not exhale for longer than 6 seconds, FVC may be underestimated.
            - With no other error code generated and current best meets the acceptability criteria outlined above.
        - Best FVC: Artifact/Cough during effort, with no other acceptable FVC performed.
            - When the Best FEV1 and Best FVC are coming from the same effort this will be graded as Borderline Acceptable when the Artifact/Cough occurs after the first second.
            - When FEV1 and FVC are on different efforts this will be Borderline Acceptable when there are no other errors affecting FEV1.
        - Best FVC: Artifact/Cough, effort should have been deselected.
            - When an artifact or cough is present that seems to have artifactually added volume to the FVC
        - Best FVC: Abrupt end of exhalation.
            - This will be graded as Borderline Acceptable data when the FEV1 and FVC do not equal each other.
            - If the FEV1 and FVC equal each other this will be graded as Unacceptable data.
        - Best FVC: Poor subject effort, effort should have been deselected.
            - This will be graded as Unacceptable the subject's efforts appears to be poor or inconsistent with the performance of a forced vital capacity maneuver.
        - Best FVC: Poor subject effort with no other acceptable FVC performed
            - The will be graded as Borderline acceptable if the best FEV1 is acceptable.
        - Best FVC: Drift in baseline, effort should have been deselected.
        - Best FVC: Subject breathing on wrong side of pneumotach effort should have been deselected.
- **Unacceptable Forced Spirometry measurement received.**
    - All Efforts: Subject breathing on wrong side of pneumotach.
    - All Efforts: Baseline drift.
    - All Efforts: Poor subject effort.

- All Efforts: Poor start of effort, late time to peak flow (≥ 120 ms).
- All Efforts: Hesitation during start of forced exhalation, back extrapolated volume out of acceptable range.
- All Efforts: Artifact/Cough during all efforts.
- All Efforts: No efforts available for analysis.
- Best FEV1: Subject breathing on wrong side of pneumotach effort should have been deselected.
- Best FEV1: Subject breathing on wrong side of pneumotach with no other acceptable efforts performed.
- Best FEV1: Baseline drift, effort should have been deselected.
- Best FEV1: Baseline drift with no other acceptable efforts performed.
- Best FEV1: Poor subject effort, effort should have been deselected.
- Best FEV1: Poor subject effort with no other acceptable efforts performed.
- Best FEV1: Poor start of effort, late time to peak flow (≥ 120 ms), effort should have been deselected.
- Best FEV1: Poor start of effort, late time to peak flow (≥ 120 ms) with no other acceptable efforts performed.
- Best FEV1: Hesitation during start of forced exhalation, back extrapolated volume is out of acceptable range, effort should have been deselected.
- Best FEV1: Hesitation during start of forced exhalation, back extrapolated volume is out of acceptable range with no other acceptable efforts performed.
- Best FEV1: Artifact/Cough during effort; effort should have been deselected.
- Best FEV1: Artifact/Cough during effort with no other acceptable efforts performed.
- Best FEV1: Abrupt end of exhalation.
- Best FVC: Subject breathing on wrong side of pneumotach effort should have been deselected.
- Best FVC: Subject breathing on wrong side of pneumotach with no other acceptable FVC performed.
- Best FVC: Baseline drift: effort should have been deselected.
- Best FVC: Baseline drift with no other acceptable FVC performed.
- Best FVC: Poor subject effort, effort should have been deselected.
- Best FVC: Poor subject effort with no other acceptable FVC performed.
- Best FVC: Artifact/Cough, effort should have been deselected.
- Best FVC: Artifact/Cough during effort with no other acceptable FVC performed.

55.3 Lung Volumes by Plethysmography Measurement Quality Grades

Quality Control Grades

1. Acceptable Lung Volume by Plethysmography Measurement Received
   A lung volume by plethysmography measurement that was transferred to the PVDOMICS database that meets the ATS/ERS Guidelines for acceptability and repeatability with the current Best effort of Acceptable quality as outlined below.
2. Borderline Acceptable Lung Volume by Plethysmography Measurement Received
   A Lung Volume by Plethysmography Measurement that was transferred to the PVDOMICS database meets the ATS/ERS Guidelines and the study specific criteria for acceptability but not repeatability or meets the ATS/ERS Guidelines and the study specific criteria for usable data with the current Best effort of Acceptable quality as outlined below.
3. Unacceptable Forced Spirometry Measurement Received
   A Lung Volume by Plethysmography Measurement that was transferred to the PVDOMICS database where the Current Best effort does not meet the ATS/ERS

Guidelines and the study specific criteria for usable measurement as outlined below.

4. Unable to Rate
   A Lung Volume by Plethysmography Measurement that was received without sufficient documentation to allow a QC rating to be assigned.

How the Quality Control Checks are performed:

- Plethysmography measurements will be performed according to the ATS/ERS 2005 recommendations (ERJ 2005; 26(3):511-22).The measurement phase will be reviewed:
  - Thoracic Gas Volume (FRC PLETH) determination
    - Tidal breathing is recorded for at least 30s and a stable end-expiratory lung volume (EELV) is observed for 3 to 5 breathings before activating the shutter.
    - Proceeding to the TGV phase, while still panting, during closure of the shutter, an artifact free Volume shift/Mouth pressure curve should be observed.
    - After opening of the shutter, the subject should perform no more than one or two tidal breaths followed by:
      - a full inspiration to TLC and then a complete, unforced expiration to RV
      - a complete, unforced expiration to RV followed by a complete inspiration to TLC.
    - SVC values ≤ 0.150L difference between the largest and smallest SVC's.

• The "Best" values from the FRC PLETH measurement are calculated from the selected recordings as follows:

- TLC: RV + largest VC
- ERV: Average of ERVs from technically acceptable efforts.
- FRC PLETH: Average of repeatable and technical acceptable FRC PLETH efforts.
- RV: FRCpleth - RV
- IC: TLC -FRC PLETH
- VC (or SVC): the largest VC from an acceptable effort.
- Comments which were entered by the site personnel are considered when reviewing and grading the measurements.

- PVDOMICS Overreader will choose one QC statement for the specific grade for each FRC PLETH effort that was performed.
  - If there are no errors on an effort then the comment "OK" will be chosen for that effort.
- PVDOMICS PFT Overreader will only report those errors that in their best clinical judgment were due to technical, subject or operator error and have a significant impact on the results.

  - The QC statements for lung volume determination are grouped by all efforts and each individual effort.
    - If there is an error on a particular effort, a statement will be chosen from the statements for that effort.
    - For example: 4 FRC PLETH efforts were collected and the FRC PLETH line of effort 1 had a significant artifact, and efforts 2, 3 and 4 were OK, the Overreader will choose a statement from the effort 1 list for artifact and will chose OK for effort 2,3 and 4.
    - If the error is found on all effort then the statement will be chosen from the all efforts category.

Detailed Description of Errors Reported

- During the QC process each individual FRC PLETH effort that was performed will be commented on.
- "Best" values for TLC, FRC PLETH, RV and IC are calculated as;
  - Reported FRC PLETH is the mean of at least 3 acceptable FRC PLETH values in Liters.
  - Reported ERV is the mean of all ERVs from acceptable VC maneuvers
  - Reported VC is the largest of all acceptable VC maneuvers
  - Reported RV is the difference between the mean FRC PLETH and the mean ERV
  - TLC is the sum of the largest VC and the reported RV

QC statements for all FRC PLETH Efforts:

1. OK

2. Irregular breathing.
   a. QC Report Statement: "All Efforts: Irregular breathing."
3. Baseline drift.
   a. QC Report Statement: "All Efforts: Baseline drift."
4. Artifacts/leak during shutter maneuver.
   a. QC Report Statement: "All Efforts: Artifact/leak during shutter maneuver."
5. Only one or two acceptable FRC PLETH maneuvers performed.
   a. QC Report Statement: "All Efforts: Only 1 or 2 acceptable FRC PLETH maneuvers performed."
6. Less than 3 tidal breaths before shutter maneuver.
   a. QC Report Statement: "All Efforts: < 3 tidal breaths prior to shutter maneuver."
7. Respiratory Rate > 30 breaths per minute prior to shutter closure.
   a. QC Report Statement: "All Efforts: > 30 breaths per minute prior to shutter closure."
8. Efforts during shutter closure > 60 efforts per minute.
   a. QC Report Statement: "All Efforts: > 60 efforts per minute during shutter closure."
9. Improper procedure after shutter maneuver.
   a. QC Report Statement: "All Efforts: Improper procedure after shutter maneuver."
10. No VC performed after shutter maneuver.
    a. QC Report Statement: "All Efforts: No VC performed after shutter maneuver."
11. FRC PLETH is not repeatable ($\Delta > 5\%$).
    a. QC Report Statement: "FRC PLETH not repeatable within 5%."
12. SVC not repeatable within .0150L.
    a. QC Report Statement: SVC not repeatable within 0.150L.
13. No valid lung volume efforts performed
    a. QC Report Statement: "All Efforts: No valid lung volume efforts performed."
14. No stable baseline prior to shutter maneuver
    a. QC Report Statement: "All Efforts: No stable baseline prior to shutter maneuver."

Individual FRC PLETH Efforts:

In order to save space each individual effort error code list will not be listed in this section. These will be listed in Appendix B of this document. For this section the phrase of Individual Effort will be used to represent the phrase Effort 1, Effort 2 etc. for each effort.

QC statements for FRC PLETH Effort x:

- OK.

2. Baseline drift. a. QC Report Statement: "Individual effort X: Baseline drift."
3. No stable baseline prior to shutter maneuver.
   a. QC Report Statement: "Individual effort X: No stable baseline prior to shutter maneuver."

4. Less than 3 breaths before shutter maneuver.
    a. QC Report Statement: “Individual effort X: < 3 breaths before shutter maneuver.”
5. Artifact/Leak detected during shutter maneuver.
    a. QC Report Statement: “Individual effort X: Leak detected during shutter maneuver.”

6. VC maneuver not performed.
    a. QC Report Statement: “Individual effort X: VC maneuver not performed.”
7. Start of VC maneuver not within 20 s after shutter opened.
    a. QC Report Statement: “Individual effort X: Start of VC maneuver not within 20 s after shutter opened.”
8. Improper VC maneuver performed.
    a. QC Report Statement: “Individual effort X: Improper VC maneuver performed.”
9. No valid lung volume effort.
    a. QC Report Statement: “Individual effort X: No valid lung volume effort.”
10. Resting Respiratory Rate > 30 breaths per minute prior to shutter closure.
    a. QC Report Statement: “Individual effort X: > 30 breaths per minute prior to shutter closure.”
12. Efforts during shutter closure > 90 per minute.
    a. QC Report Statement: “Individual effort X: > 90 efforts during shutter closure.”
13. FRC Pleth is not repeatable
    a. QC Report Statement: “Individual effort X: FRC Pleth is not repeatable”.

Body Plethysmography Lung Volumes QC Grade

Each test set will be assigned a grade based on Quality Control Statements generated during the Quality Control of the data. These grades will be:

- Acceptable lung volume data.
- Borderline Acceptable lung volume data.
- Unacceptable lung volume data.

1. Acceptable FRC PLETH data received:
    a. No QC statements other than OK.
2. Borderline Acceptable FRC PLETH data received:
    a. Only 2 valid FRC PLETH maneuvers with no additional individual effort error.
    b. SVC not repeatable; not within 0.150L.
    c. FRC PLETH not repeatable > 5% but within 10%.
3. Unacceptable FRC PLETH data received:
    a. ≤ 1 valid FRC PLETH maneuver.
    b. All Efforts: Baseline drift.
    c. Individual Effort: Baseline drift
    d. All Efforts: No VC performed after shutter maneuver.
    e. Individual Effort: No VC performed after shutter maneuver.
    f. All Efforts: Start of VC not within 20 s after shutter opened.
    g. Individual Effort: Start of VC not within 20 s after shutter opened.
    h. All Efforts: Resting Respiratory Rate > 30 breaths per minute prior to shutter closure.
    i. Individual Effort: Resting Respiratory Rate > 30 breaths per minute prior to shutter closure.
    j. All Efforts: Efforts during shutter closure > 60 efforts per minute.
    k. Individual Effort: Efforts during shutter closure > 60 efforts per minute.
    l. All Efforts: FRC variability exceeds variability limit of 10%.
    m. Individual effort: FRC exceeds variability limit of 10%.
    n. All Efforts: Artifact/Leak detected during shutter maneuver.
    o. Individual effort: Artifact/Leak detected during shutter maneuver.
    p. All Efforts: Less than 3 breaths before shutter maneuver.
    q. Individual effort: Less than 3 breaths before shutter maneuver.

r. All Efforts: No stable baseline prior to shutter maneuver.
s. Individual effort: No stable baseline prior to shutter maneuver.
t. All Efforts: No valid lung volume efforts.
u. Individual effort: No valid lung volume effort.
v. All Efforts: Improper VC maneuver performed.
w. Individual effort: Improper VC maneuver performed

Reporting of Quality Control Results

Best Test Review (BTR)

Description of Best Test Review "BTR" Process

1. During the BTR process a. All measurements are reviewed.
    b. If there is an effort with an error this effort will be deselected if:
        i. There are other efforts present which are acceptable.
        ii. By removing this effort the BTR grade will be Borderline Acceptable or Acceptable.
2. Unacceptable efforts will not be reactivated during the BTR process.
3. If an effort is deselected, the PVDOMICS Overreader will be required to choose a statement indicating that the effort has been deselected as well as one or more statements indicating the reason(s) for the change.
4. If the PVDOMICS Overreader does not change the data, a statement indicating that the data has not been changed will be made.

Body Plethysmography Best Test Review

This section of the document will list the BTR statements will be generated during BTR. Each test set will have one of the following statements generated during BTR.

1. Body Plethysmography data unchanged.
2. Body Plethysmography data changed.
3. Body Plethysmography original data was reactivated because BTR data changes were rejected by Principal Investigator. DO NOT REPLY TO THIS FAX.

Statements used when an effort is removed

When an effort is deselected or modified the PVDOMICS Overreader will be required to select a reason why from the list below:

FRC PLETH maneuver removed due to:

a. No stable baseline prior to shutter maneuver.
b. Baseline drift.
c. Less than 3 breaths before shutter maneuver.
d. VC maneuver not performed.
e. Start of VC maneuver not within 20 s after shutter opened.
f. Improper VC maneuver performed.
g. No valid measurement.
h. Resting Respiratory Rate > 30 breaths per minute prior to shutter closure.
i. Efforts during shutter closure > 60 breaths per minute.
j. Artifact/Leak during shutter maneuver.

Body Plethysmography BTR Grade

Each test set will be assigned a grade based on BTR Statements generated during the BTR of the data. This grade will be: Acceptable, Borderline Acceptable and Unacceptable. The following is a list of BTR statements and the grade that would be assigned if they were chosen.

Body Plethysmography FRC PLETH BTR Grades:

1. Acceptable FRC PLETH data after BTR.
    a. ≥ 3 acceptable FRC PLETH efforts after BTR process demonstrating < 5% variability.
- Borderline acceptable FRC PLETH data after BTR.
    a. 2 acceptable FRC PLETH efforts after BTR process.
    b. Variability of >2 acceptable FRC PLETH efforts is greater than 5% but less than 10%.
3. Unacceptable FRC PLETH data after BTR.
    a. ≤ 1 acceptable FRC PLETH effort after BTR process.
    b. Variability of acceptable FRC PLETH efforts exceeds 10%.

a) Establishing a stable EELV.

Lung Volumes by Multiple Breath Washout measurement Quality Grades

1. Quality Control Grade
    a. Acceptable Lung Volumes by Multiple Breath Washout measurement received.
        i. A Lung Volumes by Multiple Breath Washout measurement that was transferred to the PVDOMICS database that has all efforts that meet the Acceptability and Repeatability criteria outlined .
    b. Borderline Acceptable Lung Volumes by Multiple Breath Washout measurement received.
        i. A Lung Volumes by Multiple Breath Washout measurement that was transferred to the PVDOMICS database that has at least 2 efforts that meet the Acceptability criteria outlined and not the Repeatability criteria.
    c. Unacceptable Lung Volumes by Multiple Breath Washout measurement received.
        i. A Lung Volumes by Multiple Breath Washout measurement that was transferred to the PVDOMICS database that has ≥1 effort that do not meet the study specific Acceptability criteria outlined .
2. Best Test Review Grades
    a. Acceptable Lung Volumes by Multiple Breath Washout measurement after Best Test Review
        i. A Measurement that after BTR that has ≥2 efforts that meet the Acceptability and Repeatability criteria .
    b. Borderline Acceptable Lung Volumes by Multiple Breath Washout measurement after Best Test Review
        i. A Measurement that after BTR that has ≥1 efforts that meet the Acceptability criteria .
    c. Unacceptable Lung Volumes by Multiple Breath Washout measurement after Best Test Review
        i. A Measurement that after BTR that has 0 efforts that meet the Acceptability criteria .

Pulmonary Function Definitions

1. **Functional Residual Capacity measured by multiple breath washout of nitrogen from the lungs: FRC_{MBW}.**

The functional residual capacity is the volume of air in the lungs at the end of a normal resting expiration. This volume is set by the balance between the elastic properties of the lung and chest wall. The FRC is comprised of two volumes: the expiratory reserve volume (ERV) and the residual volume (RV).

2. **Expiratory Reserve Volume: ERV**
   The maximum volume of air that can be voluntarily exhaled from beyond the FRC. This volume is limited by the duration of the expiratory effort of the patient and by airway closure caused increased expiratory pressure. Coaching to obtain a maximum ERV is best done by coaching for a sustained submaximal expiratory effort.

3. **Inspiratory Capacity: IC**
   The maximum volume of air that can be inspired from FRC. This volume is limited by the inspiratory effort of the subject and can be maximized by vigorous coaching.

4. **Residual Volume: RV**
   The volume of air left in the lungs after a maximal exhalation. The residual volume is calculated by subtracting the expiratory reserve volume (ERV) from the functional residual capacity (FRC).

5. **Percent Predicted (% Predicted):**
   The ratio of a value to a mean predicted normal value which was calculated from a gender-specific regression equation that incorporates the subject's age and height. The regression equation is obtained from a study of subjects determined to be free of cardiopulmonary disease.

6. **Total Lung Capacity: TLC**
   The volume of air attained in the lungs after a maximal inhalation. This value is calculated as the sum of the vital capacity (VC) and the residual volume (RV).

7. **Vital Capacity: VC**
   The volume of air measured from a slow, complete expiration after a maximal inspiration, without a maximal forced effort. Sometimes specified as the Slow Vital Capacity (SVC). In this study, VC EX is used to designate the VC maneuver performed after the IC maneuver.

8. **Tidal Volume: VT or TV**
   The volume of air the subject breaths during relaxed, resting breathing. No coaching should be done during the collection of tidal breathing to prevent the subject from consciously varying the size of the breath or the rate of respiration.

Best Test Review

1. All study subjects will have their measurements reviewed for BTR on a continuing basis in a second step after QC has been performed for a given measurement. Internal Data Review

55.4 Diffusion Capacity Test (DLCO)

Quality Control

1. The following will be evaluated on the DLCO measurement:
   a. Phase 1 tidal breathing
   b. Phase 2: the ERV maneuver and has a plateau prior to inhaling the gas mixture.
   c. Phase 3: quick and deep inhalation after the ERV maneuver.
   d. Phase 4: a stable breath hold without an increase in mouth pressure.
   e. Phase 5: after the breath hold an exhalation of minimal 1.5 L.

How are the Quality Control Checks Performed:

1. The DLCO data will first be analyzed by computer algorithms based on the ATS/ERS 2005 criteria for single breath diffusion testing (ERJ 2005; 26: 720–735).
2. When reviewing a measurement, the CHRS Clinical OverRead Specialist will be guided by the following criteria in accordance with their clinical judgment:
    a. Complete exhalation to RV and plateau.
    b. Breath hold at TLC for 10 seconds.
    c. Artifacts / Morphology.
    d. Technical errors.
    e. Procedural errors.
3. Comments which were entered by the site personnel are considered when reviewing and grading the measurements.
4. PVDOMICS Overreader will choose a QC statement for each effort that was performed and submitted for each measurement.
    a. If there are no errors on an effort then the comment of OK will be chosen for that effort.
    b. PVDOMICS Overreader will only report errors that in their best clinical judgment were due to technical, subject or operator error and have a significant impact on the saved results.
5. The QC statements are grouped by all efforts and each individual effort.
    a. If there is an error on a particular effort a statement will be chosen from statements for that effort.
    b. For example: a subject performed 4 efforts and effort 1 had an artifact/cough, and efforts 2, 3, and 4 were OK, the PVDOMICS Overreader will choose a statement from the effort 1 list for artifact/cough and will chose OK for effort 2, 3 and 4.
    c. If the error is found on all efforts then the statement will be chosen from the all efforts category for that specific error.
6. This computer generated information along with clinical judgment will be used by the Clinical Specialist to determine if there are any errors present with data as it was received from the investigator sites.

Detailed Description of Errors Reported

During the QC process each individual effort that was performed will be commented on. This is done because average values are reported and each effort has an influence on the average.

All Efforts:

1. Baseline drift.
    a. QC Report Statement: “All Efforts: Baseline drift.”
        i. This comment is made when there is a drifting baseline on all efforts.
2. Only one DLCO measurement performed.
    a. QC Report Statement: “All Efforts: Only one DLCO measurement performed.”
        i. This comment is made when there is only 1 acceptable DLCO effort present.

- No valid measurements.
    a. QC Report Statement: “All Efforts: No valid measurements performed.”
        i. This comment is made when there are no valid efforts present.

4. Artifact/Cough.
    a. QC Report statement: “All Efforts: Artifact/Cough.”
        i. This comment is made when there all efforts show an artifact/cough that in the clinical judgment of the PVDOMICS Overreader is affecting the data. This statement will be chosen from the all efforts list.
5. Subject did not fully exhale to RV.
    a. QC Report Statement: “All Efforts: Subject did not fully exhale to RV.”
        i. This comment is made when the subject does not fully exhale to residual

volume on all efforts. This may be evident due to no Plateau at RV.

6. Subject did not inhale to at least 85% of the highest VC measured at the visit (VCmax).
    a. QC Report Statement: "All Efforts: Subject did not inhale to at least 85% of VC."
        i. This comment is made when the subject does not meet the minimum 85% inhalation of VC on all efforts.
7. Subject held breath for >12 seconds.
    a. QC Report Statement: "All Efforts: Subject held breath for more than12 seconds."
        i. This comment is made when the subject holds their breath for more than 12 seconds from RV to TLC on all efforts.
8. Leak detected during breath hold.
    a. QC Report Statement: "All Efforts: Leak detected during breath hold."
        i. This comment is made when the subject allows air to leak out around the mouthpiece at any point during the maneuver on all efforts.
9. Increased mouth pressure during breath hold.
    a. QC Report Statement: "All Efforts: Increased mouth pressure during breath hold."
        i. This comment is made when the subject does not maintain a consistent mouth pressure and plateau during the 4th phase of the maneuver on all efforts.
10. Subject did not sufficiently exhale air at the end of breath hold.
    a. QC Report Statement: "All Efforts: Subject did not sufficiently exhale air at the end of breath hold."
        i. This comment is made when the subject does not sufficiently exhale air at the end of the breath hold / plateau of phase 4 on all efforts.
11. Incorrect alveolar gas analysis.
    a. QC Report Statement: "All Efforts: Incorrect alveolar gas analysis."
        i. This comment is made when the gas analysis curve shows an artifact or abnormality that the Overreader feels invalidates the gas analysis for that effort.
12. DLCO not repeatable.
    a. QC Report Statement: "DLCO not repeatable."
        i. All values of all measurements need to be within a span of 3.0 ml/min*mmHg)of mean (Best).
13. VA not repeatable.
    a. QC Report Statement: "VA not repeatable."
        i. Comment made when values of all measurements need to be within a span of 200 mL off mean (Best).

Individual Effort:

In order to save space each individual effort error code list will not be listed in this section.
For this section the phrase of Individual Effort X will be used to represent the phrase for Effort 1, Effort 2 etc. of each measurement.

1. Baseline drift.
    a. QC Report Statement: "Effort x: Baseline Drift."
        i. This comment is made when there is a drifting baseline coming from one individual effort.

2. Artifact/Cough.
    a. QC Report statement: "Effort x: Artifact/Cough."
        i. This comment is made when the subject shows a cough/artifact that in the judgment of the PVDOMICS Overreader affects the data of one individual effort.
3. Subject did not fully exhale to RV.
    a. QC Report Statement: "Effort x: subject did not fully exhale to RV."
        i. This comment is made when the subject does not fully exhale to residual volume on an individual effort. This may be evident due to no Plateau at RV.
4. Subject did not inhale to at least 85% of previously measured VC.

a. QC Report Statement: “Effort x: Subject did not inhale to at least 85% of previous VC.”

i. This comment is made when the subject does not meet the minimum 85% inhalation of VC on an individual effort per ATS/ERS guidelines.

5. Subject did not hold breath for ≤12 seconds.
    a. QC Report Statement: “Effort x: breath hold time ≥ 12 seconds.”
        i. This comment is made when the subject does not hold their breath for a minimum 12 seconds from RV to TLC on an individual effort.
6. Leak detected during breath hold.
    a. QC Report Statement: “Effort x: Leak detected during breath hold.”
        i. This comment is made when the subject allows air to leak out around the mouthpiece at any point during the maneuver on an individual effort.
7. Increased mouth pressure during breath hold.
    a. QC Report Statement: “Effort x: Increased mouth pressure during breath hold.”
        i. This comment is made when the subject does not maintain a consistent mouth pressure and plateau during the 4th phase of the maneuver on an individual effort.
8. Subject did not exhale enough air at the end of breath hold.
    a. QC Report Statement: “Effort x: Subject did not sufficiently exhale air at the end of breath hold.”
        i. This comment is made when the subject does not sufficiently exhale air at the end of the breath hold / plateau of phase 4 on individual effort.
9. Incorrect alveolar gas analysis.
    a. QC Report Statement: “Effort x: Incorrect exhaled gas analysis.”
        i. This comment is made when the Overreader determines the gas analysis for an effort has been marred by a technical problem.

QC Grade

Each test set will be assigned a grade based on Quality Control Statements generated during the Quality Control of the data. These grades will be:

- Acceptable.
- Borderline acceptable.
- Unacceptable Data Received: All Efforts do not meet ATS criteria. This measurement cannot be improved through Best Test Review and no data will be changed.
- Unacceptable.
- Unratable.

1. Acceptable DLCO data received.
    a. No QC statement other than OK.
2. Borderline acceptable DLCO data received.
    a. Only one DLCO measurement performed.
    b. DLCO not repeatable.
3. Unacceptable DLCO Data Received: All Efforts do not meet ATS criteria. This measurement cannot be improved through Best Test Review and no data will be changed.

- Unacceptable DLCO data (selected when data can be improved by deselecting a submitted effort.
    a. Individual Effort: Baseline Drift.
    b. Individual Effort: Artifact/Cough.
    c. All Efforts Subject did not fully exhale to RV.
    d. Individual Effort: Subject did not inhale to at least 85% of previous VC.
    e. Individual Effort: Subject did not hold breath for <12 seconds.
    f. Individual Effort: Leak detected during breath hold.
    g. All Effort: Increased mouth pressure during breath hold.

h. Individual Effort: Subject did not sufficiently exhale air at the end of breath hold.
i. Individual Effort: Incorrect alveolar gas analysis.

4. Unacceptable DLCO data received.
    a. Individual Effort: Baseline Drift.
    b. Individual Effort: Artifact/Cough.
    c. All Efforts Subject did not fully exhale to RV.
    d. Individual Effort: Subject did not inhale to at least 85% of previous VC.
    e. Individual Effort: Subject did not hold breath for <12 seconds.
    f. Individual Effort: Leak detected during breath hold.
    g. All Effort: Increased mouth pressure during breath hold.
    h. Individual Effort: Subject did not sufficiently exhale air at the end of breath hold.
    i. Individual Effort: Incorrect alveolar gas analysis.

Reporting of Quality Control Results

Best Test Review

Description of Best Test Review (BTR) Process

1. During the BTR process.
    a. All measurements are reviewed.
    b. If there is an effort with an error this effort will be deselected if:
        i. There are other efforts present which are acceptable.
        ii. By removing this effort the BTR grade will be Borderline Acceptable or Acceptable.
2. If an effort is deselected, the Overreader will be required to choose a statement indicating that the effort has been deselected as well as one or more statements indicating the reason(s) for the change.
3. If the Overreader does not change the data, a statement indicating that the data has not been changed will be made.

.

DLCO BTR

This section of the document will list the BTR statements generated during BTR. Each test set will receive one of the following statements during BTR.

1. DLCO data unchanged.
2. DLCO data changed.

Statements used when an effort is deselected

When an effort is deselected the PVDOMICS Overreader will be required to select a reason why from the list below:

DLCO Effort removed due to:

1. Baseline drift.
2. Artifact/Cough.
3. Subject did not fully exhale to RV.
4. Subject did not inhale to at least 85% of previous VC.
5. Subject held breath for >12 seconds.
6. Leak detected during breath hold.
7. Increased mouth pressure during breath hold.
8. Subject did not sufficiently exhale air at the end of breath hold.
9. Incorrect alveolar gas analysis.
10. Technical difficulties.

DLCO BTR Grade

Each test set will be assigned a grade based on BTR Statements generated during the BTR of the data. This grade will be: Acceptable, Borderline Acceptable and Unacceptable. The following is a list of BTR statements and the grade that would be assigned if they were chosen.

DLCO BTR Grades:

1. Acceptable DLCO data after BTR.
   - ≥ 2 acceptable and repeatable DLCO efforts after BTR process.
2. Borderline acceptable DLCO data after BTR.
   - 1 acceptable DLCO effort after BTR process
   - ≥ 2 acceptable but not repeatable DLCO efforts after BTR process.
3. Unacceptable DLCO data after BTR.
   - No acceptable DLCO efforts after BTR process.

Chapter 60 Echo

60.1 Core Lab Contacts

Imaging Core Lab Principal Investigator:

Christine Jellis, MD, PhD

Research Coordinator II

Cathy McDowell, BSW
Office: 216-445-7842 or 1-800-223-2273 ext. 57842
Fax: 216-445-4419
Email: mcdowec@ccf.org

Research Coordinator

Dawn D'Eusanio, BA
Office: 216-444-8267
Fax: 216-445-4419
Email: deusand@ccf.org

Project Specialist

Michelle Baksar
Office: 216-444-9872
Fax: 216-445-4419
Email: baksarm@ccf.org

Project Specialist

Jill Rusticelli
Office: 216-442-5231
Fax: 216-445-4419
Email: rusticj@ccf.org

Project Manager:

Kathy Kassimatis, RDCS, FASE
Office: 216-445-5156
Fax: 216-445-4419
Email: kassimk@ccf.org

Lead Imaging Specialist:

Margaret (Koko) Park, BS, ACS, RDCS, RVT, FASE
Office: 216-445-5175
Fax: 216-445-4419
Email: parkm@ccf.org

Core Lab Manager:

Annitta Flinn, BA, RDCS, CCRC, FASE
Office: 216-445-7673 or 1-800-223-2273 ext. 57673
Fax: 216-445-4419
Email: flinna@ccf.org

When sending an email, please copy all above email addresses to ensure a prompt response.

AG Mednet Support:

US Toll Free: 1-888-924-6336
Email: **support@agmednet.com**

60.2 Hours of Operation

60.2.1 Hours of Operation

The Imaging Core Lab is open Monday through Friday, 8:00 AM to 4:30 PM, Eastern Standard Time.

60.2.2 2016-2019 Holidays

The Imaging Core Lab is closed on the following dates for holidays**:**

2016

Memorial Day	May 30, 2016
Independence Day	July 4, 2016
Labor Day	September 5, 2016
Thanksgiving	November 24-25, 2016
Christmas	December 23-26, 2016

2017

New Year's Day	January 2, 2017
Memorial Day	May 29, 2017
Independence Day	July 4, 2017
Labor Day	September 4, 2017
Thanksgiving	November 23-24, 2017
Christmas	December 25-26, 2017

2018

New Year's Day	January 1, 2018
Memorial Day	May 28, 2018
Independence Day	July 4, 2018
Labor Day	September 3, 2018
Thanksgiving	November 22-23, 2018
Christmas	December 24-25, 2018

2019

New Year's Day	January 1, 2019
Memorial Day	May 27, 2019
Independence Day	July 4, 2019
Labor Day	September 2, 2019
Thanksgiving	November 28-29, 2019
Christmas	December 24-25, 2019

60.3 Abbreviations and Acronyms

2D	Two-dimensional
3D	Three-dimensional
4C	4-Chamber
A2C	Apical 2-Chamber
A4C	Apical 4-Chamber
A5C	Apical 5-Chamber
ADM	Administration
AO	Aorta or Aortic
AS	Aortic Stenosis
ASD	Atrial Septal Defect
ASE	American Society of Echocardiography
AV	Aortic Valve
CFD	Color Flow Doppler
CVP	Central Venous Pressure
CW	Continuous Wave
DCC	Data Coordinating Center

DCF	Data Clarification Form
DCM	Dilated Cardiomyopathy
DICOM	Digital Imaging and Communications in Medicine
DICOMDIR	DICOM Directory
DOB	Date of Birth
DTF	Data Transmittal Form
DVD	Digital Video Disc
EBD	Endocardial Border Definition
EKG / ECG	Electrocardiogram
ECHO	Echocardiogram
FOV	Field of View
FPS	Frames per Second
FR	Frame Rate
HIPAA	Health Insurance Portability and Accountability Act
HV	Hepatic Vein
IAS	Interatrial Septum
ICL	Imaging Core Lab
ICS	Intercostal Space
ID	Identification
IDCM	Ischemic Dilated Cardiomyopathy
IVC	Inferior Vena Cava
LA	Left Atrium
LV	Left Ventricle
LVOT	Left Ventricular Outflow Tract
M-Mode	Motion Mode
MV	Mitral Valve
NA	Not Applicable
NATIVE DICOM format	Philips Proprietary Format
NHLBI	National Heart, Lung, and Blood Institute
mm	millimeters

PA	Pulmonary Artery
PACS	Picture Archiving and Communication System
PAP	Pulmonary Artery Pressure
PFO	Patent Foramen Ovale
PH	Pulmonary Hypertension
PLAX	Parasternal Long Axis
PM	Preventative Maintenance
PSAX	Parasternal Short Axis
PV	Pulmonic Valve
PVC	Premature Ventricular Contraction
PW	Pulsed Wave
QC	Quality Control
Qp/Qs	Ratio of pulmonary to systemic blood flow
RA	Right Atrium
RAW DICOM format	GE Proprietary Format
RIMP	Right Index of Myocardial Performance
RR	R wave to R wave timing (ms)
RV	Right Ventricle
RVIF	Right Ventricular Inflow
RVOT	Right Ventricular Outflow Tract
RVSP	Right Ventricular Systolic Pressure
STJ	Sinotubular Junction
SV	Sample Volume
SVC	Superior Vena Cava
TAPSE	Tricuspid Annular Plane Systolic Excursion
TDI	Tissue Doppler Imaging
TR	Tricuspid Regurgitation
WHO	World Health Organization
WMA	Wall Motion Abnormality

60.4 Document Revision History

60.4.1 V1.0_09Sep2016

This document is the first approved version. Amended versions will be described in this section and include a history of changes.

Version	Changes Made	Effective Date
1.0	Original	09Sep2016
2.0	1. Section 60.6.4.18, page 60.31, Clarification provided for agitated saline contrast use for shunt detection. 2. Section 60.6.6, page 60.40, Clarification provided for agitated saline contrast use for peak TR velocity jet. 3. Section 60.7.5.2, page 60.60, Clarification of boxes to check to assure 3D data transfers in Native format.	25Jan2017
3.0	1. Section 60.6.2.4, page 60.11, Change in the number of cardiac cycles and clips collected. 2. Figure 9 page 60.21, Change in the number of cardiac cycles and clips collected. 3. Figure 10, page 60.22, Change in the number of cardiac cycles and clips collected. 4. Figure 12, page 60.24, Change in the number of cardiac cycles and clips collected. 5. Section 60.6.6, page 60.39, Change in the number of cardiac cycles and clips collected.	02Mar2017

60.5 Study Overview

60.5.1 Purpose

The purpose of this C5Research (C5R) Imaging Manual is to instruct sites in: 1) protocol-specific image acquisition requirements; 2) necessary documentation, image data transfer instructions and data storage; and 3) the query resolution process for any clerical discrepancies and/or non-compliant data.

The goal of the Echocardiography Manual of Operations is to assist sites in obtaining high quality, reproducible, quantitative information about the structure, function and hemodynamics of the right and left heart. The hemodynamic (Doppler) and functional variables will be analyzed at the ICL to determine clinically useful parameters which may aide in early diagnosis, and re-classification of pulmonary hypertension. Advanced Echocardiographic measures of right ventricular performance will be compared to cardiac MRI.

60.5.2 Study Synopsis (from core PVDOMICS Protocol V1.0, April 29, 2016)

PVDOMICS is a novel NHLBI Research Initiative in Pulmonary Vascular Disease. It is recognized that patients with various forms of heart and lung disease exhibit varying degrees of pulmonary hypertension, pulmonary vascular remodeling, and right ventricular dysfunction. The genetic, molecular, and cellular processes driving these phenomena are not well understood. Rapid advances in high throughput omic methodology, combined with powerful bioinformatics and network biology capability, have created the opportunity to conduct studies that broadly search for homologies and differences across the spectrum of disease states associated with pulmonary hypertension and determinants of the spectrum of pulmonary vascular disease and RV compensation that accompanies these conditions.

The 2010 NHLBI Pulmonary Vascular Strategic Plan identified the development of a comprehensive cohort to define phenotypes integrating Omics technologies and systems approaches as a top priority. The current WHO PH classification, based solely on clinical/hemodynamic subsets, limits the ability to customize treatment for an individual patient, or to assign meaningful clinical phenotype designations, *e.g.,* Long-term survivor or Maladaptive RV Hypertrophy. **The overall goal of the PVDOMICS network is to perform comprehensive phenotyping (demographic, physicologic, clinical chemistries, and imaging) and endophenotyping (genomic, proteomic, metabolomic, coagulomic, cell and/or tissue based) across the World Health Organization (WHO) classified PH clinical groups 1 through 5 as well as intermediate phenotypes (including those without overt PH) in order to deconstruct the traditional classification and define new meaningful subclassifications of patients with PVD. The long-term goal is utilization of endophenotypes/biomarkers for early diagnosis, at-risk screening, and personalized approaches for interventions and/or preventions of PVD.**

The PVDOMICS protocol is designed to lead to new understanding of patients with PH and right heart dysfunction, based on molecular, clinical, hemodynamic, dynamic and imaging characteristics. Development of new classifications will be a product of association of these in depth phenotypic descriptions with specific molecular mechanisms of pathogenesis. The protocol will be implemented to lead to identification of both sub-phenotypes of lung vascular disease and to biomarkers of disease that may be useful for early diagnosis or for assessment of interventions to prevent or treat this condition.

The first aim will be a natural product of the protocol, to identify the molecular basis of pulmonary vascular disease regardless of WHO clinical classification, by comparison of current subsets of PH patients. The second aim is to discover biological measures of disease and therapeutic responses that may be useful not only in diagnosis but also as outcome measures in treatment and possibly prevention trials.

60.6 ECHO Process

60.6.1 Echo Qualification Submission Process

60.6.1.1 Prior to qualification, a copy of the current Preventive Maintenance (PM) document for each ultrasound system planned for use in the trial must be submitted to the Imaging Core Lab (*including serial number*). A copy of the PM document should be maintained at the site with the trial regulatory files.

60.6.1.2 The qualification process must be completed prior to sites submitting exams of enrolled subjects. **All sites will be required to submit a de-identified sample echocardiogram to the Imaging Core Lab, via AG MEDNET for *each sonographer* participating in the trial. A backup sonographer should be identified and follow the same qualification process.**

60.6.1.3 The qualification study performed should follow the PVDOMICS imaging protocol. The purpose of the Echo Qualification Process is to ensure compatibility between site echo acquisition and Core Lab analysis tools prior to subject recruitment and to ensure adherence to the imaging protocol.

60.6.1.4 The site and Data Coordinating Center (DCC) will be notified of the sonographer qualification status via email or fax.

60.6.1.5 If a sonographer does not qualify with the first submission, the Imaging Core Lab will use the critique to recommend changes for resubmission of another echo qualification study.

60.6.2 Echo Acquisition

60.6.2.1 Acquire images according to the parameters described in this manual. Only *qualified sonographers* should perform PVDOMICS study echocardiograms.

60.6.2.2 Images must be exported in RAW/NATIVE DICOM data format.

60.6.2.3 Affix a 3-lead EKG, ensuring that a clean tracing is obtained with a tall R wave and free of muscle tremor.

60.6.2.4 For digital acquisition, obtain one capture of 4-5 complete *cardiac cycles* (normal sinus rhythm) for each required parameter. If a view is suboptimal, a new imaging plane should be attempted with controlled respiration. When possible, do not submit sets of cardiac cycles that are preceded by or include cardiac arrhythmias.

60.6.2.5 Doppler and M-mode image acquisitions should be recorded at 50-100 mm/sec sweep speed (depending on heart rate) and the scale adjusted to ensure Doppler peaks are fully visualized.

60.6.2.6 All echo studies must be labeled on the ultrasound system monitor with the study name and subject ID. Be certain the *correct date* and time of image acquisition are displayed on the screen.

60.6.3 Echo Instrumentation

Echocardiographic equipment manufacturer and model varies from site to site. Each site will be required to record this information on the Data Transmittal Form. A description of this should include the brand and model of the echocardiography system used in the examination of each subject. In addition, the institution must provide documentation by a third party ensuring the equipment has been validated and calibrated. If more than one echo machine is to be used in this trial then the information above should be provided for all of the systems that will be utilized. Each machine must have the capability to record proper date, time and subject identification (ID).

Digital Capture - Typically the transthoracic images are obtained with the subject in the left lateral decubitus position during quiet respiration or end expiration. Due to the nature of the trial subjects, capturing images during end expiration (apnea) may provide the best quality images and help reduce image translation. A qualified physician or sonographer must perform all ultrasound exams. At least six sinus cardiac cycles of each view should be digitally captured during quiet respiration or at end expiration. *At least 10 cardiac cycles should be recorded if the subject is in atrial fibrillation.* For digital acquisition, obtain two

sets of three complete cardiac cycles (normal sinus rhythm) for each required parameter. For each view, the gain, compression, depth and image sector width should be optimized to ensure the best echocardiographic image. The selection of harmonics or fundamental frequency should depend upon which yields the best definition of structures.

Frame Rate - To ensure high frame rate image acquisition, that is, frame rates of 60 to 90 frames per second (FPS) narrow the sector width to include the entire left ventricular (LV) myocardium and reduce depth to include 1/3 of left atrium (LA) to ensure full visualization of basal LV. The same method will yield high frame rate imaging of the right ventricle (RV) from which 2D RV myocardial strain will be analyzed at the ICL.

ECG - All images should have a good quality ECG tracing maximizing the "R" wave.

Doppler and M-Mode - For spectral Doppler tracings, the sweep speed should be 50-100 mm/sec and the scale and baseline should be adjusted to make sure that the entire Doppler signal is visualized. Time and velocity calibration markers must be present on the Doppler tracing. For spectral and color Doppler, the appropriate gain level should be selected that detects flow without extraneous noise or extension of signal into adjoining tissue.

Contrast - If visualization of the left ventricular endocardial border is inadequate, then an approved contrast agent can be administered following institutional standards. ***However, the contrast enhanced imaging should only be performed after all other images and parameters are obtained*.** Doppler signals should be repeated after 2D contrast images are acquired. When Doppler signals are obtained during the contrast phase of the study, the gain must be reduced to optimize the velocity signal.

Table 1: ECHO Imaging Schedule

Imaging Visits	Description
Qualification	Submit a qualification echo to Core Lab before enrollment
Visit	Baseline Echo

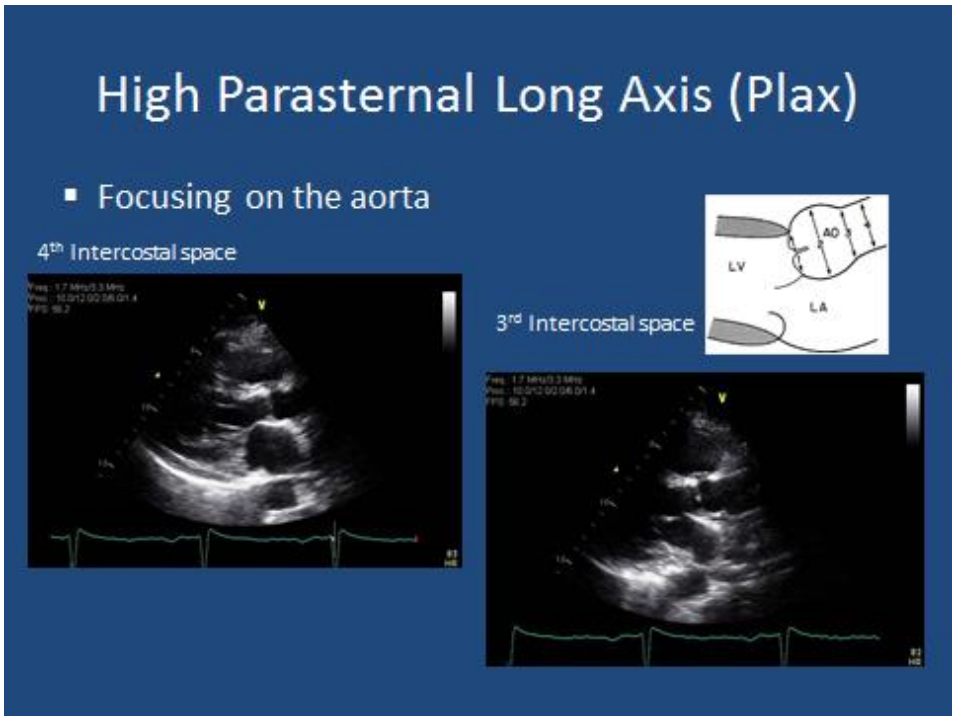
60.6.4 Echo Protocol Parameters and Imaging Guidelines

The required images to obtain the measurements which will be performed at the ICL are detailed within the PVDOMICS **TRANSTHORACIC ECHO PROTOCOL** (Appendix 1)

60.6.4.1 Begin with subject in the left lateral decubitus position. Echo bed cutout should be utilized to optimize apical views.

60.6.4.2 Obtain a high PLAX view with transducer in second or third intercostal space to focus on the ascending aorta (See Figure 1)

Figure 1



60.6.4.3 Obtain views of the LVOT and Aortic valve in both the PLAX and PSAX to identify the LVOT, RVOT proximal and distal linear dimensions. (See Figure 2 and 3)

Figure 2

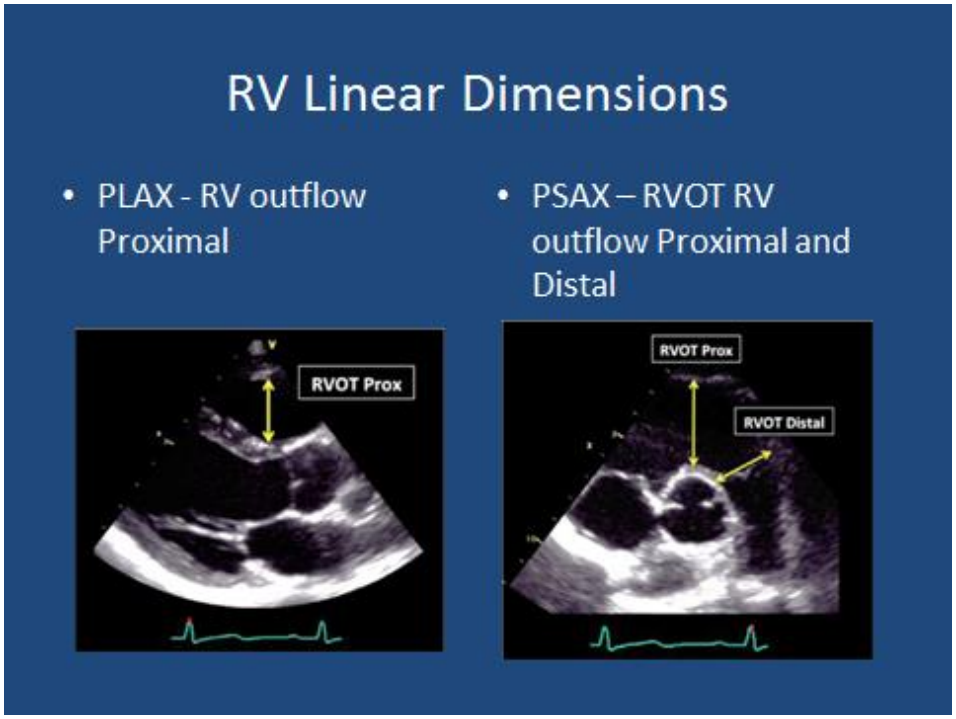
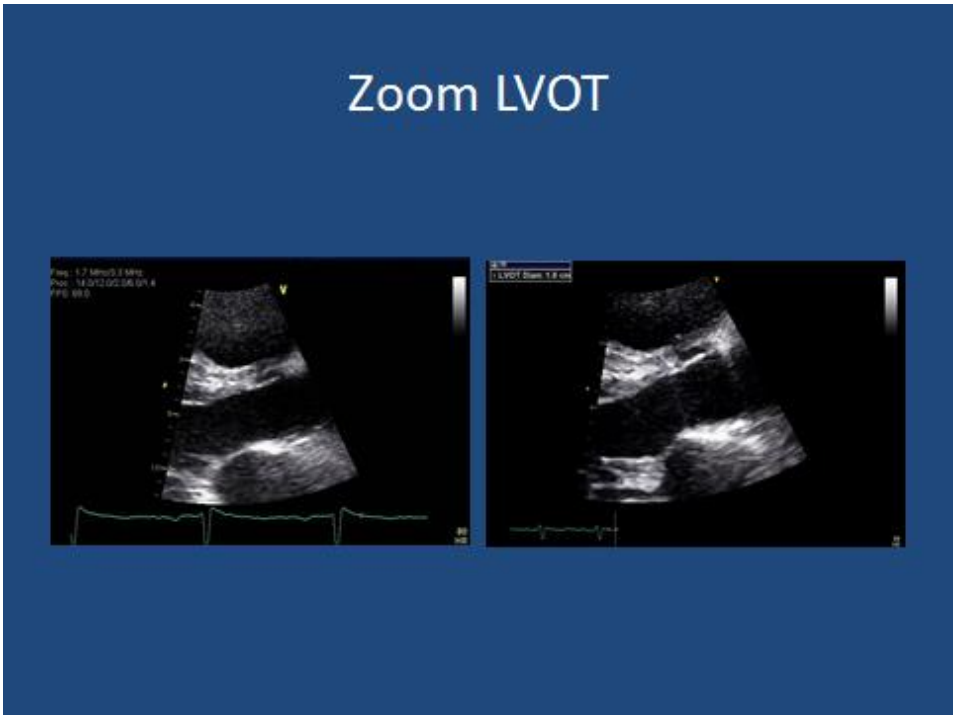
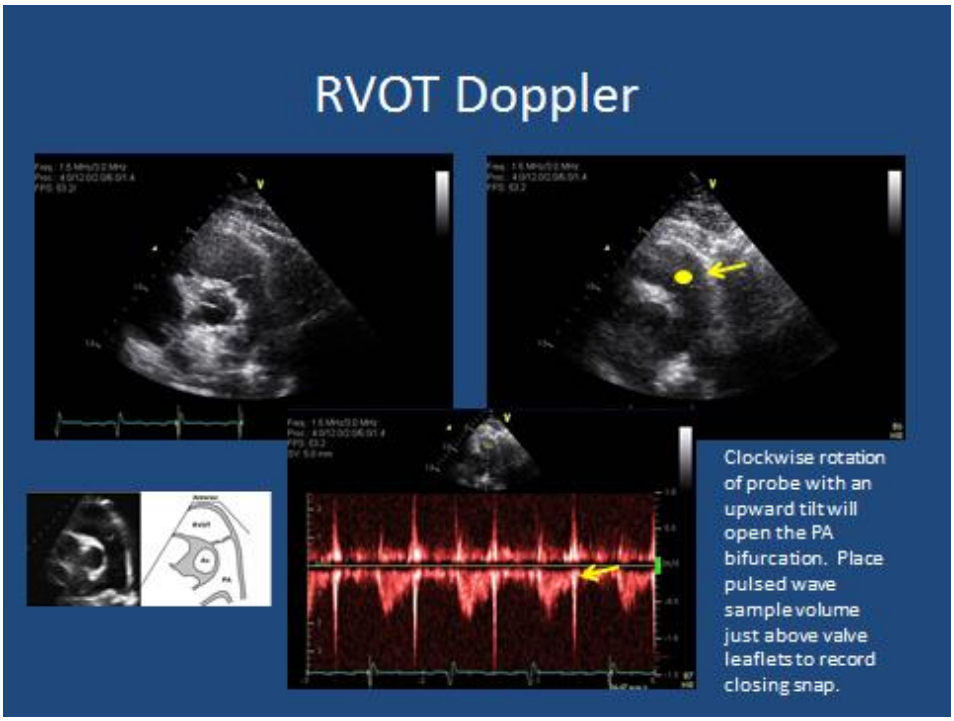


Figure 3



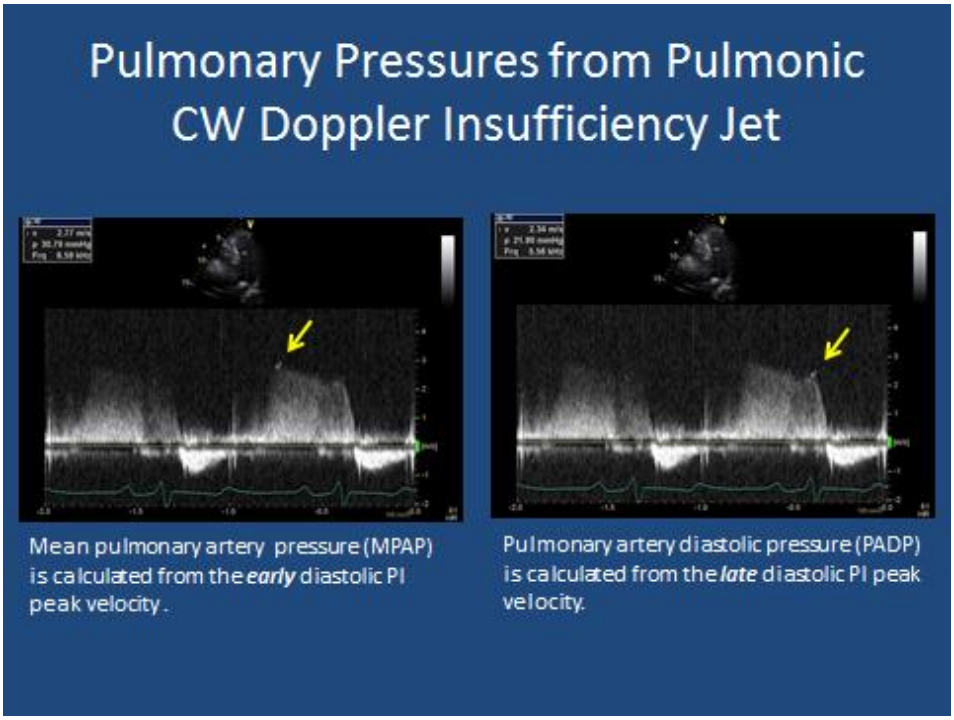
60.6.4.4 From the basal PSAX view, perform a clockwise rotation and slight anterior tilt to view the pulmonary artery and its branches. Record RVOT spectral pulsed wave (PW) Doppler with the closing snap identified. (See Figure 4)

Figure 4



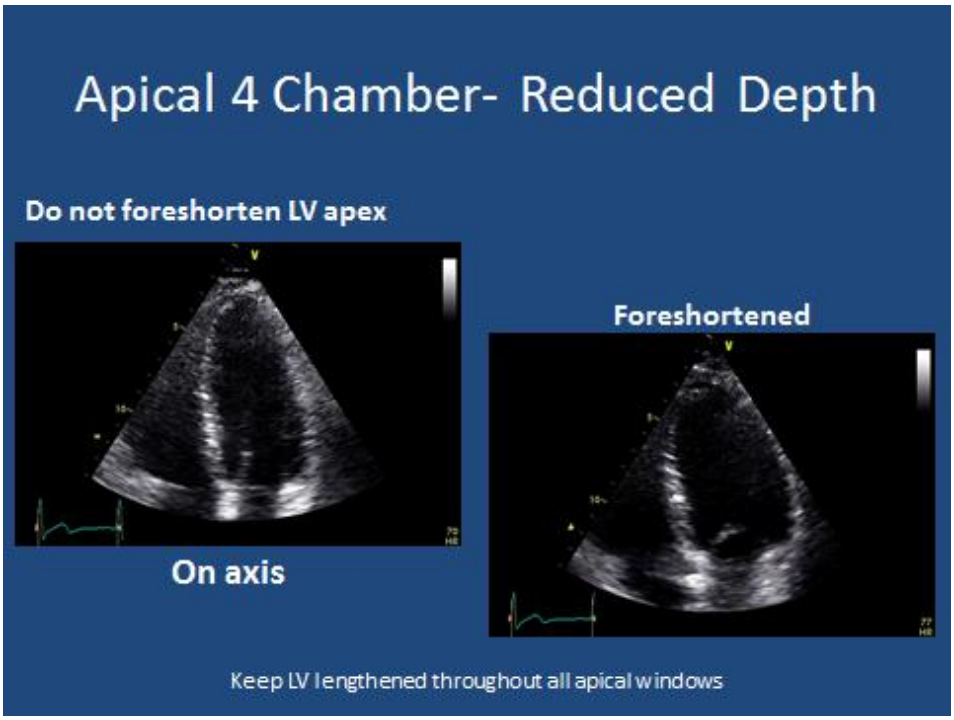
60.6.4.5 When pulmonary insufficiency is present collect Continuous Wave (CW) Doppler for additional estimation of pulmonary pressures. (See Figure 5)

Figure 5



60.6.4.6 Apical views should be acquired on axis. The apical myocardium should appear thin and pointed when in the correct plane. A foreshortened apex will appear rounded with thickened myocardium. When the image is foreshortened, apical contractility will thicken toward the mitral valve rather than toward the contralateral walls. (See Figure 6)

Figure 6



To ensure reduced depth high frame rate image acquisition (frame rate of 60 to 90 FPS), narrow the sector size to include entire LV myocardium. Remember to include 1/3 of left atrium to ensure full visualization of basal LV.

60.6.4.7 Right ventricular (RV) comprehensive imaging: includes the apical four-chamber, RV-focused apical four-chamber, modified apical four-chamber, left parasternal long and short-axis, left parasternal RV inflow, RV outflow and subcostal views.

60.6.4.8 Dedicated RV-focused apical four-chamber view: RV dimensions are best measured from an RV focused A4C view. The LV should remain long and in the center of the sector while showing the largest RV basal diameter. (See Figure 7A and 7B)

Figure 7A

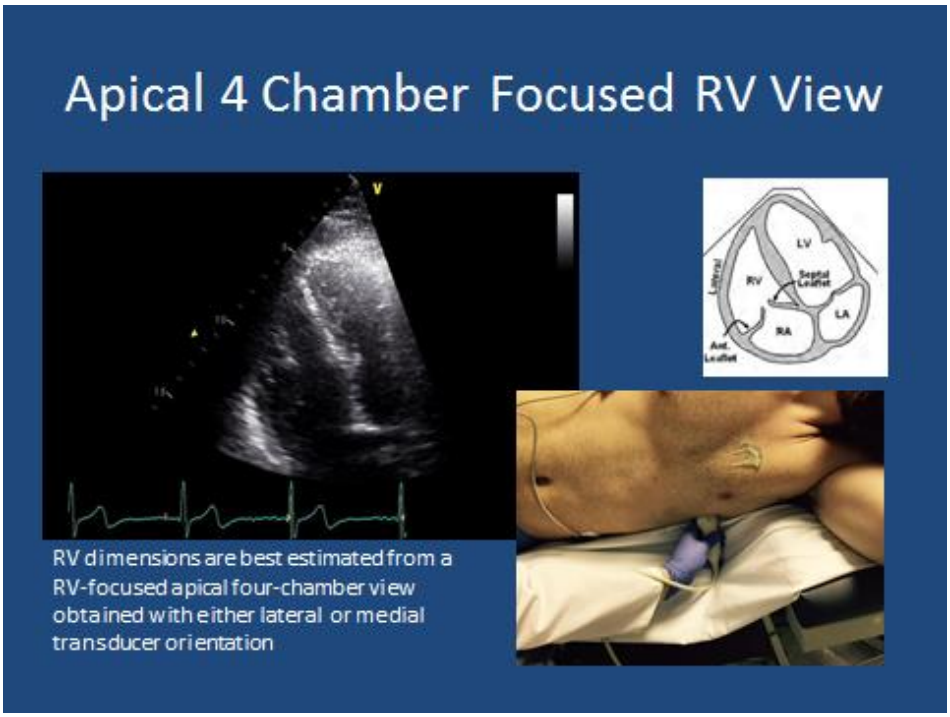
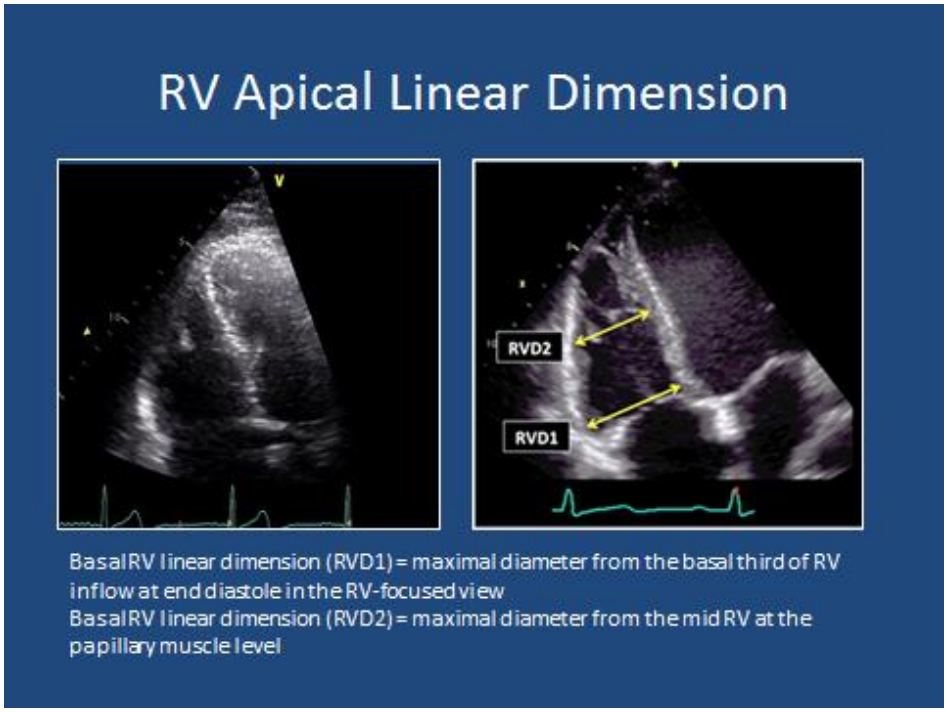
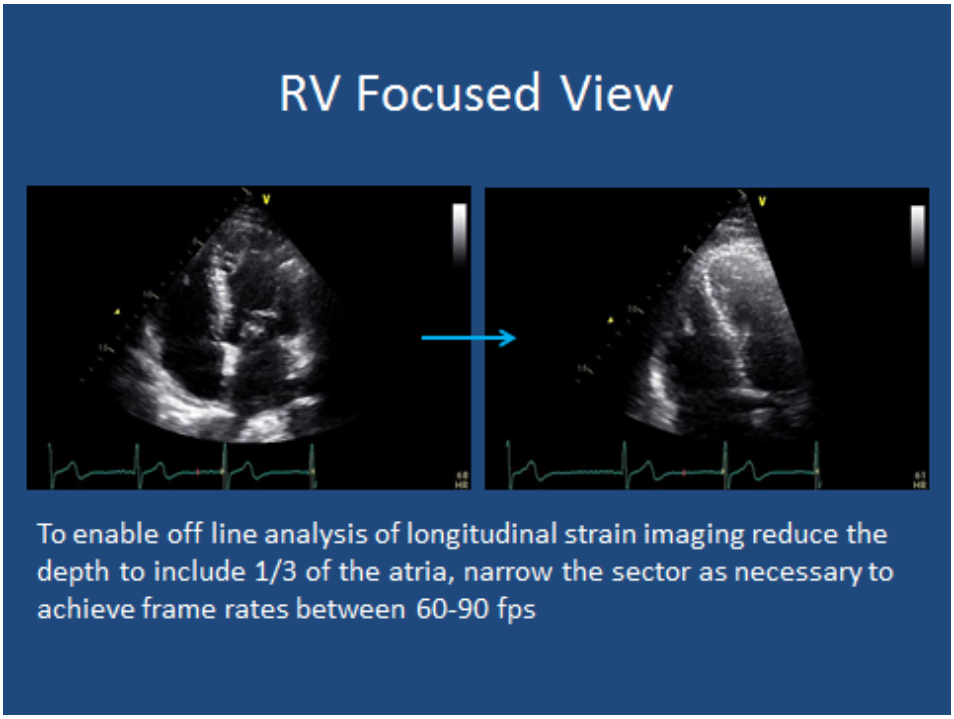


Figure 7B


RV Apical Linear Dimension
RVD2
RVD1
Basal RV linear dimension (RVD1) = maximal diameter from the basal third of RV inflow at end diastole in the RV-focused view
Basal RV linear dimension (RVD2) = maximal diameter from the mid RV at the papillary muscle level

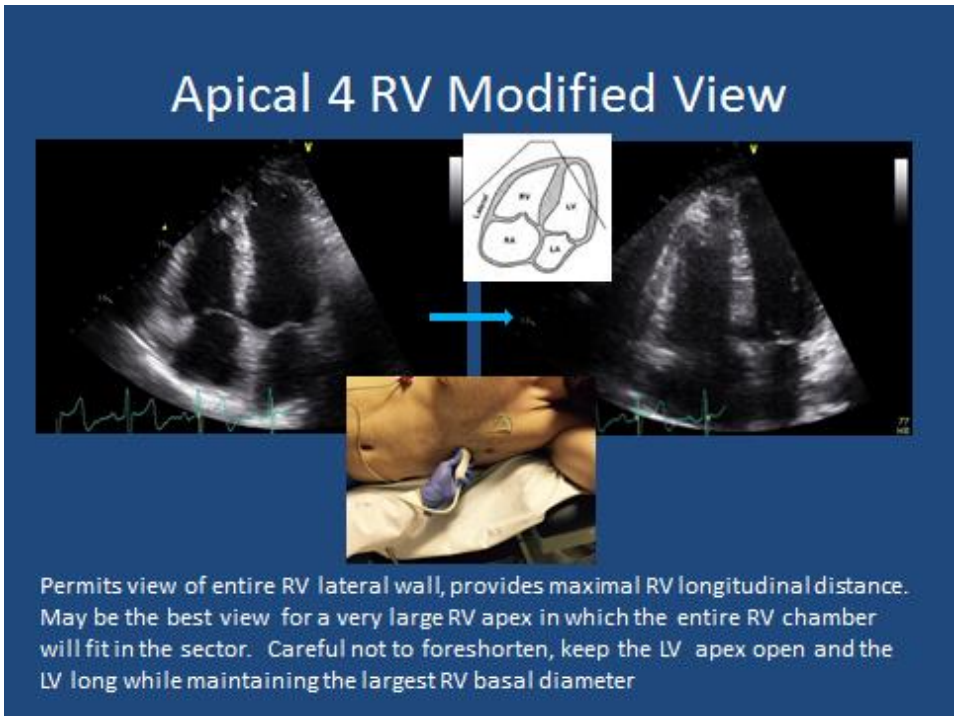
60.6.4.9 Dedicated RV-focused apical four-chamber view: To ensure reduced depth high frame rate image acquisition (frame rate of 60 to 90 FPS) narrow the sector size to include the entire RV lateral wall myocardium. Remember to include 1/3 of right atrium to ensure full visualization of basal RV. (See figure 8)

Figure 8



60.6.4.10 Apical 4C RV Modified View: Permits view of the entire RV lateral wall, and provides maximal RV longitudinal distance. For a severely dilated RV this view may allow the entire RV chamber to fit within the sector. Use care not to foreshorten the RV, keeping the LV apex open and the LV elongated while maintaining the largest RV basal diameter. (See Figure 9)

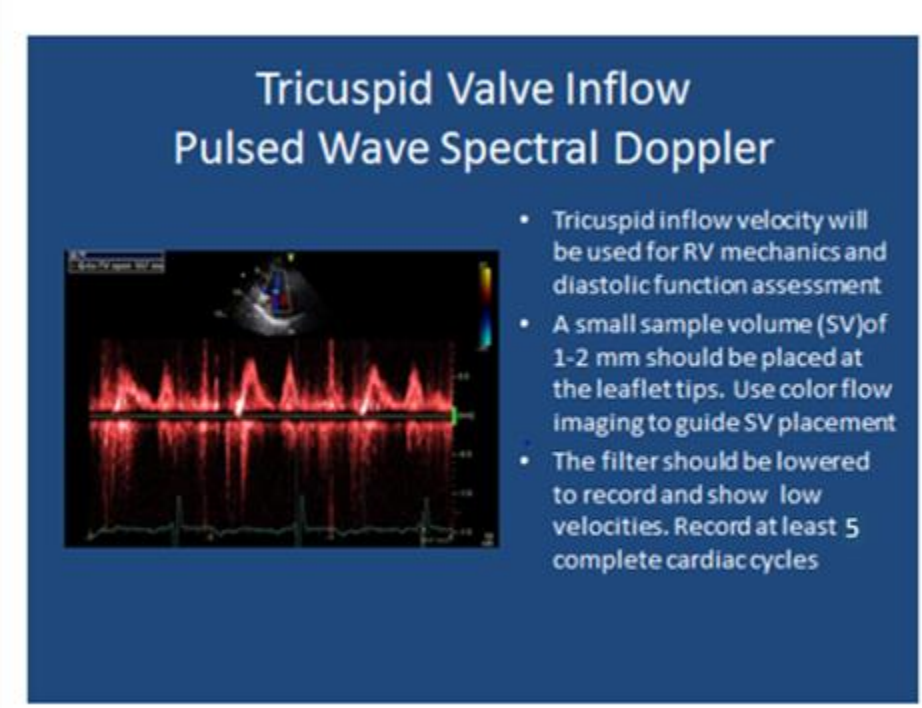
Figure 9



Note: During image acquisition maintain a clean ECG baseline free of baseline wandering and muscle tremor. Obtain a *minimum* of one capture with 4-5 complete cardiac cycles. Frame rates between 60-90 FPS.

60.6.4.11 Tricuspid Valve Inflow: PW Doppler will be used to evaluate RV performance. Spectral Doppler of RV inflow may be obtained from the PLAX RV inflow, PSAX at the aortic level, or apical views. Use color Doppler to guide SV placement in the center of flow close to the TV leaflet tips to achieve the best spectral waveform. Adjust filter to better identify valve opening and closing. (Figure 10)

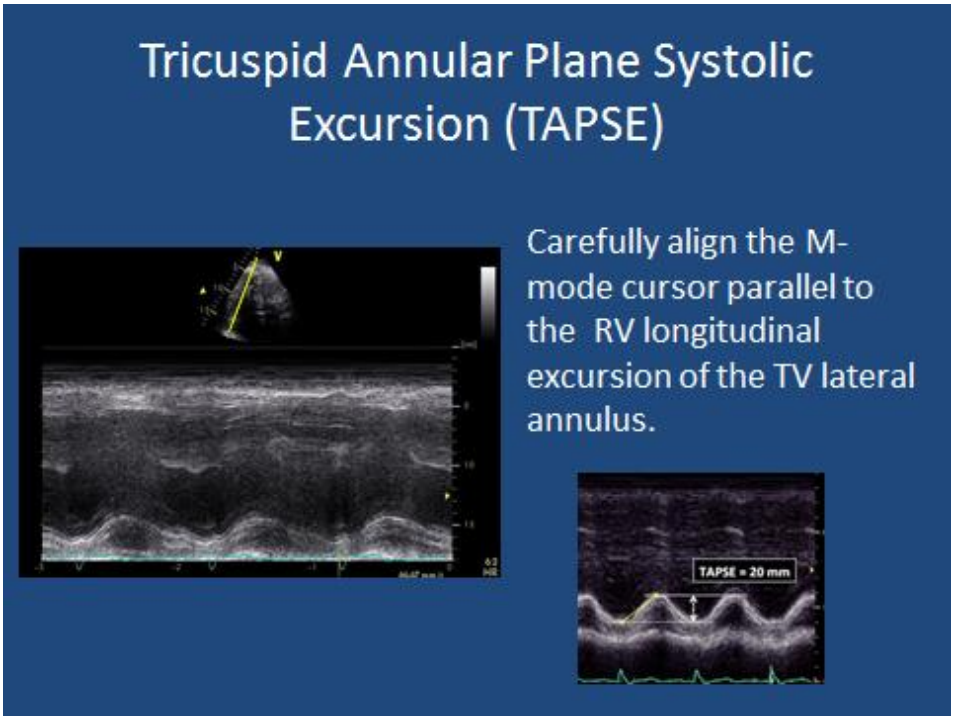
Figure 10



60.6.4.12 Tricuspid Annular Systolic Excursion (TAPSE):

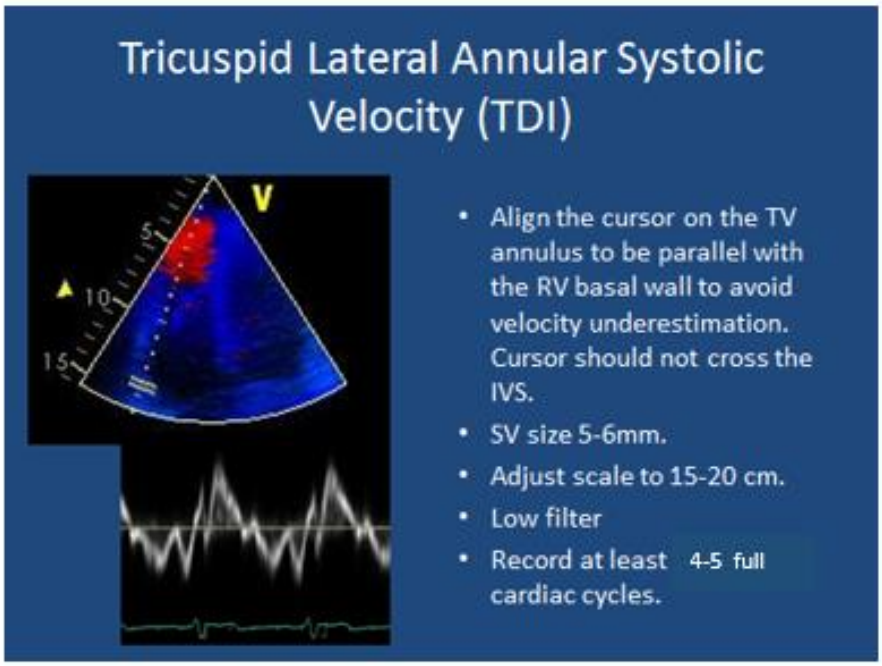
Derive from M-mode analysis of the lateral tricuspid annular longitudinal movement towards the apex. Take care to align the M-mode cursor parallel to the lateral wall. Record at 50 mm/s sweep speed. (See Figure 11)

Figure 11



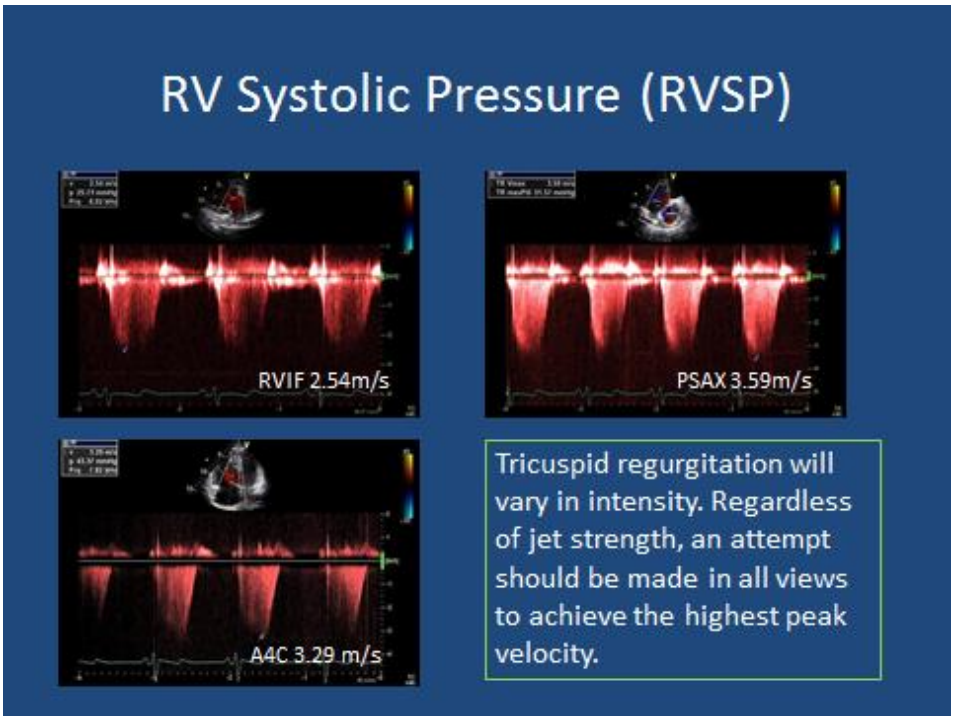
60.6.4.13 Tissue Doppler Imaging (TDI): TDI of the lateral TV annulus will be utilized to measure RV performance (RIMP, “s” wave and diastolic function). Align the cursor on the TV annulus to be parallel with the RV basal wall to avoid velocity underestimation. (See Figure 12)

Figure 12



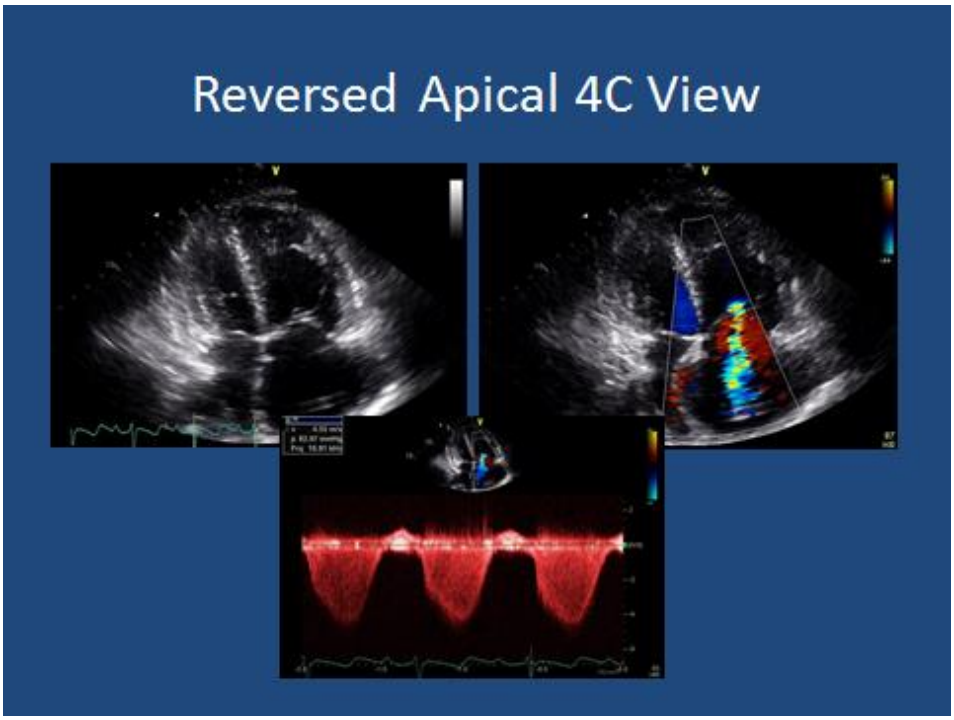
60.6.4.14 Continuous Wave Doppler (CW): CW Doppler of the TV regurgitation jet allows for estimation of RV systolic pulmonary artery pressures. CW Doppler may be obtained with the duplex imaging or non-imaging probe from the RV inflow, PSAX at the basal level, A4C, reversed A4C, and off axis imaging views to achieve the highest and cleanest signal. Respiratory variation may be alleviated when recorded at end expiration. (See Figure13)

Figure 13



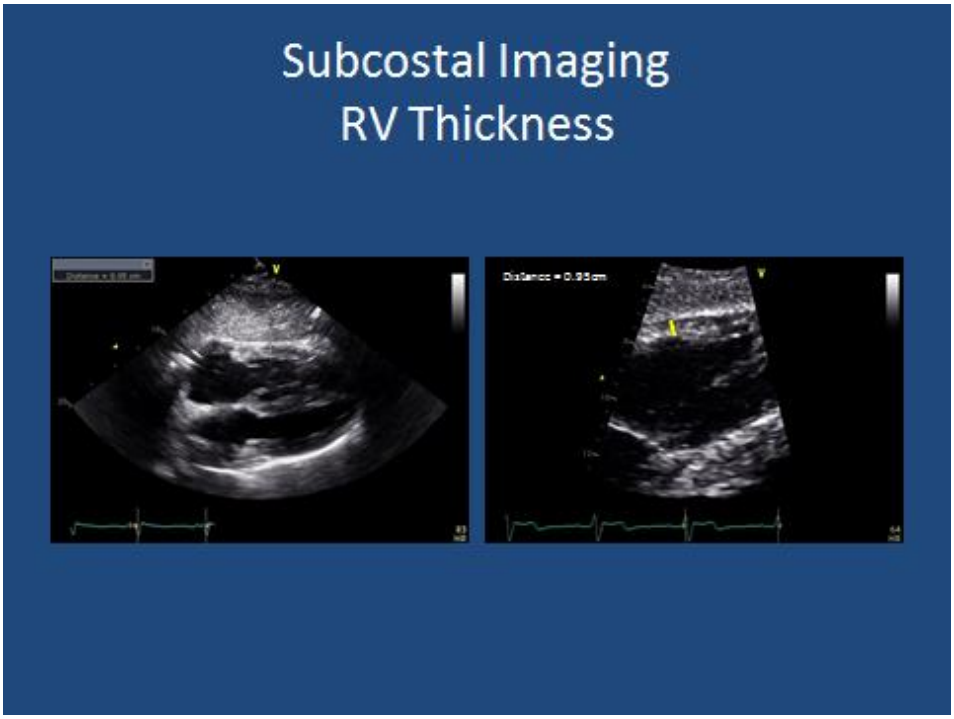
60.6.4.15 Reversed Apical 4C View: Optimize the image to best align the Doppler flow to achieve the highest velocities for RVSP estimation. This may be achieved with reversed imaging on select patients.
(See Figure 14)

Figure 14



60.6.4.16 Subcostal View: Subcostal four chamber view (*frontal view*) allows for measurement of the RV free wall thickness. Zoomed imaging helps to define the true RV wall. (See Figure 15)

Figure 15



60.6.4.17 Subcostal View: Subcostal imaging of the four chamber view (frontal view) also allows for imaging of the atrial septum along its anterior –posterior axis from the SVC to the atrioventricular valves. Color Doppler interrogation of the IAS from the subcostal imaging windows should include the four chamber view (frontal view), with short axis clockwise rotation 90 degrees (sagittal view)
(See Figure 16a, 16b and 17)

Figure 16a

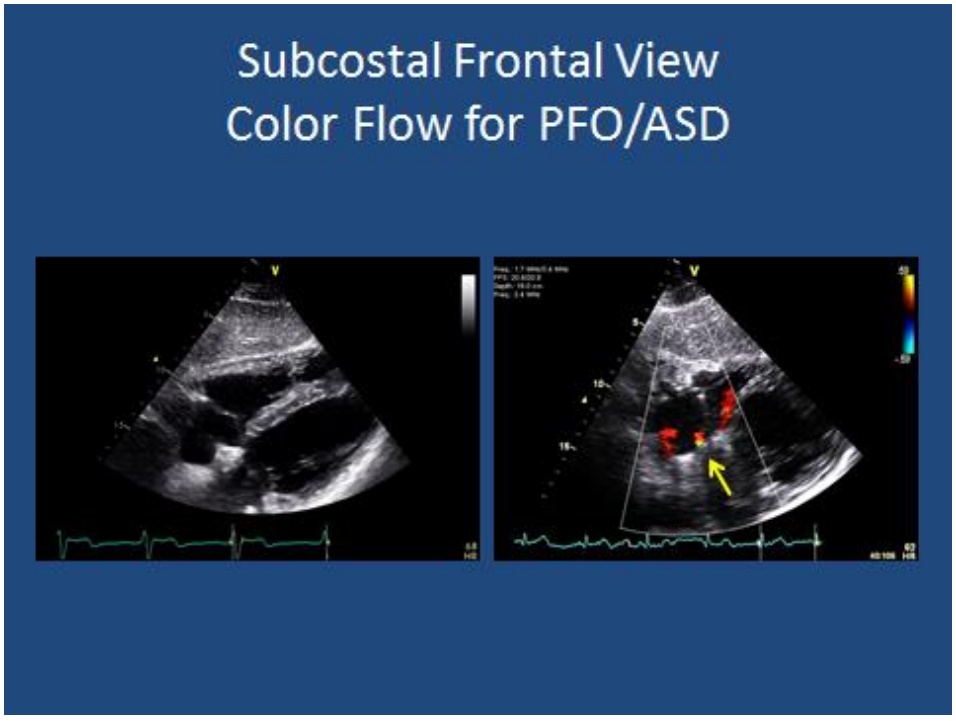


Figure 16b

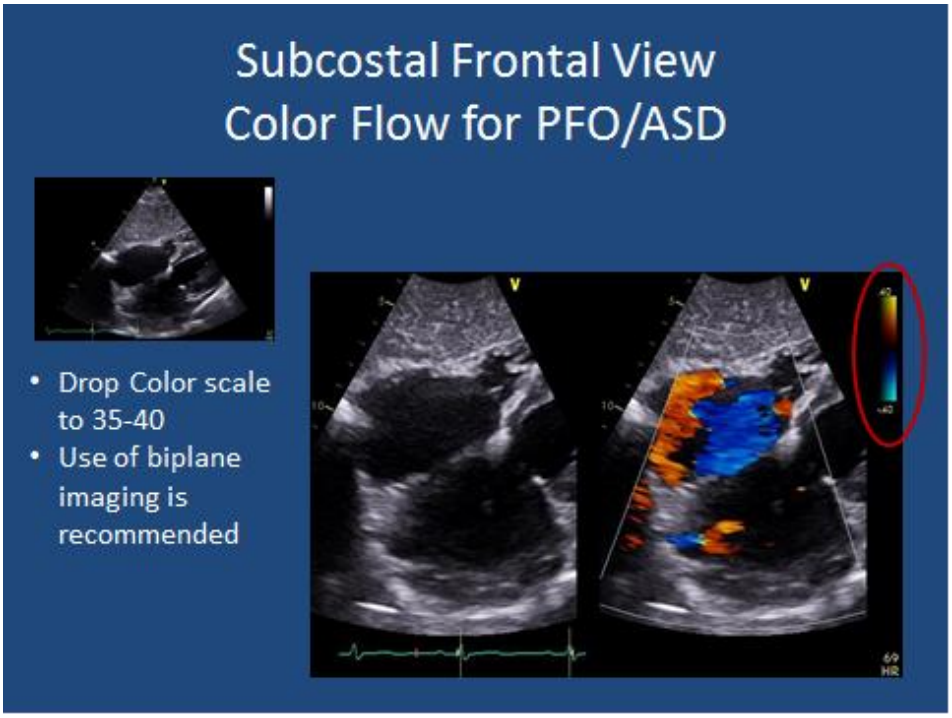
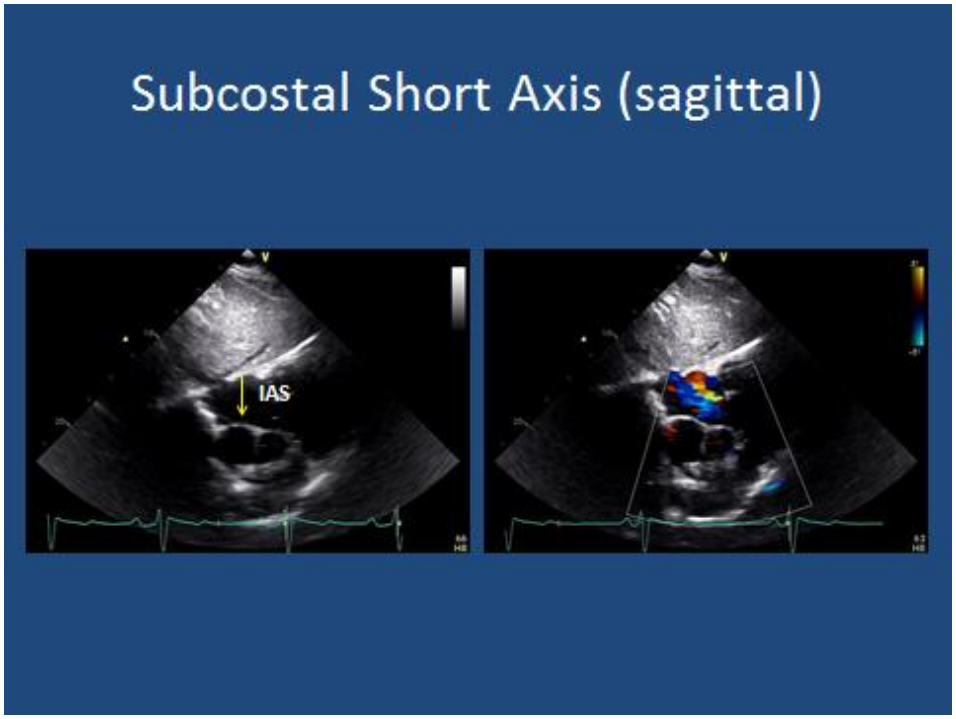


Figure 17

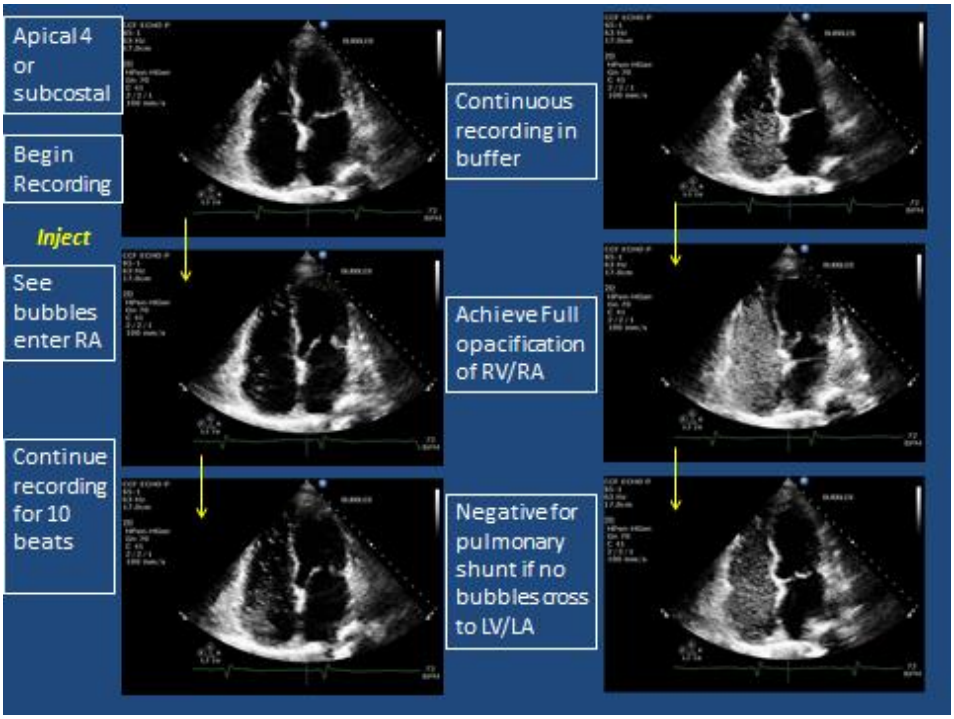


60.6.4.18 Bubble Study: Include assessment of the IAS for a PFO or ASD shunt with and without color flow Doppler.

Study subjects without known congenital systemic to pulmonary shunts, who did not have an agitated saline test on their prior echo, will need to undergo a peripheral IV line insertion and injection of the agitated saline (bubble study) in order to rule out intra-cardiac shunt.

When a shunt is suspected an agitated saline bubble study should be performed from the A4C view (or subcostal as necessary). Recording should be initiated prior to injection. After visualization of the bubbles into the right atrium continue recording for at least 10 beats to identify intra-cardiac or intra-pulmonary shunting. (See Figure 18) Study subjects without known congenital systemic to pulmonary shunts, who did not have an agitated saline test on their prior Echo, will need to undergo a peripheral IV line insertion and injection of the agitated saline ("bubble study") in order to rule out intracardiac shunt.

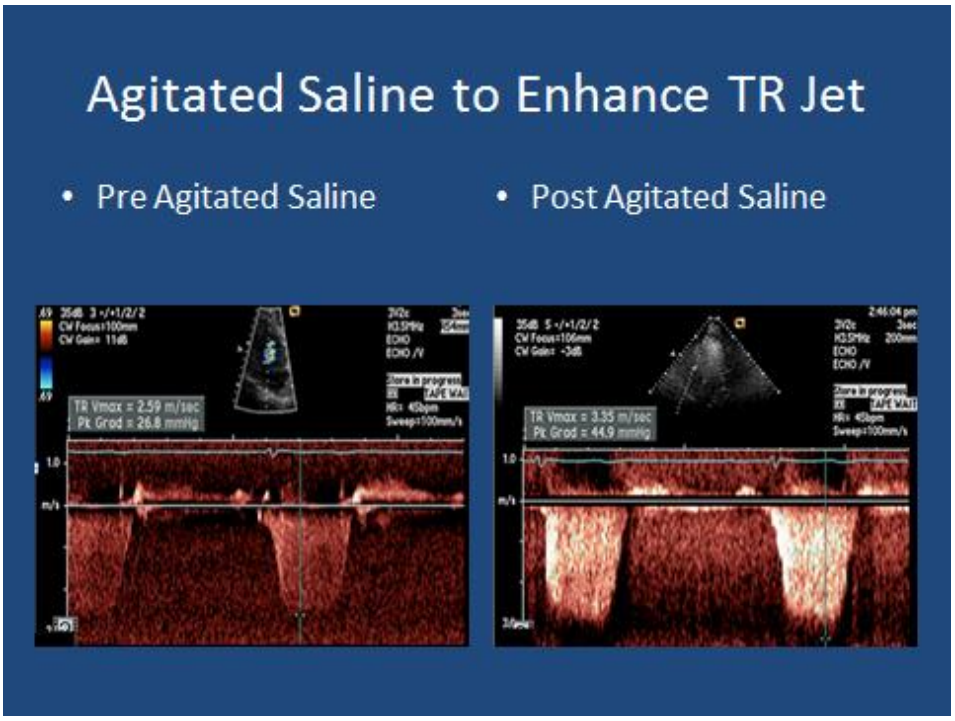
Figure 18



60.6.4.19 Agitated Saline Technique: Attach two 10-ml syringes using a three way stopcock to an intravenous line. One syringe should be filled with 8ml physiologic saline and the other with 1 ml air, draw 1 ml of blood in to the air filled syringe. Begin mixing by reverse flushing between both syringes until an adequate amount of micro-bubbles are present. (J Am Soc Echocardiogr2015;28:255-63.**)**

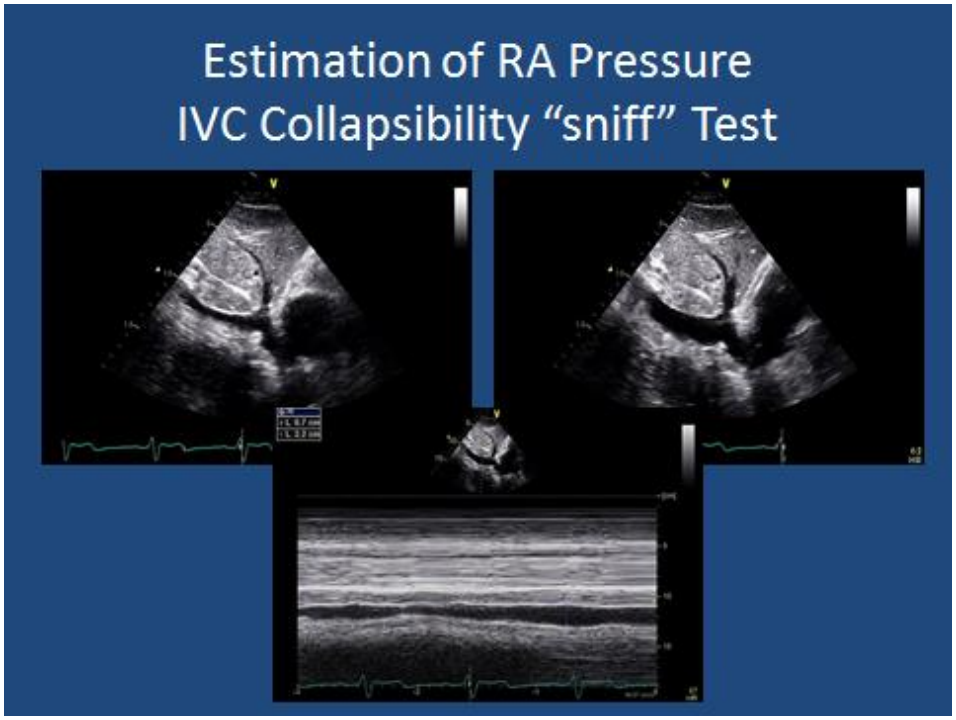
60.6.4.20 TR Enhancement: An agitated saline bubble study may enhance a weak or difficult to detect tricuspid regurgitation jet. Wait for jet washout to prevent blooming artifact. (See Figure 19)

Figure 19



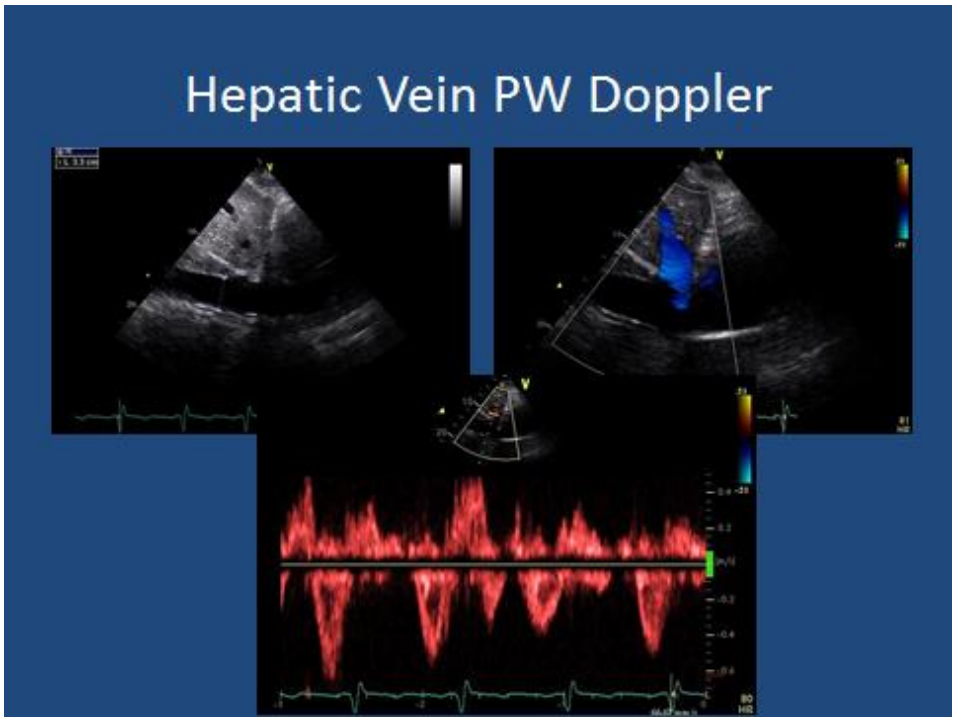
60.6.4.21 Subcostal View: The subcostal view permits imaging and measurement of the IVC, allowing for assessment of RA pressure with inspiratory collapsibility. Linear M-mode measurement of IVC is performed during inspiratory sniff. (See Figure 20)

Figure 20



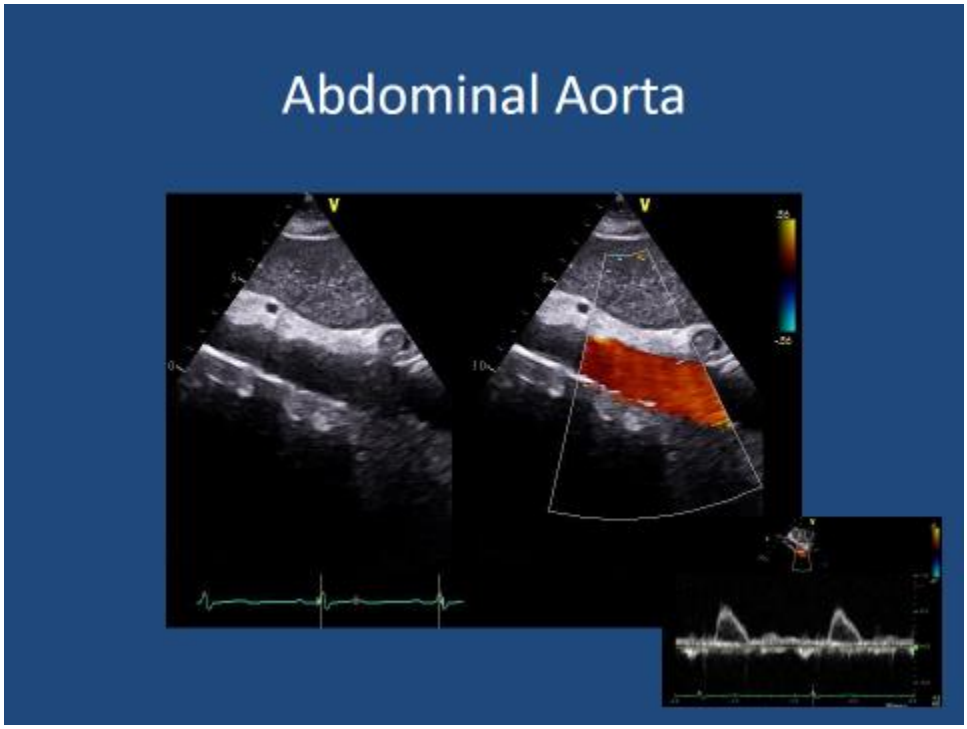
60.6.4.22 Hepatic Vein Doppler: Align the PW Doppler sample volume parallel to hepatic vein (HV) flow. (See figure 21)

Figure 21



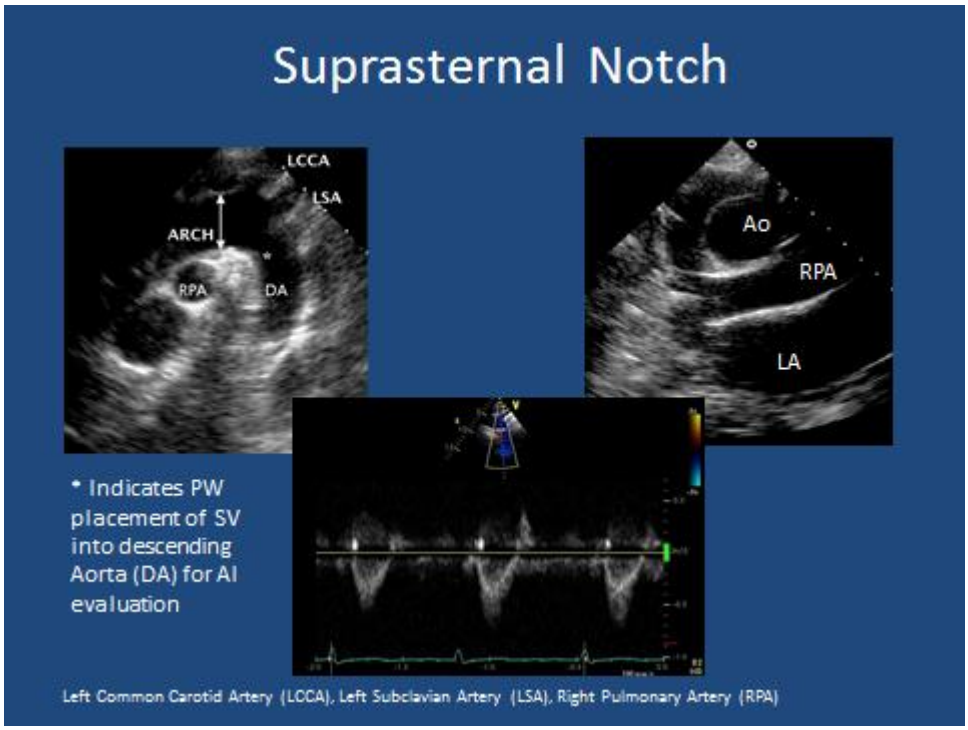
60.6.4.23 Abdominal Aorta: Just below the IVC the abdominal aorta can be seen in its long axis. Strong pulsations and continuous flow on CFD will help identify from the IVC. (See Figure 22)

Figure 22



60.6.4.24 Suprasternal Notch: PW/CW Doppler from the suprasternal notch to identify abnormal flow in valvular and congenital heart disease, PEDOFF imaging should also be considered from this window. (See Figure 23)

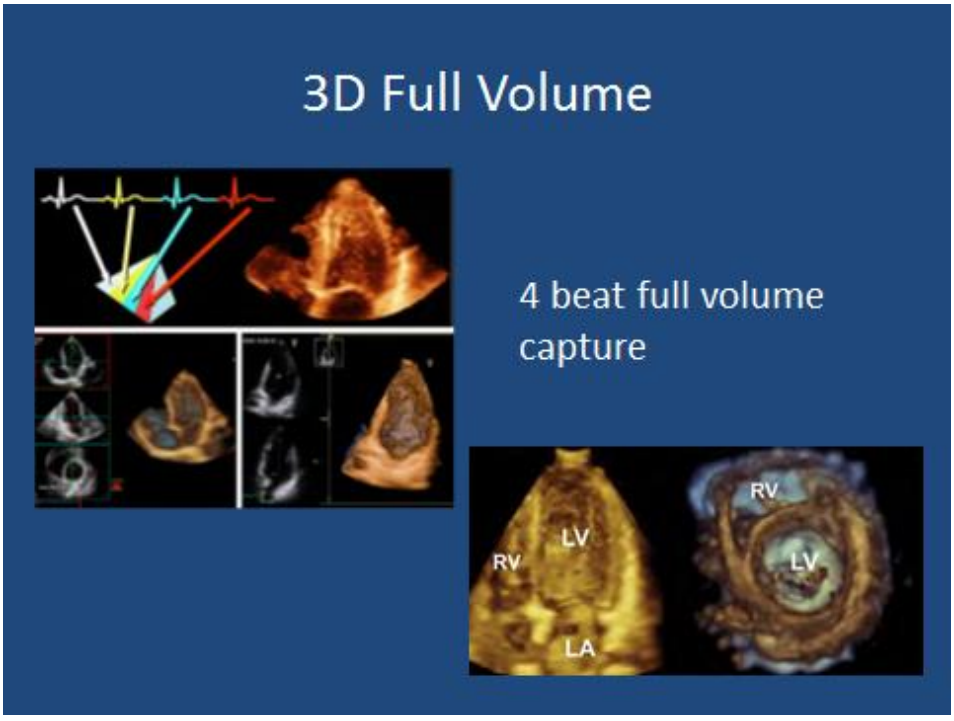
Figure 23



60.6.5 Part II 3D Optional Research Protocol

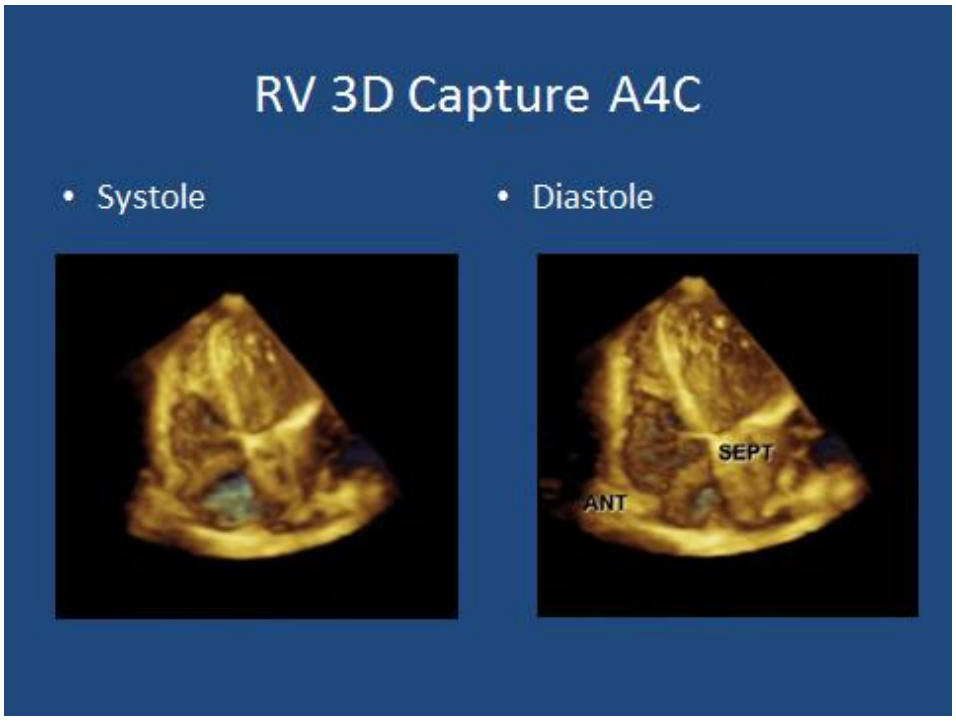
60.6.5.1 3D LV Full Volume: ECG 4 beat full volume capture. Check for stitching artifact and optimize gain settings. (See Figure 24)

Figure 24



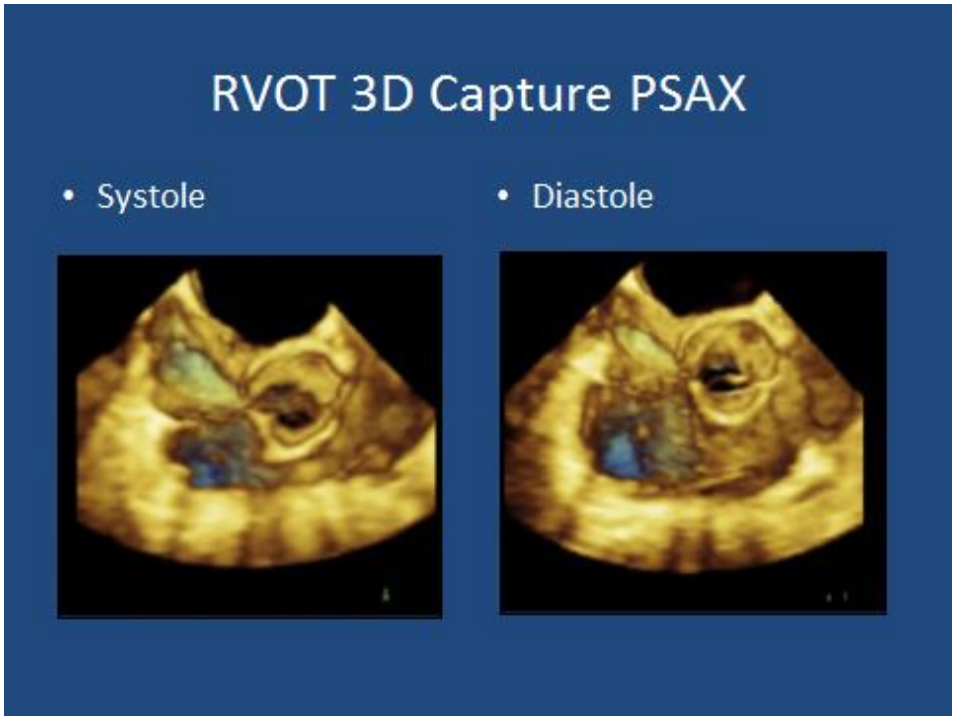
60.6.5.2 3D RV Full Volume: RV focused 4C view, ECG 4 beat full volume capture. Check for stitching artifact and optimize gain settings. (See Figure 25)

Figure 25



60.6.5.3 RVOT 3D PSAX: ECG 4 beat full volume capture. Check for stitching artifact and optimize gain settings. (See Figure 26)

Figure 26



60.6.6 (Appendix 1) PVDOMICS Transthoracic Echo Protocol

Goals:

- General cardiac and valvular anatomy and function

- Systolic function

- Diastolic function

- Hemodynamic assessment:

-Valvular pathology quantitation

-Calculation of Qp and Qs

-CVP and PAP estimate-Tricuspid valve regurgitation peak velocity

PART 1: Mandatory (clinical protocol)

- All images should be collected in one 4-5 beat loops for a total of 5 complete cardiac cycles
- Collect images during breath hold for best image optimization
- Agitated saline (with a few drops of blood) may be necessary to assure peak TR velocity jet is achieved
- Contrast enhancement when clinically indicated

Table 1: Echo Protocol Imaging Acquisition

PLAX	- Increased depth field of view (FOV) - Decreased depth FOV - Focus on LVOT with and without zoom mode (include annulus, sinus and STJ) - Move up an intercostal space to better visualize proximal ascending aorta - M-Mode AO Root - M-Mode MV - M-Mode LV - Color Doppler on Aortic Valve (AV) - Color Doppler on Mitral Valve (MV)

RV Inflow	☐ 2D RV Inflow ☐ Color Doppler across valve ☐ CW Doppler across valve- *Please record attempt, even if incomplete signal or insufficient TR*
PSAX	☐ 2D view at 3 valve level, PV, AV, TV ☐ Zoom the AV to visualize all leaflets ☐ Color AV ☐ Optimize 2D image of RVOT at PV level ☐ Color across PV level ☐ CW Doppler of PV ☐ PW Doppler across RVOT proximal to valve tips, SV 3-4mm ☐ Standard 2D of PA include bifurcation if possible-may need to move to higher ICS ☐ Color across TV ☐ CW of TV ☐ 2D view at the MV level ☐ Color across MV ☐ 2D view at the basal, mid and apical LV levels (collected at frame rates between 60-90 FPS)
Apical 4CH	☐ Apical 4 chamber view at increased depth (including entire atrial borders) ☐ Apical 4 chamber view at increased depth (including entire atrial borders) collected at frame rates between 60-90 fps. ☐ Dedicated 2D LV Image (reduced depth to focus on LV) ☐ Dedicated 2D LV Image (reduced depth to focus on LV) collected at frame rates between 60-90 FPS ☐ Color across MV, CW Doppler across MV ☐ PW MV inflow, SV at 2.0 mm at leaflet tips ☐ PW MV inflow, SV at 2.0 mm at mitral annular level ☐ PW Doppler Pulmonary Veins (SV 3-4 mm) ☐ MV annular tissue Doppler (septal and lateral mitral annuli) (SV 5-6 mm) ☐ PW TV inflow (held apnea) , CW across TV ☐ Dedicated RV 2D Image (reduced depth) ☐ Dedicated RV 2D Image (reduced depth) frame rates between 60-90 FPS ☐ TV annular tissue Doppler (lateral wall) (SV 5-6 mm) ☐ TAPSE (align M-mode cursor parallel to RV lateral wall) ☐ Zoom, Color and Doppler IAS, assess for ASD flow ☐ Zoom, Color and Doppler IVS (down to apex) assess for

	VSD flow
Apical 5CH	□ Apical 5 chamber view at increased depth □ Color Doppler LVOT □ PW Doppler LVOT □ Perform valsalva if systolic anterior motion of the MV is suspected □ CW Doppler across AV (parallel to flow) □ For suspected/known AS, obtain CW Doppler peak systolic velocities from multiple transducer positions (including PEDOFF imaging)
Apical 2CH	□ Apical 2 chamber view at increased depth (including entire atrial borders) □ Apical 2 chamber view at increased depth (including entire atrial borders) collected at frame rates between 60-90 FPS □ Dedicated 2D LV Image (decreased depth to focus on LV) □ Dedicated 2D LV Image (decreased depth to focus on LV) collected at frame rates between 60-90 FPS □ Color Doppler MV □ CW Doppler if indicated
Apical 3CH **(Apical Long)**	□ Apical 3 chamber view at increased depth (including entire atrial borders) □ Apical 3 chamber view at increased depth (including entire atrial borders) collected at frame rates between 60-90 FPS □ Dedicated 2D LV Image (decreased depth to focus on LV) □ Dedicated 2D LV Image (decreased depth to focus on LV) collected at frame rates between 60-90 FPS □ Color across MV □ Color across AV □ PW Doppler of LVOT if indicated
Subcostal	□ 2D 4 chamber image □ Zoom on RV free wall for RV thickness □ Zoom on IAS □ Color, lower color scale to 35-40 cm/sec, then PW Doppler if shunt is suspected followed by CW Doppler □ 2D image of IVC during normal respiration □ M-mode IVC to document respiratory collapse with “sniff” □ Color Doppler IVC □ Color and PW Doppler on hepatic vein

Suprasternal Notch	□ Visualize abdominal aorta, then color and PW Doppler □ 2D Image of aortic arch □ Color Doppler of aortic arch □ PW Doppler □ 2D Continuous Wave Doppler, PEDOFF if indicated
Agitated Saline	□ Bubble study at rest □ Bubble study with ***valsalva*** for suspicion of PFO or pulmonary shunt □ May be used to enhance an insufficient TR jet
Contrast Enhancement for LVO and EBD	□ Consider echo contrast study for LV/RV opacification if endocardial definition is sub-optimal per ASE guidelines □ Obtain all standard views without contrast prior to performing contrast imaging. □ Additionally contrast may be used for Doppler enhancement

Note: If contrast was administered on the initial study, please use contrast on all follow up studies.

Part II Optional Research Protocol

3D Full volume LV and RV dataset (4 beat acquisition is preferable) for the 3D LV and RV volume, function and strain measurements

Table 2 3D Protocol Imaging Acquisition

3DLV	□ Full volume PLAX of LV □ Full volume apical 4 of LV
3DRV	□ Full Volume Apical 4 of RV □ Full Volume RVOT

Above images should be obtained using best possible image optimization algorithms, including automated options offered by the vendors

Best results are expected in patients with regular RR intervals and optimal Echo windows. Optimize frame rates.

60.7 Echo Scan Submission Procedure

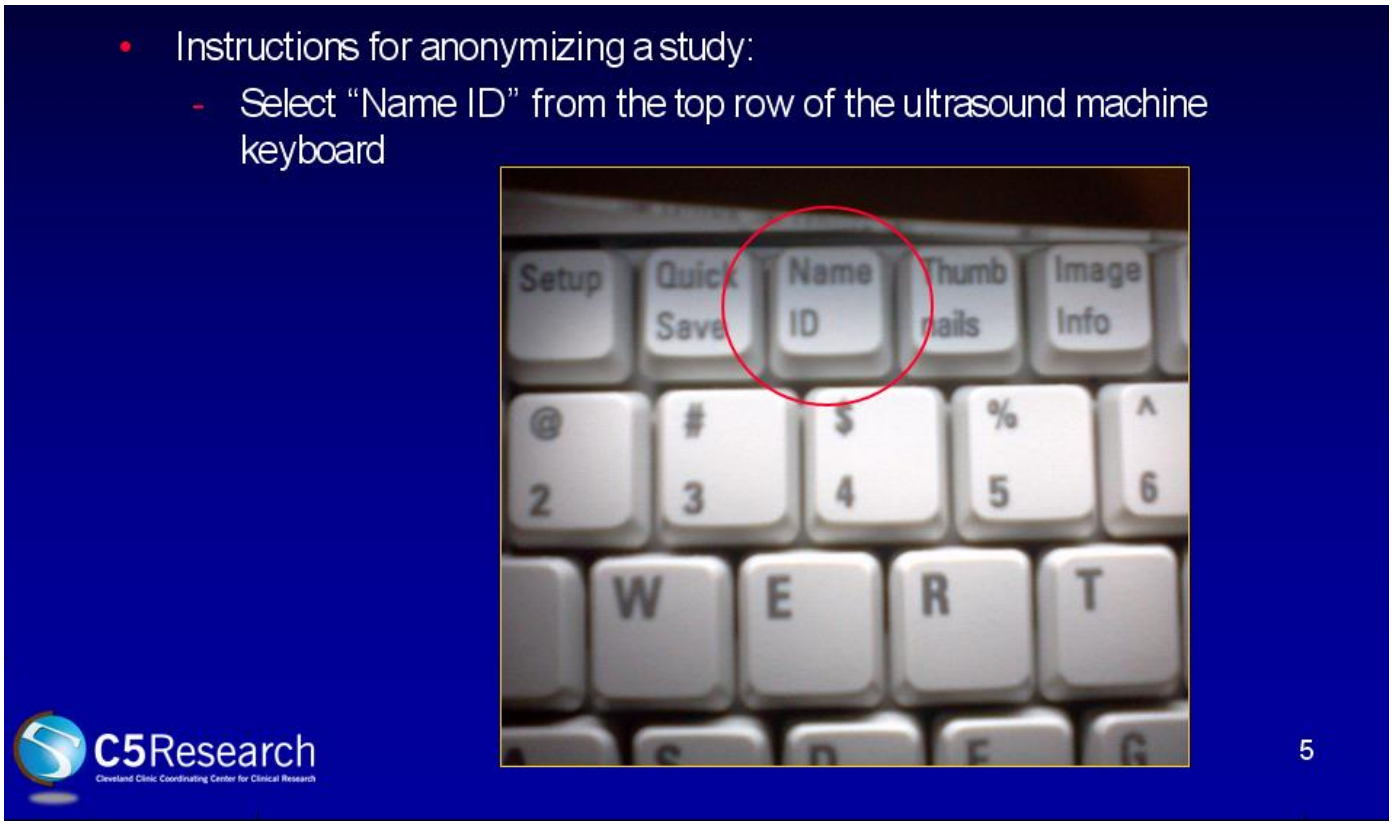
60.7.1 Echo Scan Submission Instructions

60.7.1.1 Please observe all HIPAA rules and regulations. For the purpose of confidentiality, all references to a specific subject must be made by the Subject ID Number. Please do not use subject names or any personal information to label the exam.

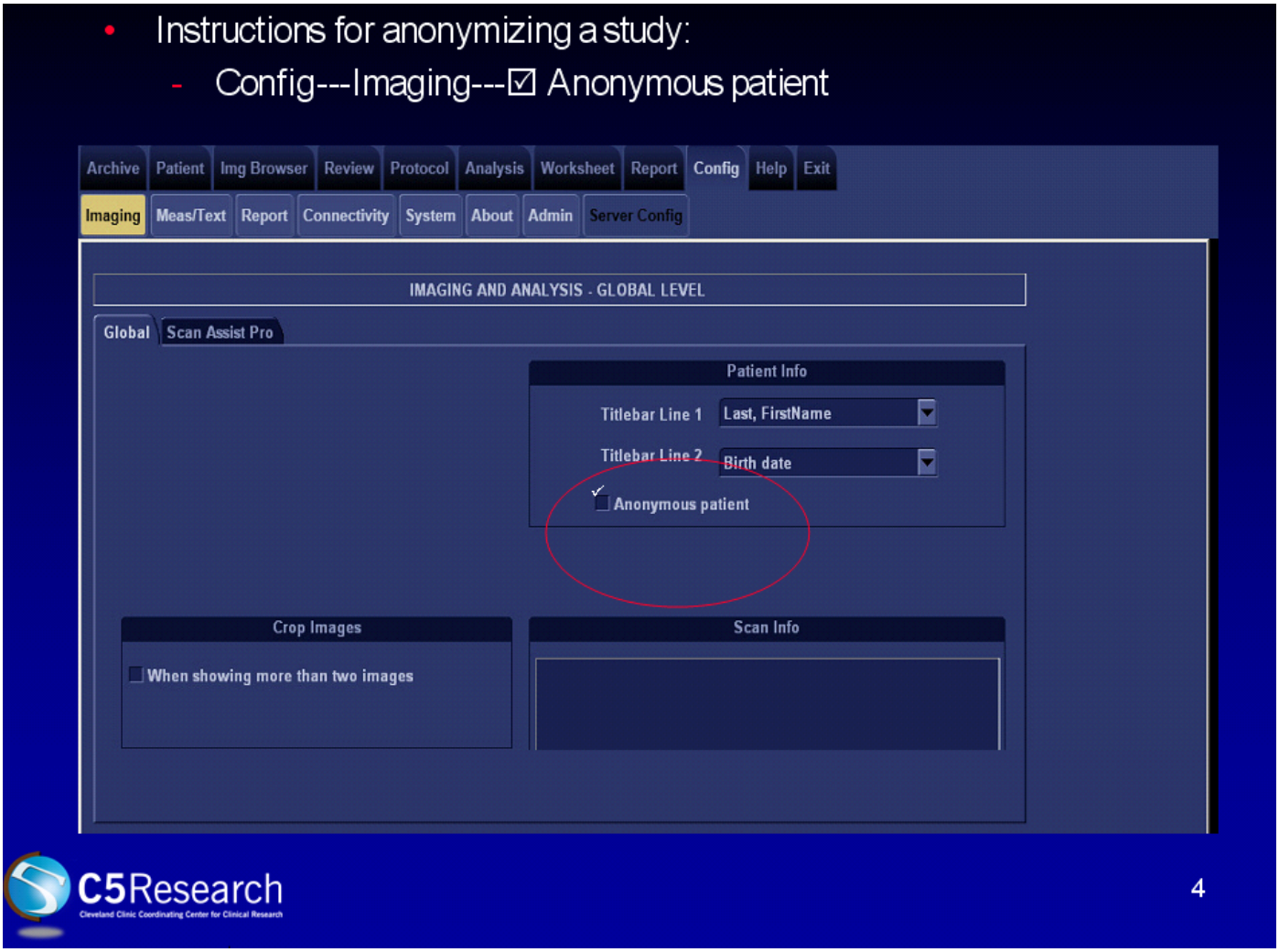
60.7.1.2 Before the sonographer begins an echo study, secure the study assigned Subject ID from the site coordinator. Enter the Subject ID in the echo system's ID field designated LAST NAME as PVD and designated FIRST NAME left blank and designated Medical Record Number (MRN) with the two digit site and four digit subject number followed by two digit alpha as assigned by the DCC. Ex: 110001-AB**.**
(See example section 60.7.2.8)

60.7.1.3 Exams that need to be labeled under patient identifiers need to be anonymized before sending to the Core Lab through AG Mednet. The instructions below show how to hide patient identifiers on the imaging screen for Philips, GE and Siemens ultrasound systems. (See anonymizing instructions section 60.7.1.3.1)

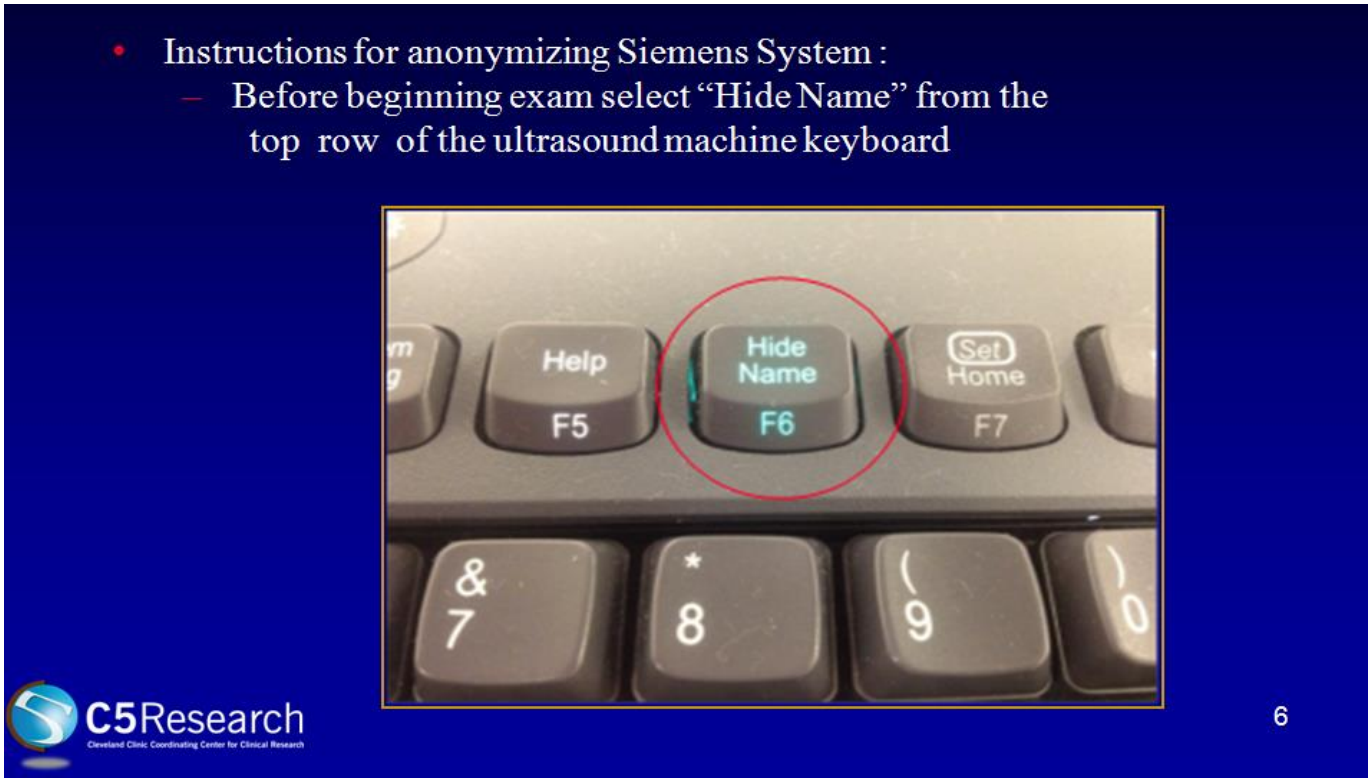
60.7.1.3.1 Anonymization Instructions for Philips Ultrasound Systems



60.7.1.3.2 Anonymization Instructions for GE Ultrasound Systems



60.7.1.3.3 Anonymization Instructions for Siemens System



60.7.1.4 Acquire images per study protocol keeping subject positioning and plane orientations optimal throughout the study.

60.7.1.5 Download the echo in RAW data format to DVD (see section 7.4 for archiving instructions)

60.7.1.6 Follow AG Mednet instructions (see section 10) for digital transmission to the Imaging Core Lab.

60.7.1.7 Make <u>one</u> copy of each echo study per DVD and upload from this media to the AG Mednet website location. Retain this copy of the study with site records.

60.7.1.8 Please copy only <u>one</u> echo study to a disc.

60.7.2 Transmitting Echo Images to Imaging Core Lab

60.7.2.1 AG Mednet is a web-based diagnostic imaging network, which enables sites to send diagnostic image exams electronically and securely to the Imaging Core Lab. AG Mednet will provide tools and training to de-identify exams, complete transmittal forms electronically and complete other trial specific tasks.

60.7.2.2 The DCC has provided an Echocardiogram (ECHO) Transmittal Form # 250 (see example 7.2.8) to be completed by the study qualified sonographer and submitted to the study coordinator (or designee) for use in completing the electronic transmittal information prior to uploading the study to AG Mednet.

60.7.2.3 No fields may be left blank. You will be unable to upload images to AG Mednet until **all required fields on the electronic transmittal form are complete.** If you have questions about completing the electronic Echo Transmittal Form, refer to the AG Mednet User Guide or contact AG Mednet.

60.7.2.4 Errors on the Echo Transmittal Form should be crossed out with a single line, not obliterated, with the correction inserted, and the change initialed and dated.

60.7.2.5 Never use correction fluid/tape, erase or obliterate information.

60.7.2.6 If there are questions about completing the hardcopy Echo Form # 250, refer to example 7.2.8, or contact an Imaging Core Lab team member for assistance.

60.7.2.7 An Imaging Core Lab Study Team Contact Information sheet is located in the front of this manual for reference.

It is important to transfer image exams to the core lab as they are collected. This practice will prevent a backlog of analysis at the core lab. Please, no bulk sending.

60.7.2.8 Echo form # 250

Revision of 01/15/2016

Form #250
Page 1 of 2

PVDOMICS

PVDOMICS Study
Echocardiogram (ECHO) Transmittal Form #250

Instructions: This form is used for both uploading data to AG Mednet for the Imaging Core Lab (ICL) and uploading data to the DCC database. Review MOP Chapter 60 prior to testing.

Study Coordinator Completes Questions 1-5.

1	1	0	0	0	1	–	A	B		1	2	0	1	2	0	1	5

1. Identification Number 2. Alphacode 3. Date of ECHO (mm/dd/yyyy)

4. Gender (0=Male, 1=Female) 0

5. Visit Type 2
   1=Qualification, 2=Baseline, 3=Follow-up

Sonographer Completes Questions 6-12.

6. a. Was blood pressure measured at the beginning of ECHO 1
      0=No, BP measures not collected, 1=Yes

   b. If yes, blood pressure measures (mmHg) (systolic/diastolic) 110/070

7. Agitated saline contrast (0=No, 1=Yes) 0

8. a. Contrast enhancement for left ventricular opacification (LVO) 1
      0=No, contrast agent not collected, 1=Yes

   b. If yes, name of contrast agent used 3
      1=Optison
      2=Definity
      3=Lumason
      8=Other, specify _____

   c. Total contrast volume (mL) 02

Comments Technically difficult study.

9. a. Username of ECHO Sonographer who performed echocardiogram ..... SMITHCA

   b. Name of ECHO Sonographer who performed ECHO Cathy Smith

Revision of 01/15/2016 Pt ID 110001 AC AB Date of ECHO 12/01/2015 Form #250
Page 2 of 2

Ultrasound Equipment Used for this ECHO

10. Ultrasound manufacturer name ..... Philips
11. Model # IE-33
12. Serial # 12345

Transmission Details for ECHO to AG Mednet – ***Coordinator completes Q13 through end of form.***

13. Method of transmission (1=Digital transfer, 8=Other, specify_____)... 1
14. Date ECHO file transmitted (mm/dd/yyyy)..... 12/01/2015
(Date file transmitted must be greater or equal to the date the form is completed.)

200. Date this form completed (mm/dd/yyyy)..... 12/01/2015

201. Username of person completing/reviewing completeness of this form ..... SMITHCA

Clinical Center Use Only
Date Form Entered (mm/dd/yyyy) __ __/__ __/__ __ __ __
Username of person entering this form__ __ __ __ __ __ __

60.7.3 Archival Instructions

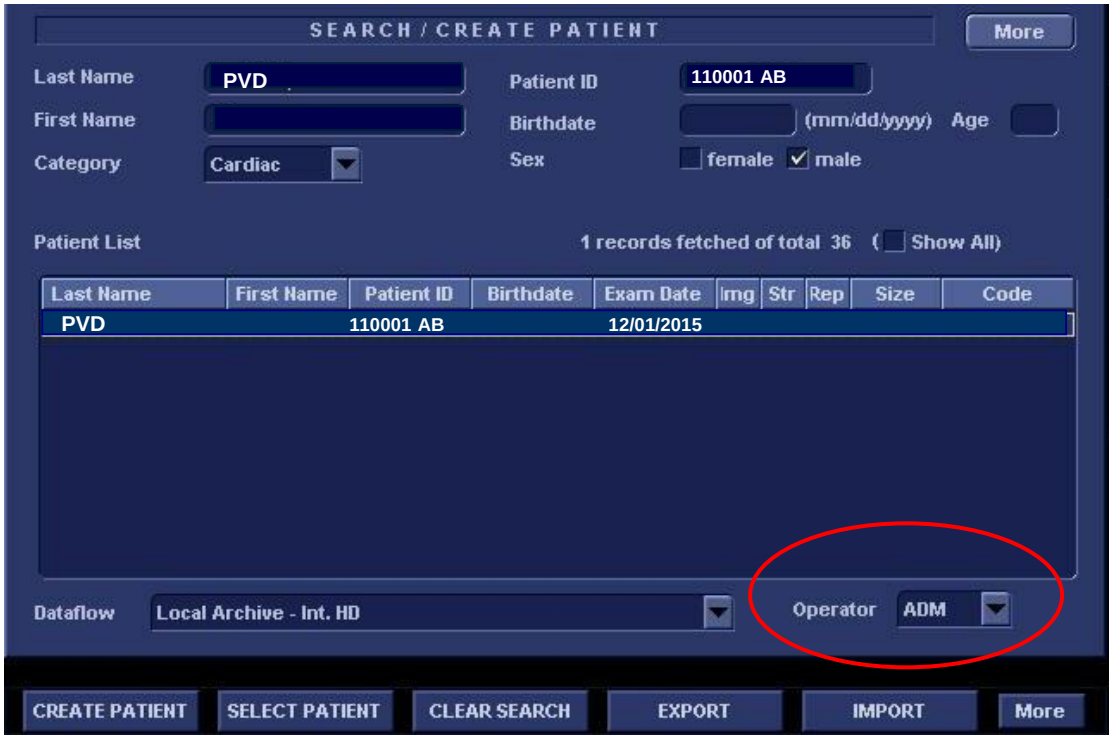
60.7.3.1 Complete the Echo Data Worksheet carefully and completely while scanning. This is treated as a source document and may be subject to inspection by regulatory authorities.

60.7.3.2 Archive the echo study to digital media (DVD) immediately from the ultrasound system that was used to acquire the images (before archiving to Picture Archiving and Communication System [PACS]). Please Note: Image files not stored in RAW/NATIVE DICOM format cannot be analyzed completely.

60.7.4 GE System Specific Instructions for Archive Export (RAW DICOM Data)

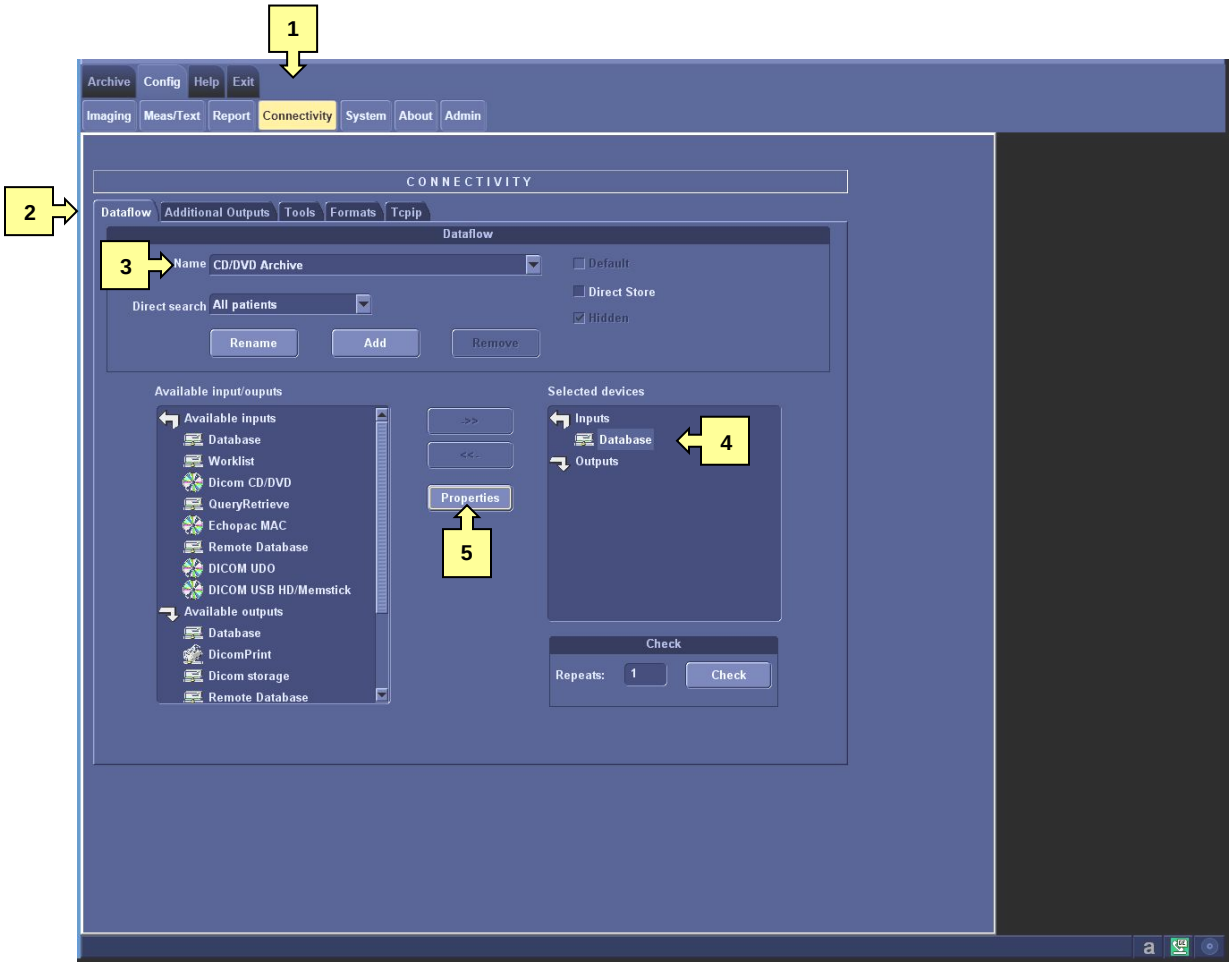
60.7.4.1 Archive all studies immediately after image acquisition.

60.7.4.2 Select Archive screen and log in as administrator (ADM). Password should be: ulsadm (all lower case)

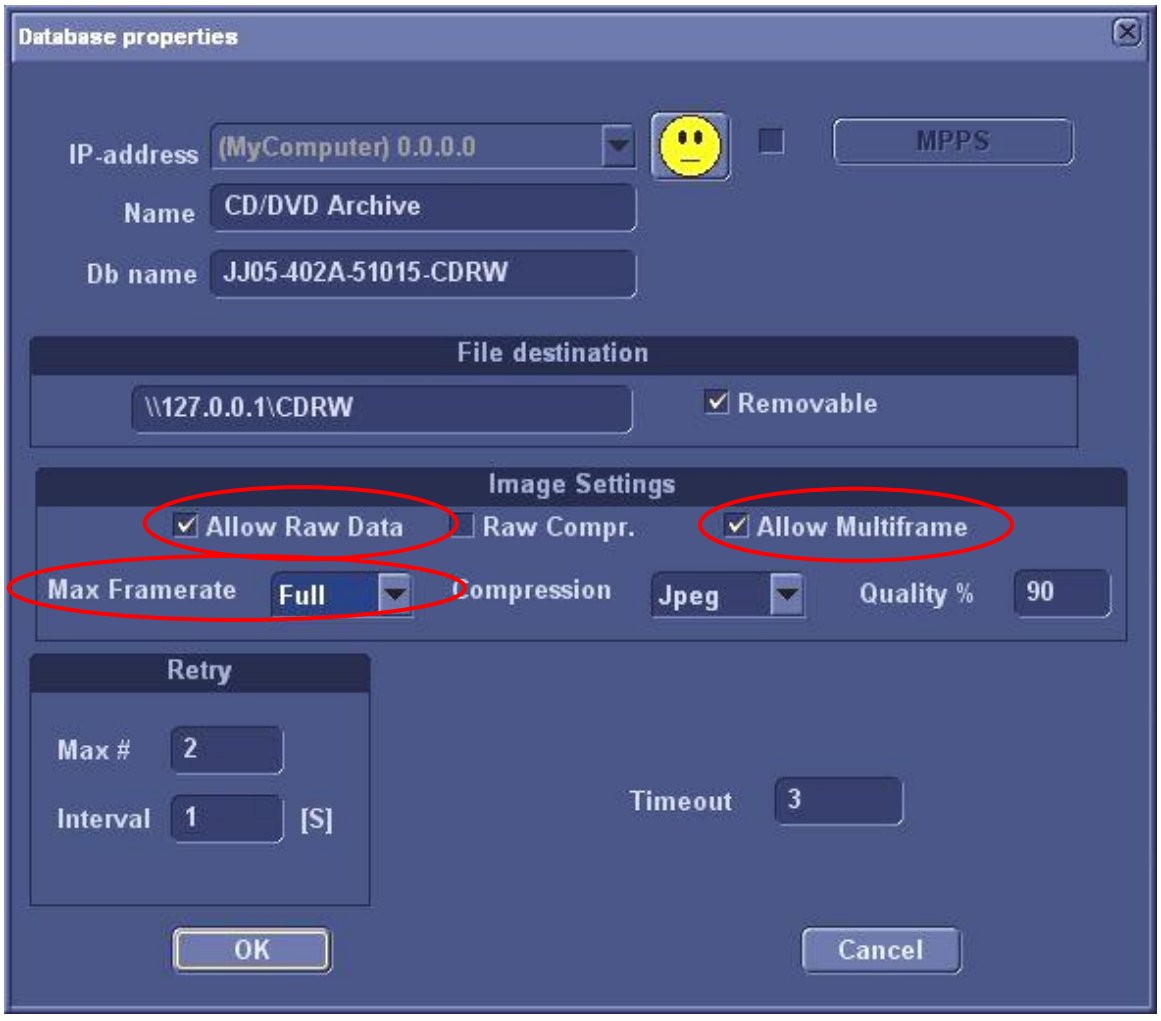


60.7.4.3 System Setup

- 1) In the **Configuration** screen, select "**Connectivity.**"
- 2) On the Connectivity screen, choose "**Dataflow**" from the top row of options.
- 3) Select **CD/DVD Archive** from the drop down menu in the **"Name"** section.
- 4) Highlight **Database** in the **"Selected devices"** region; then the Properties button will appear.
- 5) Activate the **Properties button.**

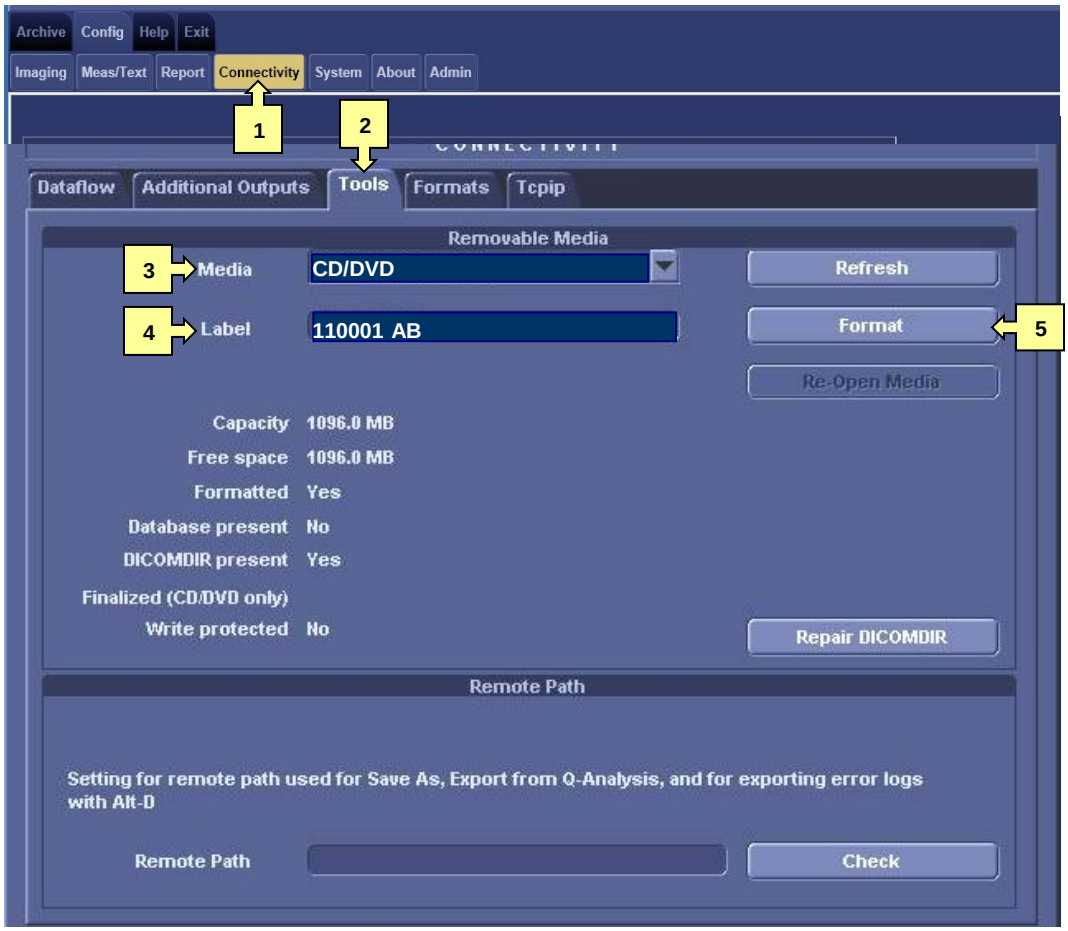


60.7.4.4 After activating the Properties button, a new window will appear. Check ☑ "**Allow Raw Data**," and "**Allow Multiframe**"; then change the "**Max Framerate**" to **Full.**



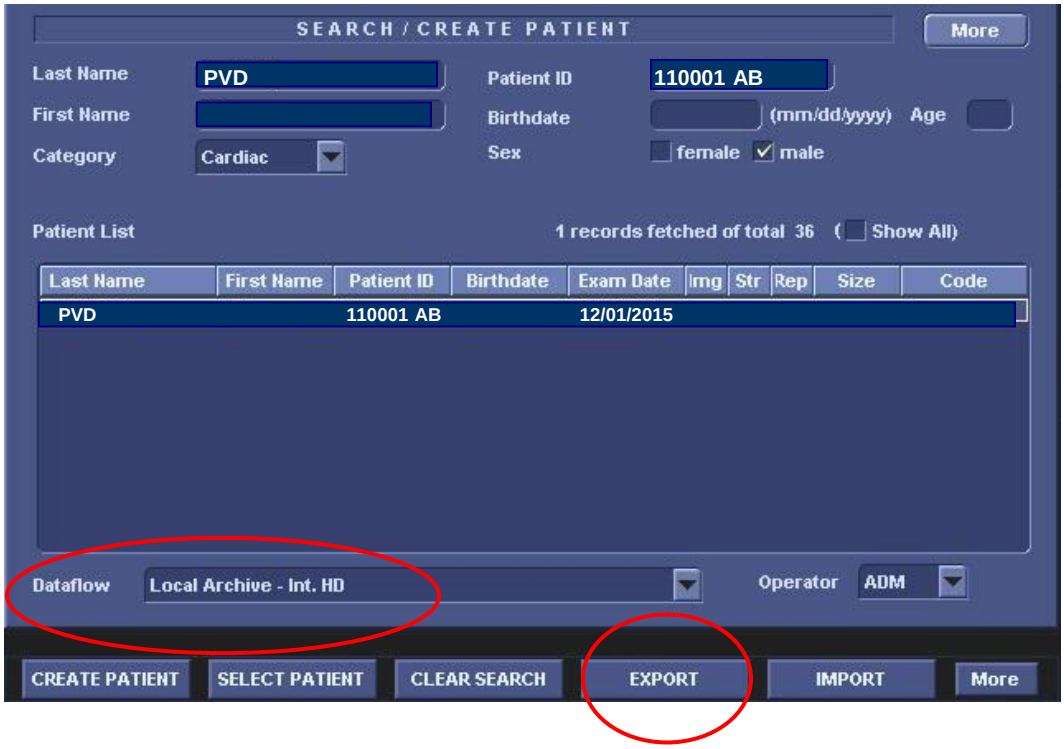
60.7.4.5 Formatting DVD

- 1) In the **Configuration** screen, select "**Connectivity.**"
- 2) On the Connectivity screen, choose "**Tools**" from top row of options.
- 3) In the Tools screen, the media type should be set to "**CD/DVD.**"
- 4) Type in the **label** for the DVD (**4 digit site and 3 digit subject number**).
- 5) Make sure the DVD is in the drive, and select "**FORMAT.**"
- A dialog box will appear to confirm that you wish to format the DVD– select OK.
- Once the DVD is formatted, exit the configuration screen.

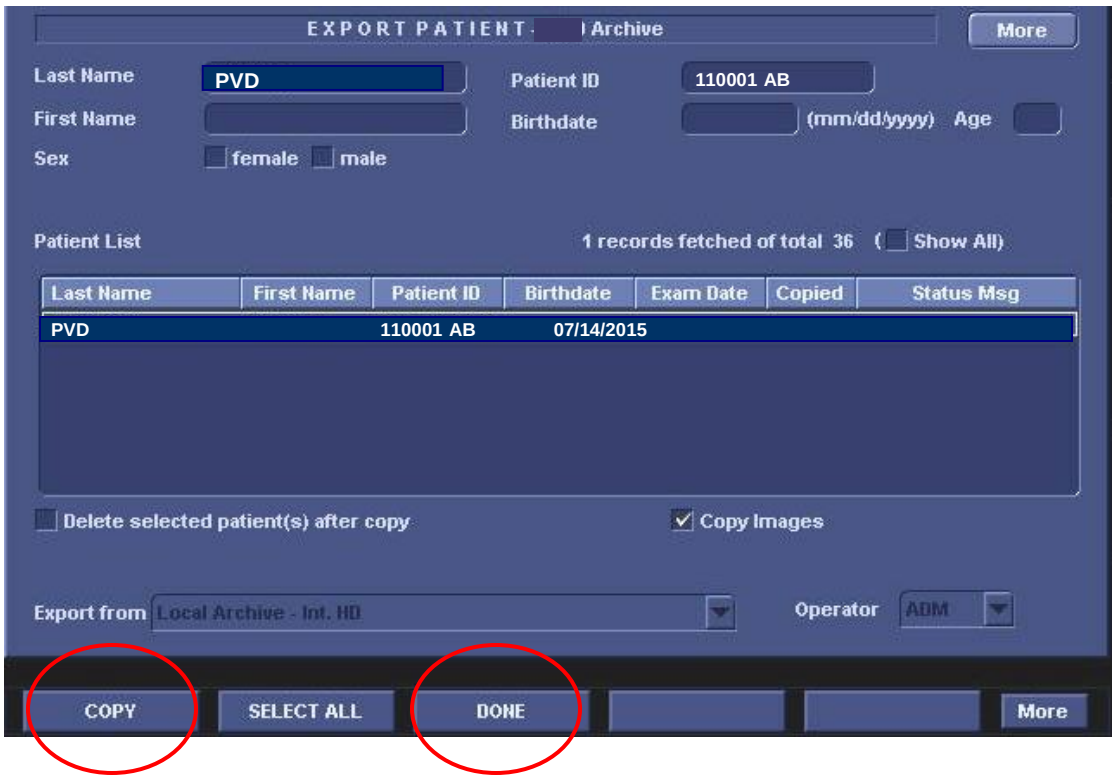


60.7.4.6 Exporting a study from Internal Hard Drive to DVD

- Select **Archive** screen and set "Dataflow" to read "**Local Archive – Int. HD**"
- Select **EXPORT** from the screen
- The export dialog box will appear. The FROM box should read "**Local Archive – Int. HD**" and the TO box should read "**CD/DVD Archive**" from the drop down menus. Select OK.



- A screen of patients on the hard drive will appear. Select the patient/subject you wish to export to the DVD, and select **COPY**.
- Once the study has been exported to a DVD, select **DONE** to finish the copy procedure.
- Select **F3 or Alt-E** from the keyboard to eject the DVD.



Retain a copy of the DVD on site with study-related records.

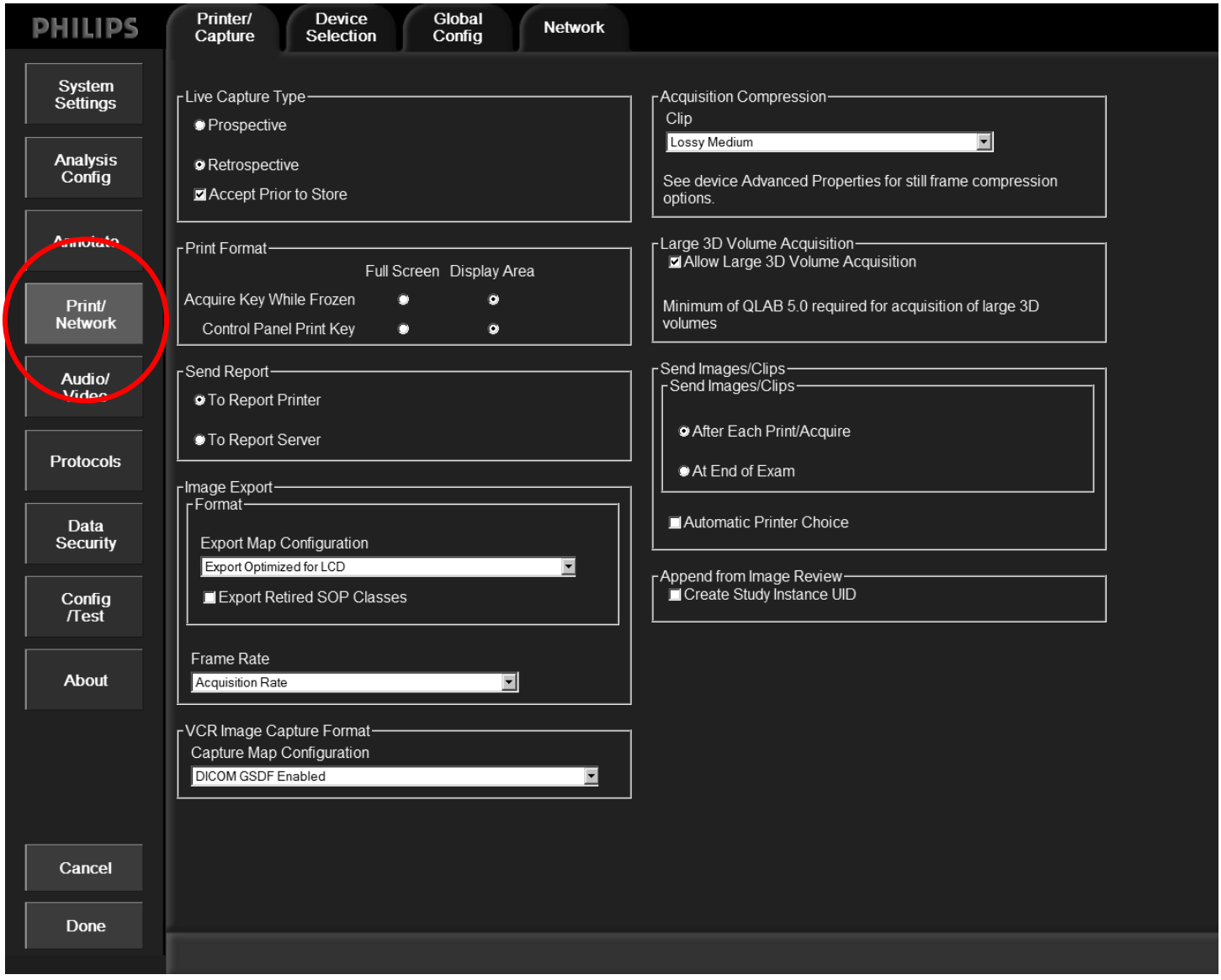
If there are problems downloading the study to a DVD, please contact your local GE application specialist.

60.7.5 Philips System Specific Instructions for Archive Export (NATIVE DICOM data)

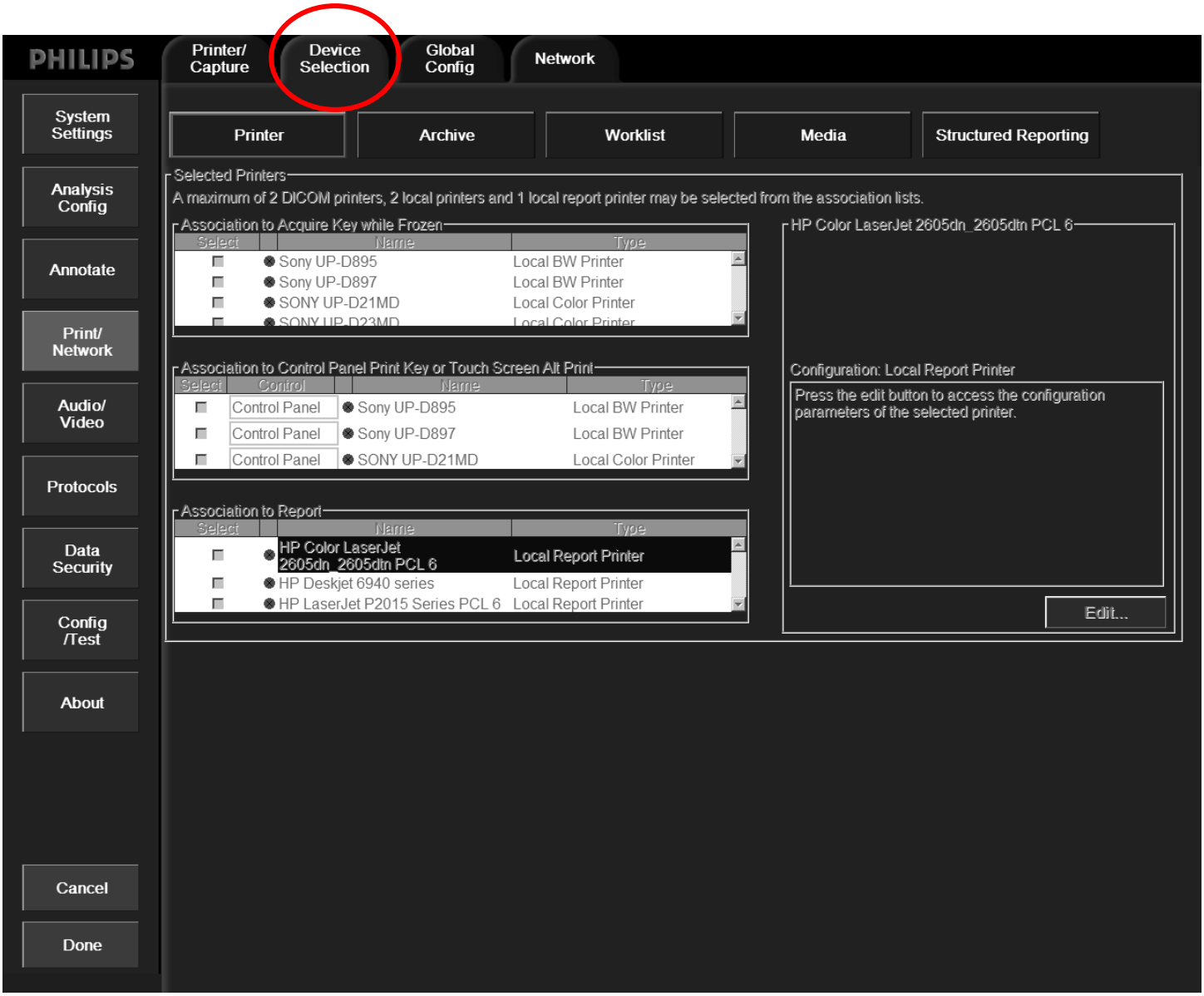
60.7.5.1 Archive all studies immediately after image acquisition

60.7.5.2 Machine set-up

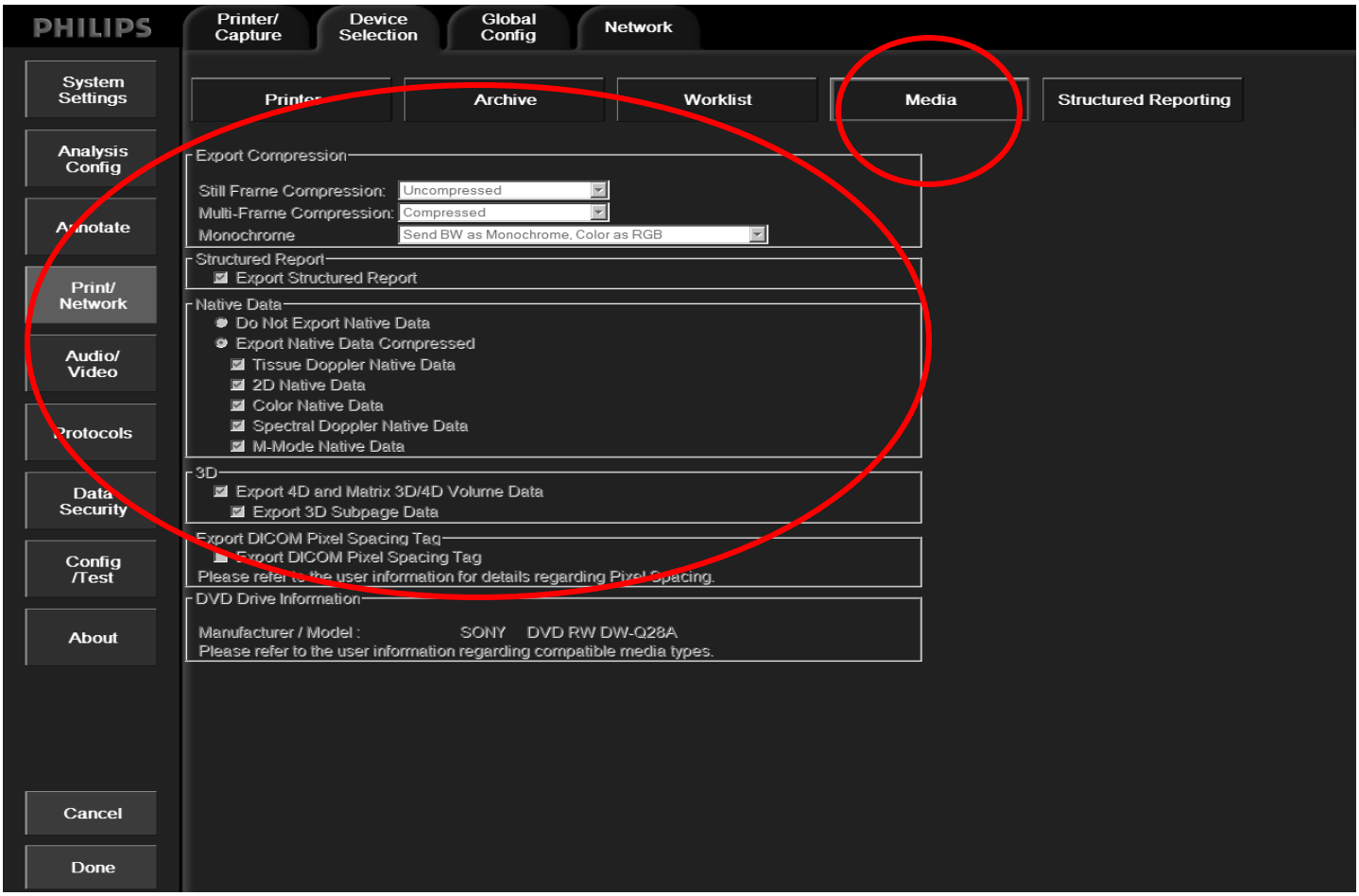
- Select machine **"setup"** on the top row of the keyboard to activate set-up screen.
- Select the **"Print/Network**" tab on the left side of the screen (fourth selection down).



- On the Print/Network screen, select **“Device Selection”** from the top row of option.

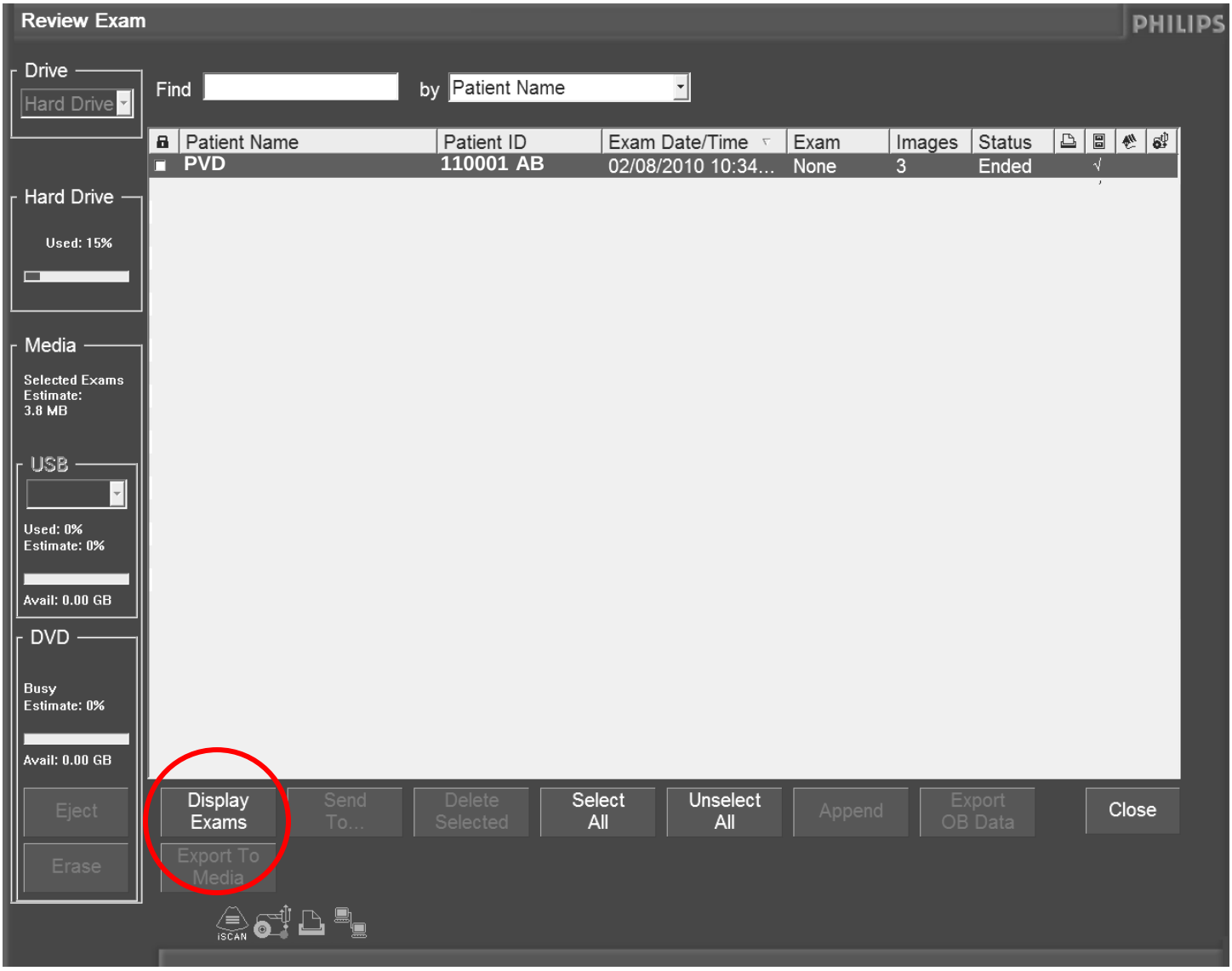


- On the Device Selection screen, select **“Media”** from the second row of options.
    - Export Compression
        - Still Frame Compression: Uncompressed
        - Multi-Frame Compression: Compressed
        - Monochrome: Send BW as Monochrome, Color as RGB
    - Native Data
        - Select Export Native Data Compressed
        - ☑ Check Tissue Doppler Native Data
        - ☑ Check 2D Native Data
        - ☑ Check Color Native Data
        - ☑ Check Export 4D and Matrix 3D/4D Volume Data
        - ☑ Check Export 3D Subpage Data



60.7.6 Exporting a study from internal hard drive to DVD

- Select **"Review"** on left side of control panel to activate the review screen.
- Select (highlight) subject from the exam list.
- On the review screen select **"Export To Media"**
    - Text box will appear
        - Choose **"DVD"** and **"Export to Media"**
        - Select **"OK"** to process selections



- Green Icon at bottom left of the screen shows active copying.



Retain the DVD on site with study-related records.

If there are problems downloading the study to a DVD, please contact your local Philips application specialist.

60.8 Echo Quality Control Process

60.8.1 Echo Critique

Echocardiograms will be monitored for adherence to the study protocol as well as quality. The Imaging Core Lab will provide feedback in the form of a critique to the sites and the DCC via email for each study submitted.

60.8.2 Query Notification

The study coordinator (or designee) and the sponsor will receive an email from the C5R ICL asking for the resolution of any issues that were found during the quality control (QC) process. Prompt response is required from the site study coordinator.

60.8.2.1 Echo Data Queries

- Review the variable name, reported value, and comments/suggestions
- Record the corrected, missing, or illegible information in the resolution box

60.8.2.2 Echo Media Queries

- Review the issue and comments/suggestions
- Record the corrected information and/or comments of action taken (for example: sent Imaging Core Lab new images via AG Mednet).

60.8.2.3 Echo Data Clarification Form (DCF)

Please print your name, sign and date (mm/dd/yyyy) in the space provided. The C5R ICL will not consider corrections recorded on the DCF unless signed and dated by site personnel completing the form. A signature indicates your agreement that the data should be changed as indicated on the DCF.

- Ensure all fields of the Data Clarification Form (DCF) are complete.
- If you have questions about completing the form, refer to the Echo Data Clarification Form example (see example

8.3.1), send an email, or telephone an Imaging Core Lab team member for assistance.

- An Imaging Core Lab Study Team Contact Information sheet is located in the front of this manual for reference.

60.8.3 Resolution and Return of Data Clarification Form (DCF)

The study center contact person must fax the completed Data Clarification Form to the Imaging Core Lab within five business days at 216-445-4419. The study center will keep a copy of the DCF on site with the corresponding study files.

60.8.3.1 Echo Data Clarification Form (DCF) Example

C5Research
Cleveland Clinic Coordinating Center for Clinical Research

Imaging Core Lab
9500 Euclid Avenue JJ-65
Cleveland, OH 44195
Fax: 216-445-4419

Data Clarification

PVDOMICS

Site Name: Brigham and Women's Hospital
Operator:
Exam Date: 12/1/2015
Visit: Baseline

Site Code: 11
Subject: 110001-AB
Modality: ECHO
Equipment: Philips IE-33
Exam Types: TTE

Media Critique

Digital Data stored in correct format?

Comment: The exam contains minimal images for this study. (29 images only).

Please re-upload the complete echo exam and forward to the Imaging Core Lab.

Sign and Date this DCF and return fax this query to the Imaging Core Lab as soon as possible for echo processing to be continued.

Response: _____

Signature: _____ **Date:** _____

Print Name: _____

60.8.4 Unresolved Query Process

60.8.4.1 If the Imaging Core Lab does not receive the faxed resolution within a reasonable time frame, a follow-up email will be sent to the site study coordinator and copied to the DCC indicating a second request for immediate attention/resolution of the data clarification.

60.8.4.2 If the DCF is returned and all the issues are not resolved, the ICL will re-send an updated DCF for complete resolution of outstanding issues. The study center will complete the form, sign it, and fax it to the ICL.

60.8.4.3 Save a copy of this DCF with the site study files.

60.8.4.4 Ensure all fields of the DCF are complete.

60.8.4.5 An Imaging Core Lab Study Team Contact Information sheet is located in the front of this manual for reference.

60.9 Imaging Core Replacement/ Inactivation Process

In the event that an image exam must be replaced or inactivated due to a submission error, this process will be followed:

- ICL to initiate query to site and DCC designee asking for clarification. ICL will not process clarification received from site until sponsor designee(s) verifies the accuracy with signature on inactivation form.
- The site monitor or designee will verify the date and subject ID on the Inventory/Quality Report to ensure accuracy.
- ICL will update the Inventory Report, PACS system and C5Research Clinical Data Management (CDM).

    1. Rename incorrect Echo as INACTIVE.

2. Proceed with normal processing of replacement Echo, i.e. check-in, import and analysis.

- Prior to data transfer, ICL will send DCC's Data Management team and C5Research CDM Replacement Echo spreadsheet containing cumulative list of studies that have been renamed.

    1. DCC will update their DM team in preparation for successful receipt of transfer.

60.10 Electronic Submission Overview

60.10.1 AG Mednet

60.10.1.1 AG Mednet is a web-based diagnostic imaging network, which enables sites to send diagnostic image exams electronically and securely to the Imaging Core Lab.

60.10.1.2 AG Mednet will provide tools and training to:

- De-identify exams
    - Site is responsible for correctly de-identifying study within the AG Mednet portal.
- Complete transmittal forms electronically
- Complete other trial-specific task

60.10.2 Electronic Submission Process

60.10.2.1 All data should be acquired in DICOM format and submitted electronically via a web-based interface to the Imaging Core Lab using the AG Mednet Desktop Agent.

60.10.2.2 Upload time is dependent on site speed network connection, but the transfer runs in the background so site staff can leave the computer running or work on other applications.

60.10.2.3 Sites are informed via email of electronic submission as soon as transfer has completed.

60.10.2.4 AG Mednet is an intuitive system and can run from a networked PC with **Java 8 plug-in installed**. This plug-in ensures AG Mednet will run within the web browser. It is likely that you already have Java 8 installed.

60.11 Forms

DCC website for all study forms for downloading and printing:

http://qhsapps.ccf.org/pvdomics/

Note to sites:

The Imaging Core Lab analysis results are intended for research purposes only and should not be used for clinical patient management.

Each site must have a plan for ensuring that clinically relevant findings are observed and managed at the site level.

60.12 References

American Society of Echocardiography Guideline and Standards documents: www.asecho.org

Guidelines for the Echocardiographic Assessment of Atrial Septal Defect and Patent Foramen Ovale: From the American Society of Echocardiography and Society for Cardiac Angiography and Interventions. (J Am Soc Echocardiogr 2015;28:910-58.)

Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography. (J Am Soc Echocardiogr 2010;23:685-713.)

Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. (J Am Soc Echocardiogr 2015;28:1-39.)

EAE/ASE Recommandations for Image Acquisition and Display Using Three-Dimensional Echocardiography. (J Am Soc Echocardiogr 2012;25:3-46.)

Guidelines for the Cardiac Sonographer in the Performance of Contrast Echocardiography: A Focused Update from the American Society of Echocardiography. (J Am Soc Echocardiogr 2014;27:797-810.)

Baumgartner et al, Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice. Eur J Echocardiogr. 2009 Jan;10(1):1-25. doi:10.1093/ejechocard/jen303. Epub 2008 Dec 8doi:10.1016/j.echo.2008 .11.029

Leibundgut et al, Dynamic Assessment of Right Ventricular Volumes and Function by Real-Time Three-Dimensional Echocardiography: A Comparison Study With Magnetic Resonance Imaging in 100 Adult Patients. (J Am Soc Echocardiogr 2010; Feb;23(2):116-126.)

Chapter 70 Cardiac MRI

70.1 Core Lab Contacts

Imaging Core Lab Principal Investigator:

Deborah Kwon, MD

Research Coordinator II

Cathy McDowell, BSW

Office: 216-445-7842 or 1-800-223-2273 ext. 57842

Fax: 216-445-4419

Email: mcdowec@ccf.org

Research Coordinator

Dawn D'Eusanio, BA

Office: 216-444-8267

Fax: 216-445-4419

Email: deusand@ccf.org

Project Specialist

Jill Rusticelli

Office: 216-442-5231

Fax: 216-445-4419

Email: rusticj@ccf.org

Project Specialist

Michelle Baksar

Office: 216-444-9872

Fax: 216-445-4419

Email: baksarm@ccf.org

Project Manager:

Kathy Kassimatis, RDCS, FASE
Office: 216-445-5156
Fax: 216-445-4419
Email: kassimk@ccf.org

Lead Imaging Specialist:

Margaret (Koko) Park, BS, ACS, RDCS, RVT, FASE
Office: 216-445-5175
Fax: 216-445-4419
Email: parkm@ccf.org

Core Lab Manager:

Annitta Flinn, BA, RDCS, CCRC, FASE
Office: 216-445-7673 or 1-800-223-2273 ext. 57673
Fax: 216-445-4419
Email: flinna@ccf.org

When sending an email, please copy all above email addresses to ensure a prompt response.

AG Mednet Support:

US Toll Free: 1-888-924-6336
Email: **support@agmednet.com**

70.2 Hours of Operation

70.2.1 Hours of Operation

The Imaging Core Lab is open Monday through Friday, 8:00 AM to 4:30 PM, Eastern Standard Time.

70.2.2 2016-2019 Holidays

The Imaging Core Lab is closed on the following dates for holidays**:**

2016

Memorial Day	May 30, 2016
Independence Day	July 4, 2016
Labor Day	September 5, 2016
Thanksgiving	November 24-25, 2016
Christmas	December 23-26, 2016

2017

New Year's Day	January 2, 2017
Memorial Day	May 29, 2017
Independence Day	July 4, 2017
Labor Day	September 4, 2017
Thanksgiving	November 23-24, 2017
Christmas	December 25-26, 2017

2018

New Year's Day	January 1, 2018
Memorial Day	May 28, 2018
Independence Day	July 4, 2018
Labor Day	September 3, 2018
Thanksgiving	November 22-23, 2018
Christmas	December 24-25, 2018

2019

New Year's Day	January 1, 2019
Memorial Day	May 27, 2019
Independence Day	July 4, 2019
Labor Day	September 2, 2019
Thanksgiving	November 28-29, 2019
Christmas	December 24-25, 2019

70.3 Abbreviations and Acronyms

ACR	American College of Radiology
AF	Atrial Fibrillation
AHA/ACC	American Heart Association/American College of Cardiology
C5R	C5 Research
MRI	Magnetic Resonance Imaging
DICOM	Digital Imaging and Communications in Medicine
DTF	Data Transmittal Form
ECV	Extracellular Volume
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HIPAA	Health Insurance Portability and Accountability Act
ICL	Imaging Core Lab
LGE	Late Gadolinium Enhancement
Mfr	Manufacturer
MOLLI	Modified Look Inversion Recovery
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MRN	Medical Record Number
NA	Not Applicable
NHLBI	National Heart Lung and Blood Institute
PACS	Picture Archiving and Communication System
PM	Preventive Maintenance
PPM/ICD	Permanent Pacemaker/Implantable Cardioverter Defibrillator
QC	Quality Control
SAEs	Serious Adverse Events

70.4 Document Revision History

70.4.1 V1.0_09Sep2016

This document is the first approved version. Amended versions will be described in this section and include a history of changes.

Version	Changes Made	Effective Date
1.0	Original	09Sep2016
2.0	1. Section 70.10.1.3, page 70.15: Clarification provided recommending sites to administer contrast within dose range (0.1 - 0.2 mmol/kg, 3–7 ml/s) according to GFR results. 2. Section 70.10.1.3, page 70.15, Added CMR Dosing Table #2 to summarize recommended dose range according to GRF results.	25Jan2017

Note to sites:

The Imaging Core Lab analysis results are intended for research purposes only and should not be used for clinical patient management.

Each site must have a plan for ensuring that clinically relevant findings are observed and managed at the site level.

70.5 Study Overview

70.5.1 Purpose

The purpose of this C5Research (C5R) Imaging Manual is to instruct sites in: 1) protocol-specific image acquisition requirements; 2) necessary documentation, image data transfer instructions and data storage; and 3) the query resolution process for any clerical discrepancies and/or non-compliant data.

The goal of the Cardiac MRI (CMR) portion of this trial is to quantify cardiac volume and mass, fibrosis and scarring, perfusion and evaluation of flow. The inherent 3-dimensional nature of CMR makes it particularly well suited for the evaluation of the RV, which is difficult to assess with other imaging modalities due to its complex shape and variable morphology. Advanced echocardiographic measures of right ventricular performance will be compared to cardiac MRI.

70.5.2 Study Synopsis (from PVDOMICS Protocol V1.1 May 12, 2016)

It is recognized that patients with various forms of heart and lung disease exhibit varying degrees of pulmonary vascular disease, leading to pulmonary vascular remodeling, pulmonary hypertension, and right ventricular dysfunction. The genetic, molecular, and cellular processes driving these phenomena are not well understood. Rapid advances in high throughput omic methodology, combined with powerful bioinformatics and network biology capability, have created the opportunity to conduct studies that broadly search for homologies and differences across the spectrum of disease states associated with pulmonary hypertension and determinants of the spectrum of pulmonary vascular disease and RV compensation that accompanies these conditions.

The 2010 NHLBI Pulmonary Vascular Strategic Plan identified the

development of a comprehensive cohort to define phenotypes integrating Omics technologies and systems approaches as a top priority. The current WHO PH classification, based solely on clinical/hemodynamic subsets, limits the ability to customize treatment for an individual patient, or to assign meaningful clinical phenotype designations, *e.g.*, Long-term survivor or Maladaptive RV Hypertrophy. **The overall goal of the PVDOMICS network is to perform comprehensive pheno-typing (demographic, physicologic, clinical chemistries, and imaging) and endophenotyping (genomic, proteomic, metabolomic, coagulomic, cell and/or tissue based) across the World Health Organization (WHO) classified PH clinical groups 1 through 5 as well as intermediate phenotypes (including those without overt PH) in order to deconstruct the traditional classification and define new meaningful subclassifications of patients with PVD. The long-term goal is utilization of endophenotypes/biomarkers for early diagnosis, at-risk screening, and personalized approaches for interventions and/or preventions of PVD.**

The PVDOMIC protocol is designed to lead to this comprehensive understanding of patients with pulmonary vascular disease based on phenotypes and endophenotypes.

The first aim will be a natural product of the protocol, to identify the molecular basis of pulmonary vascular disease regardless of WHO clinical classification, by comparison of current subsets of PH patients with healthy subjects and with non-PH diseased comparators. The second aim is to discover biological measures of disease and therapeutic responses that may be useful not only in diagnosis but also as outcome measures in treatment and possibly prevention trials.

70.6 CMR Qualification Process, Quality Control Process, and Visit Schedule

70.6.1 CMR Qualification Submission Process

70.6.1.1 Prior to Qualification, a copy of the current annual Preventive Maintenance (PM) document for each CMR scanner planned for use in the trial must be submitted to the Imaging Core (including serial number). A copy of the PM document(s) should be maintained at the site with the trial regulatory files. This satisfies the American College of Radiology recommendations and ensures the mechanical integrity of the imaging system.

70.6.1.1.1 Sites must follow American College of

70.6.1.2 The qualification process must be completed prior to sites submitting CMR exams of enrolled subjects. All participating sites will submit to the Imaging Core Lab a de-identified sample of a recently performed CMR exam completed in their institution. The purpose of the Site CMR Qualification Process is to ensure viewer and analysis compatibility between the site and the Core Lab prior to subject recruitment.

70.6.1.3 The electronic CMR data transmittal form will be completed by choosing the "Qualification" visit type prior to transferring the study to the Imaging Core lab via AG Mednet

70.6.1.4 The site and Data Coordinating Center (DCC) will be notified of the qualification status of the CMR qualification scan via email or fax.

70.6.1.5 If the site does not qualify with the first submission, the Imaging Core Lab will make recommendations for resubmission of another CMR Qualification study.

70.7 CMR Quality Control

70.7.1 CMR Critique

7.1.1.1 CMR images will be monitored for quality and adherence to the PVDOMICs imaging protocol. Imaging Core will provide feedback in the form of a critique to sites and the DCC via email for each CMR performed.

70.7.2 CMR Imaging Schedule

7.2.2.1 Acquire images at the time points listed in Table 1. The same CMR scanner should be used throughout the trial duration.

Table 1: CMR Imaging Schedule

Imaging Visits	Description
Qualification	Submit a qualification CMR to Core Lab before enrolment
Visit	Baseline CMR

70.8 CMR Contraindications (Exclusions)

- Heart rate > 120
- Atrial fibrillation or irregular heart rate due to frequent ectopy
- Brain aneurysm clips or vascular clips (however, titanium or titanium alloy clips are acceptable)
- Cochlear implants
- PPM/ICD
- Insulin pump, drug pumps
- Any metallic fragment or foreign body (Metal shrapnel or bullets)
- Pregnant women
- Indwelling pulmonary artery catheter
- Chronic Kidney Disease with GFR < 30 mL/min or known Gadolinium allergy are excluded from IV contrast, **but can be enrolled for non- contrast CMR**
- Patients with uncontrollable severe claustrophobia
- Breast tissue expanders
- Aortic stent grafts
- Patients in decompensated heart failure or with significant pleural effusions (moderate or more)
- Patients who are not able to hold their breath for 10-15 seconds at a time

Exceptions:

CMR is safe with coronary stents, joint replacements, ASD/PFO closure devices, sternal wires and most prosthetic heart valves.

70.9 Anonymization Process and Cardiac CMR Protocol

70.9.1 Anonymization Process

70.9.1.1 Before beginning imaging exam (CMR), **secure the study assigned subject ID from the site coordinator**. In the system ID last name field, type PVD. In the MRN field type: Site ID (2 digits) and Subject ID (4 digits) for a 6 digit subject identifier-followed by Alpha (2) assigned by the DCC. Ex: 110002-AB. For purposes of confidentiality and Health Insurance Portability and Accountability Act (HIPAA), all references to a specific subject must be made using the entire Subject ID. Please do not use subject names or initials to label the exam.

70.9.1.1.1 Exams clinically indicated, labeled with PHI, must be anonymized before sending to the Core Lab through AG Mednet (see section 11 for instructions)

70.9.1.2 Acquire images per study protocol keeping subject positioning optimal throughout image acquisition.

70.9.1.3 Download the study in DICOM format to CD/DVD.

70.9.1.4 Sites are to use the digital transmission method for submitting CMR exams. Follow AG Mednet instructions (see section 15) for digital transmission to the Core Lab.

70.9.1.5 Make <u>one</u> copy of each CMR study per disc and upload from this media to the AG Mednet website location. Retain disc copy of the study with site records.

70.9.1.6 Please copy only <u>one</u> CMR study per disc.

70.10 Cardiac CMR Protocol and Image Acquisition Instructions

70.10.1 Core Exam Components

70.10.1.1 Cardiac Structure/Function: Cine-CMR will be used to assess cardiac structure and function. Cine-CMR will employ an ECG gated steady state free precession (SSFP) sequence. Images will be acquired in contiguous short axis (throughout the left and right ventricle), left ventricular (2, 3, and 4 chamber) and right ventricular long axis orientations. Cine- CMR will be performed using a slice thickness of 8.0mm (inter- slice gap =0). (See Figure 1 and 2.)

Figure 1

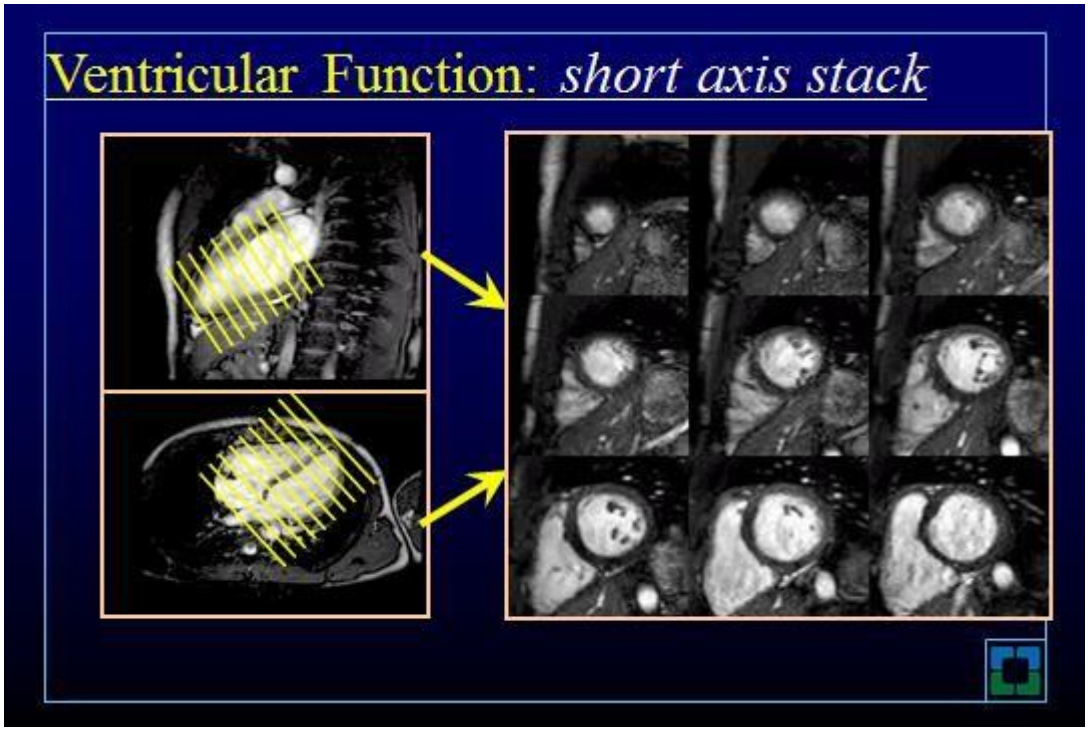
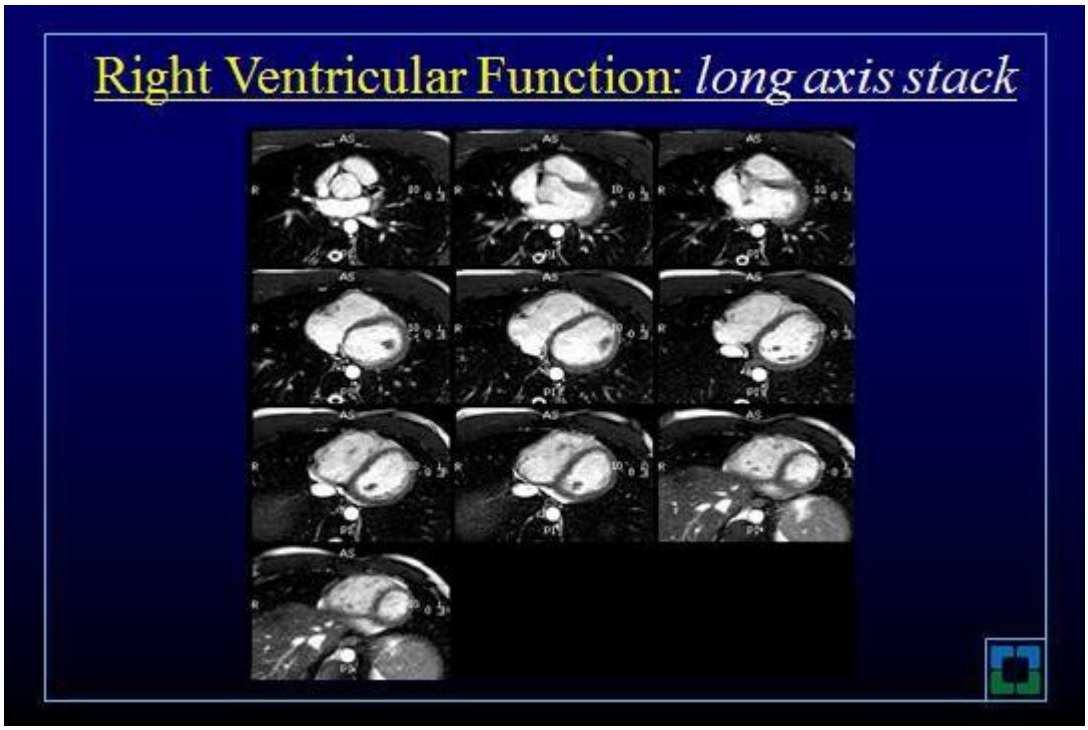


Figure 2



70.10.1.2 Valvular Flow: Phase velocity encoded CMR will be used to assess valvular flow. Images will be acquired through the aortic valve as well as the pulmonic valve (i.e. two separate images will be acquired). Images will be acquired "en-face" valve orientation at the level of the aortic and pulmonic valve leaflet tips. Making certain the temporal resolution is adequate, < 35ms, will ensure accuracy in flow data. Peak velocity encoding (VENC) limits will be tailored to avoid aliasing (typically 1.5 m/sec). **Recommend careful assessment for aliasing, and increasing the VENC level as needed (i.e. 2 m/sec or greater as needed). VENC is important to not travel too high away from the normal values on each patient.** In addition, flow quantification will be assessed of the right and left pulmonary arteries. (See Figure 3 and 4)

Figure 3

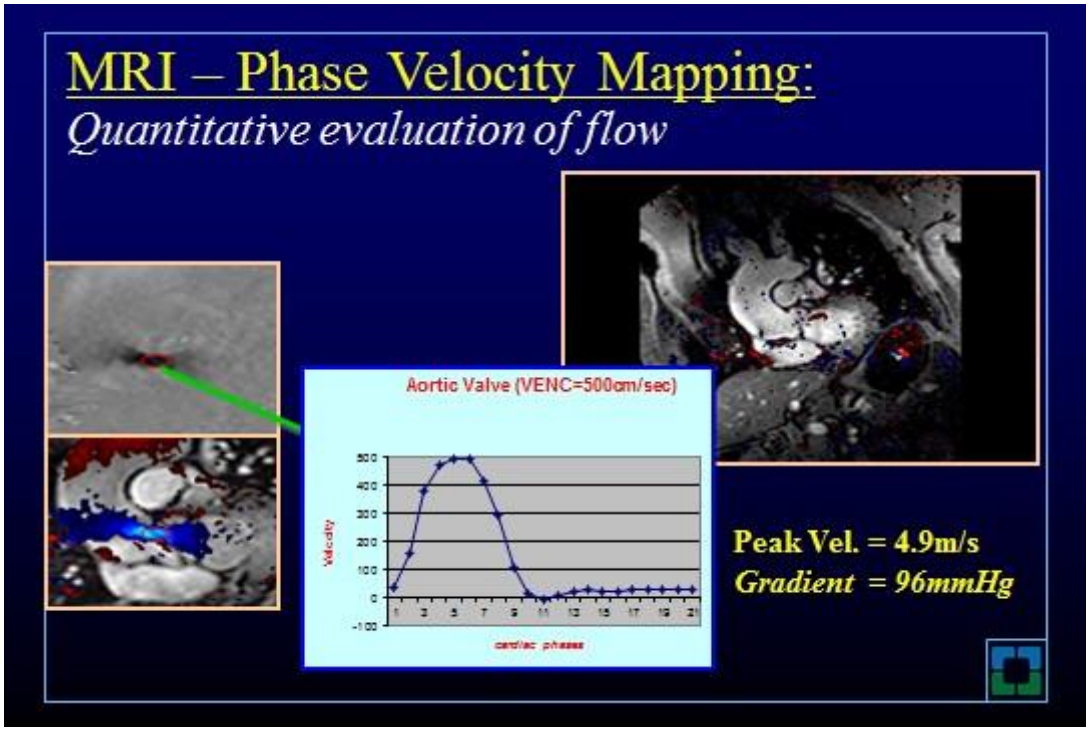
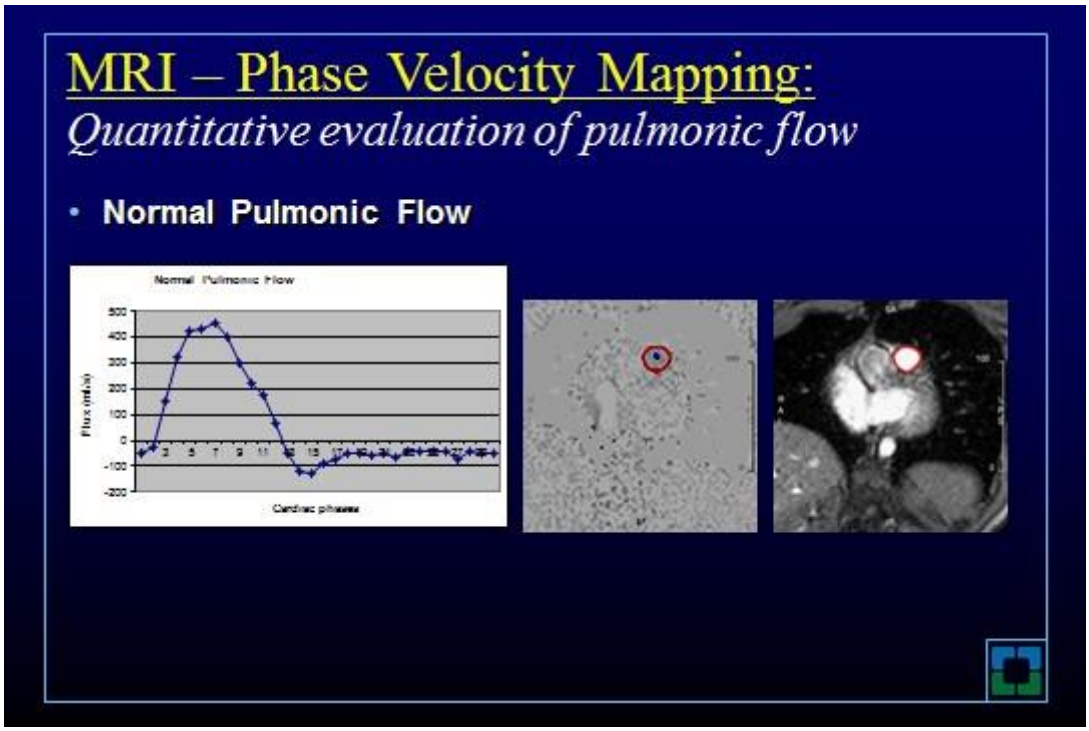


Figure 4

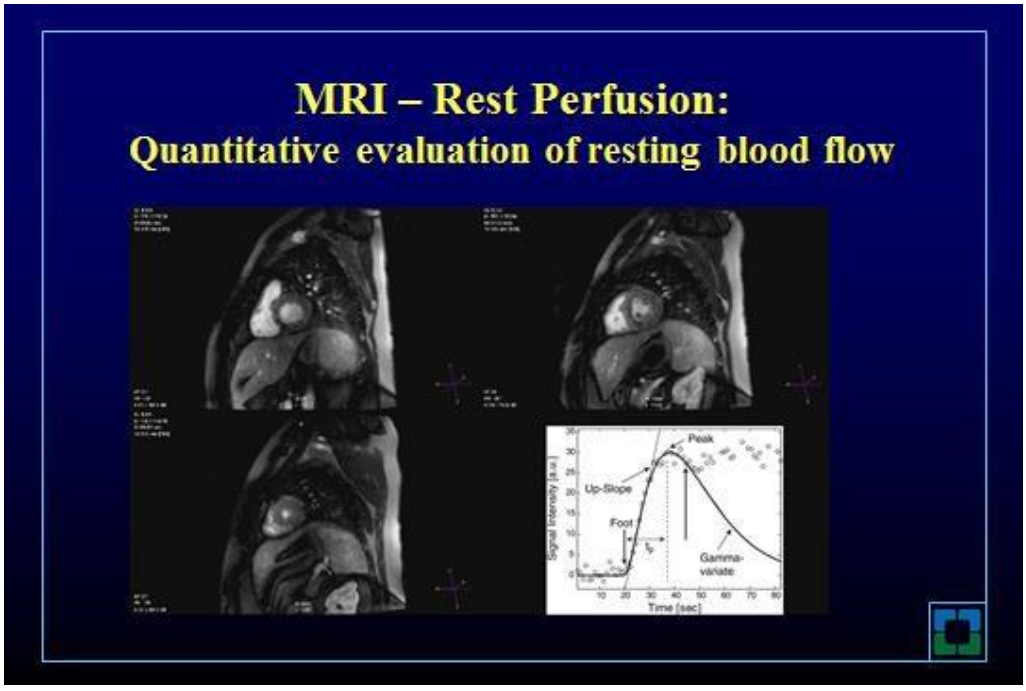


70.10.1.3 Resting Perfusion Imaging: Saturation-recovery imaging will be used to assess resting myocardial perfusion. Short-axis images will be acquired (at least 3 slices per heart beat), using a slice thickness of 8 mm and parallel imaging, 2-fold acceleration, if available with in-plane resolution, ~< 3 mm. Readout temporal resolution ~100 – 125 ms or shorter as available. Contrast will be given (0.1 -0.2 mmol/kg, 3–7 ml/s) followed by at least 30 ml saline flush (3–7 ml/sec). Breath hold will start during early phases of contrast infusion before contrast reaches the LV cavity. Images will be acquired for 40-50 heart beats to ensure that the contrast has passed through the LV myocardium. (See figure 5.)

Table 2: CMR Dosing

GFR (mL/min/1.73m^2)	Gadolinium Dosage (mmol/kg)
<30	Non contrast exam
30-60	0.10
>60	0.20
Option	If necessary follow site's institutional guidelines

Figure 5



70.10.1.4 Myocardial Scar/Infarction: Delayed enhancement (DE)-CMR will used to assess for myocardial infarction/scar. Imaging will be performed using an inversion recovery pulse sequence (Look-Locker), for which images ***will be 10-20 minutes post contrast.*** DE-CMR inversion times (TI) will be tailored to null viable myocardium (~300msec). DE-CMR will be acquired in both short and long axis orientations, matched to pre-contrast cine-CMR. **Short axis delayed images should match exactly with Cine-CMR short axis stack, acquired with a slice thickness of 8.0mm (inter-slice gap=0).**
(See Figure 1 and 2.)

Segmented (breath-held) will be required as part of the CMR protocol. Ancillary DE-CMR approaches (i.e. single shot, 3D navigator) can be used as an adjunctive (optional) approach if available at participatory sites. In addition, contiguous short axis stack of images as well as a 4 chamber image will be acquired using single shot pulse sequence with a TI of 600ms to assess for RV/LV thrombus. (See Figures 6 and 7.)

Figure 6

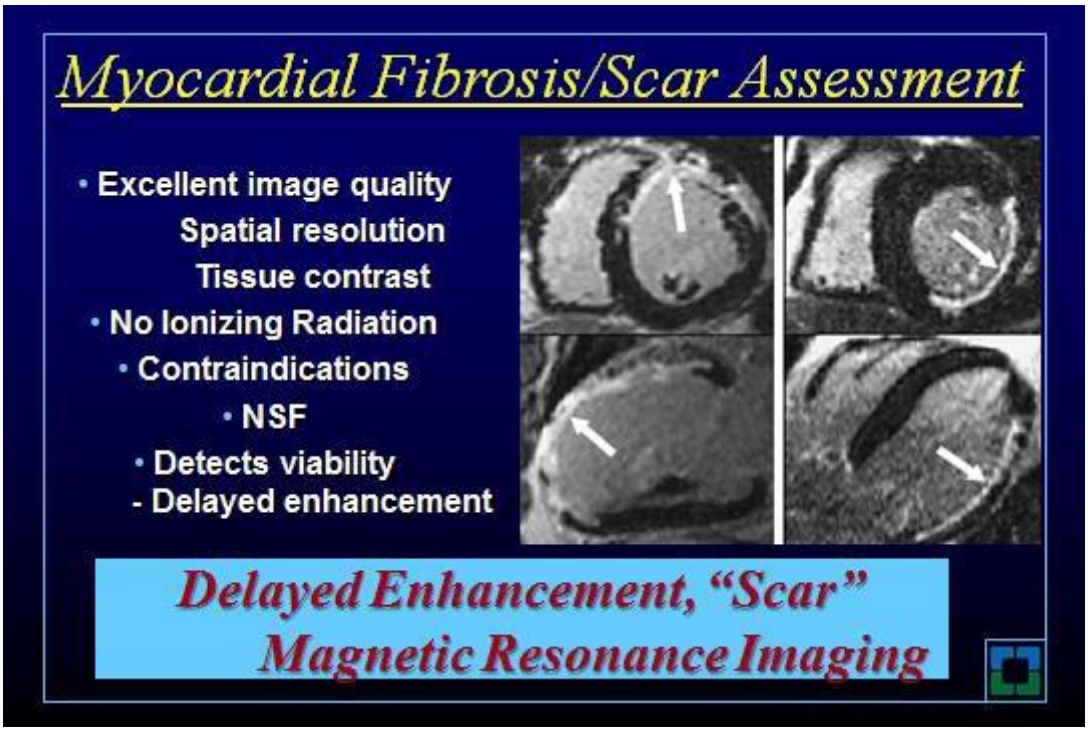
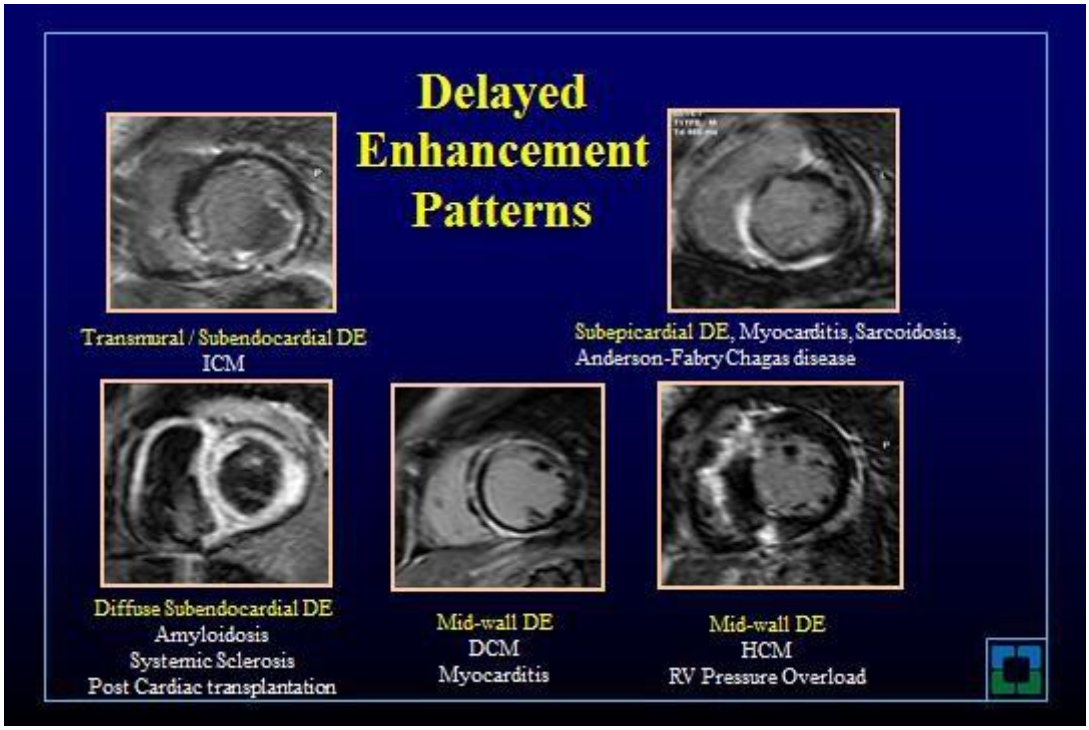


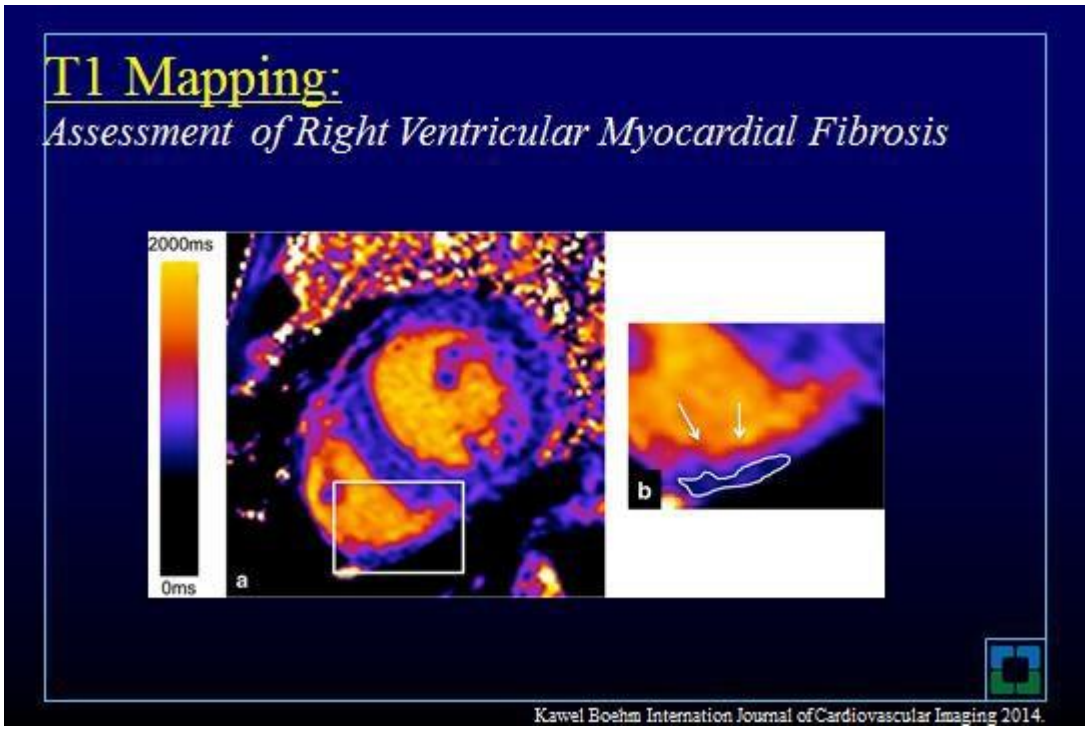
Figure 7



70.10.2 Optional

70.10.2.1 Extracellular Volume Fractionation: Pre-contrast T1 mapping will be performed to quantify myocardial extracellular volume (ECV). T1 mapping imaging will use a modified look inversion recovery (MOLLI) pulse sequence, which will be acquired in 3 short axis locations in the basal, mid, and distal left ventricle (corresponding to 16 of 17 segments within AHA/ACC segmental model). **Imaging acquired 5, 10, and at least 15 minutes** post-contrast in spatially matched locations for calculation of ECV, which will be quantified in accordance with established convention [ECV = (1- hematocrit) * [$(1/T1_{myo\ post} - 1/T1_{myo\ pre}) / (1/T1_{blood\ post} - 1/T1_{blood\ pre})$]]. **Recommend also acquiring high resolution MOLLI with in plane resolution of 1-2mm for T1 mapping/ECV quantification of the right ventricle.** (See figure 8.)

Figure 8



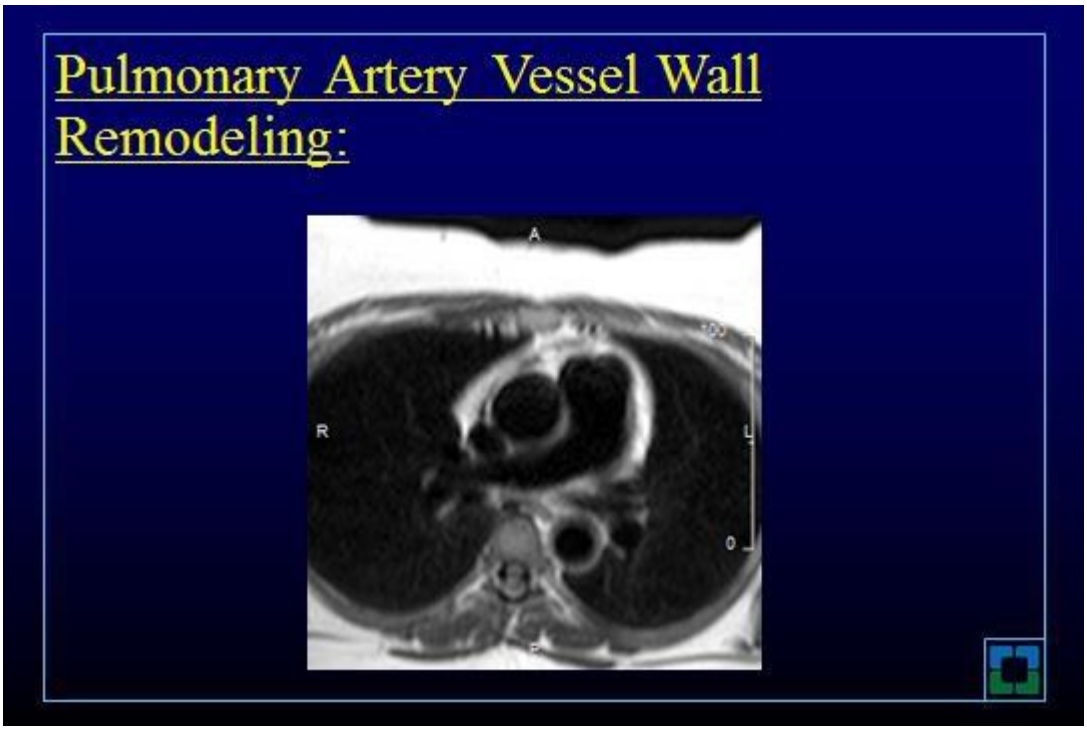
70.10.2.2 Pulmonary Artery Compliance: High temporal resolution cine-CMR (temporal resolution < 50 msec) will be performed to assess vascular compliance. Cine-CMR will be acquired in three pre-specified locations – (1) main pulmonary artery (1.0cm proximal to bifurcation), (2, 3) left and right pulmonary arteries (1.0 cm distal to bifurcation). Images will be acquired in double oblique orientation (i.e. orthogonal to the PA vessel wall, as oriented based off cine images). (See Figure 9)

Figure 9



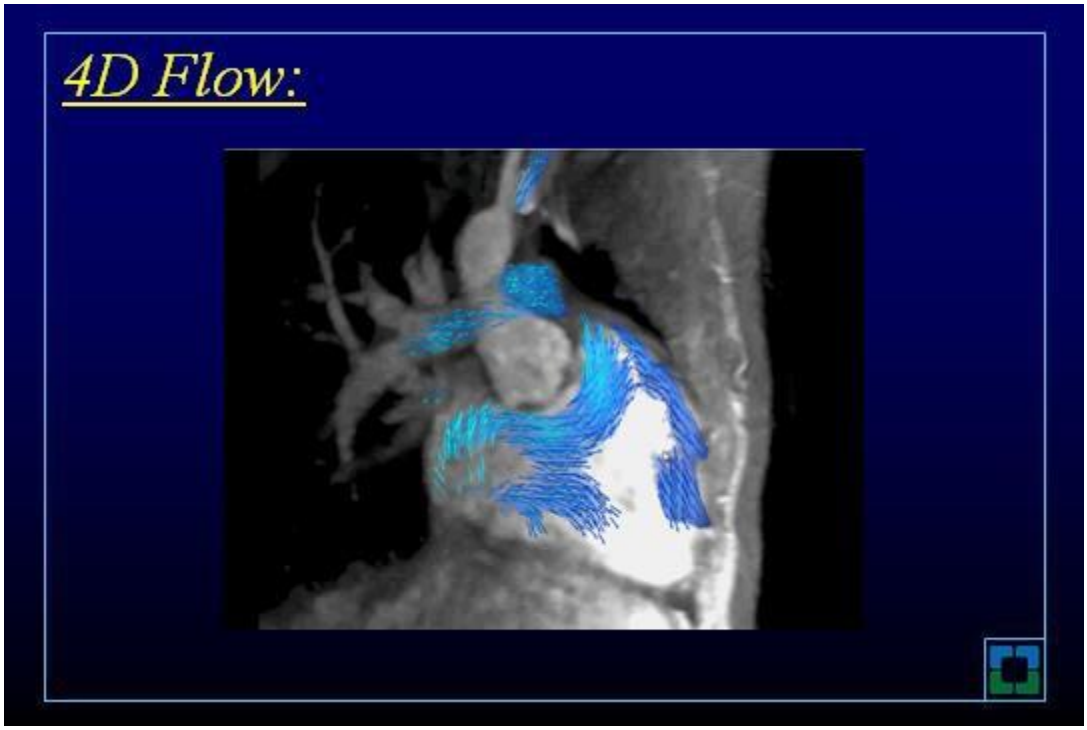
70.10.2.3 Pulmonary Artery Vessel Wall Remodeling: High anatomic resolution black blood imaging (typical in-plane resolution 1-2 mm) will be performed to assess pulmonary arterial vessel wall thickness at spatially matched locations corresponding to high temporal resolution cine-CMR (main, left, right pulmonary artery). (See Figure 10)

Figure 10

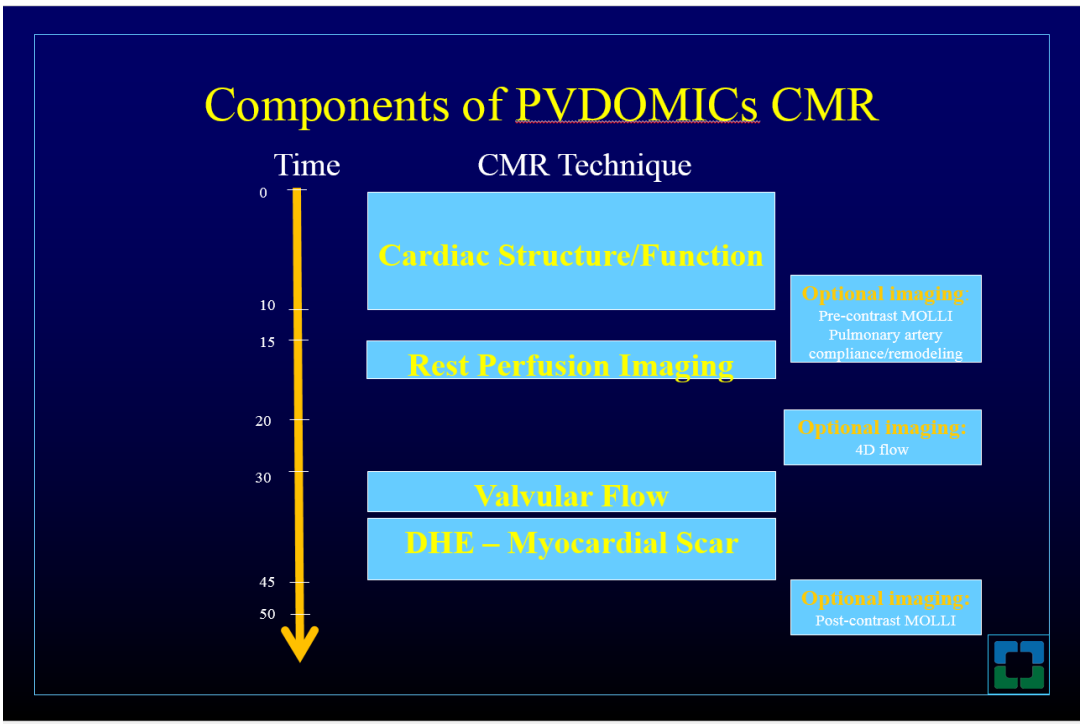


70.10.2.4 4D Flow: Anisotropic 4D segmented k-space phase contrast gradient echo sequence with retrospective ECG gating with navigator-gating of respiratory motion will be performed to assess three-directional blood flow velocity information to visualize blood flow patterns qualitatively in normal and pathological hemodynamic conditions. 3D volume will cover the apex of the heart to the aortic arch, the sternal border and spine, and the main stem of the right and left pulmonary artery until further branching in the right-to-left will be acquired (typical in-plan resolution 2-3mm). ***If this sequence is available, it should be performed immediately after the resting perfusion sequence. (See figure 11).***

Figure 11



70.10.3 Image Acquisition Sequence



70.10.4 Image Acquisition Instructions

1. Acquire images using consistent imaging parameters.
    a. Subject positioning and plane orientations must remain consistent throughout the study.
2. All subjects will be examined in the supine position.
3. EKG monitoring will be performed; lead placement is critical. Poorly placed leads result in blurred images and inaccuracies in data. Breath holding must be consistent. Placement of slices can be off as much as 2 cm when inconsistency with breath holds occurs.
4. Three-plane scout
5. Localizer: Axial single-shot blood (HASTE) images through the chest
6. 8 mm thick, spaced to cover the aortic arch through the diaphragm
7. **Acquisition during breath-hold is optimal for accuracy.**
8. Localizer: Axial bright blood images through the chest
9. Single-shot SSFP
10. (8 mm thick slices) spaced to cover the aortic arch through diaphragm
11. SSFP cine imaging (3 orientations)
12. Vertical long-axis orientation (2 chamber)
13. Horizontal long-axis orientation (4 chamber)
14. Left ventricular outflow tract (LVOT) orientation (3 chamber view)
15. Common sequence parameters for cine imaging
16. 8-mm slice thickness
17. 2.3 mm minimum spatial resolution (for both phase and frequency encoding directions)
18. 25-35 ms temporal resolution preferred; can be obtained by dropping views per segment captured between R to R intervals.
19. CMR with Late Gadolinium Enhancement (LGE)

Delayed short axis and long axis views should match slice locations of SSFP cine images. Copying the slice location is an industry standard. Cine images can be ordered to select the end diastolic trigger time by simply scrolling through a short axis image slice location. The selected time for end diastole can be entered into the actual trigger delay time prior to acquiring the delayed image set. This will enable a more accurate representation of the tracing to copy.

20. Segmented Inversion-Recovery Sequence
21. Should be acquired during breath hold approximately 10 minutes post IV administration of 0.15 mmol/kg of gadolinium chelate to optimize blood pool contrast myocardium nulling. If possible, capture a second set of late SAX stack of delays in single breath, acquiring 2 and long axis in between.
22. Inversion Time (TI) optimized by Look-Locker sequence (TI scout) to null normal myocardium. Proper selection of TI time for optimal nulling cannot be over emphasized.
23. Contiguous LV short axis stack to cover complete LV
    a. myocardium from valve plane to apex. (0 mm inter-slice gap)
24. Vertical long-axis orientation (2 chamber)
25. Horizontal long-axis orientation (4 chamber))
26. Left Ventricular outflow tract (LVOT) orientation (3 chamber view)
27. Common sequence parameters for cine imaging
28. Recommended LGE Imaging Parameters
29. TR 4.3 ms
30. TE 2.1 ms
31. Flip Angle 45 degrees to optimize effectiveness of contrast agent
32. FOV 300-350 mm
33. Matrix 128 x 256
34. 8 mm slice thickness
35. 0 mm inter-slice gap (for contiguous stack)

70.11 Image Transmittal Instructions

70.11.1 CMR Transmittal Instructions

70.11.1.1 AG Mednet is a web-based diagnostic imaging network, which enables sites to send diagnostic image exams electronically and securely to the Imaging Core Lab. AG Mednet will provide tools and training to anonymize exams, complete transmittal forms electronically and complete other trial specific tasks.

70.11.1.2 The electronic Cardiac MRI Transmittal-DCC Form #251 (see example 11.2) should be downloaded and completed by

the site technologist, then submitted to the study coordinator (or designee) for use in completing the electronic transmittal form prior to uploading the study to AG Mednet.

70.11.1.3 **No fields may be left blank. You will be unable to upload images to AG Mednet until all required fields on the electronic transmittal form are complete.**

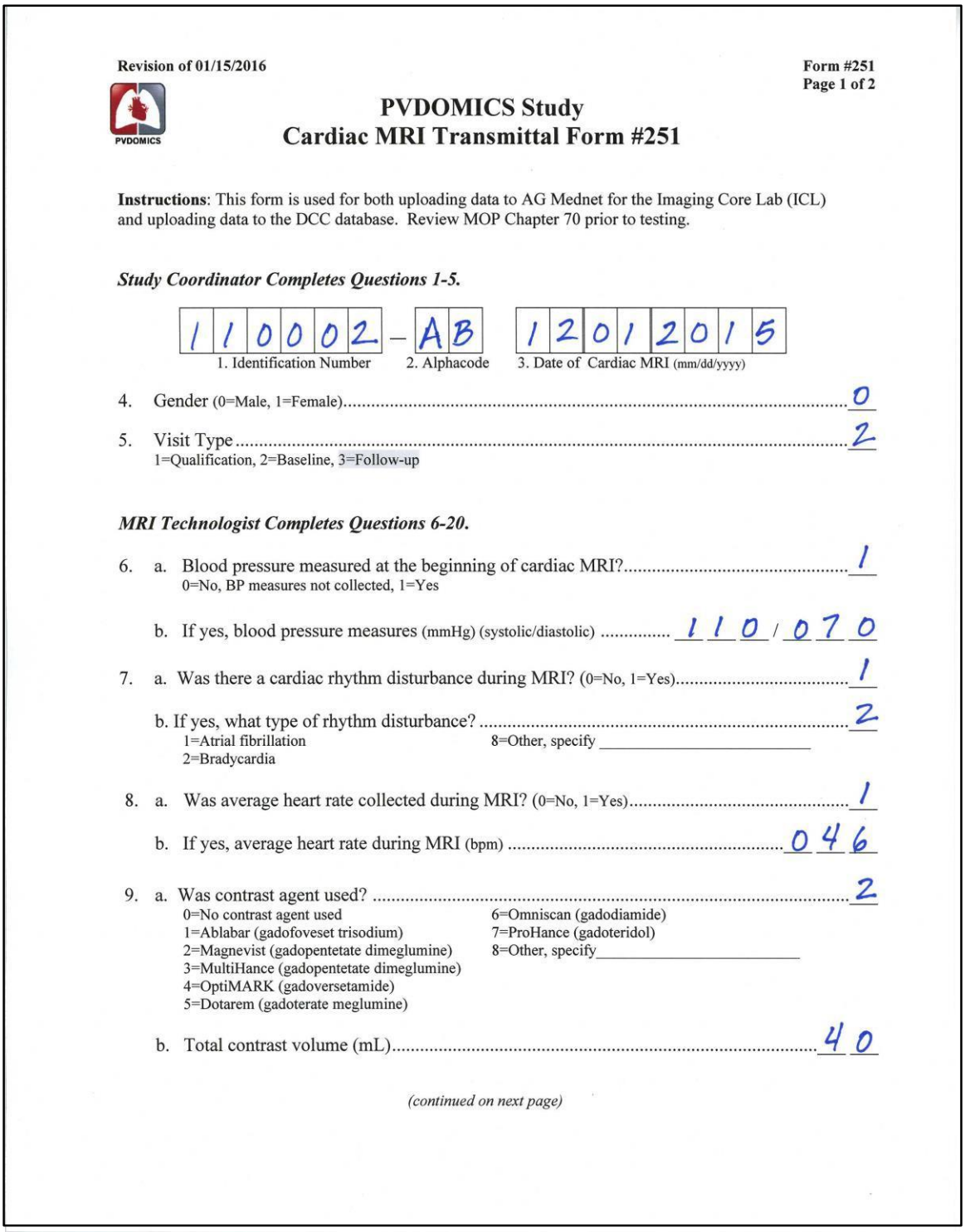
70.11.1.4 In accordance with Good Clinical Practices (GCP), errors on the hard copy should be crossed out with a single line, not obliterated, with the correction inserted, and the change initialed and dated.

70.11.1.5 If you have questions about completing the electronic data form, refer to the Data Transmittal Form example or contact AG Mednet Support for assistance. (See contact information on page 2)

70.11.1.6 An ICL Study Team Contact Information sheet is located in the front of this manual for reference.

It is important to transfer image exams to the core lab as they are collected. This practice will prevent a backlog of analysis at the core lab. Please, no bulk sending.

70.11.2 Cardiac MRI Transmittal Form #251 Example



Revision of 01/15/2016

Form #251
Page 1 of 2

PVDOMICS

PVDOMICS Study
Cardiac MRI Transmittal Form #251

Instructions: This form is used for both uploading data to AG Mednet for the Imaging Core Lab (ICL) and uploading data to the DCC database. Review MOP Chapter 70 prior to testing.

Study Coordinator Completes Questions 1-5.

1	1	0	0	0	2	–	A	B	1	2	0	1	2	0	1	5

1. Identification Number 2. Alphacode 3. Date of Cardiac MRI (mm/dd/yyyy)

4. Gender (0=Male, 1=Female)..... 0

5. Visit Type..... 2
   1=Qualification, 2=Baseline, 3=Follow-up

MRI Technologist Completes Questions 6-20.

6. a. Blood pressure measured at the beginning of cardiac MRI?..... 1
   0=No, BP measures not collected, 1=Yes

   b. If yes, blood pressure measures (mmHg) (systolic/diastolic) ..... 110 / 070

7. a. Was there a cardiac rhythm disturbance during MRI? (0=No, 1=Yes)..... 1

   b. If yes, what type of rhythm disturbance? 2
   1=Atrial fibrillation
   2=Bradycardia
   8=Other, specify _____

8. a. Was average heart rate collected during MRI? (0=No, 1=Yes)..... 1

   b. If yes, average heart rate during MRI (bpm) 046

9. a. Was contrast agent used? 2
   0=No contrast agent used
   1=Ablabar (gadofoveset trisodium)
   2=Magnevist (gadopentetate dimeglumine)
   3=MultiHance (gadopentetate dimeglumine)
   4=OptiMARK (gadoversetamide)
   5=Dotarem (gadoterate meglumine)
   6=Omniscan (gadodiamide)
   7=ProHance (gadoteridol)
   8=Other, specify _____

   b. Total contrast volume (mL)..... 40

(continued on next page)

Cardiac MRI Transmittal Form Example, page 2

Revision of 01/15/2016 Pt ID 110002 AC AB Date of MRI 12/01/2015 Form #251 Page 2 of 2

10. MRI start time (24-hr clock) (hh:mm) 08:00
11. Injection start time (24-hr clock) (hh:mm) 08:15
12. Look-Locker sequence start time (24-hr clock) (hh:mm) 08:28
13. Delayed enhancement sequence start time (24-hr clock) (hh:mm) 08:30
14. MOLLI sequence start time (24-hr clock) (hh:mm), if performed 08:35
15. MRI end time (24-hr clock) (hh:mm) 09:00

Comments _____

_____

16. a. Username of MRI Technologist who performed cardiac MRI ..... SMITHCA
    b. Name of MRI Technologist who performed cardiac MRI ____Cathy Smith____

Imaging Equipment Used for this Cardiac MRI

17. MRI manufacturer 3
    1=GE
    2=Philips
    3=Siemens
    8=Other, specify _____
18. Model # ..... Avanto
19. Serial Number # 12345
20. Field Strength: Tesla (1=1.5 T, 2=3.0 T) 1

Transmission Details for Cardiac MRI to AG Mednet- ***Coordinator completes Q21 through end of form.***

21. Method of transmission (1=Digital transfer, 8=Other, specify_____) .. 1
22. Date MRI file transmitted to AG Mednet (mm/dd/yyyy) 12/01/2015
    (Date file transmitted must be greater or equal to the date the form is completed.)

200. Date this form completed (mm/dd/yyyy) 12/01/2015
201. Username of person completing/reviewing completeness of this form ..... SMITHCA

Clinical Center Use Only
Date Form Entered (mm/dd/yyyy) __/__/____
Username of person entering this form_____

70.12 Cardiac MRI Archival Instructions

70.12.1.1 Complete the electronic Data Transmittal Form carefully and completely. (This is treated as a source document and is subject to audit by regulatory authorities.)

70.12.1.2 Archive the cardiac MRI scan to digital media (CD/DVD) immediately from the imaging system that was used to acquire the images (before archiving to Picture Archiving and Communication System [PACS]).

Please retain the CMR discs with the subject research records.

70.13 CMR Data Clarification Process

70.13.1 Query Notification

70.13.1.1 The study coordinator (or designee) and the DCC will receive an email from the C5R ICL asking for the resolution of any issues that were found during the quality control (QC) process. Prompt response is required from the site study coordinator.

70.13.1.2 Data Tracking Form Queries

- Review the variable name, reported value, and comments/suggestions
- Record the corrected, missing, or illegible information in the resolution box

70.13.1.3 Media Queries

- Review the issue and comments/suggestions
- Record the corrected information and/or comments of action taken (Example: Sent Imaging Core Lab new images via AG Mednet).

70.13.1.4 Please print your name, sign and date (DD/MMM/YYYY) in the space provided. The C5R ICL will not consider corrections recorded on the DCF unless signed and dated by site personnel completing the form. A signature indicates your

agreement that the data should be changed as indicated on the DCF.

70.13.1.5 Ensure all fields of the DCF are complete.

70.13.1.6 If you have questions about completing the form, refer to the Data Clarification Form (see example 13.4), send an email, or telephone a Core Lab team member for assistance.

70.13.1.7 An ICL Study Team Contact Information sheet is located in the front of this manual for reference.

70.13.2 Resolution and Return of DCF

70.13.2.1 The study center contact person must fax the completed Data Clarification Form to the Core Lab within five business days at +1 216.445.4419. The study center will keep a copy of the DCF with the corresponding study files.

70.13.3 Unresolved Query Process

70.13.3.1 If the ICL does not receive the faxed resolution, a follow up email will be sent to the site study coordinator and copied to the DCC indicating a second request for immediate attention/resolution of the DCF.

70.13.3.2 If the DCF is returned and all the issues are not resolved, the Imaging Core Lab will re-send an updated DCF to resolve the outstanding issues. The study center will complete the form, sign it, and fax it to the ICL.

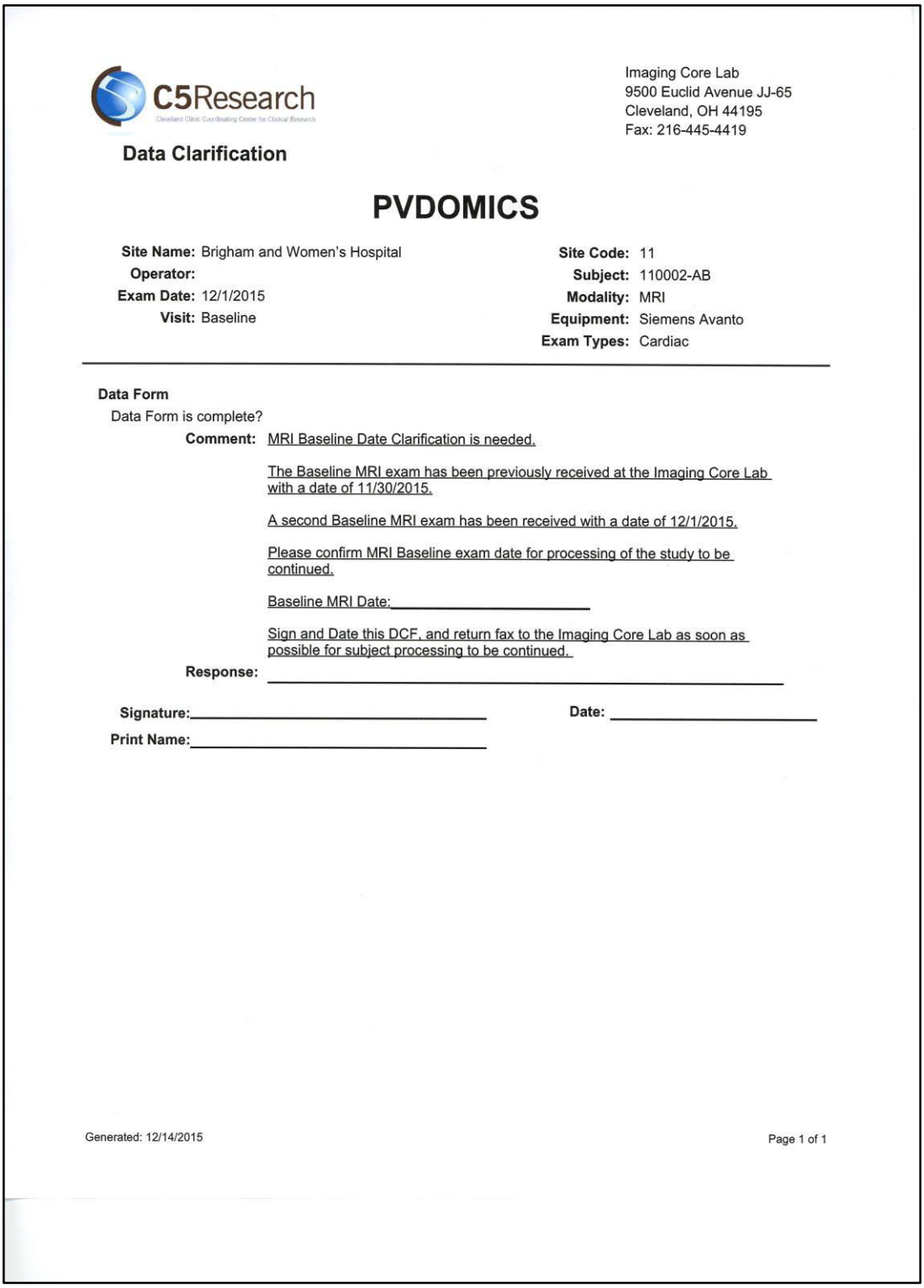
70.13.3.3 Site will save a copy of this DCF with the site study records.

70.13.3.4 Site will ensure all fields of the DCF are complete.

70.13.3.5 If you have questions about completing the form, refer to the Data Clarification Form example, send an email, or telephone an ICL team member for assistance.

70.13.3.6 An ICL Study Team Contact Information sheet is located in the front of this manual for reference.

70.13.4 Data Clarification Form (DCF) Example



C5Research
Cleveland Clinic Coordinating Center for Clinical Research

Imaging Core Lab
9500 Euclid Avenue JJ-65
Cleveland, OH 44195
Fax: 216-445-4419

Data Clarification

PVDOMICS

Site Name: Brigham and Women's Hospital
Operator:
Exam Date: 12/1/2015
Visit: Baseline

Site Code: 11
Subject: 110002-AB
Modality: MRI
Equipment: Siemens Avanto
Exam Types: Cardiac

Data Form

Data Form is complete?

Comment: MRI Baseline Date Clarification is needed.

The Baseline MRI exam has been previously received at the Imaging Core Lab with a date of 11/30/2015.

A second Baseline MRI exam has been received with a date of 12/1/2015.

Please confirm MRI Baseline exam date for processing of the study to be continued.

Baseline MRI Date:_____

Sign and Date this DCF, and return fax to the Imaging Core Lab as soon as possible for subject processing to be continued.

Response: _____

Signature:_____ **Date:** _____

Print Name:_____

Generated: 12/14/2015

Page 1 of 1

70.14 Imaging Core Replacement/ Inactivation Process

In the event that an image exam must be replaced or inactivated due to a submission error, this process will be followed:

i. ICL to initiate query to site and DCC designee asking for clarification. ICL will not process clarification received from site until sponsor designee(s) verifies the accuracy with signature on inactivation form.

ii. The site monitor or designee will verify the date and subject ID on the Inventory/Quality Report to ensure accuracy.

iii. ICL will update the Inventory Report, PACS system and C5Research Clinical Data Management (CDM).

1. Rename incorrect CMR as INACTIVE.
2. Proceed with normal processing of replacement CMR, i.e. check-in, import and analysis.

iv. Prior to data transfer, ICL will send DCC's Data Management team and C5Research CDM Replacement CMR spreadsheet containing cumulative list of studies that have been renamed.

1. DCC will update their DM team in preparation for successful receipt of transfer.

70.15 Electronic Submission Overview

70.15.1 AG Mednet

70.15.1a AG Mednet is a web-based diagnostic imaging network which enables sites to send diagnostic image exams electronically and securely to the Imaging Core Lab

70.15.1b AG Mednet will provide tools and training to:

- De-identify exams
  - Site is responsible for correctly de-identifying study within the AG Mednet portal.
- Complete transmittal forms electronically

- Complete other trial-specific tasks

70.15.2 Electronic Submission Process

70.15.2.1 All data should be acquired in DICOM format and submitted electronically via a web-based interface to the Imaging Core Lab using the AG Mednet Desktop Agent.

70.15.2.2 Upload time is dependent on site speed network connection, but the transfer runs in the background so site staff can leave the computer running or work on other applications.

70.15.2.3 Sites are informed via email of electronic submission success as soon as transfer has completed.

70.15.2.4 AG Mednet is an intuitive system and can run from a networked PC with Java 8 plug-in installed. This plug-in ensures AG Mednet will run within the web browser. It is likely that you already have Java 8 installed.

70.16 Forms

70.16.1 CMR Data Tracking Forms

70.16.1a Hard copy transmittal forms should be downloaded from QHS website and used as worksheets, at site's discretion, in preparation for electronic data transfer. Link to the PVDOMICS webpage: http://qhsapps.ccf.org/pvdomics/. Click on information page and select forms from choices.

70.17 References

American College of Radiology—North American Society for Cardiovascular Imaging Society for Pediatric Radiology Practice Parameter for the Performance and Interpretation of Cardiac Magnetic Resonance Imaging (MRI). Amended 2014 (Resolution 39)*).

ACCF/ACR/AHA/NASCI/SCMR, 2010 Expert Consensus Document on Cardiovascular Magnetic Resonance. Journal of the American College of Cardiology Vol 55, No. 23, 2010

PVDOMICS CMR ACQUISITION REFERENCE GUIDE

Cardiac Structure and Function

1. **Acquire images using consistent imaging parameters. Subject positioning and plane orientations must remain consistent throughout the study.*All subjects will be examined in the supine position.**
2. **EKG monitoring will be performed; lead placement is critical. Poorly placed leads result in blurred images and inaccuracies in data. *Breath holding must be consistent. Placement of slices can be off as much as 2 cm when inconsistency with breath holds occurs.**
3. **Three-plane scout, (True Fisp) or vendor related scout from axial, coronal, sagittal**
4. **Localizer: Axial single-shot blood (HASTE) images through the chest. Plan from sagittal and axial scout.**
5. **8 mm thick, spaced to cover the aortic arch through the diaphragm. *Acquisition during breath-hold is optimal for accuracy.**
6. **Localizer: Axial bright blood images through the chest**
7. **Single-shot SSFP (True Fisp), or vendor related cine Plan from coronal scout, *8 mm thick slices, spaced to cover the aortic arch through diaphragm**
8. **SSFP (True Fisp) or vendor related cine imaging (3 orientations)**
9. **Vertical long-axis orientation (2 chamber)**
10. **Horizontal long-axis orientation (4 chamber)**
11. **Left ventricular outflow tract (LVOT) orientation (3 chamber view)**
12. **Common sequence parameters for cine imaging**
    a) **8-mm slice thickness**
    b) **2.3 mm minimum spatial resolution (for both phase and frequency encoding directions)**
    c) **25-35 ms temporal resolution preferred; can be obtained by dropping views per segment captured between R to R intervals.**

*****If performing Optional Imaging do Pre-contrast MOLLI and pulmonary artery compliance remodeling next.**

Rest Perfusion Imaging

1. Saturation-recovery imaging will be used to assess resting myocardial perfusion.
2. Short-axis images will be acquired (at least 3 slices per heart beat), using a slice thickness of 8 mm and parallel imaging, 2-fold acceleration, if available with in-plane resolution, ~< 3 mm. Readout temporal resolution ~100 – 125 ms or shorter as available.
3. Contrast will be given (0.1 - 0.2 mmol/kg, 3–7 ml/s) followed by at least 30 ml saline flush (3–7 ml/sec). (See GFR dosing table on page 3.)
4. Breath hold will start during early phases of contrast infusion before contrast reaches the LV cavity.
5. Images will be acquired for 40-50 heart beats to ensure that the contrast has passed through the LV myocardium.

*****If performing Optional Imaging do 4D Flow Imaging next**

Valvular Flow

1. Use Phase velocity encoded images to assess valvular flow.
2. Two separate images will be acquired, through the aortic valve and the pulmonic valve.
3. Images will be acquired "en-face" valve orientation at the level of the valve leaflet tips.
4. Temporal resolution < 35ms, will ensure accuracy in flow data.
5. VENC limits will be tailored to avoid aliasing (typically 1.5 m/sec). **Recommend careful assessment for aliasing, and increasing the VENC level as needed (i.e. 2 m/sec or greater as needed). VENC is important to not travel too high away from the normal values on each patient.**
6. Flow quantification will be assessed of the right and left pulmonary arteries.

DHE-Myocardial Scar

1. **CMR with Late Gadolinium Enhancement (LGE)**
   Delayed short axis and long axis views should match slice locations of SSFP cine images. Copying the slice location is an industry standard. Cine images can be ordered to select the end diastolic trigger time by simply scrolling through a short axis image slice location. The selected time for end diastole can be entered into the actual trigger delay time prior to acquiring the delayed image set. This will enable a more accurate representation of the tracing to copy.
2. **Segmented Inversion-Recovery Sequence (tfi_psir_single-shot_PSIR) or vendor related delayed imaging**
3. **Should be acquired during breath hold approximately 10 minutes post IV administration of 0.15 mmol/kg of gadolinium chelate to optimize blood pool contrast myocardium nulling. If possible, capture a second set of late SAX stack of delays in single breath, acquiring 2 and long axis in between.**
4. **Inversion Time (TI) optimized by Look-Locker sequence (TI scout) to null normal myocardium. Proper selection of TI time for optimal nulling cannot be over emphasized.**
5. **Contiguous LV short axis stack to cover complete LV myocardium from valve plane to apex. (0 mm inter-slice gap)**
6. **Vertical long-axis orientation (2 chamber)**
7. **Horizontal long-axis orientation (4 chamber)**
8. **Left Ventricular outflow tract (LVOT) orientation (3 chamber view)\Common sequence parameters for cine imaging**
9. **Recommended LGE Imaging Parameters**
   a. **TR 4.3 ms**
   b. **TE 2.1 ms**
   c. **Flip Angle 45 degrees to optimize effectiveness of contrast agent**
   d. **FOV 300-350 mm**
   e. **Matrix 128 x 256**
   f. **8 mm slice thickness**

g. 0 mm inter-slice gap (for contiguous stack)

*****If performing Optional Imaging do Post Contrast MOLLI now.**

Optional Protocol

1. **Extracellular Volume Fractionation**: Pre-contrast T1 mapping will be performed to quantify myocardial extracellular volume (ECV).
   - **a.** Use a modified look inversion recovery (MOLLI) pulse sequence, acquired in 3 short axis locations: basal, mid, and distal LV
   - **b.** Imaging acquired 5, 10, and at least 15 minutes post-contrast in spatially matched locations for calculation of ECV, which will be quantified in accordance with established convention [ECV = (1-hematocrit) * [$(1/T1_{myo\ post} - 1/T1_{myo\ pre}) / (1/T1_{blood\ post} - 1/T1_{blood\ pre})$]]. **Recommend also acquiring high resolution MOLLI with in plane resolution of 1-2mm for T1 mapping/ECV quantification of the right ventricle.**
2. **Pulmonary Artery Compliance**: High temporal resolution cine-CMR (< 50 msec) performed to assess vascular compliance.
   - **a.** Cine-CMR will be acquired in three pre-specified locations – (1) main pulmonary artery (1.0cm proximal to bifurcation), (2, 3) left and right pulmonary arteries (1.0 cm distal to bifurcation). Images will be acquired in double oblique orientation (i.e. orthogonal to the PA vessel wall, as oriented based off cine images).
3. **Pulmonary Artery Vessel Wall Remodeling**: High anatomic resolution black blood imaging (typical in-plane resolution 1-2mm) performed to assess pulmonary arterial vessel wall thickness at spatially matched locations corresponding to high temporal resolution cine-CMR (main, left, right pulmonary artery).
4. **4D Flow:** Anisotropic 4D segmented k-space phase contrast gradient echo sequence with retrospective ECG gating with navigator-gating of respiratory motion to assess three-directional blood flow velocity information to visualize blood flow patterns and qualitatively assess flow.
5. 3D volume will cover apex to the aortic arch, the sternal border and spine, and the main stem of the right and left pulmonary artery until further branching in the right-to-left will be acquired (typical in-plan resolution 2-3mm). ***If this sequence is available, it should be performed immediately after the resting perfusion sequence.***

CMR Dosing

GFR (mL/min/1.73m^2)	Gadolinium Dosage (mmol/kg)
<30	Non contrast exam
30-60	0.10
>60	0.20
Option	If necessary, follow site's institutional guidelines.

Chapter 80. Chest Computed (CT) Tomography

80.1 General Overview and Logistics

Purpose

1. To obtain thin slice high resolution chest computed tomography (CT) scans of the chest in participants with pulmonary vascular disease.

2. To provide standardized reading/data interpretation.

Rationale

Refinements in CT image acquisition and post processing have enabled the identification and quantification of clinically relevant features of acute and chronic conditions such as pulmonary vascular disease. These include vascular enlargement, tortuosity and pruning that selectively affect the arterial and venous circulatory beds in the lung. Associated changes in lung density and overall lung morphology may aid in disease characterization as well. Diffuse lung diseases such as obstructive physiology from emphysema or chronic bronchitis, or restrictive physiology from chronic fibrotic interstitial lung disease may contribute to the etiology in pulmonary hypertension and will likely be evident on CT imaging. As core imaging investigators, we hypothesize that these features may be used to discriminate the etiology and pathophysiology of disease. Objective assessments of these features may also be used in therapeutic trials as an intermediate study endpoint (i.e. change in tortuosity or distribution of blood vessel volume) and potentially even as a metric of disease that may predict response to therapy (i.e. severity of arterial pruning may predict vasodilator response).

Introduction

Detailed CT parameters and procedures can be found in Sections *80.5 and 80.6.* Briefly, there are some scanner to scanner variations in image acquisition and reconstruction. These differences may influence qualitative and quantitative analysis of vascular and lung morphology. To account for and try to adjust for these differences, imaging investigators will be using predefined CT parameters that may provide comparable images for analysis. The most important aspect of image standardization is that each participant undergoes the same imaging protocol. Inter-subject consistency is critical for the most accurate measures of change in vascular and lung morphology.

CT scans will be collected at all participating centers, stored locally and digitally transferred to the Lung Imaging Core (LIC) at the Cleveland Clinic for further analysis. The Lung Imaging Core Lab, under the direction of Jason Lempel, MD, will serve as the radiology core to provide standardization, secondary interpretation and data analysis of all chest CT imaging obtained and performed for the PVDOMICS Study.

The Lung Imaging Core's contact information is located in the PVDOMICS Address Directory located at http://qhsapps.ccf.org/pvdomics/General_info.htm. Click on 'Address Directory.'

Additionally, the LIC will provide qualitative and quantitative CT analysis following these predefined CT parameters and provide these data to the PVDOMICS DCC.

Use of historical Chest CT scans will be permitted for the study provided the following criteria are met:

- CT scan slices must be thin (1 mm) or less
- Images obtained can be uploaded to LIC using iUploader software
- Local radiologist analysis and interpretation is available
- Scan is within 1 year prior to Form 100-General Enrollment date
- Historical CT scans obtained from outside institutions may be uploaded if all other criteria are met

80.2 System and Personnel Requirements

80.2.1 Local Center provides:

- Dedicated room
- Scanner(s) (current manufacturer information as provided on Form 20, *changes to type of scanner and/or software must be kept current, see appendix X*)
- Computer with windows operating system, version 7-10 *(contact LIC if other operating system on computer is used for PVDOMICS Study as there may be compatibility issues with iUploader software.)*
- Names and contact information of PVDOMICS CT imaging personnel (*via Form 10 and kept current as personnel may change over the course of the study*)
- Sheets/blankets/pillows for participant comfort
- PVDOMICS data collection form(s), pens
- PVDOMICS Study ID and Alphacode (provided by the Study Coordinator)

80.2.2 CT Imaging Core Provides:

- Scanning parameters
- TeraRecon iUploader software
- Instructions for standardized participant breathing
- CT Technologists training for:
  - PVDOMICS Study Participant Scanning Procedures
  - Instructions for image transfer to LIC

80.2.3 Local Center Personnel Requirements

All centers have a radiologist certified by the American Board of Radiology (ABR) with dedicated subspecialty training in thoracic imaging. ABR certified radiologists participating as part of the PVDOMICS Study should be familiar with study related procedures.

Technologists must be American College of Radiology (ACR) certified. Technologists must review PVDOMICS Chest CT Manual of Operations Chapter 80 and all appendices. The PVDOMICS Study Coordinator should have all signed attestation statements on file and record each technologist's date of review on Form 10. This documentation must be current and properly recorded before scanning study enrolled participants.
Centers should have an IT administrator/director with authority to manipulate firewalls and assist with TeraRecon iUploader software installation and trouble-shooting.

The LIC Core will provide training for techs and coordinators as follows:

- Initial PVDOMICS Study central training
- Webinar for software installation and use
- Review and provide feedback to local center on transfer of test case
- Individual guidance by LIC Radiologist(s)

80.3 Participant Exclusion from Chest CT Scan

In the instance where a participant may be obese, the study team should determine the participant's ability to safely fit into the CT scanner. If the participant exceeds the scanners weight limit, do not attempt the CT scan, regardless of whether or not a historical scan is available.

80.4 Chest CT Scanning Parameters and Procedures Overview

For the purposes of PVDOMICS study, CT scans obtained as part of routine clinical care may be performed with or without intravenous contrast as deemed appropriate by the ordering clinician at the local center. In this setting, the CT protocol utilized will be one prescribed by the local imaging department for evaluation of the clinically suspected disease, as long as the raw data is reconstructed into 1mm or thinner sections.

CT scans performed on comparator subjects or on participants with pulmonary hypertension but for research purposes only (not part of clinical evaluation), will be performed without intravenous contrast.

Furthermore, participants who have had previous CT scans performed within 1 year prior to study enrollment and for whom the study center has reconstructed and saved the images on their PACS server at 1mm thickness or less, may use these previously obtained images as part of the participants full PVDOMICS imaging evaluation. These previously obtained CT scans, whether performed with or without IV contrast, will be uploaded with their full DICOM set and sent to the Lung Imaging Core in place of new CT images. These images will be used for review by the Imaging Core Director.

Each center has specific parameters that must be implemented for the PVDOMICS chest CT scans. Scout films use default parameters. Centers have the discretion on type and number of scouts, however, must maintain ALARA principle. (*ALARA is an acronym for As Low As Reasonably Achievable. This is a radiation safety principle for minimizing radiation doses and releases of radioactive materials by employing all reasonable methods.)*

These items are provided for each center: Parameter, Scanner, Scan Type, Rotation Time (s), Detector Configuration, kV, Pitch, , Reconstruction Algorithm 1, Reconstructure Algorithm 2, Thickness (mm), Interval (mm),

80.5 Radiation Dose Selection

The Study Coordinator should assist the CT Technologist with providing the Body Mass Index (BMI) to set the effective mAs. A measured BMI is recorded on PVDOMICS Form 132-BIA or the Coordinator can provide a measured height and weight as recorded on this same

- Extra small, small, medium or large effective mAs settings for the PVDOMICS scans are based upon the participant's BMI.

Identify the correct effective mAs setting based on the patient's BMI using Table 1 below.

Table 1 Effective mAs as a function of BMI

Body Size	BMI Range	Effective Milliaperages (mAs) setting to be used
Large	>30	165
Medium	20 - 30	110
Small	15 - 19	90
Extra Small	<15	60

If the CT scan is being done for research only, the participant does not need to wait for an assessment of the image quality as the participant is scanned once and is done.

80.6 Chest CT Scanning Procedure

For the purposes of PVDOMICS study, CT scans obtained as part of routine clinical care may be performed with or without intravenous contrast as deemed appropriate by the ordering clinician at the local center. In this setting, the CT protocol utilized will be one prescribed by the local imaging department for evaluation of the clinically suspected disease, as long as the raw data is reconstructed into 1mm or thinner sections.

CT scans performed on comparator subjects or on participants with pulmonary hypertension but for research purposes only (not part of clinical evaluation), will be performed without intravenous contrast.

Furthermore, participants who have had previous CT scans performed within 1 year prior to study enrollment and for whom the study center has reconstructed and saved the images on their PACS server at 1mm thickness or less, may use these previously obtained images as part of the participants full PVDOMICS imaging evaluation. These previously obtained CT scans, whether performed with or without IV contrast, will be uploaded with their full DICOM set and sent to the Lung Imaging Core in place of new CT images. These images will be used for review by the Imaging Core Director.

Scanners of different makes and models deliver different number of photons to the subjects for a given milliamperage (mA) setting because of differences in beam infiltration, variances in tube potential, etc. Therefore, using fixed mA across scanners will result in dissimilar exposures, leading to noise differences and possible inconsistencies in the reported CT number, Hounsfield units (HU) and radiation exposures. Dose modulation is not allowed for quantitative CT study since each manufacturer modulates differently, causing increased likelihood of system differences across scanners. BMI and scan type will determine the effective mAs or mA setting. These are recommended as a function of large, medium, small or extra small BMI as detailed in Table 1. This mechanism allows for optimal doses to the various size subjects. The CT technologist will use these guidelines to choose the effect of milliamp seconds (mAs) (Siemens) or mA (GE) setting for a given BMI. Table 1 demonstrates examples of the radiation doses for a given BMI size.

Scout scans will be obtained to minimize the subject's exposure to radiation and must be performed at the lung volume for which anatomical boundaries are being evaluated. Each study site should perform scouts as deemed locally appropriate such that when spirally scanned, the full extent of the lung is acquired at the respective lung volumes and over scanning is kept to a minimum. Inadequate scout scans maybe repeated as per site-specific determination. Spiral scans however may not be repeated, unless clinically warranted as determined by an on-site thoracic radiologist.

Exposure factors (kV and mA) for the topogram should be set to the lowest available on the CT scanner that provides an acceptable image. The scanner settings utilized in PVDOMICS should

be maintained consistent throughout the duration of the study. The data shall be displayed using a display field of view (DFOV) that includes the lungs and entire chest wall in the right/left dimension so that resolution of the lung is maximum. The standard reconstruction algorithm data is all that will be used for further computer analysis. The soft tissue and lung reconstruction algorithm (B30 and B60, respectively, or standard and detail, depending on vendor) data is necessary for the supervising radiologist to interpret the image data set in standard fashion.

The specific CT scanning parameters will vary slightly from center to center based upon the differing types of CT scanners used. Manufacturer and type CT scan parameter data specific for each of the centers starts in this chapter.

Each center will be using multi-detector CT scanners (64 detectors or greater). CT scans will be obtained at maximum inspiration using the center-specific parameters in this chapter. The DFOV will be selected to include the chest wall. ***Note that dose modulation based upon body habitus is not used.***

After acquiring the CT data, images will be reconstructed using standard algorithms as detailed in using center-specific parameters in this chapter.

If the CT scan is being done for research only, the participant does not need to wait as the participant is scanned once and is done.

Scan Coverage

CT scan must include the lungs and minimize additional exposure. Start the scan slightly above the apex of the lungs and stop it once the scan is through the base of the lungs as shown in Figure 1. The DFOV should fit the lung and include some of the chest wall as shown in Figure 2.

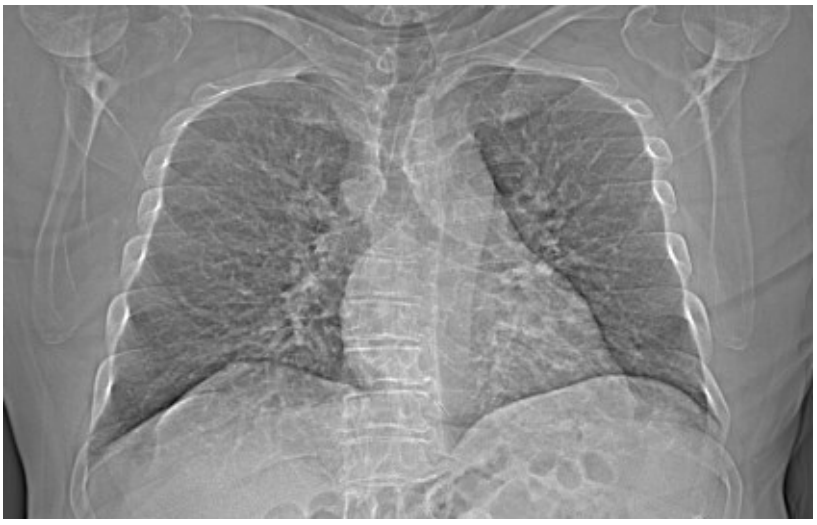


Figure 1.

The DFOV should fit the lung and include some of the chest wall as shown in Figure 2.

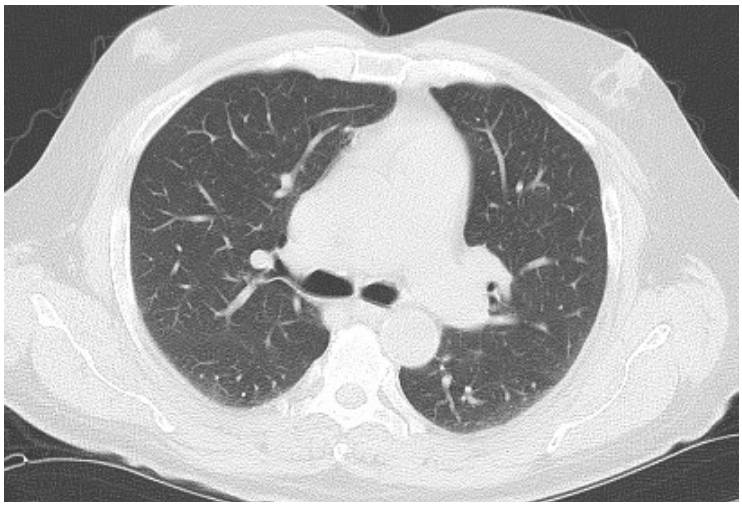


Figure 2.

80.7 Participant Preparation and Positioning on Scanner Table

Follow individual center's guidelines for participant identification and preparation for the CT scan.

It is important that the patient fully understands the breath hold and scanning procedure and that all concerns are addressed prior to performing the CT scan. It is recommended that the Study Coordinator will assist the CT technologist in the effective mAs and DFOV settings.

Patient Positioning

- Place patient in a supine position, arms positioned comfortably above the head in a head-arm rest, lower legs supported.
- Using the laser positioning lights, line up the patient so the chest is iso-center (in the middle: left-right; up-down) of the CT gantry.
- Move the table so the patient is in the correct position for a chest CT scan.



80.8 Local Center CT Scan Results Reporting

All CT images obtained as part of PVDOMICS will be reviewed and reported by a member of the local center's thoracic radiology group. All CT scans obtained will be accompanied by full clinical radiology reports. The reporting local radiologist will follow normal clinical workflow guidelines regarding notification and communication of both urgent and actionable findings to the referring physician and/or PVDOMICS center's Principal Investigator (PI).

80.9 Data De-Identification and Data Transfer Overview

All imaging (DICOM) data obtained or submitted to PVDOMICS Lung Imaging Core review will be de-identified and uploaded from the local center to LIC iNtuition Research server. This data de-identification and data transfer procedure is detailed in Chapter 80 Appendix A.

(Note: it is anticipated that a center's PVDOMICS Study-trained CT Technologist will complete these steps but a study coordinator may work with the CT tech to complete the process.)

80.10 Chest CT Data Collection Forms

The Study Coordinator or CT technologist should fill out Form 252-Center the appropriate form for each CT scan in the study as they are obtained. This process will help ensure quality data and minimize deviations from the desired CT protocol.

Form #252 should then be given to the study coordinator. The coordinator needs to obtain a final radiologist's report and de-identify it by marking through identifying information and placing PVDOMICS Study ID and alphacode. This anonymized copy should be scanned into pdf format and submitted to secure PVDOMICS location (to be determined), Form #252 should be completed and entered into PVDOMICS database and transmitted to the Lung Imaging Core.

If a historical CT scan was used, Form #253 should be completed by the coordinator and entered into PVDOMICS database along with an accompanying anonymized center CT scan final report.

80.11 Image and Data Storage at Local Centers

Images used for the purposes of the PVDOMICS Study should be maintained locally in DICOM format until the study has been completed. It is recommended that a document be maintained to identify both the local center's identifying information and the PVDOMICS Participant's identifying information (Study ID, alphacode, date of CT). This document is for local use only and not provided to the Lung Imaging Core.

A de-identified copy of the report from the local center should be stored with participant's study IDand alphacode.

Appendix A. Data De-Identification and Data Transfer Procedure

1. Obtain a copy of DICOM Images and make available either on CT console, local drive, cd or other destination folder.

2. Make sure the patient identification on the DICOM images match the PVDOMICS Study participant number and alphacode.

3. De-identify the DICOM images by dragging and dropping the DICOM data into the iNtuition uploader to be manually anonymized (with removal of pre-configured DICOM tags). PVDOMICS ID # is added during this same step.

4. Transmit through secure digital network to the LIC iNtuition server. This complete step-by-step process is detailed in *Appendix D.*

These next steps are generally completed by the Study Coordinator:

5. Obtain a copy of the radiologist's finalized clinical report. This report will be used by the Core for review and to assure correct interpretation of the radiology images.

6. Review report thoroughly to catch any participant identifiers. There may be redacting capabilities via your site's adobe software or you may have to print the report and blacken out any patient information. Date of image on the report must match the DICOM images.

7. Write the PVDOMICS participant number and alphacode on the top of each page of the report.

8. Submit this report electronically in a .pdf format.T*his section will be updated*.

9. Complete and enter Form 252 into the PVDOMICS database to alert the Core that an image is sitting in a queue on the research server. (Once a form is saved in the database, an email notification will be sent automatically to local site, Core, and DCC.)

The email message to the local center will be the only notification sent that a participant's images, radiology report and transmitted data have been received. The center will be notified only if there were any discrepancies identified such as PVDOMICS ID/alphacode mismatches.

Routine, weekly reports will be generated by the database identifying any problems with missing reports or Form 252's. Each enrolled participant will have either a Form 252 or 253 entered into the database even if the CT scan was not done.

(Center Specific Scanning parameters to follow after data transfer section) Each will be linked for center to print out its own center information.

Chapter 81. Lung Imaging Core - Chest Computed (CT) Tomography

81.0 General Information

The PVDOMICS Study Lung Imaging Core (LIC) is located at the Cleveland Clinic in Cleveland, Ohio. It is under the direction of Jason Lempel, MD, who serves as its director. He oversees LIC personnel and provides standardization, secondary interpretation and data analysis of all chest CT imaging performed for the PVDOMICS Study.

Dr. Lempel provides direction and training on chest CT imaging for the PVDOMICS Study to the local study centers' CT technologists.

Local center chest CT imaging procedures are described in detail in Chapter 80.

Dr. Lempel's contact information is located in the PVDOMICS Address Directory located at http://qhsapps.ccf.org/pvdomics/General_info.htm. *Click on 'Address Directory.'*

81.1 Training of Local Site Personnel

The Lung Imaging Core will provide training for local sites techs and coordinators as follows:

- Initial PVDOMICS Study central training
- Webinar for software installation and use
- Review and provide feedback to local center on transfer of test case
- Individual guidance by LIC Radiologist(s)

81.2 Core Image Analysis

Upon receipt of the CT scan at CT Core, a Core radiologist will review the CT data to ensure that the correct protocol for image acquisition and reconstruction was performed. An additional review of the CT images will then be performed looking for motion artifacts and incomplete imaging of the lungs.

Note: Core radiologists will provide feedback regarding image quality if suboptimal/inadequate. At the minimum, a full lung field of view is necessary for core imaging interpretation of PVDOMICS data in order to accurately categorize the type of lung disease.

Following image review for quality assurance, objective measures of vascular and pulmonary morphology will be performed.

81.3 CT Imaging Core Reporting

The DCC will not provide a clinical report on any current or historical CT scan. Specific questions regarding local CT scans obtained as part of PVDOMICS can be directed toward each center's lead PVDOMICS radiologist(s) or the LIC's radiologist(s).

Data collected following review of CT scans are obtained for research purposes only. Therefore, the Chest CT Imaging Core will not provide a detailed reading of the CT scans for abnormal findings that may be of medical concern. Each one of these scans should be reviewed by the Clinical Radiology service at each institution. Examples of these findings include, but are not limited to: incidental lung nodules, incidental breast masses and vascular abnormalities.

All actionable, clinically important findings that are discrepant between the submitted clinical report and the Chest CT Imaging Core over read will be emailed to the local center's PI and study coordinator.

Deviations from PVDOMICS MOP must be reported to the Lung Imaging Core. Follow clinical center guidelines for reporting to IRB.

81.4 Lung Imaging Core QC and Feedback

After data has been reviewed by a LIC radiologist, Form #262 will be completed and entered into the PVDOMICS database at the DCC. In addition to data analysis, review will include image quality and level of adherence to scanning parameters. Significant deviations from prescribed CT scanning parameters which may include, but are not limited to, excessively large or small imaging field of view, abnormal radiation dose and inadequate data transmission will be documented and emailed to the local center's study coordinator and PI.

81.5 Storage of Chest CT Images and Data at Lung Imaging Core

Images, data analysis and reports evaluated at and provided by the Core will be stored on a dedicated iNtuition research server within a secured, password encrypted PVDOMICS folder. These data will also be backed up on a secured encrypted Cleveland Clinic network server during the duration of the PVDOMICS study.

At completion of the PVDOMICS study, data images will be transferred to the NHLBI's Biobank for long term data storage.

.

Chapter 90. Ventilation Perfusion (V/Q) Scan

All PH and disease control participants are required to have data from a V/Q scan. These data will be used in analyses, as well as to classify participants with WHO Class IV PH. It is anticipated that most of the participants will have V/Q scans available, or will be undergoing V/Q scan as part of their regular clinical care.

- All PVDOMICS participants are required to have a ventilation-perfusion lung scan for detection of possible pulmonary emboli. V/Q scans performed within 4 years prior to enrollment can be used provided acceptable results (DICOM images and final report) are made available to the DCC Lung Imaging Core and there has been no change in clinical status of the participant. Note: historical scan can be from either PVDOMICS or non-PVDOMICS sites.

- A V/Q scan is not required if the participant has known parenchymal lung disease or has had a positive CT angiogram in the past year for which the results (DICOM images and final report) are provided to the DCC Lung Imaging Core.

- If the CTA is non-diagnostic or negative, then a V/Q scan is required.

The V/Q scan is comprised of two scintigraphic scans: one for ventilation and another for pulmonary perfusion. The ventilation scan may be performed as an Aerosol Ventilation or Gas Ventilation Scintigraphy. In Aerosol Ventilation, the bronchopulmonary distribution of an inhaled radioactive aerosol [99mTc diethylenetriamine-pentaacetic acid (DTPA)] is evaluated within the lungs. In Gas Ventilation, the pulmonary distribution of radioactive xenon (133Xe) gas is evaluated during breathing maneuvers. Pulmonary Perfusion Scintigraphy uses 99mTc macro-aggregated albumin (MAA) to record the distribution of pulmonary arterial blood flow.

Although the V/Q test uses radiopharmaceuticals, the total amount of radiation exposure to the participant is low. If the scan is done at a PVDOMICS site during the study protocol, the amount of radiopharmaceutical (mCi) administered will be recorded to maintain record of total radioactivity exposure of volunteers. **It is very important to note that any urine or blood products drawn after a V/Q scan will be radioactive. Therefore, the PVDOMICS protocol recommends that V/Q scanning that is performed during the 6-week protocol be done on the day of the participant's last scheduled visit. However, if urine or blood products must be collected and handled after V/Q scan administration of radioactive material, the urine or blood should be collected at the minimum 3 days after the scan.** The radionuclide 99mTc has a half-life of 6 hours. The time to ensure minimal to undetectable radioactivity in the biologic samples is 10 half-lives (or ~60 hours). The 133Xe radionuclide has a half-life of 5.2 days but the biological half-life is a few hours because 133Xe is exhaled (washout) [1, 2]. However, if blood is drawn immediately after a 133Xe scan, the blood sample collected will stay radioactive for weeks based on its physical 5 day half-life (and no elimination by ventilation).

Thus, blood draws after 3 days will also ensure that blood collected from those individuals have XeV/Q that is not radioactive, and likely allowable to mail. **Nevertheless, the site's local radiation safety committee should be made aware if urine or blood will be collected following V/Q in the study, as they may recommend survey of these samples before mailing to the DCC. Given these considerations, it is highly recommended that the V/Q scan be done after completion of all study urine or blood and draws.**

Form 254-Ventilation/Perfusion (V/Q) Report Transmittal Form

The report of the V/Q includes a description an overall assessment of the likelihood of pulmonary embolism based on the scintigraphic findings. This assessment will be recorded on **Form 254** along with the date the final V/Q report was transmitted to the DCC secure portal.

Form 254 is used for V/Q study done for the PVDOMICS as well as to report historical V/Q data.

References:

1. Aitkins HL, Robertson JS, Croft BY et al. Estimates of radiation absorbed doses form radioxenons in lung imaging. J Nucl Med 1980; 21:459-465.

2. Goddard BA, Ackery DM. Xenon-133, 127Xe, and 125Xe for lung function investigations: A dosimetric comparison. J Nucl Med 1975; 16:780-786.

Chapter 100. Right Heart Catheterization (RHC)

This manual is intended to serve as both a training and a reference document for persons who perform the right heart catheterization for the PVDOMICS study using standardized procedures and techniques. This will aid in obtaining accurate test results and a safe testing environment.

100.1 Right Heart Catheterization Overview

Right heart catheterization is a clinical test used to determine the pressures in the chambers of the heart and the lungs. A pulmonary artery catheter is introduced into the right side of the heart and then passes into the pulmonary artery.

In addition to the pressures in the heart and lungs, other tests may be done during the right heart cath to further determine the health of the patient. For example, vasodilators may be given to determine the patient's response.

The most common indications for the right heart cath include assisting in the diagnosis and/or management of[1,2]:

1. Heart failure
2. Pulmonary Hypertension
3. Shock
4. Cardiomyopathy
5. Congenital heart disease
6. Valvular heat disease
7. Pre or post heart transplant assessment

100.2 Quality Control

Quality Control (QC) is the periodic testing of a system to verify that it meets specifications. For example, all machines used for the right heart cath procedures should be regularly calibrated per manufacturer's instructions to ensure proper function.

All personnel performing QC checks should be familiar with all procedures to ensure that no technique errors are made. All QC testing data should be saved per the study site's normal protocol.

100.3 Personnel Qualifications

a. All persons performing the right heart catheterizations will be licensed medical practitioners in the state where the procedure is taking place.

b. Residents or fellows will be supervised by an attending physician who will be present during the entirety of the procedure.

c. All persons performing the right heart catheterizations will be trained in the specific study procedures by the data coordinating center (DCC) via webinar instruction.

100.4 Site Certification for the PVDOMICS Study

Before right heart catheterizations may be performed on study participants, each site will be required to complete the following list of requirements:

1. Review and become familiar with this MOP and study all procedures
2. Establish a primary contact person at their site who will be responsible for communication with and transmission of data to the DCC.
    a. This individual should ensure that they have completed Form 10 (Study Personnel Form) prior to transmitting any data.
3. Obtain training on the study protocol.
4. Send two example files following the protocol described in Manual of Operations Chapter 101 (Right Heart Catheterization Transmission). These files will be reviewed by the DCC Cardiovascular Physiology Core (CPC) for quality and readability.
5. Receive approval from the DCC to proceed with testing of participants.

100.5 DCC Over-read Procedure

Each right heart catheterization report sent to the DCC will be reviewed by a cardiology fellow and a cardiology staff member to verify data quality and reliability.

100.6 Equipment and Supplies

1. Pulmonary Artery (Swan-Ganz) catheter
    a. Size is at least 6F
2. Monitor, transducer, and pressure tubing
3. ECG cart & supplies
    a. Must be able to capture ECG waveform during each pressure measurement
4. Pulse oximeter
5. Blood pressure cuffs (assorted sizes)
6. Skin prep (e.g. 2% chlorhexidine)

7. Local anesthesia (e.g. 2% lidocaine solution)
8. Sterile supplies (for staff and participant)
    a. gown, gloves, hat, and mask
    b. drape for participant
    c. flush for catheter
    d. ultrasound probe cover and gel
9. Introducer sheath and needle
    a. Sheath size used should be at least one French size larger than the size of the PA catheter to enable simultaneous RA measurements at the side port of the sheath.
10. Resuscitation cart
    a. Airway management equipment
    b. Defibrillator
    c. Airway suction apparatus, tubing, and disposable ends
    d. Emergency medications (e.g. epinephrine, lidocaine, and nitroglycerine)
11. Supplemental O_2 equipment and delivery systems

100.7 Participant Contraindications and Safety

The contraindications for performing the right heart cath include those below. However, this list should not replace good clinical judgment. Any questions regarding exercise eligibility should be brought to the attention of the site principal investigator.

1. Absolute Contraindications[3]
    a. Infection at the insertion site
    b. Presence of a right ventricular assist device or total artificial heart
    c. Inability to provide consent
2. Relative Contraindications
    a. Coagulopathy (INR > 3.0)
    b. Thrombocytopenia (< 50,000)
    c. Electrolyte imbalances/disturbances
    d. Acid-base disturbance
    e. Other conditions that may make passage of the swan difficult (e.g. tricuspid valve prosthesis or vegetation)

100.8 Pre-Test Instructions for the Participant

1. Participant instructions:
    a. Loose-fitting, wrinkle resistant and comfortable clothing is recommended for the participant's comfort.
    b. The participant should abstain from eating for at least 6 hours prior to the test or as required by the study site's normal catheterization protocol.
    c. Anticoagulant medications (warfarin, NOACs, Lovenox, heparin, DTIs) should be managed prior to the right heart cath by the performing physician. This management will include determining acceptable INR values for each participant and deciding whether or not anticoagulant medications will be withheld prior to the procedure. However:
        i. Participants must be off of heparin for *at least 30 minutes* prior to procedure.
        ii. Participants must be off of low molecular weight heparin for *at least 8 hours* prior to the procedure.

        Other medications (diuretics, diabetic medications) should also be held or continued at the discretion of the site PI or performing physician.
    d. For participants who receive sedation during the procedure, a responsible adult must be available to drive the participant home following the procedure unless otherwise stipulated by the study site.
2. Obtain consent for the right heart catheterization procedure.
    a. Explain the procedure and answer the participant's questions before the test.
    b. If the participant will be sedated, the consent process must be done prior to any sedation.

100.9 Participant Assessment and History

1. The participant's medical history, clinical diagnosis, and reason for the test should be reviewed by the performing physician or designated trained professional. The review should include the following:
    a. Current medications (e.g., aspirin, medications for control of blood pressure, beta-blockers, etc.) and time of last dose.
        i. This may already have been noted for a prior study procedure. Verify that the information is still correct.
    b. Fasting status. Participants should be fasting for the omics blood draws associated with the right heart catheterization.

c. Pulmonary function tests, blood gas data, blood chemistry results, echocardiogram, baseline ECG, etc.

d. Current symptoms including chest pain, discomfort, edema, or wheezing.

e. Any other results required by the study site's normal catheterization protocol.

2. If there is a language barrier an interpreter will be used as per the study site's normal protocol.
3. Ask each participant if they complied with the preparation procedures.
    a. Record the time of the participant's last meal.
    b. Record if heparin/low-molecular weight heparin was withheld as instructed.

100.10 PVDOMICS RHC Procedure Overview

1. The participant should be in the same position for each set of hemodynamic measurements at each study time point. Participants will be in a supine position for resting right heart catheterization measurements.
2. Exclude participants on any positive pressure ventilation (CPAP, BiPAP or ventilator) during the procedure.
3. Per protocol of the study site, participants will have continuous monitoring of their heart rate, EKG, blood pressure (noninvasive cuff and/or arterial line at some sites), and pulse oximetry.
4. Venous access will be obtained via the internal jugular vein, femoral vein, or antecubital vein.
    a. The right internal jugular vein is the preferred access as this will easily allow venous blood to be sampled from the superior vena cava via the large-bore side-port of the introducer, which will decrease the risk of "shearing" of the blood sample.
    b. Femoral vein access is the <u>least</u> preferred option.
    c. The pulmonary artery catheter size should be <u>at least 6F</u> to prevent shearing of blood samples.
    d. The participant will be prepped and draped in a sterile fashion.
    e. Use of moderate conscious sedation will be at the discretion of the study site and per their protocol.
    f. The area of venous access will be anesthetized with local anesthetic.
    g. The introducer will be placed using the modified Seldinger's technique.
    h. The pulmonary artery catheter will be placed through the introducer, the catheter will be oriented so that its curve facilitates passage through the cardiac chambers, and the catheter will be advanced through the introducer while the pressure at its tip is transduced.

i. Fluoroscopy will be used for insertion of catheter.

5. The operator must have an unobstructed view of the hemodynamic monitor during the entire procedure.
6. The balloon should be fully inflated whenever the catheter is advanced and completely deflated whenever the catheter is withdrawn.
7. Once the catheter tip has reached the pulmonary artery (PA), it will be advanced until the pulmonary capillary wedge pressure (PCWP) is identified by a decrease in the pressure combined with a change in the waveform.
8. The following pressures will be measured during the study procedures:
    a. Right atrium (RA) pressure
    b. Right ventricle (RV) pressure (systolic and end-diastolic)
        i. Measured during the resting RHC only
    c. Pulmonary capillary wedge pressure (PCWP)
    d. Pulmonary artery (PA) pressure (systolic and diastolic)
9. The following saturations will be measured during the resting RHC only, while the participant is breathing spontaneously:
    a. SVC oxygen saturation (SVC sat)
    b. RA oxygen saturation (RA sat)
    c. PA oxygen saturations (PA sat)
    d. PCWP oxygen saturations (PCWP sat)
10. Thermodilution cardiac output (TDCO) will measured in triplicate during all study procedures.
    a. If there is >10% variability between measurements additional measurements should be taken until three (3) are in agreement. The three in agreement will then be averaged.
11. The following blood samples will be obtained during the resting RHC per the blood protocol. All blood samples must reach the lab within 1 hour of the draw time.
    a. Venous sample from the superior vena cava (*before* RHC) (27.5mL) The venous "OMICS" blood sample should be drawn from the side-port of the introducer if the internal jugular is accessed and the PA catheter advanced into the SVC in the event of femoral or antecubital access.
    b. Systemic Arterial (optional, *before* RHC) (6.5mL)
    c. Pulmonary Capillary (Wedge) (6.5mL)

d. Pulmonary Arterial (Mix) (6.5mL)

100.11 Order of Procedures

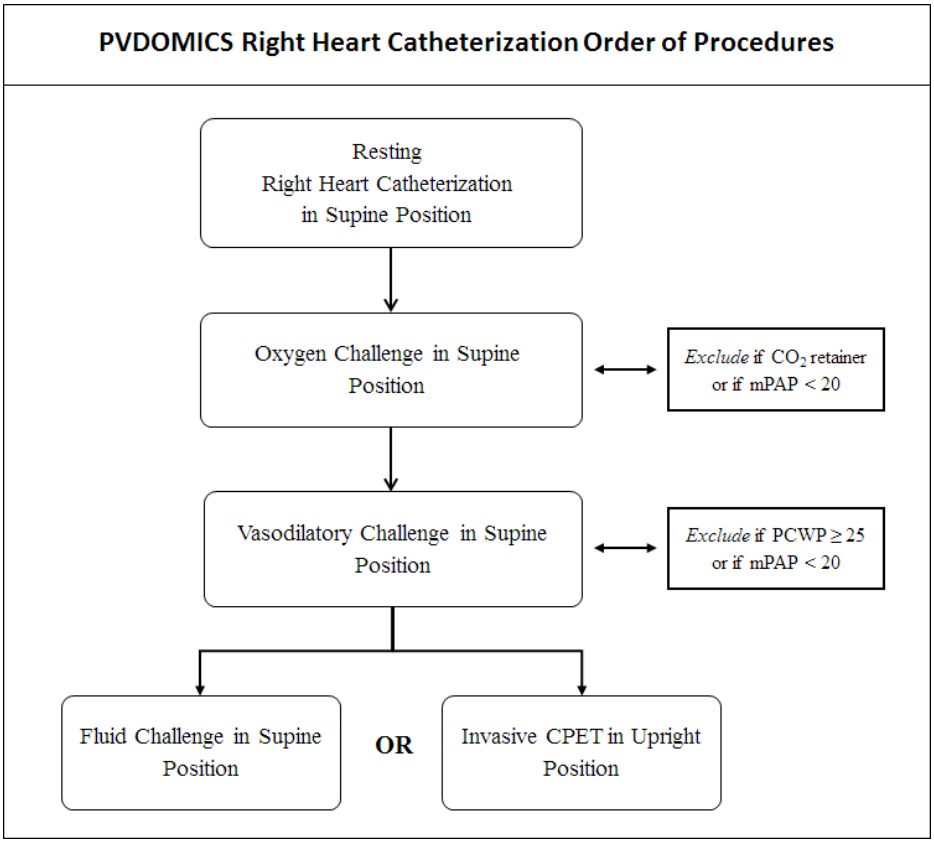
1. All participants, excluding normal controls, will undergo right heart catheterization in the supine position at rest.[1]
    a. All pressures and cardiac outputs as described in section 100.13 "Individual measurements" below will be measured.
2. Participants will then receive an oxygen challenge with 100% oxygen by face mask for 5 minutes. CO_2 retainers (i.e. pH < 7.32 and pCO_2 > 50) and those with mPAP < 20 mmHg will be excluded from the oxygen challenge unless, in the judgment of the site PI, the test can be performed safely.
    a. Remeasure all pressures, saturations and cardiac outputs as described in section 100.13 "Individual measurements" below.
3. Participants with PCWP < 25 mmHg will then undergo a vasodilator challenge. Participants will be excluded from the vasodilator challenge if their PCWP ≥ 25 mmHg or if their mPAP < 20 mmHg.
    a. Continue 100% oxygen through face mask. Oxygen should not be stopped between the oxygen challenge and the vasodilator challenge.
    b. Add inhaled nitric oxide (NO) at 40 ppm through face mask along with 100% oxygen for 5 minutes.
    c. Remeasure all pressures, saturations and cardiac outputs as described in section 100.13 "Individual measurements" below.
4. Participants will then undergo either an invasive CPET (iCPET) or a fluid challenge.
    a. Participants will be excluded from the fluid challenge if they have a baseline RAP ≥ 15 or a PCWP ≥ 18 mmHg.
    b. For participants undergoing invasive CPET:
        i. iCPET will be performed using the metabolic cart at each site per their protocol.
        ii. Participants with femoral access cannot undergo invasive CPET.
        iii. Remeasure all pressures and cardiac outputs as described below after settling on ergometer.
        iv. Variables and data for CPET must also be measured and recorded. (Reference: Manual of Operations Chapter 111)

[1] Note: RHC should be completed before angiography if a left heart catheterization is to be done at the same time.

c. For participants undergoing the fluid challenge:

i. Give 500 ml of 0.9% room temperature saline over 10 minutes through the side arm of the introducer. Infusion can begin immediately following iNO challenge with no waiting period.

ii. Remeasure all pressures, saturations and cardiac outputs as described in section 100.13 "Individual measurements" below.



100.12 Operator Measurements and Recording Data

1. All pressure tracings must be accompanied by a simultaneous ECG tracing (directly above or below the pressure tracing) which is used for timing and analysis of waveforms.
2. All pressure tracing recordings or "snapshots" should contain at least three (3) entire respiratory cycles.
    a. If the recordings contain premature ventricular contractions (PVCs), the tracings should be re-recorded unless PVC burden is too high to allow for a PVC-free recording.

b. Measurements will be recorded by sites and paper waveforms will be sent to the study coordinator for each pressure measurement.

3. Hemodynamic measurements during the resting RHC should be taken twice, once at end-expiration while the participant is breathing spontaneously and once during an end-expiratory breath hold. The resting RHC is the only time an end-expiratory breath hold will be used.
    a. Patients will be coached on the proper way to perform a breath hold. They will be asked to inspire and then relax as they expire. Care must be taken to avoid Valsalva. A suggested coaching script is attached (Appendix 3).
4. Hemodynamic measurements during the oxygen challenge, vasodilatory challenge, fluid challenge and/or iCPET will only be measured while the participant is breathing spontaneously.
5. Digitized or computer generated "mean line" should be on and recorded with all tracings.
    a. The mean line should always be recorded.
    b. If there is disagreement between the mean line and the interpretation by the reader, the human reader's interpretation will take precedence.
        i. If this is the case, saved images and paper waveforms sent to the study coordinator or the DCC should be representative of the human reader's interpretation.
6. Prior to recording any measurements:
    a. Ensure that all recording equipment has been calibrated as per manufacturer's instructions.
    b. Check the pressure transducer level to ensure it is at the level of the right atrium.
    c. "Zero" the transducer. To do this:
        i. The stopcock closest to the transducer is closed to the patient.
        ii. Remove the sterile protective cap from the stopcock port, exposing the hemodynamic monitoring system to air.
        iii. The monitor's zero function key is activated to offset pressure in the transducer, setting the pressure to zero.
        iv. Open the stopcock to the patient and replace the sterile cap on the stopcock port.
        v. Zeroing ensures that when the transducer stopcock is open to the patient and closed to air, the only pressure on the transducer will be from the vessel/heart chamber being monitored.
        vi. The transducer should be "zeroed" before each condition.

1. For participants undergoing an invasive CPET, the following procedure will be used for calibration. The PA and PCWP are recorded under fluoroscopy to ensure proper location of the catheter tip. The patient is then moved to the upright position, and the pressure calibrator is opened to ambient air ("zeroed"), calibrated, and leveled to the fourth intercostal space at the midaxillary line, approximately 5 cm below the angle of Louis or 3 finger breadths below the axilla. (see Manual of Operations Chapter 111 (iCPET))

7. Do not record any data while the patient is restless, talking, or coughing.
8. If pressure tracings appear dampened (for example, no dicrotic notch is seen on the PA pressure tracing), re-flush the catheter and ensure that there are no air bubbles in the pressure tubing.
9. If excessive catheter whip or "ringing" is noticed, attempt to reposition catheter to a less turbulent area. Introducing a small amount of blood into the line may be helpful although care must be taken to not overdamp the signal.

100.13 Individual measurements

1. Venous "OMICS" Blood Draw
    a. Make sure the participant has been resting by laying down on the cath lab table for 10 minutes before drawing the blood. During this resting period, patients can be prepped and draped, and the sheath can be placed.
    b. Draw the venous blood sample from the SVC. The preferred site of access for right heart catheterization is the right internal jugular vein. In this position, the venous "OMICS" blood sample should be drawn from the side-port of the introducer, which lies in the superior vena cava. Using the large-bore side-port of the introducer decreases the risk of "shearing" of the blood sample, which is why this site is preferred. There are differences between femoral, inferior vena cava and superior vena cava blood from an "OMIC" perspective. Therefore, if a femoral or antecubital approach is being used, the PA catheter will need to be advanced into the SVC for the "OMICS" venous blood draw before advancing into the pulmonary artery.
    c. Draw back 3mL of blood using a sterile syringe and discard the sample. Then, using a second sterile syringe, draw 27.5mL of blood for "omics" analysis.
    d. Transfer the blood from the sterile syringe to the appropriate blood collection tubes using a blood transfer device.
        i. We suggest having a study coordinator or other team member designated to transfer the blood from the syringe to the appropriate vacutainers and then transport the blood samples to the lab.

ii. Fill the blood collection tubes in the following order, taking care to note which tubes go on ice and which are kept at room temperature.

Order of Right Heart Catheterization Venous Blood:

Order	Blood Type	Color	Additive	Volume	Core	Transport to Lab
1	Resting Venous	Red *PAX gene*®	RNA Preservative Solution	2.5 mL	Genomic	Room Temperature
2	Resting Venous	Lavender	EDTA	10 mL	OMICS	Wet Ice
3	Resting Venous	Lavender	EDTA	10 mL	OMICS	Wet Ice
4	Resting Venous	Gold	SST	5 mL	Bank	Wet Ice

2. Optional Arterial Blood Draw for Arterial Blood Gas (ABG) Analysis
    a. At the same time as the venous blood draw, after 10 minutes of rest and before any other procedures or measurements are performed, arterial blood may be drawn for an ABG. This is not required.
    b. If arterial blood for ABG analysis was already obtained during PFT testing it should not be repeated during the RHC.
    c. Draw 1mL of blood for ABG in a heparinized syringe and then 6.5mL of blood for "omics" analysis in a non-heparinized syringe.
        i. ABG analysis should be done at the local site and the values recorded on the appropriate PVDOMICS form.
        ii. The rest of the blood should be transferred to the appropriate blood collection tubes using a blood transfer device and delivered to the lab with the venous blood for processing and shipping to the Biorepository Core.
            1. Fill the blood collection tubes in the following order, taking care to note which tubes go on ice and which are kept at room temperature.

Order of Systemic Arterial Blood Collection:

Order	Blood Type	Color	Additive	Volume	Core	Transport to Lab
1	Resting Systemic Arterial	Lavender	EDTA	4 mL	OMICS	Wet Ice
2	Resting Systemic Arterial	Red *PAX gene*®	RNA Preservative Solution	2.5 mL	Genomic	Room Temperature

3. Superior Vena Cava Oxygen Saturation (SVC sat)

a. During the baseline hemodynamic measures, all participants should have at least one SVC and at least one mid-RA oxygen saturation measured to exclude significant intracardiac shunting.
    i. SVC sat can be obtained from either the IJ sheath or from the right atrium.
    ii. Draw 1mL of blood for a SVC sat.
        1. If your site requires more than 1mL for a SVC sat, draw the minimum amount of blood allowed by your site's lab for this analysis.

4. Right Atrial Pressure Tracing (RAP)
    a. Record mean pressure (defined as the mean of the a wave).
        i. If the participant is in atrial fibrillation, use mid c wave or the Z point (point which corresponds to the end of the QRS).
    b. Record peak a wave and peak v wave.
    c. Apart from baseline measurements during the resting RHC, all subsequent RAP measurements (i.e. those measured during the challenges) will be simultaneously performed via transduced pressures from side port of venous sheath. Therefore, direct calibration between side port RAP/CVP pressure and PA catheter derived RAP should be made at baseline before advancing the catheter.

5. Right Ventricular Pressure (RVP) Tracing
    a. Record peak RV systolic pressure at end-expiration.
    b. Record RVEDP (pressure just prior to rise of the RV pressure).
    c. RV pressures are only recorded during the resting RHC (baseline measurements).

6. Pulmonary Capillary Wedge Pressure (PCWP) Tracing
    a. After RV pressure tracing, catheter is advanced with balloon inflated into the pulmonary artery and immediately out to the PCWP position.
    b. After PCWP recording, a pulmonary capillary wedge oxygen saturation (PCWP sat) should be measured.
        i. While the balloon is inflated, and from the distal port of the PA catheter, slowly draw back at least 3mL of blood until the blood sample turns bright red. Discard this sample.
        ii. Draw 1mL of blood for a PCWP sat.
            1. If your site requires more than 1mL for a PCWP sat, draw the minimum amount of blood allowed by your site's lab for this analysis.

iii. PCWP sat should be at least 90% (assuming the arterial saturation measured by pulse oximetry is at least 90%). If PCWP saturation is < 90%, reposition the catheter, re-record PCWP tracing, and re-draw PCWP saturation.

1. After two attempts, if PCWP sat is still < 90% but operator deems fluoroscopy and waveforms are sufficient to confirm wedge, you may proceed without obtaining PCWP sat ≥ 90%.
2. If PCWP saturation cannot be obtained after 3 attempts, please note "PCWP sat is unable to be obtained" and continue.

iv. Deflate balloon and flush catheter.

c. Record mean pressure (defined as the mean of the a wave).

i. If the participant is in atrial fibrillation, use mid c wave or the Z point (point that corresponds to the end of the QRS).

d. Record peak a wave and peak v wave.

7. Pulmonary Capillary Wedge "omics" Blood Draw

a. Blood draw must be done after all pressure measurements have been completed.

b. If PCWP saturation remained < 90% after 3 attempts (as described above), do <u>not</u> draw the PCW "omics" blood.

c. Draw back 3mL of blood using a sterile syringe and discard the sample. Then, using a second sterile syringe, draw 6.5mL of blood for "omics" analysis as per blood protocol.

i. If at any time during the blood draw the participant becomes intolerant (e.g. coughing), the blood draw can be stopped. In this case the full blood sample will not be collected.

d. Transfer the blood from the sterile syringe to the appropriate blood collection tubes using a blood transfer device. Fill the blood collection tubes in the order noted in the following table, taking care to note which tubes go on ice and which are kept at room temperature.

Order of Pulmonary Capillary (Wedge) Blood Collection:

Order	Blood Type	Color	Additive	Volume	Core	Transport to Lab
1	Pulmonary Capillary "Rest Wedge"	**Lavender**	EDTA	4 mL	OMICS	Wet Ice
2	Pulmonary Capillary "Rest Wedge"	**Red** *PAX gene*®	RNA Preservative Solution	2.5 mL	Genomic	Room Temperature

8. Diastolic Pressure Gradient (DPG)
    a. Measure pulling back from PCWP to PA tracing at end-expiration.

9. Pulmonary Artery Pressure (PAP) Tracing and Saturation
    a. After PCWP measurement, deflate balloon and pull back catheter approximately 1 cm. Record PAP tracing.
    b. Record PA systolic pressure and PA diastolic pressure, measured at end-expiration
    c. Record mean PA pressure (use the AUC provided by the computer).
        i. The mean PA pressure will be verified by the core lab using the equation: mPAP= 1/3(PASP) + 2/3(PADP).
    d. After PAP tracing is recorded, pull back and discard 3mL of blood from the distal port. Then draw 1mL of blood, analyze, and record saturation.
        i. If your site requires more than 1mL for the PA sat, draw the minimum amount of blood allowed by your site's lab for this analysis.

10. Pulmonary Artery (PA) "omics" Blood Draw
    a. Blood draw must be done after all pressure measurements have been completed.
    b. Draw back 3mL of blood using a sterile syringe and discard the sample. Then, using a second sterile syringe, draw 6.5mL of blood for "omics" analysis as per blood protocol.
        i. Note that if the catheter is not flushed between drawing the blood for the PA sat and drawing the "omics" blood it is not necessary to draw back the 3mL of waste prior to the "omics" draw. If the catheter *is* flushed after drawing the PA sat then 3mL of blood must be drawn and discarded before the "omics" blood is collected.
    c. Transfer the blood from the sterile syringe to the appropriate blood collection tubes using a blood transfer device. Fill the blood collection tubes in the order noted in the following table, taking care to note which tubes go on ice and which are kept at room temperature.

Order of Pulmonary Arterial (Mix) Blood Collection:

Order	Blood Type	Color	Additive	Volume	Core	Transport to Lab
1	Pulmonary Artery "Rest Mix"	**Lavender**	EDTA	4 mL	OMICS	Wet Ice
2	Pulmonary Artery "Rest Mix"	**Red** *PAX gene*®	RNA Preservative Solution	2.5 mL	Genomic	Room Temperature

11. Cardiac Output

    a. All sites will obtain thermodilution cardiac output (TDCO). A direct Fick cardiac output will also be obtained if the site is able to do so. Fick cardiac output cannot be obtained while the participant is receiving supplemental oxygen.

    b. Thermodilution Cardiac Output (TDCO)

        i. Prior to each participant enrollment, software should be checked to ensure proper information is input into computer system for proper calibration of cardiac output including type and size of pulmonary artery catheter, size of saline bolus (i.e. 10cc), temperature of saline, computational constant, etc.

        ii. TDCO should be made in triplicate and the final result will be the average of three measurements.

        iii. If individual measures vary more than 10% from each other, additional measurements should be taken until three (3) are in agreement. The three in agreement will be used to determine the average.

        iv. TDCO measurements can be skipped in the presence of known systemic to pulmonary shunt with Qp/QS >1.5 as TDCO may not be reliable if there is a large shunt.

    c. Direct Fick Cardiac output

        i. VO_2 will be obtained using the metabolic cart. Arterial saturation will be either directly measured from an arterial line if available or pulse oximetry will be used as the arterial saturation.

        ii. See below in “Calculations” section for direct Fick calculation.

100.14 Recording Results:

1. Results will be recorded on the paper copy of Form 280 (Right Heart Catheterization) and will then be entered into the electronic database by the study coordinator.
2. File the paper copy of the participant’s results in their study file maintained on site.

100.15 Procedure Notes:

1. Record thorough notes of the procedure including:
    a. Medications taken prior to procedure

b. All procedure notes required for clinical documentation

2. Note any results that could not be obtained.
    a. Include the reason the results could not be obtained. Be specific.
    b. File a protocol deviation.
3. Make note of any other protocol deviations or unexpected findings.

100.16 Calculations

In general, calculations will be performed by a computerized data acquisition system or database software and will not need to be calculated by the technician. However, if the values below are not automatically calculated by either the system software or the database, manual calculations will be performed according to the equations below from measurements obtained during the RHC.

1. Body Surface Area (BSA)

$$\text{BSA} = \frac{\sqrt{\text{height (cm) x weight (kg)}}}{60}$$

2. Direct Fick Cardiac Output

$$\text{Fick (L/min)} = \frac{\text{measured VO2 (ml/min)}}{(\text{Art O2 sat} - \text{MVO2}) \text{ x } 1.34 \text{ x Hb x } 10)}$$

3. Stroke Volume (SV)
    a. Use direct Fick cardiac output if available, otherwise use thermodilution cardiac output. Note which is used.

$$\text{SV} = \frac{\text{Cardiac Output (CO)}}{\text{Heart Rate (HR)}}$$

4. Stroke Volume / Pulmonary Artery Pulse Pressure (SV/PP)

$$\frac{\text{SV}}{\text{PP}} = \frac{\text{SV}}{(\text{PASP} - \text{PADP})}$$

5. Pulmonary Vascular Resistance (PVR)
    a. Use direct Fick cardiac output if available, otherwise use thermodilution cardiac output. Note which is used.

$$\text{PVR} = \frac{(\text{mean PAP} - \text{mean PCWP})}{\text{CO}}$$

6. Systemic Vascular Resistance (SVR)
    a. Use direct Fick cardiac output if available, otherwise use thermodilution cardiac output. Note which is used.

$$\text{SVR} = \frac{(\text{MAP} - \text{mean RAP})}{\text{CO}}$$

7. Right Ventricular Stroke Work Index (RVSWI)

$$\text{RVSWI} = \frac{(\text{mean PAP} - \text{mean RAP})}{(\text{SV/BSA})}$$

8. Shunt Fraction (Qp/Qs)
    a. Art O_2 sat may be obtained from an arterial line, or the pulse oximetry O_2 saturation may be used instead.

$$\frac{\text{Qp}}{\text{Qs}} = \frac{(\text{Art O2 sat} - \text{SVC sat})}{(\text{Art O2 sat} - \text{PA sat})}$$

9. Mean PA Pressure (mPAP)
    a. This formula will be utilized by the PVDOMICS database to calculate mean PA.

$$\text{mPAP} = \frac{(\text{PASP} + 2\text{PADP})}{3}$$

100.17 Terms and Definitions

1.	ABG	Arterial Blood Gases
2.	Art O_2 sat	Arterial oxygen saturation
3.	BSA	Body Surface Area
4.	DBP	Diastolic Blood Pressure
5.	DPG	Diastolic pressure gradient
6.	Fick CI	Direct Fick Cardiac Index
7.	Fick CO	Direct Fick Cardiac Output
8.	FIO_2	Fraction of inspired Oxygen
9.	Hb	Hemoglobin
10.	HR	Heart Rate
11.	MAP	Mean Blood Pressure
12.	mPAP	Mean pulmonary artery pressure
13.	Mean PCWP	Mean Pulmonary capillary wedge pressure
14.	Mean RAP	Mean Right Atrial Pressure
15.	O_2 sat	Oxygen Saturation
16.	PA O2	Pulmonary artery saturation
17.	PADP	Pulmonary artery diastolic pressure
18.	PASP	Pulmonary artery systolic pressure
19.	PCWP a	Pulmonary capillary wedge pressure, a wave
20.	PCWP sat	Pulmonary capillary wedge saturation
21.	PCWP v	Pulmonary capillary wedge pressure, v wave
22.	PVR	Pulmonary vascular resistance
23.	Qp/Qs	Shunt fraction
24.	RA a	Right Atrial a wave
25.	RA v	Right Atrial v wave
26.	RVEDP	Right ventricular end-diastolic pressure

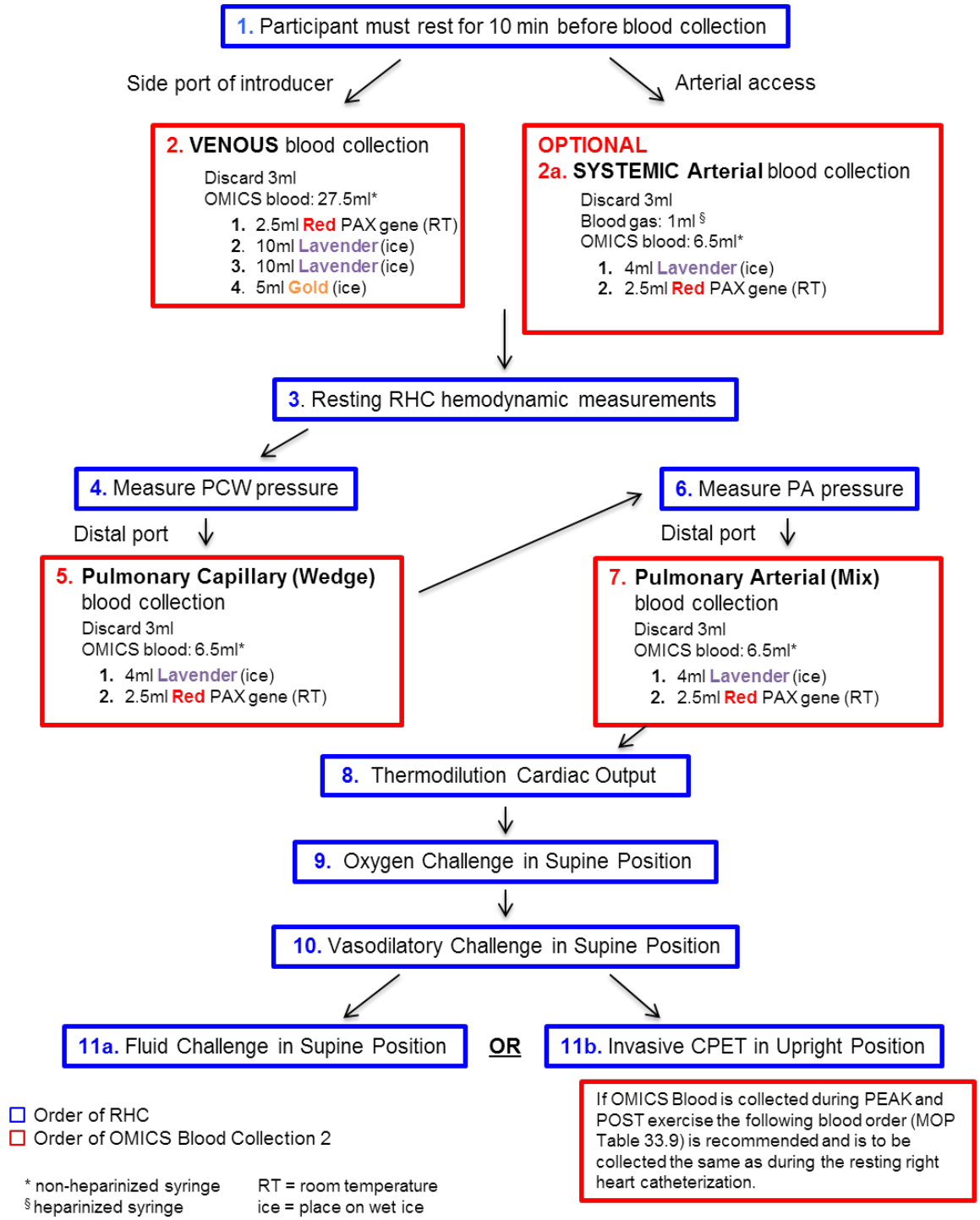
27. RVSP — Right ventricular systolic pressure
28. RVSWI — Right ventricular stroke work index
29. SBP — Systolic Blood Pressure
30. SV — Stroke Volume
31. SV/PP — Stroke volume / Pulmonary Artery Pulse Pressure
32. SVC sat — Superior vena cava saturation
33. SVR — Systemic vascular resistance
34. TD CI — Thermodilution CI
35. TD CO — Thermodilution CO
36. VO_2 — Oxygen Consumption

100.18 References:

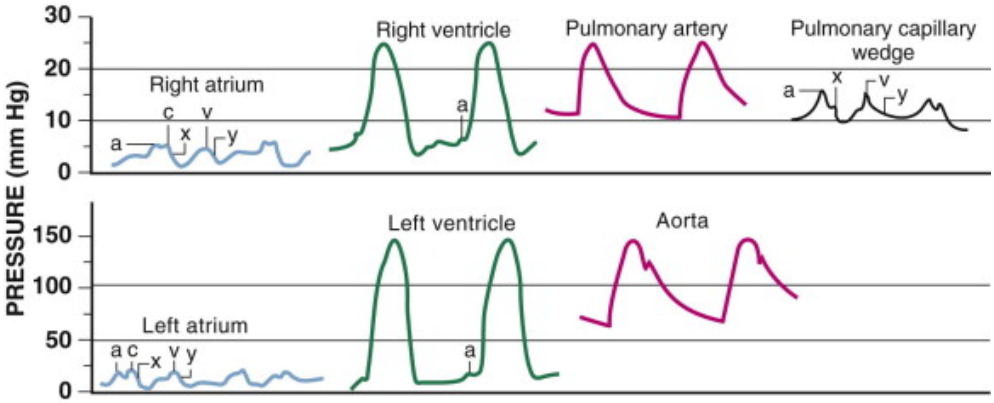
1. *Right Heart Catheterization*. Retrieved 8/25/2015, from Johns Hopkins Medicine Health Library: https://www.hopkinsmedicine.org/healthlibrary/test_procedures/cardiovascular/right_heart_catheterization_135,40/
2. Chen, M. A. (2014). *Swan-Ganz - right heart catheterization*. Retrieved 8/25/2015, from NIH: Medical Encyclopedia: https://www.nlm.nih.gov/medlineplus/ency/article/003870.htm
3. Weinhouse, G. L. (2015, August 20). *Pulmonary artery catheterization: Indications, contraindications, and complications in adults*. Retrieved August 25, 2015, from Up To Date: http://www.uptodate.com/contents/pulmonary-artery-catheterization-indications-contraindications-and-complications-in-adults

Appendices appear on the following pages.

100.A.1 Appendix 1 – RHC Blood Draw Flow Sheet



100.A.2 Appendix 2 – Example Pressure Waves



from Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Davidson, CJ, Bonow, RO, Published Jan 1, 2015, Pages 364-91, Figure 19-10.

100.A.3 Appendix 3 – End-Expiratory Hold Coaching Script

During the resting RHC, hemodynamic measurements must be measured during an end-expiratory breath hold. Here is a suggested script for coaching participants on the proper way to perform an end-expiratory breath hold:

Explain to the participant: "In order to obtain accurate measurements, we will ask that you pause your breathing for short periods of time during the procedure. We would like for you to take a breath in, let it out, and then pause your breathing while we do the measurement. Please do this without bearing down or tightening up the stomach muscles."

Have the participant practice the procedure: "Please try this now: Take a breath in, let it out, and pause your breathing."

Take the measurement: "Again: Take a breath in, let it out, and pause your breathing." (Take measurement) "Breath normally now."

Do <u>not</u> use an end-expiratory hold for measurements taken during the challenges (oxygen challenge, vasodilatory challenge, fluid challenge, or invasive CPET).

Chapter 101. Right Heart Catheterization (RHC) Data Transmission

This chapter is intended to serve as both a training and a reference document for persons who transmit the right heart catheterization data to the Cardiovascular Physiology Core (CPC) at the Data Coordinating Center (DCC). This will aid in obtaining accurate, good-quality test results.

101.1 Recording Results:

1. Results are recorded on a paper copy of Form 280-Clinical Center Right Heart Cath Results and then manually entered into the PVDOMICS database by the study coordinator. The paper version of Form 280 will be considered the source document.
    a. If centers create their own worksheet for recording study data, this worksheet may be used as the source document instead, meaning that clinical centers will not be required to fill out a paper copy of Form 280.
        i. Note: If centers use their own worksheet for recording data, it is recommended that results not be recopied onto Form 280 for 'neatness'. Data transcription/transposition can occur during copying.
    b. All results must be entered into the PVDOMICS database regardless of paper document used.
2. File the paper copy of the participant's results (source document) in the study file maintained locally.

101.2 Procedure Notes:

1. Record thorough notes of the procedure including:
    a. Medications taken prior to procedure
    b. Condition of participant (e.g. had illness/cold a few days ago)
    c. All procedure notes required for clinical documentation
2. Note any results that could not be obtained.
    a. Include the reason the results could not be obtained. Be specific.
    b. File a protocol deviation with your center's IRB as appropriate per your center's IRB policies.
    c. Make note of any other protocol deviations or unexpected findings at the bottom of the paper copy of Form 280 (Clinical Center Right Heart Catheterization Results Form).

101.3 RHC Data Transmission to Data Coordinating Center's Cardiac Physiology Core

1. What to Transmit
    a. Documentation of hemodynamic measurements for each condition (resting, oxygen challenge, vasodilatory challenge, and oxygen challenge or iCPET) at each position (RA, RV (resting only), PCWP and PA).
    b. One copy of the most representative wave form for each pressure measurement under each

condition (resting, oxygen challenge, vasodilatory challenge, and fluid challenge or iCPET)

i. Images must capture 3 consecutive breath cycles (may be split across pages)

ii. Images must include ECG tracing at the top (minimum of 3 leads)

2. De-Identify All Records
    a. All identifying information, other than the PVDOMICS specific study identifications, must be removed/redacted before transmitting the documents to the Cardiovascular Physiology Core at the DCC.
    b. Make sure **each page** has the correct PVDOMICS study identification information (PVDOMICS ID, alphacode, and date of testing) on it.
    c. Affixing labels with the PVDOMICS identifying information is acceptable.
        i. Example label: RHC_987654_AC_12102016
3. Naming and Saving Files
    a. If possible, save study results directly as a **PDF** file.
    b. If results cannot be directly saved as a PDF document:
        i. Print out results
        ii. Scan results onto a desktop computer
        iii. Save in PDF format
    c. Name the file according to the following convention:
        i. RHC_[*PVDOMICS 6 digit ID number*]_[*two letter alphacode*]_[*date in mmddyyyy format*].pdf
        ii. For example: RHC_987654_AC_12102016.pdf
        iii. Do not use any special characters in the file name.
4. Transmit Data to Cardiovascular Physiology Core (CPC) at the DCC
    a. Files will be transferred electronically to the Cardiovascular Physiology. This will allow the transfer of files in a secure and traceable fashion.
    b. Upload Right Heart Catheterization PDF file and send to CPC via secure data transfer protocol (see MOP Chapter 6, Appendix 1)

Following transfer, data files will be stored on a secure server that is protected within the firewall of Cleveland Clinic. The Cardiovascular Physiology Core will review each file received to verify that all data is complete and accurate. DCC programmers have internal protocols that are used to move and securely store PVDOMICS study data.

Chapter 110. Clinical Center Cardiopulmonary Exercise Test (CPET) – Non-Invasive

This manual is intended to serve as a training and a reference document for persons who perform the CPET for the PVDOMICS Study using standardized procedures and techniques. This will aid in obtaining accurate test results and a safe testing environment.

110.1 Introduction to CPET

The cardiopulmonary exercise test (CPET) involves the assessment of cardio-pulmonary function during incremental exercise and combines the routine measurements of the electrocardiogram (ECG), blood pressure and power output with the analysis of exhaled gases.[1,2] It is useful in a wide spectrum of clinical settings and helpful in clinical decision making. In clinical practice, CPET is considered when specific questions persist after consideration of basic clinical data (e.g., physical examination, chest radiograph, pulmonary function tests and ECG).

Cellular respiration involves the oxidation of carbohydrates, fats and glycogen stores using both aerobic and anaerobic metabolic pathways.[3,4] The volume of oxygen (O_2) taken up each minute by the muscles for the oxidative process (VO_2), increases during exercise proportionate to the work rate that is being performed.[5] In order to satisfy the increased metabolic needs of the exercising muscle, the lungs, heart, pulmonary circulation and peripheral circulation must respond in a coordinated fashion appropriate to the increase in metabolic demand.[3] As exercise intensity increases, one or more of these essential systems may reach its maximal response, imposing a limitation to exercise. The assessment of maximum O_2 consumption (VO_2 max) and determining any limitations to further increases in VO_2 is an important diagnostic tool. The quantification and physiologic response of VO_2, carbon dioxide (CO_2) production (VCO_2), and the minute ventilation (V_E) and other cardiopulmonary variables measured during a CPET allows the clinician to study the response of these systems under controlled metabolic stress.

Clinically, the most common indications for the CPET include:

1. Determination of the exercise capacity
2. Determination of the cause of a cardiopulmonary limitation to exercise
3. Identification of abnormal cardiopulmonary responses to exercise
4. Exercise prescription and monitoring response to exercise for training and rehabilitation
5. Evaluation of results of therapeutic intervention
6. Pre-operative evaluation
7. Impairment/disability evaluation
8. Selection of participants for cardiac transplantation
9. Evaluating unexplained dyspnea when initial cardiopulmonary testing is nondiagnostic

110.2 Quality Control

Quality Control (QC) is the periodic testing of a system to verify that it meets specifications. It is recommended that a mechanical calibration be performed following any movement or jarring of the equipment and a biologic calibration be performed every six months. Flow calibration and gas analyzer calibration should be performed prior to each test.

Ideally, each clinical center will have two biologic standards (lab personnel), so that if one of them is ill or leaves the area the center will still have a second person available to provide physiological calibration.

A biologic standard should be a healthy volunteer who does not smoke or have a respiratory disease (including asthma).

1. Biologic standards (two healthy laboratory personnel)
    - 1.1 Obtain consent to repeated testing.
    - 1.2 Test at least once every six months or as required by the manufacturer or your clinical center's protocol. Testing once every one to two months is encouraged, but not required.[20,27,28]
    - 1.3 The biologic standards should initially perform a maximal study, then use 40% to 50% of the maximum workload as their steady-state work rate.
    - 1.4 For the steady-state tests, collect gas exchange and work intensity data on each biologic standard as 6 minutes of constant work rate is performed.
    - 1.5 If the VO_2 or VCO_2 value obtained by averaging the last 2 minutes of the 6 minute test are outside the 95% confidence limits for a historical average for a particular biologic standard, repeat the test or use another biologic standard.
    - 1.6 Take corrective action if the repeat values or other biologic standard's values are also outside the 95% confidence limits, and then repeat the test of the biologic standard to verify adequacy of the corrective procedure.
    - 1.7 Add data to the quality control database only after the system is again performing properly. Recalculate averages and standard deviations to obtain updated values for the 95% confidence limits.
    - 1.8 The time of day used to test the biologic standard should be consistent from session to session.
2. Collection of exhaled gases: utilizing appropriate valving, a 1 to 2 minute collection of exhaled gas can be obtained while a participant is in the steady state of exercise. Assessment of gas bag volume and fractional concentrations of O2 and CO2 can be used to calculate VO_2, VCO_2, and V_E. Though technically challenging, this method may be considered the gold standard validation method.[26]
3. Establish mean and SD by repeated testing and apply rules for adequate quality assurance responses.

The QC technician should be familiar with all procedures to ensure that no technique errors are made. All QC testing data should be saved per the clinical center's normal protocol and should be readily available for review at all times.

110.3 Clinical Center Certification

Before CPET studies are performed on participants, each clinical center is required to complete the following list of requirements:

1. Review and become familiar with this MOP and study procedures
2. Establish a primary and a secondary contact person at each center who will be responsible for communication with and transmission of data to the Data Coordinating Center (DCC).
3. Submit one non-invasive CPET test on a "standard normal participant". The standard participant should be a healthy adult. You may use a laboratory employees for qualification testing if you like.
    a. Prospective CPET laboratories will be evaluated based on their ability to: (1) follow a study qualification protocol, (2) generate good quality CPET data, and (3) transmit data to the core laboratory.
    b. Test results will be compared to data available on normal individuals from the core laboratory and the published literature.
4. Await feedback from the core laboratory confirming that their center has qualified prior to scheduling study participants for testing.

110.4 Contraindications and Safety

Monitored exercise testing is considered relatively safe with a reported complication rate of 0.5 to 1.0 in 10,000 tests.[20,23-25] Contraindications for performing cardiopulmonary exercising testing include those listed below. However, this list should not replace good clinical judgment. Any questions regarding exercise eligibility should be brought to the attention of the center's primary investigator.

110.4.1. Contraindications

1. Abnormal resting ECG
2. Current exercise-induced angina
3. Inability to cycle (e.g. arthritis)
4. Exertional syncope
5. Known potentially lethal exercise-induced arrhythmia (e.g., ventricular tachycardia)
6. Severe symptomatic aortic stenosis
7. Resting systolic blood pressure ≥ 200 mmHg

110.4.2 Criteria for immediately stopping the exercise test

In the vast majority of CPETs, participants should be verbally encouraged, both before and during the test, to give a maximal effort with the goal of achieving physiologic limitation. The most accepted criteria for exercise termination before symptom limitation are:

1. Chest pain suggestive of ischemia
2. Ischemic ECG changes
3. Complex ectopy or increasing ectopy with decreasing SpO_2
4. Second or third degree heart block
5. Fall in systolic blood pressure >20 mmHg from the highest value during exercise
6. Hypertension (>250 mmHg systolic; >120 mmHg diastolic)
7. Severe desaturation (SpO2 ≤ 80% when accompanied by symptoms and signs of severe hypoxemia)
8. Sudden pallor
9. Loss of coordination
10. Mental confusion
11. Dizziness or faintness
12. Signs of respiratory failure

Note that exceeding a preset heart rate is not a useful criterion for stopping exercise. In situations in which the exercise is terminated because of the criteria listed above, the participant should be observed until they are stable and their physiologic variables have returned to baseline conditions.

110.4.3 Personnel Qualifications

The director of the laboratory performing the CPET should be a physician, preferably a pulmonologist or cardiologist certified in advanced cardiovascular life support, with knowledge of exercise physiology and with training in calibration, quality control, performance, and interpretation of CPET.

The director, based on the clinical situation and clinical judgment, should determine whether a physician needs to be present during the actual test or whether it is sufficient for the physician to be physically available in the proximity of the exercise laboratory, so as to be able to respond immediately in case of emergency.

The technicians should be trained in a field related to CPET such as exercise physiology, respiratory therapy, or pulmonary function testing. The technicians must have the basic knowledge of normal and abnormal exercise responses and be certified in basic cardiac life support. They should be able to recognize an abnormal rhythm and ST depression on an

ECG. The technician must have a minimum of 3 months of experience or internship in CPET before being given full responsibility for conduct of tests, and be competent in calibrating the equipment and performing quality control procedures.

110.5 Terms and Definitions

AT	Anaerobic Threshold
AT VO_2	O_2 Uptake at the Anaerobic Threshold
ATPS	Ambient Temperature and Pressure, Saturated
BP	Blood Pressure
BTPS	Body Temperature and (ambient barometric) Pressure, Saturated
HR	Heart Rate
HRR	Heart Rate Reserve
MVV	Maximum Voluntary Ventilation
OUES	Oxygen Uptake Efficiency Slope
RER	Respiratory Exchange Ratio (VCO_2/VO_2)
VCO_2	CO_2 Output
V_D	Respiratory Dead Space
V_E	Minute Ventilation, Expired (L/min)
V_E / VCO_2	Ventilatory Equivalent for Carbon Dioxide
V_E / VO_2	Ventilatory Equivalent for Oxygen
V_I	Inspired Ventilation (L/min)
VO_2	O_2 Uptake
VO_2 / HR	O_2 Pulse
V_T	Tidal Volume

Continued on next page.

110.6 Equipment and Supplies

1. Cycle ergometer
    1.1. Mechanical or electromagnetically braked (the electronically braked ergometer is strongly preferred because of its compatibility with incremental protocols)
        1. An upright cycle ergometer is preferred. A supine bicycle is an acceptable alternative in the case of invasive CPET.
    1.2. Capable of calibration
    1.3. Handlebars and seat that adjust to height
2. ECG system
    2.1. Instrumentation should meet the specification set by the American Heart Association (AHA).[11,12]
        1. Continuous display of a minimum of 3 leads
        2. Capacity to print copy of a 12-lead ECG
3. Blood pressure
    3.1. Sphygmomanometer (cuff measurement method)
        1. Assorted cuff sizes
        2. Mercury column or calibrated Bourdon pressure gauge OR automatic blood pressure monitoring system
    3.2. Direct method using in-dwelling arterial catheter
        1. Pressure transducer
        2. Recorder
        3. Intravenous (IV) administration set and associated pressure tubing
        4. 500 mL IV bag of heparinized saline solution with 1,000 units of heparin (2 units/mL) to be put under pressure for catheter flushing apparatus.
4. Pre-heparinized (dry heparin) syringes for arterial blood gas (ABG) harvesting are preferred
5. Appropriate standard precaution (SP) attire and gloves for technicians
6. Gas analyzers
    6.1. O_2 and CO_2
    6.2. Calibration tanks for 2 points within the physiologic range
7. Flow measurement device, typically including pneumotachograph or hot-wire anemometer, directional valves, and tubing (which may be provided as part of a commercial metabolic exercise system)

8. Data-acquisition computer, monitor and keyboard

9. Resuscitation cart

    9.1. Airway management equipment

    9.2. Defibrillator

    9.3. Airway suction apparatus, tubing and disposable ends

    9.4. Emergency medications (e.g., epinephrine, lidocaine, and nitroglycerine)

10. Supplemental O_2 equipment and delivery systems

11. Pulse oximeter

    11.1. Finger and ear probes

12. Chart displaying the Borg modified ratings of perceived exertion (RPE) scale[14]

13. Other optional tests require specific equipment

    13.1. Cardiac output determination using either CO2 equilibration or foreign gas uptake techniques

    13.2. Spirometer for flow-volume curves before, during, and after exercise

14. Barometer (or other valid method to obtain barometric pressure) and accurate thermometer

110.7 Participant Preparation (Pre-Test Instructions)

110.7.1. Participant Instructions

1. The participant should be wearing loose-fitting and comfortable clothing and shoes suitable for exercise.
2. The participant should abstain from smoking and/or consuming alcohol at least 4 hours prior to test, and from eating a heavy meal 2 hours prior to test.
3. Typically, no medications are withheld prior to the CPET.

110.7.2. Procedure Explanation

1. Briefly explain the procedure, including the purpose of the procedure and the risks involved with CPET.
2. Answer the participant's questions before the test.
2. The explanation should be provided by personnel who are familiar with CPET and this PVDOMICS protocol and can accurately describe the test and all potential risks.

110.8 Participant Assessment and History

The participant's medical history, clinical diagnosis, and reason for the test should be reviewed by a physician or other trained professional prior to exercise testing. The review should include:

1. Current medications (especially bronchodilators, medications for control of blood pressure, and beta-blockers)
2. PF tests, blood gas data, chest radiograph, blood chemistry results, etc.
3. Current symptoms including chest pain, discomfort, or wheezing
4. The participant's exercise limitations and activities of daily living
5. If the participant needs to use supplemental oxygen during the procedure

The clinical center primary investigator or a designated certified professional should assess each participant to determine their ability to perform the CPET. Rescheduling may be necessary if the participant has not complied with the preparation criteria.

When speaking with the participant, utilize an interpreter if there is a language barrier. Ask the participant if they have complied with the preparation procedures and document the time of their last meal, all medications taken in the last 24 hours, and if they have exercised in the past 8 hours. Please note that recent exercise is participant reported and each participant may have a different definition of "exercise". This is okay, we are interested in ascertaining if they have recently tired themselves out.

110.9. ECG electrode placement

The modified 10-electrode (Mason-Likar) configuration is the preferred method of electrode placement for obtaining a 12-lead ECG.[10,13,17]

The positions of the precordial leads are in the standard locations. The right arm (RA) and left arm (LA) limb electrodes are usually placed slightly below the right and left clavicle. The right leg (RL) and left leg (LL) limb electrodes are usually placed at the lower edge of the rib cage, or alternatively, at the level of the umbilicus at the mid-clavicular line.

Skin preparation is essential to reduce surface resistance and ensure a good ECG signal. To obtain the best ECG signal, the following steps may be used at the discretion of the personnel performing the ECG.

1. Shave hair (if applicable).
2. Use alcohol wipes to remove surface oils.
3. Abrade skin with fine emery cloth (240 grit sandpaper or mechanical skin preparation device). There are commercially available skin preps which include an abrasive and alcohol.

In addition, ensure that cables are adequately stabilized to reduce motion artifact.[10]

110.10. Arterial Line Placement (optional)

If arterial blood gases are indicated, arterial line placement to obtain multiple arterial blood samples may be required to fully assess gas exchange. This is especially true during the invasive CPET procedure (see MOP Chapter 111). In some situations, however, a single arterial blood sample may be taken during heavy exercise by radial artery puncture.

110.11. Pulmonary Function Tests (PFTs)

Pulmonary Function Tests will be obtained as per the PVDOMICS Pulmonary Function Testing MOP. Before proceeding with the CPET, ensure that the maximum voluntary ventilation (MVV) from the participant's most recent PFT is available.

110.12. Pulse oximetry

Pulse oximetry may be monitored during testing with either a finger probe or an ear probe. If an ear probe is used, rub the ear to improve perfusion prior to attachment of probe.

Ensure a good baseline reading for pulse oximetry probe by noting that the instrument indicates an adequate signal, pulsing with the heartbeat, and that heart rate measured by pulse oximeter agrees with ECG readings.

110.13 Pre-Test Procedures	
Confirm consent	Check to make sure that a current signed consent is on file for the participant.
Demographics	Identify the participant using two separate identifiers and record demographic information.
Participant instruction	Explain the purpose of the test. Explain that it is a maximum stress test and that the mouthpiece or mask must be in place for the duration of the test.
	Explain the end-points (attainment of maximal heart rate, development of limiting symptoms, or blood pressure, ECG or O_2 saturation out of range) and reassure the participant about safety.
	Explain how to use of the Modified Borg Scale (Appendix 1). This scale will be used to assess both dyspnea (shortness of breath) and Rate of Perceived Exertion (RPE). The modified Borg scale will be used for all dyspnea and RPE assessments prior to, during, and immediately following exercise. Explain that they will need to point to a number on the scale because

	they will have a mouthpiece or mask in place.
Position participant on cycle ergometer	An upright bicycle will be used in order to ensure consistent measurements across clinical centers. However, a supine bicycle is an acceptable alternative in the case of invasive CPET (see MOP chapter 111). 1. Adjust handlebar and saddle height a. When the pedal is at bottom center, knee flexion should be about 20°. 2. Instruct the participant on pedal speed. 60 rpm is the target. a. Have the participant cycle briefly with no power to familiarize themselves with the equipment and to check the ECG signal for motion artifact.
Attach participant to mouthpiece/mask	Place mouthpiece in participant's mouth or attach mask and apply nose clip. Although sometimes uncomfortable, the mouthpiece is preferred to the mask since leaks can occur with a mask and cause erroneous results. Instruct the participant to maintain a tight seal around the mouthpiece to reduce the incidence of air leak. If the participant is using a mask, ensure that it fits tightly. Instruct the participant to breathe quietly for 2 to 3 minutes; feedback may be needed to avoid inappropriate breathing patterns (e.g., hyperventilation). Remind participant that they should not talk while the mouthpiece is in or during the test. Go through alternative communication signals with them (such as pointing at a number on the modified Borg scale rather than saying it, or nodding when you point to or say the correct number).
Pulse oximeter	Place pulse oximeter, if applicable. Finger or ear probe can be used. The ear probe is preferred because the contraction of the hand muscles while holding the handlebar of the cycle can alter blood flow to the finger. If the ear is used, prep the site by rubbing to ensure good blood flow. Pulse oximetry may or may not be accurate in exercise testing[36-38] (Check pulse tracing to assess quality of signal if O_2 saturation reading seems inappropriate.)

Select Ramp Protocol	Participants will be assigned to one of three continuous ramp protocols depending on their current, self-reported physical abilities. The three ramps that will be used are a 10 watts per interval ramp, a 15 watts per interval ramp, and a 20 watts per interval ramp. An interval is defined as the time spent at a specific work rate. Follow the guidelines below to select the appropriate ramp for each patient based on their self-reported abilities. • If the participant becomes short of breath or fatigued moving between rooms in their house, use a 10 W ramp. • If the participant is able to walk around their house without difficulty but becomes short of breath or fatigued climbing one (1) flight of stairs, use a 15 W ramp. • If the participant is able to climb one (1) flight of stairs without difficulty (they do not become short of breath or fatigued in doing so) use a 20 W ramp. See Appendix 2 for further details.

110.14 Resting Measurements	
ECG	Obtain resting ECG, which may differ morphologically (e.g., T-wave inversion) from standard ECG performed in the supine position with limb-lead configuration. Obtaining supine, upright, and hyperventilation ECGs has been recommended to document morphological changes.
Blood Pressure	Obtain resting blood pressure and assess for absolute or relative contraindication for testing.
	Cuff blood pressure measurement a. The AHA recommends that the width of the bladder should be 40% of the circumference of the arm and the length of the bladder should be at least 80% of the arm circumference. b. Measure blood pressure with the participant's arm relaxed and not on the cycle handlebar. c. If using, mercury manometer or Bourdon gauge should be at eye level to avoid parallax d. Note that if using an automated blood pressure unit, they are acceptable to use but may be unreliable at higher power outputs, likely because of motion artifact.

	Direct measurements of blood pressure are available with an arterial catheter.[40] a. Pre-flush gauge and tubing with heparinized solution, clearing all bubbles. b. View pulse wave-form to detect overdamping or underdamping of the signal. c. Mount the pressure gauge at the left atrium level and set electrical output to read zero when gauge is opened to atmosphere.
Dyspnea	Assess and record resting dyspnea score using the modified Borg scale (Appendix 1) as feasible. Ask participant: "Using this scale from 0-10, where 0 is none at all and 10 is maximal, what number best describes your current shortness of breath?"
Rate of Perceived Exertion (RPE)	Assess and record resting RPE score using modified Borg scale (Appendix 1) as feasible. Ask participant: "Using this scale from 0-10, where 0 is none at all and 10 is maximal, what number best describes your current level of fatigue?"

110.15 Exercise Procedure	
Start exercise	Begin exercise following the appropriate ramp protocol (10 watts/interval, 15 watts/interval, or 20 watts/interval)
Monitor and record blood pressure, dyspnea, RPE, HR and ECG	Obtain blood pressure, dyspnea score, RPE score, heart rate, and work rate every 2 minutes, as feasible, during exercise as outlined in Appendix 3. Additionally, record VO_2 every 2 minutes as outlined in Appendix 4. 12-lead ECG should be continuously monitored during exercise. Obtain ECG, blood pressure, dyspnea score, RPE score, and VO_2 at the maximal work rate, as feasible. a. Maximal work rate (aka peak exercise) is defined as the point in time at which the participant is unable to maintain 60 revolutions per minute cycle rate.
Encourage participant	Encouragement may be needed with certain individuals to obtain a maximal effort. Encourage participant to reach an RER >1.10 and to maintain it for 30+ seconds.

Termination of test	At the termination of exercise ask the participant the reason for stopping the test (e.g., legs hurt, shortness of breath, or fatigue). Document the reason given. Obtain and record dyspnea and RPE scores immediately after the cessation of exercise.

110.16 Post-Exercise Procedures	
Cool down	Recovery should include ECG and symptom monitoring during a cool-down phase of 2 minutes of unloaded pedaling (at 0 watts) followed by 3 minutes of rest.
ECG	12-lead ECG should be monitored continuously for 5 minutes post-exercise (cool down period).
Blood pressure, dyspnea, RPE, and HR	Blood pressure, dyspnea score, RPE score, and heart rate should be measured and recorded at each minute, as feasible, after cessation of exercise until the end of the cool down period.
Discontinue monitoring	Recovery values do not have to reach pretest levels but should be stable before monitoring is discontinued.

110.17 Reporting Results

Form 290 (Center Cycle Ergometer Non-Invasive Cardiopulmonary Exercise Test (CPET) Procedure Notes) or Form 291 (Center Cycle Ergometer Invasive Cardiopulmonary Exercise Test (iCPET) Procedure Notes) must be completed and entered into the study database. Note that only one of these forms will be filled out per participant. The paper copy of Form 290 or Form 291 should be maintained in the participant's study record at the clinical center.

At a minimum, the following results must be recorded either by the exercise system and software (data sent to the cardiovascular physiology core) or by the study coordinator on Form 290 or 291.

1. Maximum watts achieved during exercise
2. Duration of exercise in minutes
3. Reason for exercise termination
4. Whether or not the RER reached/exceeded 1.10
5. Resting RER (30 second average)
6. Peak RER (30 second average)
7. Resting HR (beats per minute)

8. Peak HR (beats per minute)
9. Resting oxygen saturation
10. Peak oxygen saturation
11. Resting respiratory rate (breaths per minute)
12. Peak respiratory rate (beats per minute)
13. Resting VO_2
14. Peak VO_2
15. VO_2 at AT (if identifiable)

110.18 Procedure notes

Record thorough notes on the procedure as several factors may influence test results. For example:

1.1. Participant effort

1.1.1. Participant should be encouraged to give a maximal performance, unless early termination is warranted.

1.1.2. Example variables to detect a maximal performance:

1. HR must be close to the maximal predicted.

a. predicted HR = 210 - 0.65 x age

2. $V_{E,max}$: between 60% - 80% of ventilatory capacity.

a. Ventilatory Capacity = MVV or FEV1 x 35 to 40

3. SaO_2 <80% (In cases of severe hypoxemia a participant may terminate exercise.)
4. Metabolic work: RER equal to or greater than 1.10 to 1.15
5. Supervising clinician's observation of apparent effort.

1.2. Medications

1.2.1. Beta-blockers, calcium channel blockers, and similar medications may affect the heart rate response.

1.2.2. Bronchodilators may affect the ventilatory response

1.3. Exercise device selection and usage

1.3.1. Participant performance, coordination, and physical limitation with a particular exercise device can affect results:

1. Weight support on handrails
2. Inability to coordinate pedaling effort

3. Orthopedic constraints

1.3.2. Exercise device calibration

1. A poorly calibrated exercise device will affect reported work rate but not the overall VO_2max.

1.4. System leaks

1. Leaks associated with participant, connection interface, tubing, valves can affect results.

Cardiopulmonary exercise testing should be performed under the supervision of a physician appropriately trained to conduct clinical exercise tests and certified in advanced cardiac life support. The degree of supervision will be determined by the clinical condition of the participant being tested. It is recommended that the physician be present when participants are tested.

110.19 Referenced Documents

1. Sue DY, Wasserman K. Impact of integrative cardiopulmonary exercise testing on clinical decision making. Chest 1991;99:981-992.
2. Weisman IM, Zeballos RJ. Cardiopulmonary exercise testing. Pul Crit Update 1995;11:1-8.
3. Wasserman K, Hansen JE, Sue DY, et al (Eds.). Principles of Exercise Testing and Interpretation. 2nd Ed. Philadelphia,Lea & Febiger, 1994.
4. Weber KT, Janicki JS. Cardiopulmonary exercise testing. Physiologic Principles and Clinical Applications. Philadelphia, WB Saunders Co, 1986.
5. Whipp BJ. The bioenergetic and gas exchange basis of exercise testing. Clin Chest Medicine1994;15:173-192.
6. Wasserman K, Van Kessel AL, Burton GG. Interaction of physiological mechanisms during exercise. J Appl Physiol 1967;22:71-85.
7. Wagner PD. Central and peripheral aspects of oxygen transport and adaptations with exercise. Sports Med 1991;11:133-142.
8. Weisman IM, Zeballos RJ. An integrative approach to the interpretation of cardiopulmonary exercise testing. Clin Chest Medicine 1994;15:421-445.
9. Fletcher GF, Balady G, Froelicher VF, et al. Exercise Standards: A Statement for Healthcare Professionals From the American Heart Association. Circulation 1995;91:580-615.
10. Pina IL, Balady GJ, Hanson P, Labovitz AJ, Madonna DW, Myers J. Guidelines for clinical exercise testing laboratories. A statement for healthcare professionals from the Committee on Exercise and Cardiac Rehabilitation, American Heart Association, Circulation 1995;91:912-921.
11. Committee on Electrocardiography, American Heart Association. Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography: Circulation 1967;35:583-602.
12. Bailey JJ, Berson AS, Garson A Jr, Horan LG, Mcfarlane PW, Mortara DW, Zywietz C. Recommendations for standardization and specifications in automated electrocardiography: bandwidth and digital signal

processing. A report for health professionals by an ad hoc writing group of the Committee on Electrocardiography and Cardiac Electrophysiology of the Council on Clinical Cardiology, American Heart Association. Circulation 1990;81:730-739.

13. American College of Sports Medicine, Guidelines for Exercise Testing and Prescription. 4th Ed. Philadelphia,Lea & Febiger, 1991.
14. Borg GAV. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982; 14:377-381.
15. Aitken RCB. Measurement of feelings using visual analogue scales. Proc R Soc Med 1969;62:989-993.
16. European Society of Cardiology Working Group on Exercise Physiology, Physiopathology and Electrocardiography. Guidelines for cardiac exercise testing. Eur Heart J 1993;14:969-988.
17. Mason RE, Likar I. Experimental and laboratory reports: A new system of multiple-lead exercise electrocardiography. Am Heart J 1966;71:196-205.
18. Blackie SP, Fairbarn MS, McElvaney NG, et al. Normal values and ranges for ventilation and breathing pattern at maximal exercise. Chest 1991;100:136-142.
19. Sterk PJ, Fabbri LM, Quanjer PhH, Cockcroft DW, O'Byrne PM, Anderson SD, Juniper EF, Malo J-L. Airway responsiveness. Standardized Challenge Testing with Pharmacological, Physical and Sensitizing Stimuli in Adults. Report Working Party Standardization of Lung Function Tests. European Community for Steel and Coal: Official statement of the European Respiratory Society. Eur Respir J 1993;6(Suppl 16):53-83.
20. Jones NL. Clinical Exercise Testing, Philadelphia, WB Saunders Co., 1988.
21. Zavala DC. Manual on Exercise Testing: A Training Handbook, 3rd Ed. University of Iowa, 1993.
22. Zeballos RJ, Weisman IM: Behind the scenes of cardiopulmonary exercise testing. Clin Chest Medicine;1994:15:193-213.
23. Gibbons L, Blair SN, Kohl HW, et al. The safety of maximal exercise testing. Circulation 1989;80:846-852.
24. Thompson PD. The Safety of Exercise Testing and Participation. In: American College of Sports Medicine Resource Manual for Guidelines for Exercise Testing and Prescription, Durstine JL, King AC, Painter PL, et al (Eds). 2 Ed. Philadelphia, Lea & Febiger, 1993.
25. Ellestad MH. Stress Testing: Principles and Practice. 3rd Ed. Baltimore, Williams and Wilkins, 1986.
26. American Thoracic Society/American College of Chest Physcians. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. Am J Respir Crit Care Med 2003;167:211-277.
27. Mottram C. Exercise testing. Respiratory Care Clinics of North America, Philadelphia, WB Saunders Co, 1997.
28. Beck KC. Evaluating exercise capacity and airway function in the athlete. Chapter 2. In: Allerigc and Respiratory Disease in Sports Medicine. Weiler J (Ed). Marcel Dekker, 1997.
29. Huszczuk A, Whipp BJ, Wasserman K. A respiratory gas exchange simulator for routine calibration in metabolic studies. Eur Respir J 1990;3:465-468.
30. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973; 85:546-562.
31. Patterson JA, Naughton J, Pietras RJ, and Gumar RN. Treadmill exercise in assessment of patients with cardiac disease. Am J Cardiol 1972;30:757-762.
32. Balke B. Correlation of static and physical endurance. I. A test of physical performance based on the cardiovascular and respiratory response to gradually increased work. Project No. 21-32-004, Report No. 1. San Antonio, TX, United States Air Force School of Aviation Medicine, April 1952.
33. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. J Appl Physiol 1983;55:1558-1564.

34. Astrand PO. Textbook of Work Physiology. New York, Mcgraw-Hill, 1977.

35. James FW, Kaplan S, Glueck CJ, Tsay J-Y, Knight MJS, Sarwar CJ. Responses of normal children and young adults to controlled bicycle exercise. Circulation 1980;61:902-912.

36. Hansen JE, Casaburi R. Validity of ear oximetry in clinical exercise testing. Chest 1987;91:333-337.

37. Zeballos RJ, Weisman IM. Reliability of noninvasive oximetry in black patients during exercise and hypoxia. Am Rev Respir Dis 1991;144:1240-1244.

38. Ries AL, Farrow JT, Clausen JL. Accuracy of two ear oximeters at rest and during exercise in pulmonary patients. Am Rev Respir Dis 1985;132:685-689.

39. Perloff D, Grim C, Flack J, et al. AHA Medical/Scientific Statement. Special Report. Human blood pressure determination by sphygmomanometry. Circulation 1993;88:2460-2467.

40. Rasmussen PH, Staats BA, Driscoll DJ, et al. Direct and indirect blood pressure during exercise. Chest 1985;87:743-748.

41. Wasserman K. The anaerobic threshold measurement to evaluate exercise performance. Am Rev Respir Dis 1984;129:S35-S40.

42. Lewis DA, Sietsema KE, Casaburi R, Wasserman K. Inaccuracy of non-invasive estimates of VD/VT in clinical exercise testing. Chest 1994;106:1476-1480.

43. Magalang UJ, Grant BJB. Determination of gas exchange threshold by nonparametric regression. Am J Respir Crit Care Med 1995;151:98-106.

44. Sue DY, Wasserman K, Moricca RB, Casaburi R. Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination. Chest 1988;94:931-938.

45. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020-2027.

46. Beaver WL, Wasserman K, Whipp BJ. Improved detection of lactate threshold during exercise using a log-log transformation. J Appl Physiol 1985;59:1936-1940.

47. Dempsey JA, Reddan W, Balke B, Rankin J. Work capacity determinants and physiologic cost of weight-supported work in obesity. J Appl Physiol 1966;21:1815-1820.

48. Casaburi R, Barstow TJ, Robinson T, Wasserman K. Dynamic and steady-state ventilatory and gas exchange responses to arm exercise Med Sci Sports Exerc 1992;24:1365-1374.

49. Porszasz J, Casaburi R, Somfay A, et al. A linear treadmill ramp protocol using simultaneous changes in walking speed and grade. Med Sci Sports Exerc 2003;35:1596-1603.

50. Tomassoni TL. Introduction: the role of exercise in the diagnosis and management of chronic disease in children and youth. Med Sci Sports Exerc 1996;28:403-405.

51. Washington RL, Bricker JT, Alpert BS, Daniels SR, Deckelbaum RJ, Fisher EA, et al. Guidelines for exercise testing in the pediatric age group. From the Committee on Atherosclerosis and Hypertension in Children, Council on Cardiovascular Disease in the Young, the American Heart Association. Circulation 1994;90:2166-2179.

52. Weisman IM, Zeballos RJ. Clinical evaluation of unexplained dyspnea. Cardiologia 1996;41:621-634.

53. Goldman L, Hashimoto B, Cook EF, Loscalzo, A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. Circulation. 1981;64:1227-1234

54. American Thoracic Society, Standardization of spirometry: 1994 update. Am J Respir Crit Care Med 1995;152:1107-1136.

55. American Thoracic Society. Quality assurance in pulmonary function laboratories. Amer Rev Respir Dis 1986;134:625-627.
56. Proctor DN, Beck KC. Time delays adjustment to minimize errors in breath-by-breath measurement of V. O2 during exercise, J Appl Physiol 1996;81:2495-2499.
57. American College of Sports Medicine, Resource Manual for Guidelines for Exercise Testing and Prescription, Durstine JL, King AC, Painter PL, et al (Eds). 2nd Ed. Philadelphia, Lea & Febiger, 1993.
58. Russell JC, Dale JD. Dynamic torquemeter calibration of bicycle ergometers, J Appl Physiol 1986;61:1217-1220.
59. Van Praagh E, Bedu M, Roddier P, Coudert J. A simple calibration method for mechanically braked cycle ergometers. Int J Sports Med 1992;13:27-30.
60. Weisman IM, Zeballos RJ: Cardiopulmonary exercise testing: The need for standardization. Pul Persp 1992;9:5.
61. Neuberg GW. Cardiopulmonary exercise testing. An idea whose time has almost come. Chest 1990;97:257-258.
62. Kroeker EJ, Wood EH. Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in man. Circ Res 1955;3:623-632.
63. Rowell LB, Brengelmann GL, Blockmon JR, Bruce RA, Murray JA. Disparities between aortic and peripheral pulse pressures induced by upright exercise and vasomotor changes in man. Circulation 1968;37:954-964.
64. Lightfoot JT, Tuller B, Williams DF: Ambient noise interferes with auscultatory blood pressure measurement during exercise. Med Sci Sports Exer 1996;28:502.
65. Roca J, Whipp BJ, Agusti, AGN, et al. Clinical exercise testing with reference to lung disease: indications, standardization and interpretation strategies. Eur Respir J 1997;10:2662-2689.
66. Casaburi R, Cotes JE, Prefaut C. Equipment, measurements and quality control in clinical exercise testing. In: Clinical Exercise Testing with Reference to Lung Diseases. Eur Respir Mon. 1997;6:72-87.

Appendices appear on the following pages.

110.A.1 Appendix 1 – Modified Borg Scale

Modified Borg Scale

0	Nothing at all
0.5	Very, very slight
1	Very mild
2	Mild
3	Moderate
4	Somewhat severe
5	Strong
6	-
7	Severe
8	-
9	Extremely severe
10	So severe you need to stop

Use this scale to measure both perceived dyspnea and rate of perceived exertion (RPE) before, during, and after exercise.

110.A.2 Appendix 2 – Selecting the Appropriate Exercise Protocol

Follow the procedure below in order to select the appropriate exercise protocol for each participant in the PVDOMICS study.

Ask each participant:

1) *Do you become short of breath or fatigued when you walk around your house?*

If the answer to question 1 is "yes" → STOP, select a 10 watt/minute continuous ramp protocol
If the answer to question 1 is "no" → ask question 2

2) *Do you become short of breath or fatigued when you climb 1 flight of stairs?*

If the answer to question 2 is "yes" → select a 15 watt/minute continuous ramp protocol
If the answer to question 2 is "no" → select a 20 watt/minute continuous ramp protocol

110.A.3 Appendix 3 – PVDOMICS Non-Invasive Cycle Ergometer CPET Data Collection Schedule

Data should be captured as indicated below during the last 30 sec of each interval if possible.

Time Elapsed	**Work Rate**	**Heart Rate**	**Pulse O_2 sat**	**SBP**	**DBP**	**Dyspnea (Borg scale)**	**RPE (Borg scale)**
(min)	(watts)	(bpm)	(%)	(mmHg)	(mmHg)	(0-10)	(0-10)
Pre-Exercise							
-1	Rest						
Exercise							
0	0						
	Start ramp						
2							
4							
6							
8							
10							
12							
Recovery							
+1	0						
+2	0						
+3	Rest						
+4	Rest						
+5	Rest						
Peak							
____ : ____ minutes : seconds							

110.A.4 Appendix 4 – PVDOMICS Non-Invasive Cycle Ergometer CPET Additional Data Collection Schedule

All data should be captured during the last 30 sec of each interval

Time Elapsed (min)	**VO_2** (ml/kg/min)
Pre-Exercise	
-1	
Exercise	
0	

Time Elapsed (min)	**VO_2** (ml/kg/min)
Start ramp	
2	
4	
6	
8	
10	
12	

Time Elapsed (min)	**VO_2** (ml/kg/min)
Recovery	
+1	
+2	
+3	
+4	
+5	
Peak	
____ : ____ minutes : seconds	

110.A.5 Appendix 5 – Goldman Specific Activity Scale

This scale will be utilized by the study database to calculate the participant's NYHA functional class based on the maximum METS they achieve during the exercise testing.

METS Achieved	**NYHA Functional Class**	**Summary of Criteria for Specific Activity Scale Classifications[53]**
≥ 7	Class I	Patient can perform to completion any activity requiring ≥ 7 metabolic equivalents
≥ 5	Class II	Patient can perform to completion any activity requiring ≥ 5 metabolic equivalents but cannot or does not perform to completion activities requiring ≥ 7 metabolic equivalents
≥ 2	Class III	Patient can perform to completion any activity requiring ≥ 2 metabolic equivalents but cannot or does not perform to completion any activities requiring ≥ 5 metabolic equivalents
< 2	Class IV	Patient cannot or does not perform to completion activities requiring ≥ 2 metabolic equivalents

110.A.6 Appendix 6 – CPET Calculations

In general, all calculations will be performed by a computerized data acquisition system or database software and will not need to be calculated by the technician. However, if the values below are not automatically calculated by either the system software or a database, manual calculations will be performed according to the equations below.

1. Expired volume (V_E) is calculated from the timed collection of expired gas, with gas volumes being corrected to BTPS conditions:

$$V_{E,BTPS} = \frac{V_{E,ATPS} \text{ X (ATPS to BTPS factor)}}{t \text{ (min)}}$$

where:

$V_{E,BTPS}$ = expired minute ventilation (L/min) at BTPS

$V_{E,ATPS}$ = expired minute ventilation (L/min) at ATPS

$$\text{Conversion from ATPS to BTPS conditions} = \frac{(PB - PH_20) \text{ X } (310)}{(PB - 47) \text{ X } (TA + 273)}$$

where:

PH_2O = water vapor pressure at the ambient temperature (AT). This MUST be obtained from tables of water vapor pressure versus temperature.

PB = barometric pressure

2. Inspired volume (V_I) is needed for other calculations and, if room air is inspired, can be obtained from:

$$V_I = V_E \text{ X } \frac{1 - FEO_2 - FECO_2}{0.7904}$$

where:

FEO_2 = mixed expired O_2 concentration

$FECO_2$ = mixed expired CO_2 concentration.

3. VCO_2 and VO_2 are calculated from timed gas collection and concentration of mixed expired gases (either direct measurement of a mixed expired gas sample, or calculated from

analysis of expired gas flow and concentration), corrected to mL/min at STPD conditions:[20]

$$VO_2 = [(V_{I,BTPS} \text{ X } FIO_2) - (V_{E,BTPS} \text{ X } FEO_2)] \text{ X } \frac{PB-47}{0.863}$$

$$VCO_2 = [(V_{I,BTPS} \text{ X } FICO_2) - (V_{E,BTPS} \text{ X } FECO_2)] \text{ X } \frac{PB-47}{0.863}$$

where:

V_E and V_I are calculated as above

0.863 = conversion from L/min to mL/min and the ratio of (760 X 310/273) X 0.001 is the factor for the conversion from BTPS to STPD conditions

FIO_2 = fractional concentration of inspired O_2

$FICO_2$ = fractional concentration of inspired CO_2

FEO_2 = fractional concentration of mixed expired O_2

$FECO_2$ = fractional concentration of mixed expired CO_2

4. There are variables of interest that are derived from V_E, VCO_2, VO_2 and heart rate (HR): the ventilatory equivalents (V_E/VO_2, and V_E/VCO_2), the oxygen pulse (VO_2/HR), and the gas exchange ratio or respiratory exchange ratio ($RER = VCO_2/VO_2$)[3,8,21]

5. Measures of pulmonary dead space to tidal volume ratio can be done by analysis of arterial blood gases using the classic Bohr equation (which gives the physiological dead space exactly):[41]

$$V_D/V_T\% = \{[(PaCO_2 - P_ECO_2)/PaCO_2] - (V_{D,valve}/V_T)\} \text{ X } 100$$

where:

$V_{D,valve}$ = respiratory valve and mouthpiece dead space

Utilization of the erroneously named "non-invasive V_D/V_T" is inappropriate in CPET. It is usually misleading and can lead to radically wrong V_D/V_T values because $P_{ET}CO_2$ can be considerably different than $PaCO_2$ in the presence of significant gas exchange abnormalities which yield alveolar dead space.[42]

6. Anaerobic threshold (AT), also known as ventilatory threshold (VT) or gas exchange threshold (GET), is determined from graphical analysis of data.[43] This study will use the term AT rather than VT or GET.

    6.1. The conventional method[41] for determining AT uses ventilatory equivalents plotted against VO_2. Usually, data are smoothed or averaged to reduce breath-by-breath variability, facilitating location of the AT. The AT coincides with the minimum of V_E/VO_2. The V_E/VCO_2 should either be constant or declining in the region around the AT. An increasing VE/VCO_2 suggests the increase in both parameters is due simply to hyperventilation rather than to a change caused by lactic acidosis.

    6.2. AT can also be located using V-slope analysis,[44,45] where the VCO_2 (vertical axis) is plotted versus the VO_2 (horizontal axis). The AT is the point where the slope of VCO_2 versus VO_2 increases; this can be located either manually or by using computerized analytic routines. If computerized analysis routines are used, the AT should always be verified by visual inspection of the data.

    6.3. Another approach is to plot the lactate concentration values in arterial blood against VO_2 (using either manual or computerized data analysis routines). The AT is the point where the rate of rise in lactate increases or the total lactate concentration exceeds a threshold value (usually about 2 mEq/L). Presenting the log(lactate) versus log(VO_2) amplifies the change in slope, allowing easier identification of the threshold.[46]

7. The normal alveolar-arterial O2 gradient [$P(A\text{-}a)O_2$] increases with age and during exercise. At 20 to 39 years of age, the mean $P(A\text{-}a)O_2$ is 8 mmHg at rest, and 15 mmHg at maximal exercise. At 40 to 69 years of age, the mean $P(A\text{-}a)O_2$ is 13 mmHg at rest, and 19 mmHg at maximal exercise. In this older group, at maximum exercise the upper limit of normal (i.e., 95% confidence interval) is 28 mmHg.[3] A general guideline for the upper limit of adults is a $P(A\text{-}a)O_2 < 35$ mmHg.[8]

Chapter 111. Clinical Center Cardiopulmonary Exercise Test (CPET) - Invasive

Adapted from the Protocol for Invasive Cardiopulmonary Exercise Test in Clinical Practice; David M. Systrom, M.D.,[§ǂ] Bradley A. Maron, M.D. [§*] Used with permission.

Divisions of §Cardiovascular and ǂPulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 75 Francis Street, Boston, MA 02115; Department of ‖Pulmonary Medicine and *Cardiology, Veterans Affairs Boston Healthcare System, Boston, MA 02115; #Department of Cardiology, Boston Children's Hospital, Boston, MA 02115

This manual is intended to serve as a training and reference document for persons who perform invasive CPET for the PVDOMICS Study using standardized procedures and techniques. Before performing invasive CPET for the PVDOMICS study, both this chapter on invasive CPET and Chapter 110 on non-invasive CPET should be reviewed.

111.1 Contraindications to Invasive CPET testing

Participants who are excessively anticoagulated or with severe thrombocytopenia are at increased risk. Participants without central venous access are not candidates. Additional common relative contraindications to exercise testing apply to iCPET, including severe/symptomatic aortic stenosis (though the question is usually whether symptoms are related or unrelated to valve disease), decompensated congestive heart failure, unstable coronary syndromes, inability to exercise, severe pulmonary hypertension, unstable arrhythmias or syncope.

The following is a stepwise approach to the application of iCPET testing in clinical practice.

111.2 Participant Counseling

Discuss sequential phases of the iCPET study and obtain consent.

1. Right heart catheterization and radial artery access placement:
    a. In participants for whom the diagnosis of unexplained dyspnea is unresolved despite alternative testing, including non-invasive CPET, right heart catheterization during iCPET is required to evaluate for specific forms of cardiopulmonary disease. Right heart catheterization is safe and, although complication rates vary by center, the risk of death in one large clinical study (n = 7,218) of patients with severe pulmonary hypertension was 0.055% (n = 4); serious adverse events occurred in 1.1% (n = 76), predominately due to bleeding at the site of vascular access[1]. Additional complications include accidental arterial catheterization and transient arrhythmia during passage of the catheter through the right cardiac chambers. To minimize the risk of complication, cardiac catheterization is performed uniformly with the assistance of ultrasound and fluoroscopic guidance at our center.
    b. Radial artery canalization is generally well tolerated; complications are uncommon and include, but are not exclusive to, temporary or permanent vessel occlusion, pseudoaneurysm formation, infection, or, rarely, air embolism. Local pain at the site of cannulation, however, is common and may persist for days.

2. If the exercise testing is not performed in the catheterization laboratory, the patient is transported with appropriate healthcare provider supervision from the cardiac catheterization laboratory to the iCPET suite with continued cardiac rhythm and pulmonary artery monitoring, the latter to avoid inadvertent and sustained wedging of the catheter.
3. Each vascular access site (i.e., radial, internal jugular) is monitored at each stage.
4. The participant should be familiarized with study devices (e.g., cycle ergometer, pneumotachograph, metabolic cart, waveform screen for pulmonary arterial catheter and radial line, electrocardiography [ECG] leads).
5. Review stages of iCPET Test:
    a. Preparatory phase/set up
    b. Warm up phase
    c. Exercise phase
    d. Recovery phase

111.3 Components of an iCPET

1. Cycle ergometer
    a. An upright cycle ergometer is used for exercise stress where the resistance (i.e., work) is continually and linearly increased until symptomatic exhaustion. A supine or semi-supine cycle ergometer may be used at sites where cycle ergometry is regularly performed supine, but is not preferred.
2. Metabolic cart
    a. Contains gas analyzers and a pneumotachograph for breath-by-breath measurements of expired O_2 and CO_2 and ventilation with calculation of VO_2 and VCO_2. The metabolic cart can also be used to perform spirometry to measure or calculate maximum voluntary ventilation (MVV = 35 × FEV1).
3. Continuous 12-lead electrocardiography to monitor heart rate, rhythm, and signs of ischemia.
4. Peripheral non-invasive oxyhemoglobin saturation level (SpO_2) monitoring
5. Hemodynamic monitoring and vascular access
    a. Continuous measurements of systemic blood pressure through the radial artery catheter; central venous, right atrial, right ventricular, and pulmonary arterial pressures are measured at rest and during exercise via the pulmonary artery catheter. The PCWP is determined by balloon inflation every minute during exercise.
6. Vascular access
    a. Blood samples from radial and pulmonary arterial catheters are also drawn every minute to measure blood gases and pH. Cardiac output is calculated every minute via the direct Fick method using co-oximeter measured SaO_2 and $S\bar{v}\ O_2$ and measured VO_2. Plasma lactate is also measured, generally via the radial artery.

111.4 Pulmonary Function Testing, and Right Heart and Radial Artery Catheterization

1. Prior to catheterization, spirometry is performed to record Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), FEV1/FVC), and maximum ventilatory volume (MVV, either measured or estimated by FEV1 x 35). In participants for whom neuromuscular disease is a consideration, the MVV should be measured before and after exercise.
2. Exercise flow volume loops and inspiratory capacity measurements may be obtained during exercise in specific participants, such as those where there is suspicion for a vascular ring or with pulmonary disease of unclear severity.
3. Standard sterile technique applies to right heart catheterization and radial artery cannulation, performed in a cardiac catheterization laboratory by an experienced operator.
4. Blood pressure and oxyhemoglobin saturation levels are recorded in each of the following vascular compartments with the participant supine: superior vena cava, right atrium, right ventricle, main pulmonary artery, and cardiac output is measured using the Fick method according to the following formula: $Qt = \dot{V}O_2/C(a\text{-}\bar{v})O_2$, where Qt is cardiac output; $\dot{V}O_2$, volume of oxygen consumption; $C(a\text{-}\bar{v})O_2$, O_2 content of arterial – mixed venous blood.[2]
5. In the absence of a contraindication to further testing on resting RHC (*e.g.*, severe pulmonary hypertension, decompensated HF), the catheter port is disconnected from the pressure monitoring system and reconnected to a portable pressure transducer and monitor.
6. Calibration: The pulmonary artery and PCWP are recorded under fluoroscopy to ensure proper location of the catheter tip. The participant is then moved to the upright position and the pressure calibrator is opened to ambient air ("zeroed"), calibrated, and leveled to the 4th intercostal space at the mid-axillary line, approximately 5 cm below the angle of Louis or 3 finger breadths below the axilla, which is in the plane of the right atrium in most participants.
7. The monitored participant is then transferred under the supervision of appropriate healthcare provider escort to the iCPET suite.

111.5 Invasive CPET Suite

In addition to the components required for iCPET testing (see above), the iCPET suite should contain a system for pressure measurements and an advanced cardiopulmonary life support (ACLS) emergency cart.

1. Staff required includes the following appropriately trained medical personnel:
    a. An exercise physiologist supervises the metabolic cart and timer, coordinates the timing of blood draws and PCWP measurements, provides encouragement and direction ("coaching") to the participant, anticipates the end of the test based on symptoms and metabolic data, and is positioned to obtain arterial blood gas, pH and lactate samples appropriately (See Section 111.7.3 below).
    b. A second exercise physiologist manages the waveform recorder, records the systemic, pulmonary artery and PCW pressures at the appropriate time intervals (See section 111.7.3

below)

c. A physician assistant, nurse practitioner, or physician performs the pulmonary artery catheter balloon inflation to obtain wedge pressure tracing at the appropriate time intervals (See section 111.7.3), as well as obtaining mixed venous blood gases and pH from the distal pulmonary artery catheter port at the appropriate time intervals.

d. A physician is present and supervises the test.

111.6 Determining the Exercise Protocol

1. Pedal resistance increases during the exercise test at a linear rate after a period of freewheel. The rate of increase is determined according to each participant's prior exercise test performance or self-reported baseline fitness level to aim for a 6-8 minute symptom-limited test as follows:
    a. 10 watts/interval increase for sedentary participants
    b. 15 watts/interval if participants are able to perform light exercise (walking slowly, cooking, washing dishes, or other low aerobic activities of daily living).
    c. 20 watts/interval if participants are able to perform moderate exercise (walking briskly, vacuuming or mopping, using a powered lawn mower, etc.).
2. For the PVDOMICS study, follow the guidelines below to select the appropriate ramp for each participant based on their self-reported abilities. One interval is defined as the time spent at a specific work rate.
    a. If the participant becomes short of breath or fatigued moving between rooms in their house, use a 10 watts/interval ramp.
    b. If the participant is able to walk around their house without difficulty but becomes short of breath or fatigued climbing one (1) flight of stairs, use a 15 watts/interval ramp.
    c. If the participant is able to climb one (1) flight of stairs without difficulty (they do not become short of breath or fatigued in doing so) use a 20 watts/interval ramp.
    d. See Appendix 111.A.1 for further details..
3. Participants pedal at a continuous rate of approximately 60 cycles per minute as resistance increases. The exercise physiologist plays an important role in monitoring the cycling rate. The goal exercise time duration is at least 5 minutes.

111.7 Invasive CPET Test

In addition to the information provided below please refer to MOP Chapter 110 (CPET – non-invasive) sections 110.13-110.16 for additional directions for PVDOMICS specific testing. Note that, if doing supine iCPET, resting measurements should be taken with feet up before any pedaling has begun.

1. Preparation Phase	a) Record demographic and other patient characteristics on a

	participant report form. b) Participant is positioned on ergometer with seat height adjusted to comfort, with total or near-total leg extension at nadir of pedal trajectory. c) 12-lead ECG system is activated with standard lead positioning. The modified 10-electrode (Mason-Likar) configuration is the preferred method of electrode placement[3]. d) With participant on the cycle ergometer, radial and pulmonary artery catheter waveform recorders are connected, zeroed, and leveled according to the methods and landmarks described in Section 111.4.6. e) Pulse oximeter is connected to the recording system for continuous SaO_2 monitoring. The validity of non-invasive SaO_2 assessment is supported by comparing reported HR to the ECG HR and subsequently validated in comparison to radial artery measurements. f) The mouthpiece for the pneumotachograph and metabolic cart should be fitted and nose clip placed followed by baseline ventilation and pulmonary gas exchange measurements recorded over a 1-minute period. g) Measure baseline ABG (optional), $S\bar{v}\ O_2$, and plasma lactate. h) Measure baseline systemic and pulmonary arterial pressures, right atrial pressure (central venous pressure), and PCWP.
2. Warm up or 'Free wheel' phase	a. Participants will warm up without resistance (aka "free wheel") for 2 minutes; during this time, re-level all pressure transducers to account for subtle changes in posture that may occur with movement of exercise. b. Continuously record ventilation and pulmonary gas exchange measurements. c. Repeat systemic and pulmonary arterial pressures, central venous pressure, and PCWP after 60 seconds of free wheel. d. Optional: Repeat ABG, VBG, pH and plasma lactate after 60 seconds of free wheel.
3. Exercise Phase	a. Metabolic cart-driven resistance is added to the pedal stroke at the predetermined rate (10 watts/interval, 15 watts/interval or 20 watts/interval). b. Optional: Blood for ABG, VBG, pH, and plasma lactate measurements are drawn at 2-minute intervals (or more frequently if

	desired). c. PAP (mean, systolic, diastolic), PCWP and RAP are measured at 2-minute intervals (or more frequently if desired). d. Central venous (right atrial pressure), systemic arterial, and pulmonary artery pressures are recorded continuously through passive exhalation. e. Peak exercise is defined as the point in time at which the participant is unable to maintain 60 revolutions per minute cycle rate. f. Hemoglobin, ABG, VBG, pH, $S\bar{v}\ O_2$, and plasma lactate are measured at peak exercise g. PAP (mean, systolic, diastolic), PCWP, and RAP are measured at peak exercise. h. Coaching is permissible; the goal is achieve at least 5 minutes, though preferably 6-8 minutes, of exercise prior to the completion of the test.
4. Recovery Phase	a. The cycle ergometer resistance returns to 0 watts. b. The participant cycles for two minutes at 0 watts, then rests for three additional minutes. Monitoring continues during this time with data recorded every minute per CPET protocol (see MOP chapter 110). c. After two minutes of recovery PAP (mean, systolic, diastolic), PCWP, and RAP are measured. d. After five minutes of recovery PAP (mean, systolic, diastolic), PCWP, and RAP are measured. 1 ml of blood may be sampled for ABG, VBG, pH, $S\bar{v}\ O_2$, and plasma lactate (optional). e. Participant is then transferred, with appropriate escort, to an area for recovery. Blood pressure and heart rhythm are monitored frequently. PAP and blood lactate levels may be monitored at 30 min and 60 min time points if the catheters are tolerated by the participant. The PA catheter is then removed while the participant is instructed to hum. The catheter insertion site is compressed with direct pressure for at least 5 minutes and occlusive dressing is applied and maintained at the puncture site for 24 hours. The radial artery catheter is then removed and firm but not occlusive pressure is applied to the insertion site for a minimum of 10 minutes, and a pressure bandage is applied and maintained for 24 hours. The participant should be instructed against lifting for 48 hours and asked to contact the exercise staff in the event of bleed, hematoma, redness, rash, finger pain, and/or cyanosis at either the

	pulmonary artery or radial artery insertion sites.

111.8 Indications for study cancellation or termination

1. ECG signifying myocardial injury current or potentially lethal arrhythmias
2. Systemic hypotension (e.g., systolic blood pressure < 90 mmHg)
3. Extreme hypertension (e.g., systolic blood pressure > 220 mmHg)
4. Syncope or pre-syncope or lightheadedness
5. Peripheral oxyhemoglobin saturation level <88%
6. Severely elevated PCWP during exercise (> 40 mmHg)

Invasive CPET is an important consideration in the clinical evaluation of patients with unexplained exertional intolerance despite conventional diagnostic testing. By leveraging the simultaneous assessment of full cardiopulmonary hemodynamics and gas exchange performance during exercise, iCPET is well positioned to diagnose exercise-induced pulmonary arterial hypertension, heart failure with preserved left ventricular ejection fraction, and failure to augment right ventricular pressure as occult causes of exertional dyspnea. Our experience is that a multi-disciplinary approach to the application of iCPET in clinical practice that involves pulmonologists, cardiologists, physicians assistants, and exercise physiologists is critical to the completion of a safe and accurate study. With an expanding pool of patients diagnosed with unexplained dyspnea, the implementation of a standardized iCPET protocol is anticipated to enhance the dialogue by which clinicians discuss the pathophysiology of exertional dyspnea and empiric efforts to identify novel treatments for patients afflicted with this condition.

111.9 Referenced Documents

1. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, Barst RJ, Ghofrani HA, Jing ZC, Opitz C, Seyfarth HJ, Halank M, McLaughlin V, Oudiz RJ, Ewert R, Wilkens H, Kluge S, Bremer HC, Baroke E, Rubin LJ. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol. 2006;48:2546-2552
2. Maron BA, Cockrill BA, Waxman AB, Systrom DM. The invasive cardiopulmonary exercise test. Circulation. 2013;127:1157-1164
3. Mason RE, Likar I. A new system of multiple-lead exercise electrocardiography. Am Heart J. 1966;71:196-205

See also:

Argiento P, Vanderpool RR, Mulè M, Russo MG, D'Alto M, Bossone E, Chesler NC, Naeije R. Exercise stress echocardiography of the pulmonary circulation: limits of normal and sex differences. Chest 2012;142(5):1158-1165.

Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher G, Forman D, et al. Clinician's guide to cardiopulmonary exercise testing in adults: A scientific statement from the American Heart Association. Circulation 2010;122(2):191-225.

Bidart CM, Abbas AE, Parish JM, Chaliki HP, Moreno CA, Lester SJ. The noninvasive evaluation of exercise-induced changes in pulmonary artery pressure and pulmonary vascular resistance. J Am Soc Echocardiogr 2007;20(3):270-275.

Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart

failure with preserved ejection fraction. Circ Heart Fail 2010;3(5):588- 595.

D'Andrea A, Naeije R, D'Alto M, Argiento P, Golia E, Cocchia R, Riegler L, et al. Range in pulmonary artery systolic pressure among highly trained athletes. Chest 2011;139(4):788-794.

Fowler RM, Maoirana AJ, Jenkins SC, Gain KR, O'Driscoll G, Gabbay E. Implications of exercise-induced pulmonary arterial hypertension. Med Sci Sports Exerc 2011;43(16):983-989.

Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation 2012;126(18):2261-2274.

Guenette JA, Chin RC, Cory JM, Webb KA, O'Donnell DE. Inspiratory capacity during exercise: measurement, analysis, and interpretation. Pulmonary Med 2013;2013:956081.

Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62(25Suppl):D42- D50.

Kane DW, Tesauro T, Koizumi T, Gupta R, Newman JH. Exercise-induced pulmonary vasoconstriction during combined blockade of nitric oxide synthase and beta adrenergic receptors. J Clin Invest 1994;93(2):677-683.

Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary artery pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009;34(4):888-894.

Lewis GD, Bossone E, Naeije R, Grünig E, Saggar R, Lancellotti P, Ghio S, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary disease. Circulation 2013;128(13):1470-1479.

Manetos C, Dimopoulos S, Tzanis G, Vakrou S, Tasoulis A, Kapelios C, Agapitou V, Ntalianis A, Terrovitis J, Nanas S. Skeletal muscle microcirculatory abnormalities are associated with exercise intolerance, ventilator inefficiency, and impaired autonomic control in heart failure. J Heart Lung Transplant 2011;30(12):1403-1408.

Masuki S, Eisenach JH, Schrage WG, Johnson CP, Dietz NM, Wilkins BW, Sandroni P, Low PA, Joyner MJ. Reduced stroke volume during exercise in postural tachycardia syndrome. J Appl Physiol 2007;103(4):1128-1135.

Mehra MR, Park MH, Landzberg MJ, Lala A, Waxman AB, for the International Right Heart Failure Foundation Scientific Workshop Group. Right heart failure: toward a common language. J Heart Lung Transplant 2014;33(2):123-126.

Naeije R, Vanderpool R, Dhakal BP, Saggar R, Saggar R, Vachiery JL, Lewis GD. Exercise- induced pulmonary hypertension: physiological basis and methodological concerns. Am J Resp Crit Care Med 2013;187(6):576-583.

Oldham WM, Lewis GD, Van Horn TL, Pappagianopoulos PP, Systrom DM. Cardiovascular limit to exercise due to preload failure. Chest. 2010;138:184A (Abstract).

Rich S, Rabinovitch M. Diagnosis and treatment of secondary (non-category 1) pulmonary hypertension. Circulation 2008;118(12):2190-2199.

Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23(7):685-713; quiz 786-788.

Ryan JJ, Rich JD, Thiruvoipati T, Swamy R, Kim GH, Rich S. Current practice for determining pulmonary capillary wedge pressure predisposes to serious errors in the classification of patients with pulmonary hypertension. Am Heart J 2012;163(4):589-594.

Santos M, Opotowsky AR, Shah AM, Tracy J, Waxman AB, Systrom DM. A central cardiac limit to aerobic capacity in patients with exertional pulmonary venous hypertension: implications for heart failure with preserved ejection fraction. Circ Heart Fail 2014; Epub ahead of print.

Scheer BV, Perel A, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. Crit Care 2002;6(3):199-204.

Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM. Exercise-induced pulmonary arterial hypertension.

Circulation 2008;118(21):2183-2189.

Udelson JE. Heart failure with preserved ejection fraction. Circulation 2011;124(21):e540-543.

Waxman AB. Exercise physiology and pulmonary arterial hypertension. Prog Cardiovasc Dis 2012;55(2):172-179.

111.10 Figures & Figure Legends

Figure 1. A diagnostic algorithm for interpreting iCPET results. (A) Assessment of functional capacity is determined by calculating the maximum volume of oxygen consumed per minute ($\dot{V}O_2$), which may be performed during conventional or invasive cardiopulmonary exercise testing (iCPET). **(B)** A disproportional increase in the minute ventilation relative to maximum ventilatory capacity ($\dot{V}$ E:MVV) indicates a pulmonary mechanical limitation to exercise. Alternatively, early achievement of the anaerobic threshold (AT) suggests disordered oxygen (O_2) flux that may be a consequence of **(C)** decreased cardiac output (i.e., abnormal O_2 delivery) and/or **(D)** impaired O_2 extraction by skeletal muscle tissue from arterial blood. This determination, and subsequent analyses presented in the diagnostic algorithm, require iCPET and cannot be performed by conventional exercise stress testing alone. In patients with a central cardiovascular limit to exercise, specific cardiopulmonary hemodynamics profiles observed during exercise are suggestive of **(E)** exercise-induced PAH, **(F)** exercise-induced heart failure with preserved ejection fraction (HFpEF) if the left ventricular ejection fraction is normal, or **(G)** a preload limitation to exercise. COPD, chronic obstructive pulmonary disease; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; $\dot{V}CO_2$, volume of exhaled carbon dioxide; RV, right ventricle; MVV, maximum voluntary ventilation. Figure and legend *reproduced with some modifications with permission from* Ref. [1].

Figure 1. A diagnostic algorithm for interpreting iCPET results.

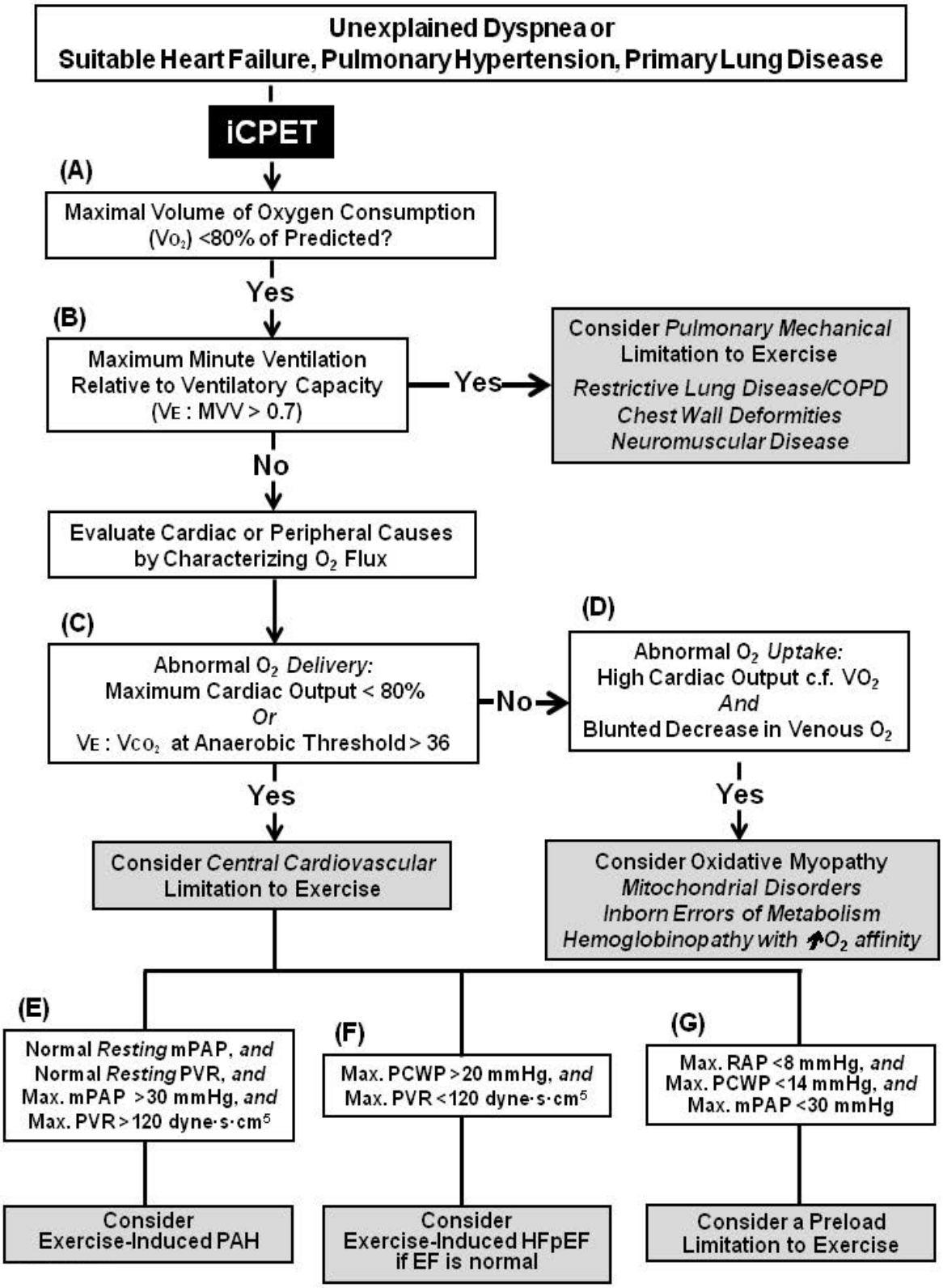


Figure 2. Modeling of the relationship between cardiac output and mean pulmonary artery pressure.

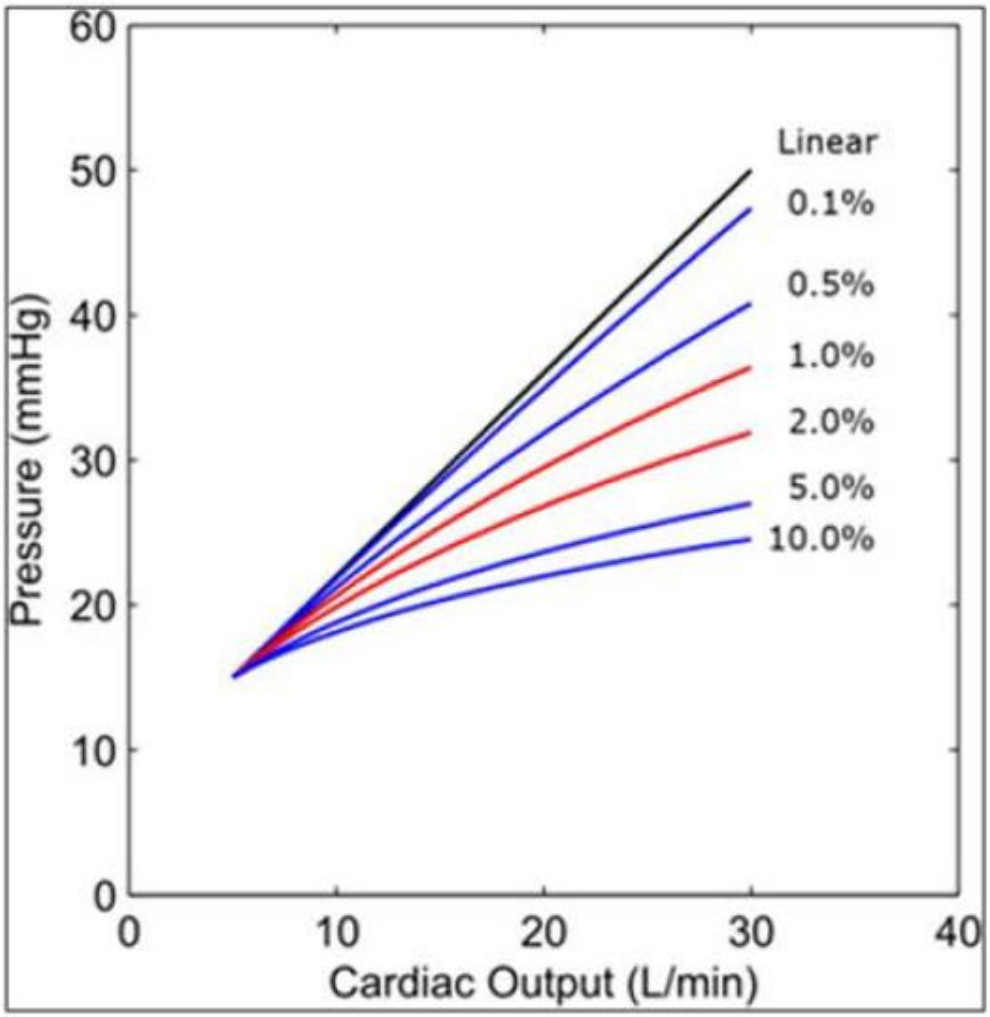


Figure 2. Modeling of the relationship between cardiac output and mean pulmonary artery pressure. Under physiological conditions, the pulmonary vascular distensibility coefficient approximates 1-2%, which results in a curvilinear relationship between cardiac output and mean pulmonary artery pressure. *Adapted with permission from the Protocol for Invasive Cardiopulmonary Exercise Test in Clinical Practice; David M. Systrom, M.D., Bradley A. Maron, M.D.*

111.A.2 Appendix 1 – Selecting the Appropriate Exercise Protocol

Follow the procedure below in order to select the appropriate exercise protocol for each participant in the PVDOMICS study.

Ask each participant:

1) *Do you become short of breath or fatigued when you walk around your house?*

If the answer to question 1 is "yes" → STOP, select a 10 watts/interval continuous ramp protocol
If the answer to question 1 is "no" → ask question 2

2) *Do you become short of breath or fatigued when you climb 1 flight of stairs?*

If the answer to question 2 is "yes" → select a 15 watts/interval continuous ramp protocol
If the answer to question 2 is "no" → select a 20 watts/interval continuous ramp protocol

111.A.1 Appendix 2 – PVDOMICS Invasive Cycle Ergometer CPET Data Collection Schedule

All data should be captured during the last 30 sec of each interval (e.g. between 1:30 and 2:00)

Time Elapsed	**Work Rate**	**Heart Rate**	**Pulse O_2 sat**	**SBP**	**DBP**	**Dyspnea (Borg scale)**	**RPE (Borg scale)**
(min)	(watts)	(bpm)	(%)	(mmHg)	(mmHg)	(0-10)	(0-10)
Pre-Exercise							
-1	Rest						
Exercise							
0	0						
	Start ramp						
2							
4							
6							
8							
10							
12							
Recovery							
+1	0						
+2	0						
+3	Rest						
+4	Rest						
+5	Rest						
Peak							
____ : ____ minutes : seconds							

111.A.1 Appendix 3 – PVDOMICS Invasive Cycle Ergometer Additional CPET Data Collection Schedule

All data should be captured during the last 30 sec of each interval (e.g. between 1:30 and 2:00). Intervals, including peak time, must match with the corresponding intervals on F290.

Time Elapsed	**sPAP**	**dPAP**	**VO_2**
(min)	(mmHg)	(mmHg)	(ml/kg/min)
Pre-Exercise (Resting)			
-1			
Exercise			
0			
Start ramp			
2			
4			
6			
8			
10			
12			

Time Elapsed	**sPAP**	**dPAP**	**VO_2**
(min)	(mmHg)	(mmHg)	(ml/kg/min)
Recovery			
+1			
+2			
+3			
+4			
+5			
Peak			
____ : ____ minutes : seconds			