Manual of Procedures

Pre-*Vent*

Prematurity-Related Ventilatory Control (Pre-Vent): Role in Respiratory Outcomes:

Protocol #19606: Multi-Center Common Protocol

(CRM + Chart Review Study)

Protocol #19978: Common Biorepository and Questionnaire Protocol

(DNA + Questionnaire Study)

Version Date: 23Oct2017

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List of abbreviations

Abbreviation or specialist term	Explanation
AE	Adverse Event
CRC	Clinical Research Coordinator
eCRF	Electronic Case Report Form
CTO	School of Medicine Clinical Trials Office
OSMB	Observational Safety Monitoring Board
GA	Gestational Age
ICF	Informed Consent Form
IRB	Institutional Review Board
MOP	Manual of Procedures
REDCap	Research Electronic Data Capture system
PHI	Protected Health Information
PI, Co-PI	Principal Investigator, Co-Principal Investigator
UVa	University of Virginia
VPN	Virtual Private Network

1 Introduction

The University of Virginia (UVa) would like to thank you for your participation in the Prematurity-Related Ventilatory Control (Pre-Vent): Role in Respiratory Outcomes:

- **Protocol #19606: Multi-Center Common Protocol *(CRM + Chart Review Study)***
- **Protocol #19978: Common Biorepository and Questionnaire Protocol *(DNA + Questionnaire Study)***

We plan to enroll over 500 infants in this multi-center study across 5 study sites. A Multi-Center Management Team in the UVa School of Medicine Clinical Trials Office (CTO) are available to assist you and all personnel involved in this study in the day-to-day activities of study management. Information regarding how to contact the study team is listed below.

This manual is designed to provide general information and instructions for study procedures. It contains study contacts, regulatory considerations and study specific instructions. Electronic Case Report Form (eCRF) instructions are provided in a separate document called the eCRF Guidelines. In addition, instructions for DNA collection, handling and shipment of DNA specimens collected for Protocol #19978 are outlined in the Study Laboratory Manual.

This MOP is to be used as an aide and not in lieu of the protocol. Please refer to the protocol for all IRB-approved study specifics, including the scientific background, study outcomes and statistical considerations.

We hope that your participation in the study will provide a fulfilling research experience, as we attempt to broaden our knowledge of NICU respiratory issues.

2 UVA Contact Information

CTO Multi-Center Management Team		
Steve Fowler Clinical Research Associate (Primary)	saf2qh@virginia.edu	434-243-4730
Holly Davis Clinical Research Associate (Back-Up)	haw5D@virginia.edu	434-924-9553
LDCC		
Randall Moorman, MD Co-PI, Contact PI	rm3h@virgina.edu	434-982-3367
Doug Lake, PhD Co-PI, Engineering Contact	del2k@virginia.edu	434-243-9667

3 Study Website: “UVa Box”

UVa Box is an online collaboration environment. UVa Box can be accessed through https://virginia.box.com/v/Pre-VentSharedFolder. Study personnel at each site will log in using the email address that they have provided to the UVa team, and a password created by and known only to themselves. The site contains Multi-Center Resources (study manuals, tools and templates) as well LDCC Communications.

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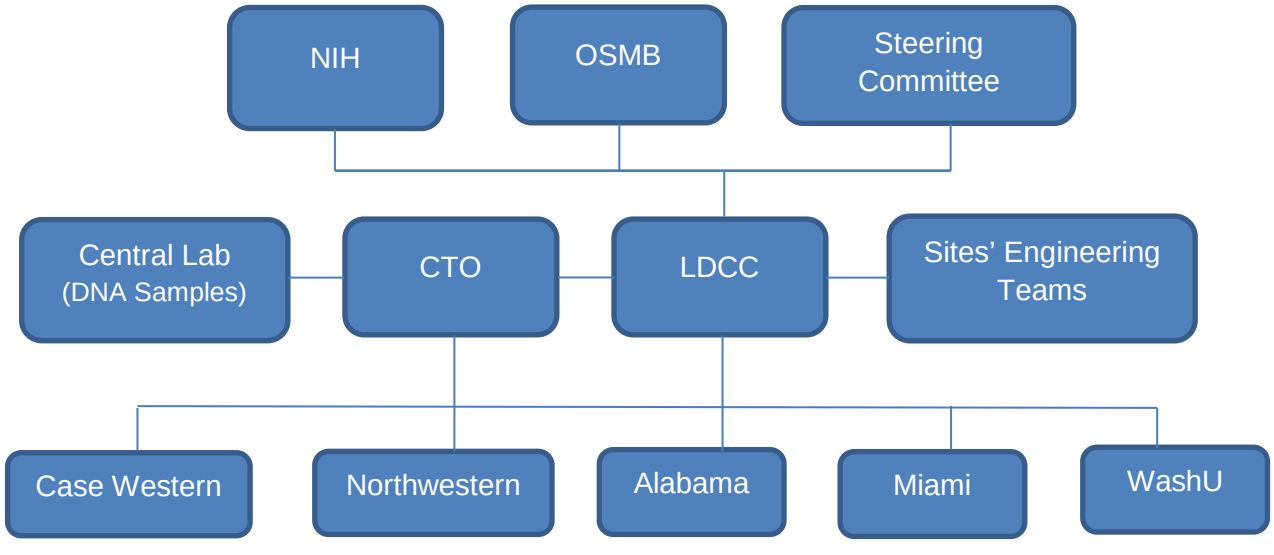
If you have not previously received access to UVa Box and would like access, please contact a member of the UVA Multi-Center Management Team listed in Section 2 above.

4 Administration

Organizational Structure

UVA is organizing this study, with participation of 5 outside centers, under the Pre-Vent umbrella. The Study Principal Investigators, J. Randall Moorman, MD and Douglas E. Lake, MD received a grant (1 U01 HL133708-01) from the National Heart, Lung and Blood Institute (NHLBI). UVa is the Sponsor, but not the Funding Source, of the Multi-Center Common Protocol at the sites.



NIH

As this is a Cooperative Agreement, the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) provides not only funding, but substantial scientific oversight and involvement.

Observational Safety Monitoring Board (OSMB)

The Observational Safety Monitoring Board is an independent board with expertise to evaluate risk and current accepted clinical practices. The OSMB provides overall monitoring of progress, interim data and safety issues and is appointed by NHLBI.

Pre-Vent Steering Committee

The Steering Committee provides governance of the study. All major scientific decisions will be determined by majority vote of the SC. The Pre-Vent Steering Committee is composed of up to two investigators from each site, the LDCC, a Chairperson appointed by NHLBI, and an NHLBI representative. The Steering Committee is responsible for discussing and approving any major changes to the protocol and responding to recommendations or mandates from the Observational Safety Monitoring Board (OSMB). The Steering Committee will meet in person twice annually, and monthly via teleconference.

Leadership and Data Coordination Center (LDCC)
The Leadership and Data Coordination Center at UVa leads the scientific design and analyses of the multicenter study, coordinates the cardiorespiratory monitoring (CRM) data collection and management, and provides support for the OSMB and SC.

Clinical Trials Office (CTO)
The Multi-Center Management Team with the Clinical Trials Office at UVa coordinates site activation, regulatory management, data review and validation as well as routine monitoring of both Multi-Center protocols.

Participating Pre-Vent Centers

Center	Name	Role
University of Virginia Charlottesville, VA	Randall Moorman, MD Doug Lake, PhD Karen Fairchild, MD Katy Krahn, MS Steve Fowler, BIS Holly Davis, BA, CCRP	Co-PI, Contact PI Co-PI, Engineering Contact Co-Investigator, Neonatologist LDCC Manager CTO Multi-Center CRA CTO Multi-Center CRA
1. Case Western Reserve University Cleveland, OH	Anna Maria Hibbs, MD Richard Martin, MD	Site co-PI, Contact PI Site co-PI
2. Northwestern University Chicago, IL	Aaron Hamvas, MD Debra Weese-Mayer, MD	Site co-PI, Contact PI Site co-PI
3. University of Alabama at Birmingham Birmingham, AB	Namasivayam Ambalavanan, MD Premananda Indic, PhD	Site Co-PI, Contact PI Site Co-PI
4. University of Miami Miami, FL	Eduardo Bancalari, MD Nelson Claure, MSc, PhD	Site Co-PI, Contact PI Site Co-PI
5. Washington University St. Louis St. Louis, MO	James Kemp, MD John Carroll, MD	Site Co-PI, Contact PI Site Co-PI

5 Responsibilities

Responsibilities of Pre-Vent Centers
The minimum staff required for participation at each clinical center are 2 Site Co-Principal Investigators (Co-PIs), a Clinical Research Coordinator (CRC), and a Site Engineering Team Member. The responsibilities of these individuals are described briefly in this section and in more detail in subsequent sections.

Site Co-PIs or designees are responsible for ensuring the proper conduct of the trial at his or her clinical center (including recruitment and treatment of patients as specified in the protocol), as well as accurate collection of data. Other specific duties include the following:

- Obtaining Institutional Review Board (IRB) approval
- Introducing the study to parents of babies who are eligible for the consented portions of the study, and obtaining signed informed consent (in some centers this responsibility may be delegated)
- Reviewing all enrolled infants to confirm their eligibility
- Oversight of data collection
- Participating in Steering Committee and OSMB meetings
- Informing the IRB of the study progress

The Site CRC is responsible for the day-to-day operations of the study at the clinical center, including data collection and management. This includes the following:

- Collecting information necessary to complete the data collection forms, and coordinating data entry
- Responding to messages and other communications from the CTO or triaging them to the Site PI
- Distributing updates of the study protocol and MOP to research team
- Reporting deviations to the CTO per guidelines in the protocol
- Managing the study screening log and providing updates to the CTO
- Assigning study ID to appropriate babies
- Assuring that the questionnaires are completed and DNA is collected from both parents whenever possible for all consented babies

The Site Engineering Team Member is responsible for the management of CRM data collection. This includes the following:

- Work directly with Doug Lake, PhD at the LDCC to ensure harmony with LDCC requirements
- Store continuous raw CRM data for the entire length of an infants' NICU stay
- Work with local institution's IT department/contact person to ensure adequate back-up of all files
- Process raw CRM files into required format
- Install and run analytic algorithms to process CRM files
- Attach correct REDCap Study ID to CRM result files
- Ensure no HIPAA identifiers are in results files other than DOB and time of birth. Bed number and monitor number are permitted.
- Oversee transfer of CRM results files to LDCC

Responsibilities of the UVA CTO Multi-Center Management Team

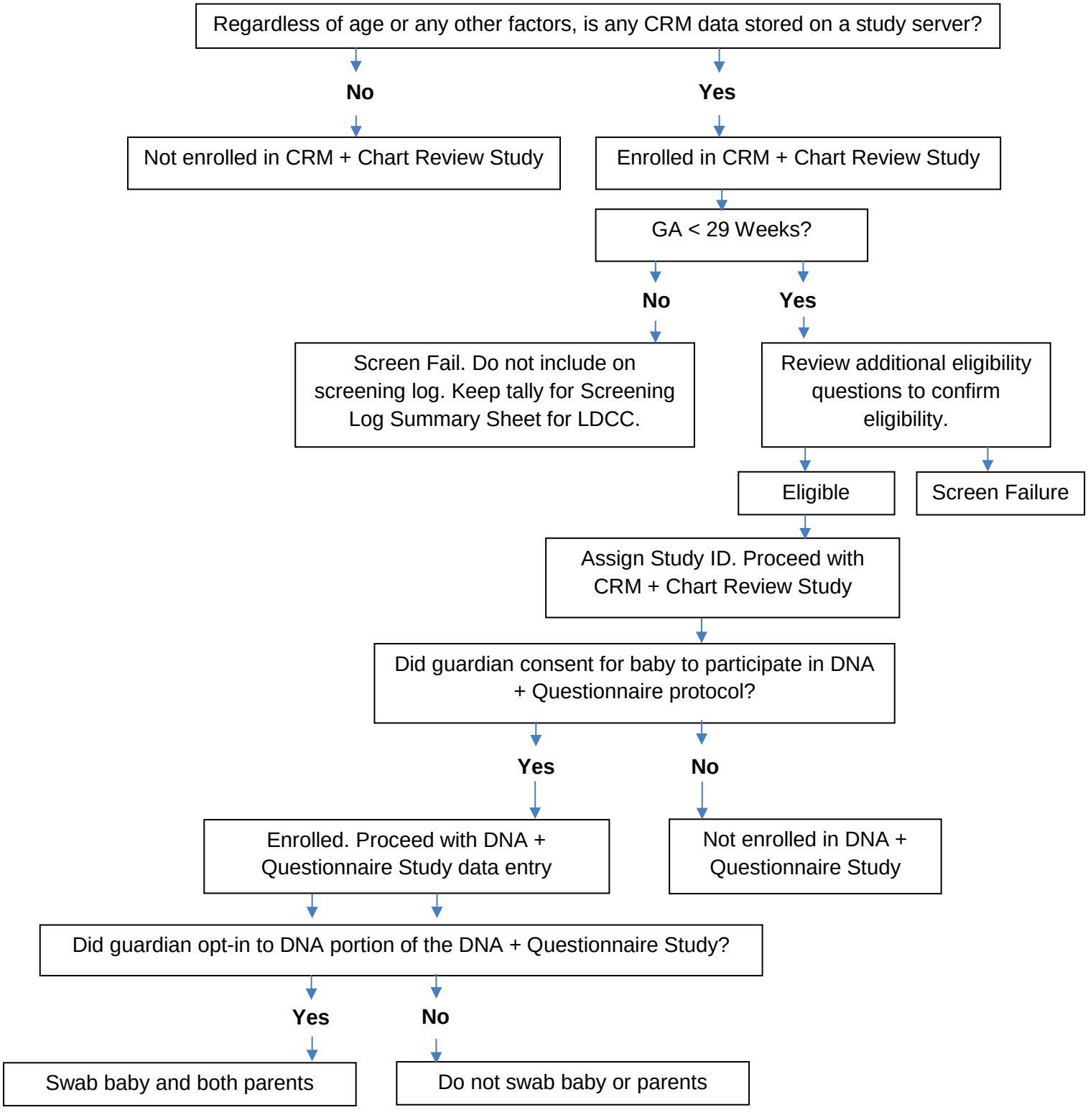
- Processing, modifying and distributing the MOP
- Developing and distributing the study tools and other manuals
- Serving as the Site Liaison/Central Contact for each site
- Providing the necessary training to CRCs in accessing and entering CRF data into the study database
- Monitoring overall data entry and protocol adherence
- Communicating messages from the UVA LDCC to the sites as requested.
- Quality review and oversight of REDCap data collection and DNA collection

Responsibilities of the UVA LDCC

- Working directly with the Site Engineering Team Member to ensure capabilities for CRM storage, processing, analysis and results transfer are enacted
- Facilitating communications among the Co-PIs, OSMB, NIH, SC, CRCs, and Site Engineering teams
- Scheduling meetings of and communicating with the OSMB and SC
- Monitoring the progress and scientific quality of the study
- Preparing interim and final analyses and reports
- Participating in the preparation of presentations and publications relating to the study

6 Screening Process

Screening and Consenting Flow Chart



Screening Procedures

All babies on whom CRM data are stored on a research server are enrolled in the Pre-Vent CRM + Chart Review Study and must be included in the overall enrollment numbers.

- All enrolled babies < 29 weeks Gestational Age* (GA) should be added to the study screening log as a part of the screening procedure.
- Enrolled babies ≥ 29 weeks GA are automatically screen-fails, and do not need to be entered on the screening log.
- Enrolled babies that are < 29 weeks GA and meet all eligibility criteria should be assigned a subject identifier (details below) and proceed with Pre-Vent CRM + Chart Review protocol case report forms.
  Note: *GA represents the time the baby spent in the womb. It does not change after birth.

Guardians with babies that are enrolled and eligible in the CRM + Chart Review Study should be approached for baby participation in the DNA + Questionnaire Study.

Consented babies are enrolled in the Pre-Vent DNA + Questionnaire Study and a questionnaire should be completed by the Guardian. If the Guardian opted to participate in the DNA portion of this protocol, the baby and both parents should be swabbed for DNA collection (See Laboratory Manual for collection, storage and shipment details).

Subject Identifiers

The baby's identifier will be a 4 digit number starting in the thousands by the site code numeric. See the site codes below. CRC will assign a REDCap Study ID sequentially. For example, the subject number for the first baby entered in REDCap at Case Western would be 1001. In the case of twins, the infant subject numbers would be 1001 and 1002.

Institution	Site Number	Sequential Study IDs
Case Western Reserve University	01	1000-1999
Northwestern University	02	2000-2999
University of Alabama at Birmingham	03	3000-3999
University of Miami	04	4000-4999
Washington University St. Louis	05	5000-5999

Screening Log

A confidential Screening Log will be maintained at each site (Screening Log Template is available in UVa Box, and an example is shown in the appendix to this MOP). On a daily basis the Site CRC or designate will assess whether any babies were enrolled through storage of CRM data. These babies will be screened for eligibility, and if eligible, the CRC will assign the study ID on the Screening Log and enter the infant in REDCap.

The screening log will contain Protected Health Information (PHI). Therefore, it must be kept in a secure location and must not be shared outside the site, including not with UVa.

The screening log will include the following data:

- Date screened: Enter todays date
- Mother Last Name: Enter mother's last name.
- Mother MRN: Enter mother's MRN.
- Baby's Last Name: Enter enrolled baby's last name.
- Mandatory: Baby MRN: Baby's MRN is mandatory to allow definitive identification of the subject by any potential future viewers of the screening log (Good Clinical Practices).
- Date and time of Delivery: Enter time or approximate time of birth, if known, to aid in determining eligibility. If not known, time will default to midnight.
- Date and time of Enrollment (first CRM data storage) Enter time or approximate time that CRM data storage began, if known, to aid in determining eligibility. If not known, time will default to midnight. If times are not known, use best judgement to determine if data storage began before age 7 days (approximately 168 hours after birth).
- Age at enrollment. This is calculated automatically if the 2 prior fields are completed, to aid in determining eligibility. If times are not known, use best judgement to determine if data storage began before age 7 days (168 hours after birth).
- GA< 29w? Should always be yes. The purpose of this column is to remind site staff of this eligibility requirement.
- Mandatory: Eligible? If baby is eligible to continue in study, choose yes. If not, choose reason why not.
    - No: ≥7 days old at enrollment If age at enrollment was 7 day or more (if data collection began more than 168 hours after birth). If times are not known, use best judgment to determine if data storage began before 7 days.
    - No: Unlikely to survive or decision not to pursue full care. Has the baby been deemed not likely to survive and a decision has been made not to provide full care?
    - No: Major congenital or chromosomal anomaly. Does the baby have any of the following?:
        - Neurologic conditions or brain anomalies likely to affect control of breathing (not including IVH)
        - Pulmonary conditions or lung or airway anomalies likely to significantly affect oxygenation (not including RDS, PIE, PTX). Ex: diaphragmatic hernia, TE fistula, significant pulmonary hypoplasia as from pre-viable PPROM.
        - Cardiac conditions or malformations likely to significantly affect oxygenation (not including PDA, ASD). Ex: right- or left-sided obstructive lesions, major valve abnormalities, large VSD likely to lead to heart failure.
        - Chromosomal or other major anomalies likely to affect control of breathing or oxygenation. Ex: Down syndrome or other trisomies.
    - No: Other reason (protocol deviation). The protocol does not list any other exclusion criteria
- Mandatory: If eligible, enter 4 digit REDCap Subject ID: Do not complete unless you chose "Yes" in Column K: "Eligible?" Enter Study ID assigned by the CRC according to the scheme provided in the MOP.
- Mandatory: If Eligible, Consented to Questionnaire Protocol? Do not complete unless you chose "Yes" in Column K: "Eligible?" If parent signed consent(s) for the DNA + Chart Review Study, choose yes. Otherwise choose reason why not.
- Mandatory: If Eligible and Consented to Questionnaire Protocol, did parent opt-in the infant to DNA Portion? Do not complete unless you chose "Yes" in Column M: "Consented to

Questionnaire Protocol?" If parent(s) opted to allow the baby to participate in the DNA portion, check yes. Otherwise choose reason why not.

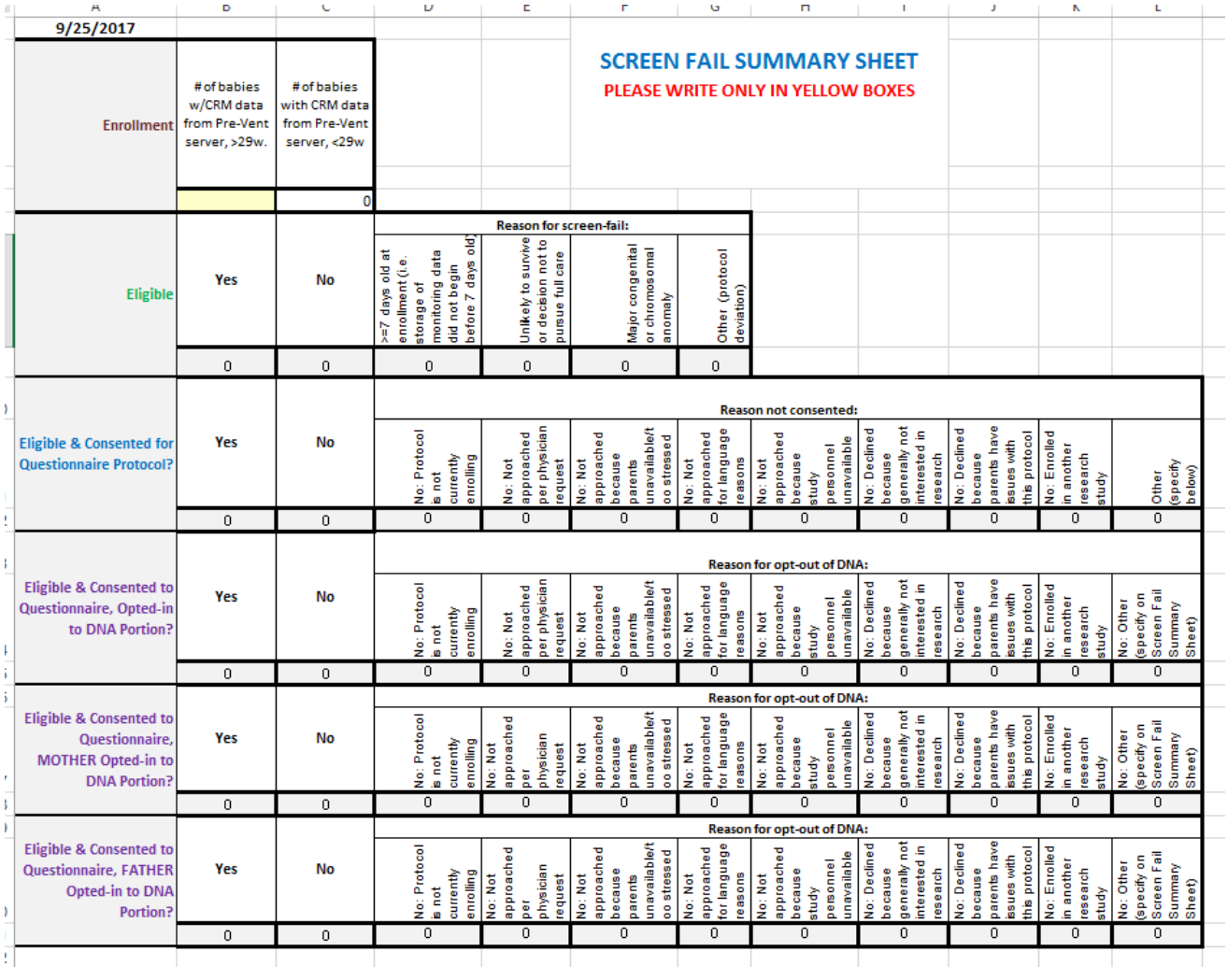
- Mandatory: If infant participating in DNA Portion, did MOTHER opt-in to DNA portion? Do not complete unless you chose "Yes" in Column N: "opt-in infant to DNA Portion?" If biological mother opted to participate, herself, in the DNA portion, check yes. Otherwise choose reason why not.
- Mandatory: If infant participating in DNA Portion, did FATHER opt-in to DNA Portion? Do not complete unless you chose "Yes" in Column N: "opt-in infant to DNA Portion?" If biological father opted to participate, himself, in the DNA portion, check yes. Otherwise choose reason why not.

Monthly Screening Report to UVA CTO

Sites will be asked to provide a monthly summary of screening activity, the Screen Fail Summary Sheet, to the UVA CTO on the **last Friday of each month**. The basic data required to be submitted are:

- Number enrolled >29 weeks (These babies are not entered on screening log, so number must be counted and entered manually)
- Number enrolled <29 weeks
- Number eligible for REDCap
- Number consented for Questionnaires
- Number consented for DNA

The last four numbers above are calculated automatically in the Screen Fail Summary Sheet as data are entered in the Screening Log. The table can be copied and pasted into an email to the UVA CTO monthly (example shown below). The table includes all information from the drop-down lists on the Screening Log.



9/25/2017

SCREEN FAIL SUMMARY SHEET

PLEASE WRITE ONLY IN YELLOW BOXES

Enrollment	# of babies w/CRM data from Pre-Vent server, >29w.	# of babies with CRM data from Pre-Vent server, <29w
		0

Eligible	Yes	No	Reason for screen-fail: >=7 days old at enrollment (i.e. storage of monitoring data did not begin before 7 days old)	Unlikely to survive or decision not to pursue full care	Major congenital or chromosomal anomaly	Other (protocol deviation)
	0	0	0	0	0	0

Eligible & Consented for Questionnaire Protocol?	Yes	No	Reason not consented: No: Protocol is not currently enrolling	No: Not approached per physician request	No: Not approached because parents unavailable/too stressed	No: Not approached for language reasons	No: Not approached because study personnel unavailable	No: Declined because generally not interested in research	No: Declined because parents have issues with this protocol	No: Enrolled in another research study	Other (specify below)
	0	0	0	0	0	0	0	0	0	0	0

Eligible & Consented to Questionnaire, Opted-in to DNA Portion?	Yes	No	Reason for opt-out of DNA: No: Protocol is not currently enrolling	No: Not approached per physician request	No: Not approached because parents unavailable/too stressed	No: Not approached for language reasons	No: Not approached because study personnel unavailable	No: Declined because generally not interested in research	No: Declined because parents have issues with this protocol	No: Enrolled in another research study	No: Other (specify on Screen Fail Summary Sheet)
	0	0	0	0	0	0	0	0	0	0	0

Eligible & Consented to Questionnaire, MOTHER Opted-in to DNA Portion?	Yes	No	Reason for opt-out of DNA: No: Protocol is not currently enrolling	No: Not approached per physician request	No: Not approached because parents unavailable/too stressed	No: Not approached for language reasons	No: Not approached because study personnel unavailable	No: Declined because generally not interested in research	No: Declined because parents have issues with this protocol	No: Enrolled in another research study	No: Other (specify on Screen Fail Summary Sheet)
	0	0	0	0	0	0	0	0	0	0	0

Eligible & Consented to Questionnaire, FATHER Opted-in to DNA Portion?	Yes	No	Reason for opt-out of DNA: No: Protocol is not currently enrolling	No: Not approached per physician request	No: Not approached because parents unavailable/too stressed	No: Not approached for language reasons	No: Not approached because study personnel unavailable	No: Declined because generally not interested in research	No: Declined because parents have issues with this protocol	No: Enrolled in another research study	No: Other (specify on Screen Fail Summary Sheet)
	0	0	0	0	0	0	0	0	0	0	0

NIH Demographic Reporting

For NIH demographics reporting, we will only report demographic data on subjects that are actually being studied (eligible subjects that are maintained in the REDCap database).

Therefore, for IRB human-subject protection purposes, enrollment begins at data storage (includes screen failures) and for NIH demographic reporting purposes, enrollment begins at assignment of a study ID and entry into the REDCap database.

7 Consenting

Informed Consent Form (ICF)

CRM + Chart Review Study: An IRB approved Informed Consent is not required for participation in this portion of the study, unless your site co-PIs specifically requested a local ICF.

Currently, Case Western and Washington must discuss consent and use ICFs for this portion. Northwestern, Alabama and Miami are approved to conduct the CRM + Chart Review Study without consent (waiver-of-consent has been approved by IRBs).

> Case Western and Washington: No CRM data may be stored on a research server prior to obtaining informed consent and a signed ICF. Study participants will be recruited by

approaching guardian before the eligible baby reaches 7 days (168 hours) post-delivery. (Please review the screening log for eligibility guidance). Each center will have an ICF approved by their local IRB.

Northwestern, Miami and Alabama: These sites do not need to approach parents or discuss consent before enrollment

DNA + Questionnaire Study: All sites will discuss consent and use an ICF approved by their local IRB. Some sites have combined consent forms.

Case Western: Babies whose guardian has signed the CRM + Chart Review protocol ICF are automatically enrolled in the DNA + Questionnaire protocol and may be included in the questionnaire portion of this protocol. For the DNA portion of the DNA +Questionnaire protocol, participants will be recruited by approaching biological parents and guardians before discharge from hospital, to discuss consent and obtain signed the DNA + Questionnaire protocol ICF for the infant and both biological parents.

Washington: Babies whose guardian has signed the CRM + Chart Review ICF are automatically enrolled in this protocol and may be included in the questionnaire portion of DNA + Questionnaire Study. If the guardian has checked the box allowing opt-in to the DNA portion of DNA + Questionnaire Study, DNA samples from the baby are permitted. Biological parents must each sign a DNA + Questionnaire Study consent from before the parental DNA sample is permitted.

Northwestern, Miami and Alabama: Participants will be recruited by approaching parents and guardians before discharge from hospital, to discuss consent and obtain signed ICF. If the guardian/parents check the box allowing opt-in to the DNA portion, DNA samples are permitted.

Note: If both biological parents are not available, either one may consent to have the baby and him or her (or just the baby) enrolled in the DNA portion of the study. However, each site is expected to continue enrolling families in the Biorepository and Questionnaire Study until it has collected 100 complete trios including baby and both biological parents.

Informed Consent Summary

Site	**19606 CRM + Chart Review**	**19978 Questionnaire**	**19978 DNA**
1. Case Western	Consent before data storage	Included in 19606 consent	Consent before DNA
2. Northwestern	No consent	Consent before questionnaires	See opt-in box on consent
3. Alabama	No consent	Consent before questionnaires	See opt-in box on consent
4. Miami	No consent	Consent before questionnaires	See opt-in box on consent
5. Washington	Consent before data storage	Included in 19606 consent	Included in 19606 consent

Individuals Obtaining Consent

At each site, a group of clinicians and the site CRC, and other qualified, approved staff will be trained in the consent process for Pre-Vent. These individuals will have completed training in research ethics required by their local IRBs. In addition, they will be familiar with the Pre-Vent study

background, aims, eligibility criteria, and conduct, having completed a computer-based learning module or similar training. They will understand the eligibility criteria and the contents of the ICF. Individuals that will be obtaining informed consent should be listed with the IRB as well as on the Personnel and Delegation of Duties Form.

Signing Informed Consent Form (ICF)
After a study team member has discussed the study with the guardian and biological parents, allowed time for the guardian/parents to read the ICF, and answered any questions about the study, the guardian/parents may elect to sign the ICF. Obtain signatures on the ICF per your site IRB requirements.

For twins, local IRB's may require that the guardian sign two ICFs, one for each infant. Once you have determined what the signature requirements are for your site please assure that consent signatures are obtained in a consistent manner.

Non-English-Speaking Mothers
If a guardian/parent, does not speak English, some study centers will have an IRB-approved process whereby a professional interpreter participates in all phases of the consent process. If this case, and if the guardian/parent consents, he/she and the interpreter will sign a form(s) in a manner approved by the local IRB.

8 Safety Reporting

9 Training

Documentation of Training

Each site is responsible for training all relevant personnel in conduct of the study, and keeping records of this training. All appropriate individuals should be adequately trained on the protocol and study procedures. Individuals not present at the initiation visit should receive training by the CRC and/or Principal Investigator. Training should be documented on the Training Log (see Attachments).

Retraining after protocol deviations or modifications
If there are significant issues with protocol deviations at individual or multiple sites, or if there are significant protocol modifications in the course of the study, providers will undergo educational updates and retraining as deemed necessary by site PIs or UVA PIs.

Personnel and Delegation of Duties Form
All appropriate individuals should be listed on the Personnel and Delegation of Duties Form (see Attachments). Individuals performing procedures that are a part of standard of care do not need to be listed on this form (Infusion nurses, Phlebotomists, etc.).

10 Regulatory Considerations

Updated Regulatory Documents
Updated regulatory documents should be sent to the UVA CRA as necessary. Updated Informed Consent Forms will need to be submitted to the UVA CRA for review and approval prior to submission.

11 Electronic Case Report Forms

Directions for completing the study case report forms are provided in the eCRF Completion Guidelines document. Additionally, you can contact the UVA PM or CRA with any additional questions.

Site staff listed on the Personnel and Delegation of Duties Form and with active REDCap account are authorized to enter data or make corrections in REDCap.

The electronic CRFs in REDCap are used to record study data and are an integral part of the study and subsequent reports. Therefore, the CRFs should be completed for each subject according to the subject's source data, within 14 days after the subject's completed visit.

Data entry will be reviewed monthly (if not more frequently) for compliance and a summary provided to the site, along with a query log, as necessary.

12 Source Documents

For every entry in the eCRFs, there must be an entry providing the same information in the source document. The source document entry must be the original recording of the information. For most clinical information, the source documentation is the medical record (which is most likely electronic). Electronic medical documents do not need to be printed and maintained for the purposes of this study.

The standard rule for completion of source documents, as well as CRFs, is "If it is not documented, it did not happen."

Questionnaires

The Inpatient Questionnaire and 52 Week Visit Questionnaire must be read verbatim as they are to the parent, guardian or appropriate caretaker of the baby.

The questions in Section I **only** (current meds, respiratory support, and feeding) of the 52 Week Visit questionnaire may be answered by reviewing the EMR instead of relying on parent response.

13 Appendices

Training tools, documents and other study-related materials are on the UVa Box website: https://virginia.box.com/v/Pre-VentSharedFolder