Clarification of Optimal Anticoagulation Through Genetics

A Randomized, Multicenter, Double-Blind Clinical Trial to Evaluate Efficacy in the Use of Clinical Plus Genetic Information to Guide Warfarin Therapy Initiation and Improve Anticoagulation Control for Patients.

http://www.coagstudy.org

Manual of Procedures (MOP)

Version 1.1.20111201

The Clinical Trial Coordinating Center (CTCC) at
The University of Pennsylvania School of Medicine,
Department for Epidemiology and Biostatistics

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Manual of Procedures (MOP)

Table of Contents

1. BACKGROUND AND STUDY ORGANIZATION 1
1.A. Background 1
1.B. Study Organization and Summary of Responsibilities 2
1.B.1. Sponsor: 2
1.B.2. Clinical Trial Coordinating Center: 3
1.B.2.a) Medical Monitor 4
1.B.3. Clinical Sites: 4
1.B.3.a) Principal Investigator (PI) 5
1.B.3.b) Research Coordinator (RC) 5
1.B.3.c) Clinical Site Research Pharmacy 6
1.B.3.d) Clinical Site Genotype Laboratory 7
1.B.4. Central Laboratory: 7
1.B.5. Investigational Drug Service: 7
1.B.6. Steering Committee: 8
1.B.7. Executive Committee: 8
1.B.8. Data and Safety Monitoring Board (DSMB): 8
2. STUDY DESIGN, OBJECTIVES, AND ENDPOINTS 9
2.A. Study Flow and Study Visit Time Line 9
3. PARTICIPANT ENROLLMENT 12
3.A. Initiation of a New Study and the Enrollment Process 12
3.B. Participant Population and Recruitment 13
3.B.1. Participant Population: 13
3.B.2. Participant Recruitment: 13
3.B.3. Pre-screening: 14
3.C. Participant Screening and Enrollment Visit 14
3.C.1. Informed Consent: 14
3.C.2. Administration of Informed Consent: 15
3.C.3. Confidentiality: 16
3.D. Participant Documents 17
3.D.1. Source Documentation 17
3.E. Assignment of Participant Identification 18
3.F. Participant Eligibility 18
3.F.1. Inclusion Criteria: 18
3.F.2. Exclusion Criteria: 18
3.F.3. Deferral Criteria: 20
3.G. Screening Failures 20
3.H. Randomization Procedure 20
3.I. Enrollment Timeframe and Venipuncture for Genotype Testing 20
3.I.1. Collection of Genotype Specimen 21
3.I.2. Communication with Site Laboratory and Central Laboratory 21
4. Dosing Interventions and Dose Requests 22
4.A.1. Dose Requests 23

4.A.2. Contact with Site Research Pharmacy 24
4.A.3. Patient Dosing Instructions 24
4.A.4. Over-ride of Dose Titration in Both Intervention Arms 25

5. Participant Follow-Up 26
5.A. Overview of Study Follow-Up Plan 26
5.B. Types of Follow-Up Visits 26
5.B.1. Scheduled Visits: 26
5.B.2. Interim Visits: 27
5.B.3. Follow-up Visit Locations: 27
5.C. Allowable Visit Windows: 27
5.C.1. VISIT WINDOW 27
5.C.2. Missed Visits: 29
5.D. Follow-Up Visit Procedures 29
5.D.1. Follow-up Procedures for Participant INRs 29
5.D.2. Forms Completion at each Follow-up 30
5.D.2.a) Week One (Day 4- visit 2) 30
5.D.2.b) Week One (Day 7- visit 3) 30
5.D.2.c) Week Two (visit 4) 31
5.D.3. Week Two (visit 5) 31
5.D.3.a) Week Three (visit 6) 32
5.D.3.b) Week Four (visit 7) – Primary Endpoint and Unblinding Visit 32
5.D.3.b.(1) Participant Unblinding Procedure at Week Four 33
5.D.3.c) Month 2 (visit 8) - Telephone Visit 33
5.D.3.d) Month 3 (visit 9)- In-person Visit: 34
5.D.3.e) Month 4 (visit 10) – Telephone Visit 34
5.D.3.f) Month 5 (visit 11) – Telephone Visit 35
5.D.3.g) Month 6 (visit 12) – In person Final Visit 35
5.E. Participant Retention 35
5.E.1. Follow-Up Procedures for Participants Who Discontinue Study Drug 36
5.E.2. Participant Transfer 36
5.F. Participant Withdrawal and Withdrawal of Consent 36
5.F.1. Voluntary Withdrawal 36

6. CONCOMITANT MEDICATIONS 38
6.A. Collecting Concomitant Medication Data 38
6.A.1. Using the Concomitant Medication Dictionary: 38

7. ADVERSE EVENTS 41
7.A. Identification of Adverse Events (AE) 41
7.B. Adverse Event (AE) Definitions 42
7.C. Classifying Adverse Events 42
7.C.1. Severity and Seriousness: 42
7.C.2. Relatedness: 43
7.C.3. Expectedness: 43
7.C.4. Known Events Associated with Warfarin Use: 43
7.C.4.a) Out-of-Range INR Values 43

7.C.4.b) Bleeding Events 44
7.D. Adverse Event Reports 44
7.D.1. Serious Adverse Events (SAE): 45
7.D.2. Unanticipated Problem Definition: 45
7.D.2.a) Unanticipated Problem Example 45
7.D.3. Filing an Unanticipated Problem Report: 46
7.E. Adverse Event Coding Using CTCAE and MedDRA 46
7.F. Medical Monitor 49
7.F.1. Patient Safety and Unblinding: 49
7.F.2. Warfarin Dosing Adjustments: 49
8. DATA COLLECTION AND ADMINISTRATIVE FORMS 51
8.A. Case Report Forms (CRFs): 51
8.A.1. Types of Case Report Forms: 51
8.A.2. General Instructions: 51
8.A.3. Directions for Completing the Header Information: 52
8.A.4. Review of Completed Case Report Forms: 53
8.B. Case Report Form (CRF) Completion Guidelines: 53
[ENROLL] Enrollment Information: 55
[ELIG] Eligibility Confirmation: 61
[RAND] Randomization: 67
[GENOTYPE] Genotyping Information: 69
[DOSREQ] Dose Requisition – Initiation Period: 73
[DOSREQ2] Dose Requisition – Titration Period: 77
[PERSHX] Personal History Form: 81
[MEDHX] Medical History Form: 83
[DIET] Diet Information: 91
[DIETFUP] Diet Information Follow-Up: 95
[EUROQOL] EQ-5D Health Questionnaire: 99
[SF-36] Health Status Questionnaire (SF-36™): 103
[INRLOG] INR Log: 111
[AE] Adverse Events: 113
[CMED] Concomitant Medications: 115
[VISIT] Follow-Up Visit Form: 117
[EVENTS] Medical Events: 121
[WARFLOG] Warfarin Log: 141
[DASS] Duke Anticoagulation Satisfaction Survey (DASS): 143
[MMS] Modified Morisky Scale (MMS): 149
[WSTOP] Early Warfarin Stop: 151
[SSTOP] Study Stop: 153
[UNBLIND] Unblinding: 157
[COAGCONS] COAG Consent: 161
[PIDLOG] Participant ID Log: 163
[PTCONT] Participant Contact Information: 165
[DPCS] Data Processing Cover Sheet: 167
[COMMENT] Comments Sheet: 169

8.C. Submission of Case Report Forms to the CTCC 170
8.D. Data Quality Management Procedures 170
8.D.1. Queries: 170
8.D.2. Types of Queries Generated by the Database: 170
8.D.2.a) Missing Fields 170
8.D.2.b) Skip Patterns 171
8.D.2.c) Range Checks 171
8.D.2.d) Logic Checks 171
8.D.3. Types of Queries Generated by Manual Monitoring: 171
8.D.3.a) Monitoring Checks 171
8.D.4. Managing Queries: 171
8.D.4.a) Receiving Queries from CDM 171
8.D.5. Making Corrections Based on Queries: 172
8.D.6. Query Response to the CTCC: 172

9. Data Management System Users Guide 173
9.A. Introduction 173
9.B. Oracle JInitiator 173
9.C. SSL Certificate: 175
9.D. Data Management System Web Site: 178
9.E. COAG -- MAIN MENU 180
9.F. Data Management System log in: 181
9.G. COAG – Clinical Center Main Menu – For Research Coordinators 182
9.H. Participant Registration: 183
9.I. Visit Entry – First Entry 184
9.J. Second entry for ENROLL and ELIG only 188
9.K. Data entry – Dose Requisition: 190
9.L. Data entry – Other Log Forms 194
9.M. Entry Status 195
9.N. Editing 198
9.O. Data Management System (DMS) Screen Module for Unblinding 199
9.P. Visit Schedule Report DMS Instructions 207

10. SPONSORED PROJECT HELP DESK 208
10.A. Technical Support 208
10.B. Assignment of Data Management System (DMS) Accounts 208

11. APPENDICES 210
11.A. Appendix 1 – Warfarin Dosing Instructions 210

1. BACKGROUND AND STUDY ORGANIZATION

1.A. Background

Warfarin sodium is one of the top 20 medications used in the US. Its use will only increase as the population ages. Warfarin is highly efficacious at preventing thromboembolism (TE), a condition associated with substantial morbidity and mortality. Numerous conditions put patients at risk for TE, including atrial fibrillation, deep venous thrombosis, mechanical heart valves, and dilated cardiomyopathies. However, warfarin must be dosed properly to avoid life-threatening complications (from overdosing) and lost efficacy (from underdosing).

The impetus for identifying clinical and genetic factors that alter warfarin dose response, thus better predicting starting dose, is that warfarin dose requirements vary widely among patients and are typically identified by trial and error, putting patients at risk for complications and drug failure. Although the average maintenance dose is 4-6 mg per day, warfarin dose requirements can vary over 30-fold and warfarin has an unusually narrow therapeutic range. Current practice relies primarily on empirical dosing (i.e., giving all patients the same starting dose, regardless of clinical and genetic factors). For example, at many centers in the US, most patients are begun empirically on 5 mg/day during the "initiation phase" of warfarin on the basis of population averages, and the dose is titrated based on response, as measured by repeated measures of the international normalized ratio (INR). Because of empiric dosing, the dose of warfarin must be changed frequently when initiating therapy in response to out-of-range INRs, and frequent (up to several times a week) monitoring is needed during this initiation phase. The practice of empiric dosing results in improper dosing in a large number of individuals, and out-of-range INRs are extremely common early in therapy (e.g., 57%5 to 69%). These improper levels of anticoagulation (AC) provoke life-threatening bleeding and thromboembolic complications, resulting in substantial morbidity and cost.

Variability in warfarin dose-response is related to both clinical and genetic factors. Many patient and environmental factors (herein referred to as "clinical factors") that can influence warfarin response have been identified over warfarin's more than 50 years of use. However, despite knowledge of these factors, a large proportion of variability in warfarin dose requirements remains, and dosing algorithms have, to date, had limited success. One possible reason for the limitations of prior dosing algorithms is that they do not incorporate genetic factors that alter warfarin dose requirement. As a result, interest has turned to understanding genetic factors that may play a role in warfarin response.

Two genes, the cytochrome P-450 family 2 subfamily C polypeptide 9 enzyme (CYP2C9) gene and the vitamin K epoxide reductase complex 1 (VKORC1) gene, have been the focus of extensive studies. Because of the difficulties of dosing warfarin and the multifactorial nature of warfarin response, the concept of dosing algorithms that use clinical and genetic variables to improve AC management, reduce complications, and enhance efficacy has real potential. The conceptual framework of this trial is that, by choosing a dose early in the course of therapy that is more likely to be an individual's ultimately required stable dose, the degree of improper anticoagulation that is common early in therapy can be reduced.

This proof-of-concept trial is important because, despite our current understanding of the influence of clinical factors and genetic factors on warfarin dosing, formal testing of the utility of a genetic-guided dosing strategy among a large, diverse group of patients using warfarin has not been rigorously performed.

In August 2007, the US Food and Drug Administration (FDA) announced the approval of revised warfarin labeling, to explain that patients' genetic makeup may influence how they respond to the

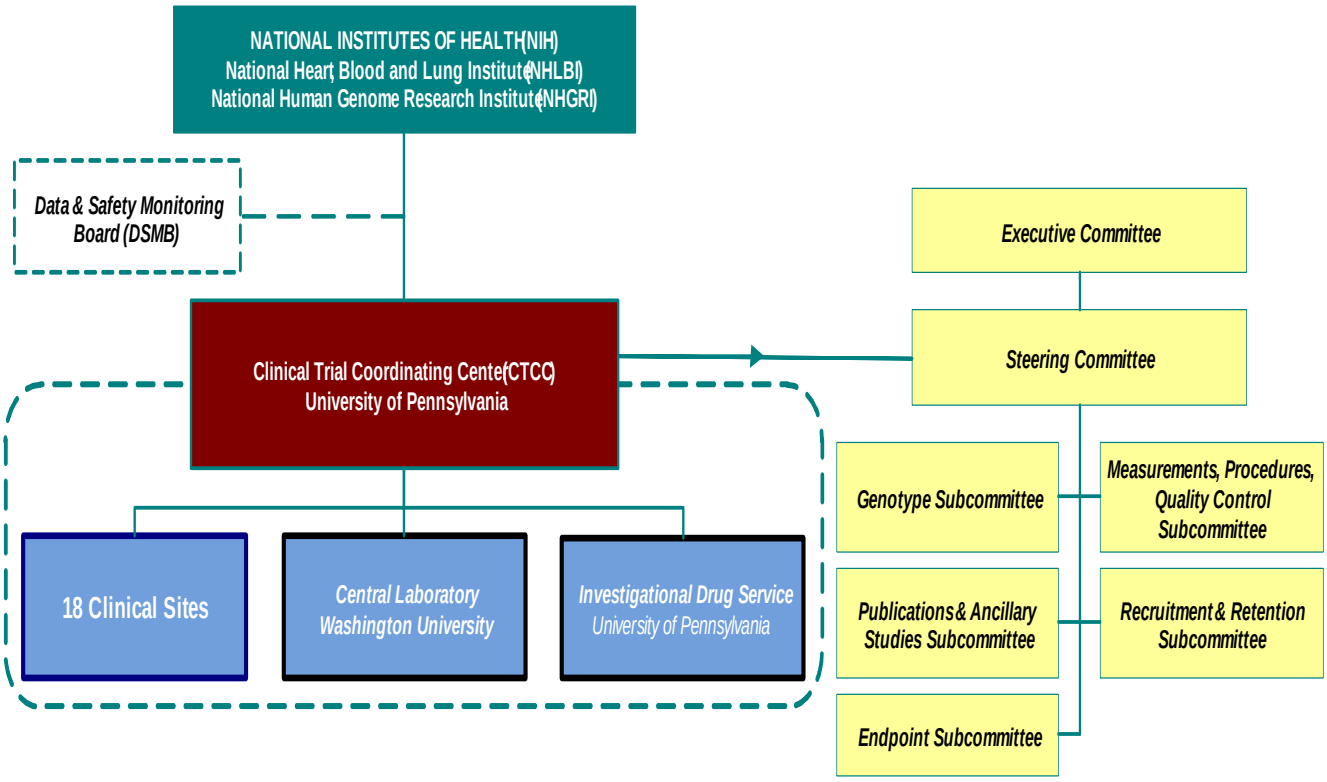
drug and that genetic information could be used to determine initial dosing. In addition, the Centers for Medicare and Medicaid Services have recently asked for public comment on pharmacogenetic testing, highlighting warfarin, because of the "relative scarcity of high-quality published evidence from outcome-related clinical trials about the clinical utility due to pharmacogenetic testing at this time."

In summary, current dosing practices for warfarin are empiric and result in the need for frequent dose changes as the INR gets too high or too low. As a result, patients are put at increased risk of TE, bleeding, and premature discontinuation of a highly efficacious therapy. Also, primarily because of difficulties using the drug, there is substantial under use of warfarin in millions of patients who would benefit from AC. There is clearly a need to improve warfarin management. In order to definitively determine if the use of clinical plus genotype-based dosing will translate into improvement of AC control, a large, rigorously controlled, randomized trial is necessary.

1.B. Study Organization and Summary of Responsibilities

The COAG study is a multi-center, randomized, double-blind, phase IIb clinical trial comparing clinical and genotype plus clinical approaches to guiding warfarin therapy initiation. The organization of the COAG study is designed to promote study collaboration and facilitate effective communication and utilization of resources among a network of clinical investigators and research scientist in the conduct and operations of the COAG clinical trial.

Figure 1: COAG Organizational Chart



1.B.1. Sponsor:

The National Institutes of Health (NIH) - National Heart, Blood and Lung Institute (NHLBI) is the primary funding agency for the COAG study. The Atherothrombosis and Coronary Artery

Disease (ACAD) Branch, Division of Cardiovascular Diseases, NHLBI will be responsible for oversight and administration of the scientific conduct of the trial. The NHLBI Project Officer and Program Director, Yves Rosenberg, M.D., M.P.H. serves on the COAG, Steering Committee, the Executive Committee, and the Data and Safety Monitoring Board and will oversee all final decisions on recommended protocol changes and on other issues of importance to the overall conduct of the COAG study.

Staff representatives from the Division of Research Activities, NHLBI, Office of Biostatistics Research, NHLBI, Office of Acquisitions, NHLBI, and office of Population Genomics National Human Genome Research Institute (NHGRI) will be involved in all major decisions affecting the course of the study.

1.B.2. Clinical Trial Coordinating Center:

The Clinical Trial Coordinating Center (CTCC) at University of Pennsylvania School of Medicine, Department for Epidemiology and Biostatistics has the responsibility for the overall coordination of study related activities. Coordinating Center staff includes professionals in biostatistics, epidemiology, data processing and monitoring, systems technology, administration, contracts, and communication coordination. Stephen E. Kimmel, MD, MSCE, is the Principal Investigator for the CTCC has primary responsibility for overall study compliance, quality assurance, and data integrity. He is responsible for providing annual progress reports to the NHLBI, and periodic progress reports to the Steering Committee and DSMB. Specific responsibilities of the CTCC include:

- Executing annual contract agreements with the Clinical Sites and Central Laboratory
- Coordinating the development of the study protocol, study forms and manual of procedures
- Develop the statistical design of the study
- Develop and maintain an Internet-base data capture system for the collection of study data
- Develop and maintain a Web site for facilitating study communications
- Provide ongoing education and training to clinical site staff in study procedures, clinical trials management, and data collection procedures
- Manage quality control aspects associated with the reporting and management of data (monitor data entry activities and error rates, data control, documentation of database changes)
- Prepare data quality reports.
- Monitor clinical site performance for participant safety, protocol adherence and data integrity
- Prepare periodic reports on clinical site recruitment and retention performance
- Organize site visits and perform study audits
- Prepare an analysis plan in conjunction with the Data and Safety Monitoring Committee for analyzing the frequency of specified events including adverse events and other study outcomes related to participant safety.
- Prepares interim and final statistical reports

- In collaboration with Principal Investigators and study leadership, prepare manuscripts of the study results for publication.
- Track and monitor reported serious adverse events
- Track IRB approvals and expirations and provide other regulatory support as necessary
- Coordinate conference calls and study meetings.
- Provide logistical support for in-person meetings; prepare and distribute meeting materials, summaries, and follow-up on action items

1.B.2.a) Medical Monitor

The Medical Monitor, Dr. Scott Kasner, is a licensed physician and Vascular Neurologist associated with the CTCC, and serves in an independent role. The Medical Monitor will be unblinded to study dose and treatment arm assignment for all patients enrolled in the study. The Medical Monitor is responsible for:

- Managing requests for warfarin dose adjustments
- Authorizing requests for dose unblinding
- Serving as a resource to investigators and coordinators for urgent concerns related to patient safety, particularly when such concerns might require interruption or cessation of the study intervention and /or any deviation from the study protocol.
- Reviewing SAE reports and major bleeding events

1.B.3. Clinical Sites:

Eighteen (18) clinical sites are responsible for recruiting, enrolling, evaluation, and follow-up of COAG study participants according to the COAG Protocol and procedures.

Each clinical site is supported by a separate Agreement with the Clinical Trial Coordinating Center. Key clinical site study team includes the Principal Investigator (PI) and the Research Coordinator (RC) and Research Pharmacist. It is the responsibility of all members of the study team to adhere to the study protocol and Manual of Procedures (MOP).

The participating clinical sites are:

Clinical Sites	Principal Investigator
University of Texas	Sherif Abdel-Rahman, PhD
Mount Sinai School of Medicine	Robert J. Desnick, PhD, MD
University of California, San Francisco	Margaret C. Fang, MD, MPH
Washington University School of Medicine	Brian F. Gage, MD, MSc
University of Maryland School of Medicine	Richard B. Horenstein, MD
University of Florida	Julie A. Johnson, PharmD
Henry Ford Hospital	Scott Kaatz, DO, MSc, FACP
Mayo Clinic College of Medicine	Robert D. McBane, MD
Hospital of the University of Pennsylvania	Emile R. Mohler, III, MD

Clinical Sites	Principal Investigator
Vanderbilt University	James A. S. Muldowney III, M.D., F.A.C.C.
Intermountain Medical Center	Scott M. Stevens, MD
Marshfield Clinical Research Foundation	Steven Yale, MD, FACP
Duke University Medical Center	Thomas L. Ortel, MD, PhD
Georgia Health Sciences University	Jaspal S. Gujral, MBBS, MRCP
University of Alabama at Birmingham	Nita A. Limdi, Pharm.D, PhD, MSPH
University of Utah Health Care	Robert Pendleton, MD
Tulane University	Patrice Delafontaine, MD
Montefiore Medical Center	Henny Billett, MD

1.B.3.a) Principal Investigator (PI)

The PI is responsible for the overall conduct of research activities at the clinical site. This includes:

- Ensuring that all site personnel assisting in the conduct of the study adhere to the study protocol and procedures
- Spend adequate time in the clinic to observe study procedures and to hold regular discussions with staff to review all aspects of the study and to resolve any problems that may arise
- Review reported adverse events, determine level of severity and assign relationship to study intervention.
- Promptly reports to the Sponsor/CTCC and IRB all changes in research activity and all unanticipated problems involving risk to human subjects
- Make no changes to the research protocol without obtaining prior Steering Committee and IRB approval except in circumstances to minimize immediate threats to the safety of human subjects
- Represent the clinical site at study steering committee meetings and assigned sub-committee meetings

1.B.3.b) Research Coordinator (RC)

The PI may delegate some or all of the responsibilities to the Research Coordinator:

- Submit copy of IRB approval letter and approved informed consent to the CTCC prior to study initiation. Also submit to the CTCC, the IRB approval letter and revised informed consent for all protocol amendments that occur throughout the study.
- Maintain IRB correspondence and regulatory documentation
- Recruit potentially eligible participants for clinical trial enrollment
- Evaluate study participants for protocol eligibility
- Obtain informed consent from the participants before initiating research-related activities

- Instruct and educate participants regarding study interventions and anticipated side effects and their management
- Develop strategies to retain study participants in a clinical trial
- Schedule tests and study visits and phone contacts for participants within timeframes required by the protocol.
- Ensure the accuracy and completeness of data; Enter study data from paper CRFs to electronic systems;
- Respond and resolve data queries with the CTCC in a timely manner.
- Perform quality inspection on aspects of data collection that were completed by other study staff
- Maintain source documentation for each study participant in accordance with the protocol.
- Ensure the collection and shipping of the genotype blood specimens within required timeframe, or if not possible, as soon as possible after initiating first drug dose
- Identify abnormal INR laboratory results and inform PI/clinician.
- Submit only investigator/clinician approved request for study agent to the research pharmacist
- Provide written instructions for taking study drug to out-patient participants
- Inform the research pharmacist of clinicians study drug change requests (over-rides) and correctly enter the request into the data management system.
- Facilitate information and communications between the PI and Medical Monitor and Medical Monitor and site Research Pharmacist for dose adjustments (over-rides) requests.
- Collect returned study drug
- Monitor participant dosing compliance
- Identify and document Adverse Events (AEs) and Serious Adverse Events (SAEs)
- Initiate SAE reporting and notify appropriate individuals stated in the protocol, and submit reports according to procedures outlined in MOP. Provide supporting information on reported SAEs as requested
- Inform PI of any protocol deviations/violations
- Participate in regularly scheduled conference calls with the Coordinators Group.
- Notify the CTCC of all changes in clinical` site study personnel.

1.B.3.c) Clinical Site Research Pharmacy

The Research Pharmacist is responsible for:

- Maintaining study drug supply, receipt, storage, preparation, dispensation, and disposal or return
- Accountability of pharmacy drug records and record security

- Dispensing dose and quantity according to data management system dose calculation module
- Accurately entering the dose dispensed for each patient into the data management system
- Communicating with the Medical Monitor when a dose adjustment (over-ride) is requested by study investigator.
- Maintaining the integrity of the blinded drug dose and not reveal participant dose information to site PI, other investigators, or Research Coordinator. Will only reveal dose information in an emergency situation wherein the medical monitor cannot be reached.

1.B.3.d) Clinical Site Genotype Laboratory

The site genotype laboratory is responsible for:

- Extracting DNA from participant specimen received and conducting genotyping
- Completing Genotype case report form information
- Entering Genotype case report form information into the data management system
- Maintaining the blinding of genotype information and will not reveal participant genotype to site PI, other investigators, or Research Coordinator.
- Contacting the Central Laboratory if genotyping fails after second attempt.
- Conducting ongoing quality assurance proficiency testing on samples specified by the Central Laboratory

1.B.4. Central Laboratory:

Washington University School of Medicine-Department of Pathology and Immunology in St. Louis, MO serves as the Central Laboratory (CL) for the COAG study The Central Lab will be responsible for implementing a quality assurance (QA) plan, ensuring accurate genotyping results from the clinical sites by replicating genotyping on samples sent from the Clinical Sites. The CL should describe a process of QA periodic random sampling and testing over the course of the study. Research Coordinator procedures for blood collection, shipping and storage as well as clinical laboratory staff genotyping and data entry procedures are provided in the Laboratory Manual of Procedures. Training and certifying clinical laboratory staff will be conducted by the Central Laboratory.

During the study the CL will coordinate with the CTCC to provide genotyping data as needed. The CL will document a process for data transfer of the comprehensive lab data set to the CTCC. At the end of the contract period, the CL will transfer all biospecimens and laboratory data to an NIH-designated repository.

1.B.5. Investigational Drug Service:

The Investigational Drug Service at the University of Pennsylvania will prepare the packaging, labeling, and distribution of blinded study drug to all clinical site research pharmacies. The IDS is responsible for providing site research pharmacists training in all study procedures related to dispensing, storage, accounting and inventory of blinded study drug. See Research Pharmacy Manual of Procedures and Data Management System Manual for Research Pharmacy.

1.B.6. Steering Committee:

The Steering Committee is the main governing body of the study. Membership of the Steering Committee will include the Steering Committee Chair, CTCC PI, the NHLBI Project Officer and staff of the NIDDK and NHGRI, the Clinical Site PIs. All major scientific decisions will be determined by vote of the Steering Committee. Except for the organizational period, the Steering Committee will meet approximately semi-annually in person and hold regularly scheduled conference calls.

Subcommittees of the Steering Committee will be established as needed by the Steering Committee. Standing subcommittees include, Genotyping, Publications and Ancillary Studies, Recruitment and Retention, Endpoints, Measurements/Procedures and Quality Control. Clinical site PIs will chair and participate in subcommittees.

Specific responsibilities of the Steering Committee include;

- Determining the scientific aims of the study
- Developing the study design and establishing participant eligibility requirements
- Developing the protocol and overseeing protocol implementation
- Addressing protocol issues and approving protocol amendments
- Establishing subcommittees and taskforces, as needed
- Serving as the scientific forum for the study for reviewing and reporting data
- Approving all ancillary study proposals
- Monitoring overall study quality control

The Steering Committee will also monitor the publishing of results, assigning priorities to the publishing of study results, settle issues regarding authorship, review and approve manuscripts before they are submitted.

1.B.7. Executive Committee:

The Executive Committee will monitor day-to-day operations related to the conduct of the study, and as appropriate, make decisions on behalf of the Steering Committee. The Executive Committee will consist of the Chair of the Steering Committee, the CTCC PI, and the NHLBI Project Officer.

1.B.8. Data and Safety Monitoring Board (DSMB):

The members of the DSMB are appointed by the NHLBI. The DSMB acts to independently monitor and assess study safety. Specific responsibilities of the DSMB include:

- Conducting in-depth reviews of the progress of the study at established intervals which includes evaluating participant accrual and adherence to protocol
- Reviewing outcome data and making recommendations to the NHLBI regarding continuation, modification, or early termination of the study should it become necessary to protect the safety and welfare of the participants

2. STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

This Clarification of Optimal Anticoagualtion through Genetics (COAG) study is a randomized, multicenter, double-blind trial comparing two approaches to guiding warfarin therapy initiation. Prior to initiating warfarin therapy, participants will be recruited from up to 12 US academically-affiliated clinical sites from both the inpatient and outpatient level of care.

Clinical and genotype data will be collected on all participants. All participants who meet eligibility criteria at baseline screening will then be randomized to one of the two study dosing intervention arms: the genotype-guided dosing arm or the clinical-guided dosing arm, which will test the effects of algorithm guided dosing over the first 4-5 days of therapy.

The primary objective of the study is to compare the two strategies with respect to the time participants spend within the therapeutic INR range (PTTR) during the first 4 weeks of therapy:

- initiation of warfarin therapy based on algorithms using clinical information and an individual's genotype using genes known to influence warfarin response ("genotype-guided dosing"), and
- initiation of warfarin therapy based on algorithms using only clinical information ("clinical-guided dosing").

Each arm will include a baseline dose initiation algorithm and a dose revision algorithm applied over the first 4-5 doses of warfarin therapy. Thus, the intervention will be applied over these first 4-5 days (the "intervention period"). Following this period, dose titration will be the same between arms and blinded treatment assignment and warfarin dose will continue for the first 4 weeks of the trial (up to the primary endpoint). By comparing the two strategies in this trial, the study will be able to determine if genetic information provides added benefit above and beyond what can be done simply with clinical information.

Secondary objectives of the study are to compare the two strategies with respect to the PTTR during the first 2 weeks and 3 and 6 months of therapy; other outcomes at 2 and 4 weeks and 3 and 6 months, including time to stable warfarin dosing and INR above range (>4.0); number of dose changes required; and major clinical outcomes, including major bleeds, combination of major and minor bleeds, combination of major bleeds and thromboembolic complications, cost, and quality of life.

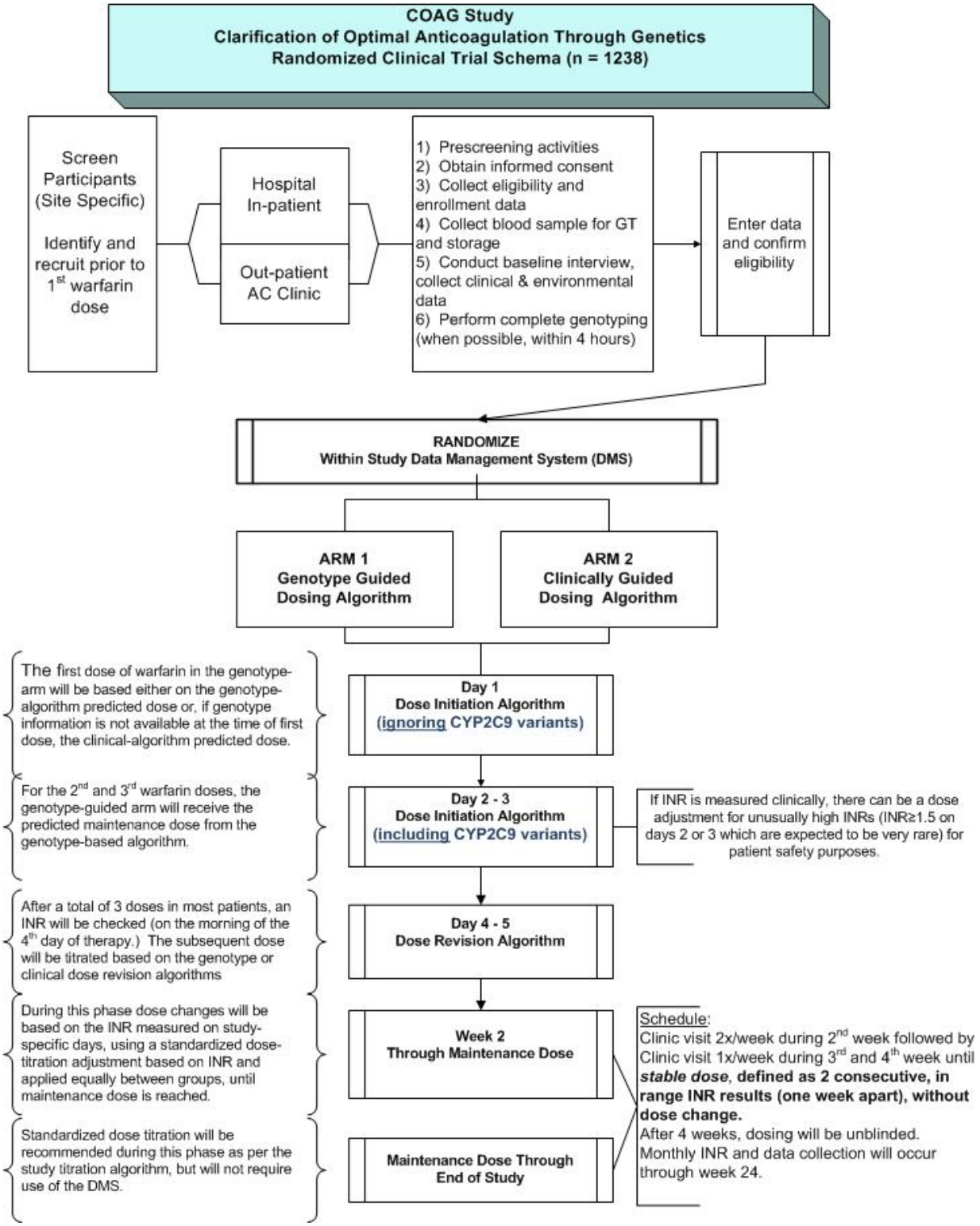
The primary endpoint of this study is the percentage of time participants spend within the therapeutic INR range (PTTR) during the first four weeks of therapy. This will be calculated from the INR values using the standard method that assumes a linear change in INR from one measurement to the next using the method of Rosendaal et al.[78]

2.A. Study Flow and Study Visit Time Line

The study will be conducted over a period of 36 months. Study visits will be followed according to the protocol visit schedule for the duration of 24 weeks. The first 4 weeks of treatment duration is a blinded study phase with 20 weeks of unblinded follow-up. Study participants, investigators and clinical site personnel will remain blinded to warfarin dose, genotype, and study arm. The site genotype laboratory technician will be unblinded to genotype only. The site research pharmacist will be unblinded to warfarin dose only. There is NO placebo capsules used in this trial. After 4 weeks (primary outcome duration), clinicians will be informed of the actual dose the patient is taking and patients will then receive their warfarin through their ususal pharmaceutical outlet. All clinicians will remain blinded to study arm until completion of the trial.

The following is a diagram of the study flow and a table of the schedule of study visits:

Figure 2: COAG Study Flow Diagram



VISIT Schedule [VSTSCH V2.0.20100816]

Visit description	Month 1			Month 1		Month 1	Month 1	Month 2[T]	Month 3	Month 4[T]	Month 5[T]	Month 6
	SCR/BL	Week 1		Week 2		Week 3	Week 4					
	Day -1/0	Day 4	Day 7	Day A	Day B							
Data collection schedule	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Informed Consent	X											
COAG Consent (***COAGCONS***)	X											
Participant Contact Information and updates (***PTCONT***)	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment Information (***ENROLL***)	X											
Eligibility Confirmation (***ELIG***)	X											
Randomization (***RAND***)	X											
Genotyping Information (***GENOTYPE***)	X											
Dose Requisition Information (***DOSREQ/DOSREQ2***)	X	X	X	X	X	X	X	PRN	PRN	PRN	PRN	PRN
Personal History Form (***PERSHX***)	X											
Medical History (***MEDHX***)	X											
Diet Information and updates (***DIET / DIETFUP***)	X					X	X		X			X
EQ-5D Health Questionnaire (***EUROQOL***)	X				X		X		X			X
Health Status Questionnaire (***SF-36***)	X						X		X			X
INR Log (***INRLOG***)	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (***AE***)	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications (***CMED***)	X	X	X	X	X	X	X		X			X
Follow-up Visit Form (***VISIT***)		X	X	X	X	X	X	X	X	X	X	X
Medical Events (***EVENTS***)		X	X	X	X	X	X	X	X	X	X	X
Warfarin Log (***WARFLOG***)		PRN	PRN	PRN	PRN	PRN	PRN	X	X	X	X	X
Duke Anti-Coagulation Satisfaction Survey (***DASS***)			PRN		PRN		PRN		PRN			PRN
Modified Morisky Scale (***MMS***)					PRN		PRN		PRN			PRN
Early Warfarin Stop (***WSTOP***)		PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	
Study Stop (***SSTOP***)		PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	X
Unblinding (***UNBLIND***)		PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN	PRN
Data Processing Cover Sheet (***DPCS***)	X	X	X	X	X	X	X	X	X	X	X	X

[T]These visits may be conducted by phone.

3. PARTICIPANT ENROLLMENT

3.A. Initiation of a New Study and the Enrollment Process

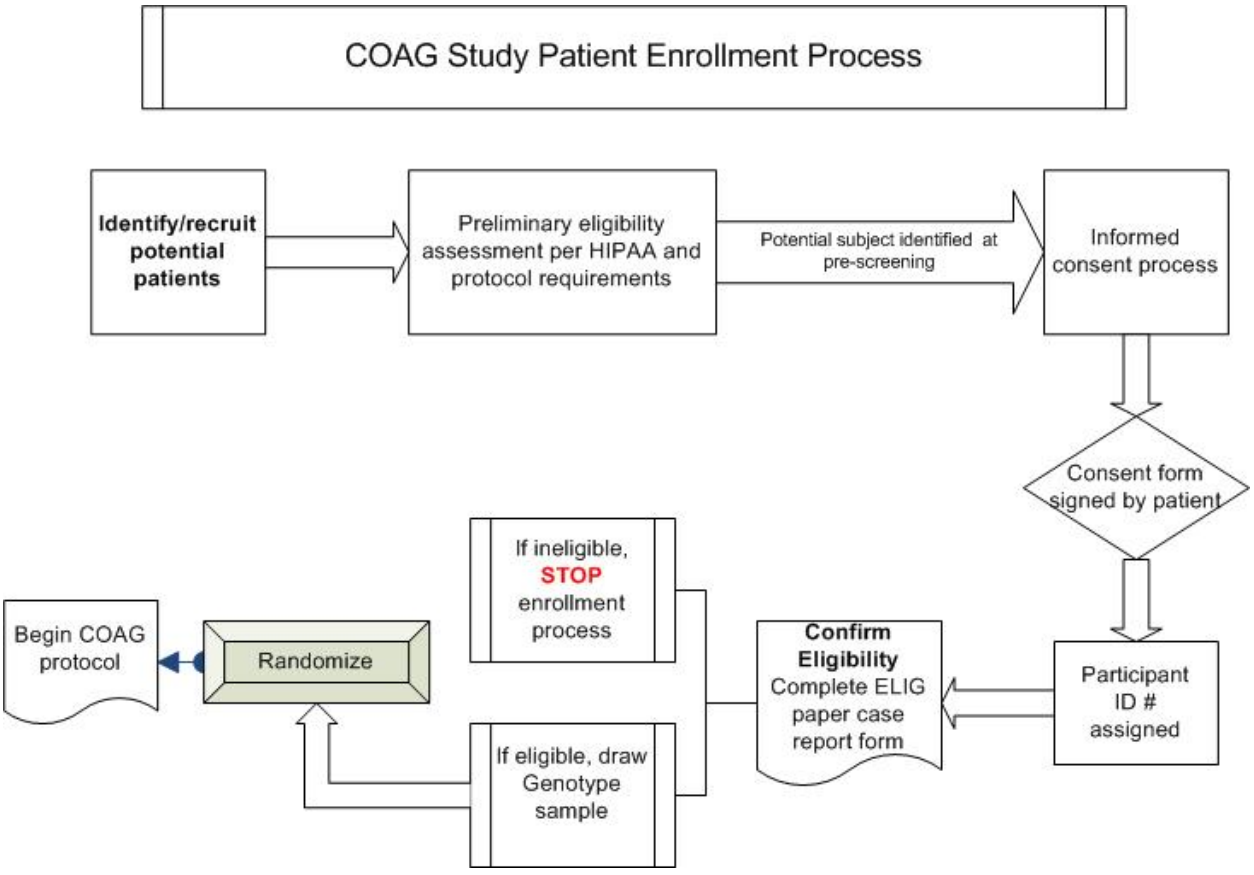
Prior to initiating the COAG study, qualified site staff is responsible for the implementation of a number of tasks that will contribute to the successful completion of the clinical trial. The Principal Investigator, Research Coordinator, and other research staff will work within existing systems within the institution in order to accomplish a successful launch of the study.

Prior to enrolling participants in the study, each Clinical Site must receive IRB approval to conduct the study and must submit to the CTCC a copy of the site IRB approval letter and copy of the IRB approved informed consent document.

The National Institutes of Health (NIH) mandates education on human subject protection for all investigators and research team members who apply for or receive NIH funds for research involving human subjects. Each research team member must document completion of training in human subject protection and this documentation must be maintained at the clinical site. This documentation must also be submitted to the CTCC prior to initiating a clinical trial. A certificate issued from the training program at the clinical site institution will satisfy this requirement, or certificate from completion of the NIH on-line Protection Human Research Participants course (http://phrp.nihtraining.com).

Participant enrollment refers to the tasks that each site undertakes to initiate participant accrual beginning with identifying and recruiting potential participants. The following figure outlines the enrollment process in the COAG study:

Figure 3: COAG Study Patient Enrollment Process



3.B. Participant Population and Recruitment

3.B.1. Participant Population:

The study population will be drawn from patients with a variety of diseases or conditions that require an expected duration of warfarin therapy of at least 3 months or long-term anticoagulation therapy with warfarin. Enrollment will reflect a racially and ethnically diverse participant population that is representative of the US population, and will include women and minorities. It is anticipated that a large proportion of enrollees will be elderly.

3.B.2. Participant Recruitment:

The successful recruitment and retention of participants who are "warfarin naïve" and have not had prior warfarin therapy is the most important factor for the success of this trial. Participants will be recruited from inpatient and outpatient levels of care. Each clinical site has recruitment goals of approximately 103 participants, at a rate of one participant per week or 4 participants per month. It is expected that approximately two years or 24 months will be needed for patient recruitment.

Each clinical site will be responsible for determining how best to recruit participants from its local population and will develop recruitment strategies that include hospital-based recruitment as well as recruitment from out-patient anticoagulation clinics. Some recruitment methods are described below:

Referral sources from in-patient primary providers and hospital inpatient anticoagulation management services.

Many potential hospitalized participants can be identified from the population of patients admitted to hospital cardiology, internal medicine, and neurovascular units with a diagnosis that will require warfarin therapy (e.g., deep venous thrombosis, pulmonary embolism, atrial fibrillation). This method of recruitment requires the coordinated effort and support of medical colleagues, treating clinicians, hospital pharmacists, and medical information systems.

Referral sources from out-patient anticoagulation clinics

Referral of potential participants who are to begin warfarin as planned out-patient therapy will come mainly from medical practices and providers in the anticoagulation clinics. Site coordination of study staff rapid response to referral notifications is needed since warfarin therapy will usually be initiated at the participant's first anticoagulation clinic visit, and may require that the participant be contacted by the study staff in advance of the first anticoagulation clinic appointment.

Success of in-patient and out-patient recruitment methods depend largely on reliable study communication systems and strong study advocacy from referral sources as well as the number of participants in the population who are eligible and willing to participate in and comply with the study protocol.

Recruitment Materials for Potential Participants

Clinical sites may prepare and utilize their own materials for the purpose of recruiting. A "Participant Recruitment Brochure" and other recruitment materials have been developed in conjunction with the Recruitment and Retention sub-committee. Recruitment materials can be distributed to referral sources and potential participants. In the brochure, the trial will be described and participant study requirements listed. Clinical sites are encouraged to use the

brochure. It should be stamped with the name and contact information of the Research Coordinator (RC) or physician's office so that referral sources or participants can contact researchers who can provide further study and enrollment information. In addition, these brochures may be used during pre-screening of potential participants or may be used at health fairs and other promotional and educational events to advertise the trial. The brochure may need to be approved by the clinical site IRB prior to use.

NIH-NHLBI Sponsored Press Release and Home Page and Study Web Site

Prior to the start of this trial, the National Institutes of Health (NIH) will arrange a press release to introduce the study to the media and public. Thereafter, the trial will be described on the NIH Home Page, NHLBI division, in the "What's New" section. In addition, the study announcement will be listed on the COAG study web site home page section: http://www.coagstudy.org

3.B.3. Pre-screening:

A general assessment of the participant's potential eligibility should be made to determine if further eligibility screening is warranted. In this study, this is considered a *pre-screening* phase during which the study coordinator reviews patient medical records or makes initial inquiries about potential participants to in-patient or out-patient physicians or clinicians. The first contact with a potential study participant will be considered a pre-screening contact and the RC should provide basic information about the study and inform the potential participant of how he/she was selected for contact (e.g. referred by primary provider). Procedures to confirm eligibility can be done only after the participant has signed the informed consent form. If pre-screening contact indicates an interest and potential eligibility of a participant, the RC will proceed with the screening/baseline visit.

3.C. Participant Screening and Enrollment Visit

The screening and baseline visit is considered the first study visit for the participant. At this visit, informed consent will be obtained from the participant, participant identification number will be assigned, eligibility will be confirmed, enrollment information will be collected, blood will be drawn for genotyping, and randomization into the study will occur. Detailed information on specific forms to be completed at this visit will be addressed in Section 8– Data Collection and Administration Forms.

3.C.1. Informed Consent:

An informed consent must be obtained from the participant before any study procedures are performed.

The initial step after recruitment is to obtain informed consent. Each clinical site is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its local Institutional Review Board (IRB), and State Department of Health requirements. The informed consent form must be obtained (signed and dated by the participant) prior to initiation of study related activity. Specifically, the following must be accomplished during the informed consent process:

- The participant must be informed that participation in the study is voluntary and that refusal to participate will involve no penalty or loss of benefits.
- The participant must be informed that the study involves research.

- The participant must be informed of any alternative procedures.
- The participant must be informed of any reasonable foreseeable risks.
- The participant must be informed of any benefits from the research.
- An outline of safeguards to protect participant confidentiality must be included, as well as an indication of which parties are allowed to review the record and of the participant's right to withdraw without penalty. This should be balanced with a discussion of the effect withdrawals have on the study, and the responsibility a participant has, within limits, to continue in the study if they decide to enroll.
- The participant must be informed of his/her right to have **questions answered** at any time and of **whom to contact** for answers or in the event of research-related injury.
- The participant must be informed that s/he will be notified of any safety-related **changes** in the protocol that might affect his/her willingness to continue in the study.
- The participant must be informed as to whether or not any **compensation** will be offered for participation in the study and whether any medical treatments are available, and if so, what they consist of.
- The participant must be provided with a HIPAA authorization to sign, either as a part of the informed consent or as a stand-alone document to be presented at the time of consent, which details all potential risks of disclosure and individuals and organizations who may have access to participant research data.

3.C.2. Administration of Informed Consent:

The RC will provide the potential participant with a copy of the Informed Consent Form so that they can read and consider participation in the COAG study.

The informed consent form should be reviewed in a setting where the participant is able to make a free choice without coercion and undue influence. Ample time should be given to allow the participant to thoroughly read and process the information. Because the enrollment process of this study must occur in a limited time period, it is important that the study staff be particularly mindful of time influence during the administration of the informed consent and not allow time limits to unduly effect how they administer the informed consent or convey study information. The RC should go over the consent with the participant and answer any questions. The participant should be made aware of his/her responsibilities throughout the Screening and Treatment/Follow-up phases of this trial. The importance of treatment compliance and continued follow-up should be stressed. This is balanced with a discussion of the effect of participant withdrawal on the study.

If at any time during the informed consent process should the participant express uncertainty about participation or indicate a need to delay in making a decision about participating, the RC will discontinue the enrollment process.

The Informed Consent Form must be signed and personally dated by the participant or his/her legal representative, and the person "obtaining consent". A participant should not be asked to sign the consent statement if s/he has any doubts about enrolling or if the clinic staff believes s/he does not understand what his/her participation would involve. Under no circumstance is study information to be collected from the participant or study procedures performed for the specific purpose of the trial before the participant has signed the informed consent form.

Problems reading the consent form

Some people may have difficulty reading the consent form. RCs should be aware of this possibility and if they sense that reading is a problem for the participant, they can offer assistance in reviewing the consent form. This should be done cautiously as some participants may be sensitive to the issue of reading. It is also permissible for participants to have a friend/relative assist them in reading or discussing the consent form.

If the participant or their legal representative cannot read the written material, then an impartial witness should be present for the entire consent process. After the participant has had a chance to ask questions and has signed the consent form, the witness would then sign and date the consent, to affirm the process.

Non-English speaking participants

For non-English speaking participants, the individual clinical site must provide a professionally translated, IRB approved version of the consent form and all supporting materials. In addition, a clinical research staff member who is fluent in the participant's native language or a professional interpreter should be utilized to explain the study and answer the participant's questions. It is permissible for non-English speaking participants to rely on a friend or family member as translator in reading and understanding the consent form and other study forms as long as the research staff is comfortable with this situation and this action is in accordance with local IRB guidelines.

Documentation of consent

The RC will maintain the original consent document in the participant's confidential file with other confidential documentation, and provide a copy of the signed and dated informed consent(s) to the participant. A second copy of all informed consent(s) should be made as a back up and stored together in the "study-confidential file". In addition, a signed/dated progress note must be made in each participant's file documenting that the informed consent was obtained before conducting any study procedures.

To ensure confidentiality, the RC will not send copies of the informed consent form(s) signed by the participant to the Clinical Trial Coordinating Center (CTCC) or keep any copies of the informed consent form with the case report forms (CRFs).

3.C.3. Confidentiality:

General Information

Extensive efforts will be made to ensure and maintain participant confidentiality, except as may be required by regulation. All identifying information must be maintained in a secure area at all times and must never appear on CRFs. Consent form(s) and source documentation must be maintained in a separate folder from the CRFs. If source documentation has to be made available for data audits, copies of the source documents should be forwarded to the CTCC with only Participant ID number visible and personal information obscured.

The CTCC staff has access to the Participant ID number for data management purposes. All communication between the CTCC staff and the clinical site staff regarding participant data occurs via the Participant ID number only.

All CRFs and source documents sent to the CTCC must have all participant identifiers, other than the Participant ID number, obscured. However, please never obscure information on the original/source documents.

The staff at the CTCC **will not** have access to any participant locator or identifying information available to the clinical site.

3.D. Participant Documents

3.D.1. Source Documentation

Source documents are the original signed and dated records of participant information (e.g.,the medical record, shadow chart) which may include electronic documents containing all the information related to a participant's protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. Source documents substantiate case report form (CRF) information. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

List of Source Documents

Source documents, which may be either paper or electronic, may include but are not limited to the following items.

- Institutional, research, hospital, clinic, or office records containing:
  - Inpatient and outpatient medical records
  - Progress notes
  - Consults
  - Nursing notes
  - Pathology reports
  - Radiology reports
  - Imaging reports
  - Medicine/radiation administration records
  - Surgical reports
  - Laboratory results
  - Admission forms
  - Flow sheets and study-specific checklists that are signed and dated
  - Discharge summaries
  - Participant diaries/calendars
- Relevant participant-specific written communication from non-study health care providers, including comments related to past medical history, entry criteria, or other referral or follow-up information;
- Participant-specific correspondence, such as documented telephone calls, email messages, and faxes;
- Obituaries, autopsy reports, and death certificates.

Chart Notes: Study staff should document every contact with a study participant in a signed and dated chart note specifying the date, type, purpose, and location of the contact, and the general status of the participant.

Chart notes also must be used to document the following:

- The study informed consent process
- Procedures performed that are not recorded on other source documents
- Pertinent data about the participant that are not recorded on other source documents
- Protocol departures/deviations/violations that are not recorded on other source documents

3.E. Assignment of Participant Identification

A Participant Log [PTLOG] has been developed for each clinical center. It includes columns for unique Participant ID numbers, for participants' initials, names, and randomization number. After the participant has signed the informed consent document, the participant is logged in the PTLOG and assigned a unique identifier referred to as a Participant ID number (PID). Each participant should be assigned the next available Participant ID number.

All communication with the CTCC regarding individual participants must be through the Participant ID number and your clinical center code. Once a Participant ID number has been assigned, that number never changes and it should never for any reason, be reassigned. The [PTLOG] form should be stored in a secure, locked filing cabinet. A backup copy of this log should be made at the end of every other week and the copy stored in a separate, secure location.

The 6-digit Participant ID number is composed as follows:

- The first 3 digits of the number is the protocol number and clinical center code.
- The last 3 digits indicate the sequential ordering of participants.

3.F. Participant Eligibility

It is the responsibility of the site Investigator and designated study staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study.

Should site staff discover that an ineligible participant has inadvertently been enrolled in the study, the Principal Investigator or designee must contact the CTCC Principal Investigator for guidance on subsequent action to be taken.

The participant is questioned to confirm his/her eligibility by reviewing the inclusion, exclusion and deferral criteria.

- If the participant meets all the inclusion criteria, then continue to the exclusion criteria section.
- If the participant meets any of the exclusion criteria, then the participant is not eligible to participate in the COAG trial.
- If the initiation of therapy is delayed, the participant is temporarily deferred from enrolling into the COAG trial until such time that the new re-screening date is reached.

3.F.1. Inclusion Criteria:

1. Age ≥ 18 years
2. Willingness and ability to sign informed consent
3. Able to be followed in outpatient AC clinic
4. Expected duration of warfarin therapy of at least 1 month
5. AC management for the patient will be performed in-hospital and as an outpatient by clinicians that will adhere to the study dosing algorithms and dose titration plans (discussed below)
6. Target INR 2-3

3.F.2. Exclusion Criteria:

1. Currently taking warfarin.
2. Prior warfarin therapy with known required stable dose

3. Clinician opinion that warfarin dosing needs to be adjusted for reasons not accounted for by dosing algorithm
4. Abnormal baseline INR (off warfarin), e.g., due to liver disease, antiphospholipid antibody
5. Contraindication to warfarin treatment for at least 3 months
6. Life expectancy <1 year
7. Pregnant women or child-bearing women not using medically-approved method of birth control (requires negative pregnancy test to exclude pregnancy in child-bearing women)**********
8. Inability to follow-up on a regular basis with anticoagulation practitioners participating in the trial
9. Any factors likely to limit adherence to warfarin. For example,
    - Dementia
    - alcohol or substance abuse
    - plans to move in the next 6 months
    - history of unreliability in medication taking or appointment keeping
    - significant concerns about participation in the study from spouse, significant other, or family members
    - lack of support from primary health care provider
10. Cognitive or other causes of inability to provide informed consent or follow study procedures
11. Participating in another trial that prohibits participation in the COAG trial or planned enrollment in such a trial within the first 6 months of warfarin therapy
12. Estimated blood loss of >1000 cc requiring blood transfusions within 48 hours prior to randomization
13. Genotype (CYP2C9 or VKORC1) known to participant from prior testing

*********Clarification of Exclusion Criteria #7**

Protocol Exclusion Criteria #7 States: *Pregnant women or child-bearing women not using medically-approved method of birth control (requires negative pregnancy test to exclude pregnancy in child-bearing women)*

Informed Consent States: *Because warfarin might be harmful to a pregnant woman and/or the unborn child, women of childbearing potential must have a negative pregnancy test at the time of screening if they wish to participate in this trial.*

- Any Medical Record documentation of a negative pregnancy test must be current documentation. Current documentation would include a documented negative pregnancy test that was performed since the patients last menstrual period or a documented negative pregnancy test performed within the prior month to starting warfarin, whichever is shorter. Any other pregnancy test documentation prior to this time point would not be acceptable proof of a negative pregnancy.

- If documentation is not available in the participant's medical records, the research coordinator must obtain a pregnancy test with negative pregnancy test results in order to confirm participant's eligibility.
- The research coordinator must follow the institutional standard for pregnancy testing. If the institutional standard requires serum testing for pregnancy, then a serum testing for pregnancy must be obtained.
- If outpatient point of care or hospital bedside urine testing for pregnancy is performed, it must be conducted according to the approved institutional practice guidelines (e.g. out-patient laboratory and hospital laboratory /JCAHO approved testing and quality control standards).

3.F.3. Deferral Criteria:

Because this study requires all patients to be enrolled at the initiation of warfarin, patients who have already received a dose of warfarin cannot be enrolled. The only reason for deferral would be if a patient is planned to start on warfarin and the initiation of therapy is delayed. These patients will remain eligible to enroll, assuming they continue to meet all inclusion/exclusion criteria at the time of warfarin initiation. **Please consult with the Medical Monitor and your Principal Investigator if for any questions or concerns related to delay in warfarin initiation for an enrolled patient.**

3.G. Screening Failures

A participant who does not complete the Screening procedures for whatever reason will be considered a screening failure and will not be randomized to the trial. All of the completed screening forms, including informed consent form, for participants who are considered screening failures, should be filed at the clinical center in the Source Documentation Binder and should not be sent to the CTCC.

3.H. Randomization Procedure

Participants will be randomized via the data management system following completion of required screening procedures. Information will need to be collected on the following case report forms (CRFs) and entered into the data management system prior to randomization:

- Eligibility Confirmation (ELIG) and
- Enrollment Information (ENROLL).
- Randomization (RAND)

Participants are successfully randomized and stratified based on the information recorded on these CRFs and entered into the data management system.

The Research Coordinator is blinded to the randomization assignment. The Research Coordinator will receive a message that the participant was successfully randomized at the time they commit the information from the Randomization (RAND) CRF to the data management system. Participants must be successfully randomized in the data management system before the first dose of warfarin can be requested.

3.I. Enrollment Timeframe and Venipuncture for Genotype Testing

Please refer to Figure 3 - COAG Study Patient Enrollment Process. Confirmation of eligibility is required before the participant can be randomized in the data management system. In order to facilitate a rapid turnaround time for genotype specimen analysis, the enrollment timeframe will

allow for genotype venipuncture to be performed soon after written informed consent is obtained from the participant. This will occur before the participant is randomized in the data management system. If the participant is confirmed to be eligible, the RC will obtain the genotype blood specimen and continue with the enrollment process to randomize the participant. However, if the participant is confirmed not eligible, the RC will stop the enrollment process, genotype venipuncture will not be performed, and the RC will stop the enrollment process and the participant will not be randomized.

3.I.1. Collection of Genotype Specimen

The goal of recruitment will be to enroll as many patients as possible who have genotyping available prior to receiving the first dose of warfarin. The Research Coordinator will ensure the timely collection and shipping of the genotype blood specimen. **If the genotype specimen cannot be obtained before the patient receives the first dose of warfarin, every effort will be made to obtain the specimen as soon as possible thereafter.** See Laboratory Manual of Procedures for details on blood specimen collection, handling, and shipping procedures.

3.I.2. Communication with Site Laboratory and Central Laboratory

The Research Coordinator will coordinate the activities needed to ensure that the collected specimens are received by the site genetics laboratory and the central laboratory. Prior to collection of the genotype specimen, the RC will contact the site genetics laboratory to inform them that a specimen will be drawn and the time the laboratory should expect the arrival of the specimen. The RC will request the site laboratory to confirm receipt of the specimen, and communicate when the genotype will be completed. Once analysis of the specimen is completed, the site laboratory enters the genotype information into the data management system and notifies the RC that the genotype is available. Since the RC is blinded to the genotype information, the site laboratory will not reveal this information. In the event of specimen damage or poor quality, the site laboratory will notify the RC if a second genotype specimen is needed. Arrangements for transporting the specimens to the local and central laboratory will be made by the RC according to procedures outlined in the Laboratory Manual, Section 3.

The RC will receive laboratory supplies for specimen collection from the central laboratory. Such supplies will not be shipped to the site laboratory. The RC must communicate directly with the designated central laboratory contact when reordering supplies. (See Laboratory Manual of Procedures)

4. DOSING INTERVENTIONS AND DOSE REQUESTS

Patients will be randomized to one of the two dosing intervention arms (genotype-guided dosing or clinical-guided dosing) that will test the effects of algorithm-guided dosing over the first 4-5 days of therapy (Please refer to Figure 2 – Study Flow). Research Coordinator activities in each phase of dosing interventions involves close communication with the clinician investigator and research pharmacy and diligence in entering dose requisition information into the data management system.

In order to blind participants, investigators and clinical site personnel to warfarin dose, and thus blind to study arm and genotype, all warfarin tablets will be blinded for the first 4 weeks for each study participant (i.e., up until Day 29 of the study). In order to do this and to replicate as closely as possible the usual way in which warfarin is prescribed and taken in practice, doses of warfarin will be encapsulated in hard gelatin capsules. NO placebo capsules are used in this trial. All capsules will look the same regardless of warfarin dose. After 4 weeks (Day 29 Unblinding), clinicians will be informed of the actual dose that the patient is taking at Day 29 and patients will then receive their warfarin through their primary care provider. Starting with Day 29, the research pharmacy will no longer provide blinded study drug.

The Data Management System (DMS) is programmed to calculate the dose of warfarin that each patient is to receive. The DMS will include several modules to calculate the daily dose of study medication for randomized subjects based on algorithms defined in the protocol. These modules will check for the availability of specific data elements that are required by the algorithms and will prevent a dose calculation from occurring if mandatory data are missing. Medication dosing will be calculated for the dosing phases of the protocol:

1. **Initial dose algorithm – (Days 1-3)** The initial dose algorithm will be used if the subject is at day one, day two, or day three of the intervention. According to the protocol, a value for INR is not expected for days 1 through 3 (initial dose phase). However, **if the patient's INR is checked for any reason on day 2 or 3, it will be used in the dose request and will be used by the DMS to modify the calculation for that day's dose. Any daily INR must be entered into DMS each day by the RC before dose is ordered.**

2. **Dose revision algorithm – (Days 4-5)** The dose revision algorithm will be used if the subject is at day four or day five of the intervention. The dosing calculated on days four and/or five will be calculated as a weekly dose for study participants. Patients must be able to have INR done and receive blinded drug on days 4 and/or 5 of therapy (dose revision phase). **If an INR is reported as 2.5 or greater on Day 4 or Day 5, please contact the medical monitor. The RC can initiate the dose request in the DMS when this occurs, but the dose request cannot be dispensed by the Research Pharmacist until after the medical monitor has reviewed the reported INR and approved the dose to be dispensed.** When recruiting patients, it is important that the RC be mindful of the the warfarin dosing schedule and the coordination of the visit schedule. For example:

   - If patients warfarin dosing would start on a Tuesday, they must return on Friday for the Day 4-5 (visit 2) dose revision.
   - If patients warfarin dosing would start on a Wednesday, only enroll them if your site has Sat/Sun clinic visit hours and your IDS is available on weekends.
   - If patients warfarin dosing would start on a Thursday, they must return on Monday for day 4-5(visit 2) dose revision.

3. **Dose titration – (Day 6 –Week 4)** During this dose titration phase, dose changes will be based on the INR measured on study-specific days, using a standardized dose-titration adjustment based on INR and applied equally between groups.

For each of these phases, the research coordinator will complete a dose request form and enter that data into the DMS. **Before executing the DMS dose requisition request, the RC must always check with the clinician beforehand**. Depending on where the subject is in the visit schedule, one of the dose calculations will be selected by the DMS and used to determine the optimum medication dose and that value will be recorded in the DMS.

Other Important Details Related to Dosing:

Patients and Research Pharmacy (IDS) must be available on the following days after starting therapy

- Day 2: if genotyping not completed on day 1
- Days 4 and/or 5 (after day 3 of therapy)
- Throughout first 4 weeks of treatment as per protocol visit schedule
- Any time patient gets INR

****

Important Principal Investigator directive regarding Principal Investigator supervision of study activities for participants enrolled at the in-patient level of care.

- The Principal Investigator will review with the Research Coordinator, on a daily basis, the status of all in-house patients enrolled in the COAG study.
- For the enrolled in-patient who will be receiving blinded study drug over a weekend or holiday, the Research Coordinator will provide the Principal Investigator with a daily report on the patient status during this time period to ensure that hospital procedures and study procedures are being followed in regard to INR reporting, submitting dose requests and distribution of blinded study drug.
- The Research Coordinator will notify the Medical Monitor and the Principal Investigator in the event that a study-required INR is not drawn for an enrolled in-patient, or if the study drug is held, stopped, not dispensed, or if the patient encounters a serious adverse event.

****

4.A.1. Dose Requests

The Research Coordinator will request a dose for a specific study day. The DMS checks to see if genetic data has been entered for the participant at the time the dose requisition screen is opened. If no genotyping form has been entered by the Genetics Laboratory, the DMS will display a message informing the Research Coordinator that the genetics form is missing. The DMS will perform this check regardless of which treatment arm is assigned to the participant to preserve the blinding of the Research Coordinator.

The Research Coordinator has the capability of submitting a dose request even though the genetics data is unavailable if it is necessary to obtain the medication due to time constraints. If the Research Coordinator initiates the dose request, the clinical algorithm will be used to calculate the dose. Once the dose has been successfully submitted, the dose calculation cannot be

attempted again for that study day. The results of the dose calculation will not be displayed to the Research Coordinator.

Usually dispensed dose will be the same as calculated dose, but will occasionally (rarely) be different (e.g. when there is a dose over-ride)

It is important to accurately enter INR data as it determines dosing and is primary outcome of the study

4.A.2. Contact with Site Research Pharmacy

Depending on the patients status when enrolled in the study (in-patient or out-patient) it is possible that more than one research pharmacy is utilized at the site.

In-patient requirements for COAG study drug

Study drug must be a written order given by an MD before an in-patient floor nurse can distribute drug to patient. Example of an order: "*Warfarin-Blinded Dose Give at 6pm each day*." This could be written as an admission order for all in-patient participants in COAG study.

If the floor nurse doesn't find the study drug available when patient is to receive it, the RC and/or hospital pharmacist will be called and they will contact the research pharmacist.

The RC must check daily on the status of each in-patient enrolled in the study and must check daily that the study drug was dispensed the night before.

If there is a request for a change in dose outside the DMS generated dose, the RC must notify research Pharmacy and initiate the dose over-ride in the DMS.

A hold and re-start on study drug can occur. In cases where study drug is held, it can be held no longer than two (2) days.

Bridging between in-patient to out-patient status for study participants

The research coordinator plays the key role in this transition. The RC will verbally notify the research pharmacy of the patients discharge from in-patient status, and will fax a patient profile sheet to the research pharmacy that contains patient name, address and phone number should the research pharmacy need to ship study drug to patient before the next scheduled clinic visit.

4.A.3. Patient Dosing Instructions

All patients must receive a dose instruction sheet and the RC must review the dose instructions with the patient every time they receive a new dose of blinded warfarin. Please see Appendix 1 Warfarin Dosing Instruction sheet. The RC or at some sites, the Research Pharmacist, will indicate on the instruction sheet the amount of pills the patient is to take and circle on the sheet each specific day of the week and what bottle (A and/or B) from which to take the pills. In some instances, the patient may also receive a single dose or a series of single dose bottles in addition to bottle A and/or B, which is also indicated on the Instruction Sheet as to individual day and pill.

The RC should copy onto the dose instruction sheet the dose information indicated on the patient's pill bottle(s) filled and distributed by the Research Pharmacist. If the RC is unclear about the dose instructions, or has questions, the Research Pharmacist must be contacted to confirm dosing information before the instruction sheet is given to the patient.

The RC will also:

- Remind patients to bring back all pill bottles at the next study visit
- Inform the patient that new bottles will be dispensed at every study visit during first 4 weeks
- Count the remaining pills in each bottle returned
- Send unused pills back to local IDS

4.A.4. Over-ride of Dose Titration in Both Intervention Arms

During the dose titration phase dosing will be based on the INR measured on study-specific days, using a standardized dose-titration adjustment based on INR and applied equally between groups. The investigator/clinician will know the INR and will be told of the relative change in dose during the dose titration phase (e.g., the DMS would report "Based on your patient's INR, their dose will be increased by 10%"). If clinicians believe that there are reasons not to follow this recommendation (e.g., a patient has been non-adherent with therapy as a cause of a low INR and the investigator wants them to simply start back on their current dose without increasing the dose, intercurrent event/illness, etc.), the Medical Monitor will be contacted to request a change. Discussion between the investigator and the Medical Monitor must occur, and an acceptable warfarin dose will be determined based on the relevant clinical issues. (Please refer to MOP Section 7.F for Medical Monitor contact information).

The RC is responsible for communicating with the site Research Pharmacist and the Medical Monitor when a clinician requests a dose override. **All deviations from the study algorithm dosing schedule must be approved by the Medical Monitor.** If a request for dose over-ride is approved, the Medical Monitor will contact the site Research Pharmacist to inform them of the change in dose.

The RC must communicate with the Medical Monitor in the event of missed doses, held doses, stopped doses, and any warfarin dosing regimen started outside of the protocol. The following are examples of when to call the medical monitor:

- If a clinician requests a dose override, call medical monitor
- Patient reports they stopped taking warfarin since last visit. If 2 or more doses were missed in one week, call medical monitor
- Patient is taken off warfarin (doses held) for a medical procedure (e.g. dental extraction). If 2 or more doses are mixed in one week, call medical monitor
- An outside clinician places patient on new regimen of warfarin dosing or patient is treated off protocol with warfarin in any other fashion, patient is taken off dosing protocol and medical monitor is contacted.
- Warfarin dose is stopped or held because of an adverse event, call the medical monitor.
- An INR is reported as **2.5** or greater on Day 4 or Day 5.

Throughout the dose adjustment phase, participants will be instructed by the site RC to contact the RC if they start any new medications or stop any current medications. If these medications interact with warfarin, the participant will return in 5-7 days for an INR check and adjustments will be made accordingly, again maintaining blinding of dosing during the first 4 weeks of therapy.

5. PARTICIPANT FOLLOW-UP

5.A. Overview of Study Follow-Up Plan

Study follow-up visits will be followed according to the protocol visit schedule for the duration of 24 weeks (see MOP Section 2 -VISIT SCHEDULE). All eligible participants who have been successfully randomized will proceed to treatment/follow-up phase of the trial. The first four weeks of treatment/follow-up is during the blinded phase of the study. The remaining 20 weeks of follow-up is during the unblinded phase of the study. All randomized patients are expected to be followed in the study for the full 6 month period.

5.B. Types of Follow-Up Visits

FOR THE FIRST MONTH OF THE STUDY (Blinded Phase), All Study Visits Are IN-PERSON VISITS. The unblinded phase visits at months 2, 4, and 5 will be conducted by telephone. Unblinded phase visits at months 3 and 6 will be in-person visits.

**************Clarification added November 2010**************

Data Collection Method After the First Four Weeks

The current study visit schedule procedure outlines the following methods of data collection:

- Telephone visits for data collection at months 2, 4, and 5
- In-person visits for data collection at month 3 and month 6

In order to ensure as complete a dataset as possible, enhance recruitment, and maximize retention, the Executive Committee the Steering Committee approve that the procedure for data collection after the first 4 weeks of follow-up be changed to allow for telephone collection of data for study visits conducted at month 3 and 6 should patients not be able to come in for a study visit. The standard will remain in-person interviews, but this change will allow telephone interviews for those patients that cannot come for in-person interviews.

Thus, the new study visit schedule procedure outlines the following methods of data collection (changes in blue):

- Telephone visits for data collection at months 2, 4, and 5
- In-person visits for data collection are preferred at month 3 and month 6. If patient cannot come for an in-person interview on those days, then a telephone interview should be done to ensure data collection at 3 and 6 months.

5.B.1. Scheduled Visits:

A Participant Follow-Up Contact Schedule will be generated for each individual participant according to the date that participant receives first dose of blinded warfarin treatment. Depending on the individual clinical circumstances related to treatment, the participant start of warfarin treatment may need to occur **after** the date of randomization. (Note: start of warfarin treatment before randomization would make participant not eligible for study).

The date of first dose is therefore considered to be Day 1 – Visit 1 for the participant. This schedule indicates the sequence of follow-up contacts, target dates for each contact, and time windows in which the contact must be completed. At the close of each contact, the RC will schedule the next contact by referencing the Participant Follow-up Contact Schedule.

5.B.2. Interim Visits:

Depending on participant INR readings, additional interim contact visits may need to be scheduled to monitor patient response to treatment.

5.B.3. Follow-up Visit Locations:

Follow-up visits for participants enrolled as in-patients in the study will be conducted during their hospital stay. Upon discharge from in-patient status, the next patient follow-up visit will be scheduled and conducted in conjunction with the outpatient Anticoagulation Clinic.

Follow-up visits for participants enrolled as out-patients in the study will be scheduled for the outpatient Anticoagulation Clinic location.

5.C. Allowable Visit Windows:

5.C.1. VISIT WINDOW

It is the responsibility of the clinical site personnel to expend considerable effort in retaining participants for the duration of the study in order to maximize on the follow-up data. Visit windows are established to allow the RC to follow a visit schedule for the study processes as well as allow for some room to see a participant for a visit while maintaining the integrity of the data. Hence a period of time is allowed before and after a target visit date for the participant to complete a study visit.

The following table illustrates the visit week/month and visit number as well as the visit window in which follow-up visits may be scheduled.

COAG VISIT WINDOW

Visit #	Weeks/Months	Visit Window
1	Week 0	First day of dosing
2	Week 1	Day 4 - 5
3	Week 1	Day 6 - 10
4	Week 2A	Day 8 - 13
5	Week 2B	Day 11 - 17
6	Week 3	Day 15 - 25
7	Week 4 – Primary Endpoint ** Unblinding	Day 22 – 32 Day 29-32
8	Month 2	± 7 Days
9	Month 3	± 7 Days
10	Month 4	± 14 Days
11	Month 5	± 14 Days
12	Month 6	± 14 Days

The COAG Data Management System (DMS) has an individual patient scheduling tool that will produce an individual patient schedule according to the above visit window. The important feature of the DMS individual patient scheduling tool is that it is database linked and developed

for standardized use, thereby preventing errors in patient scheduling from the start of day one dose. Please refer to MOP Section 9P for instructions in the use of the individual patient scheduling tool.

Week One (visits 2 & 3)

After the completion of the first -Visit #1 (Day 1-first day of dosing), there are two follow-up visits scheduled in Week 1:

- Follow up Visit #2 will occur on Day 4 of that first week. Visit #2 can occur within the window of Day 4-5.
- Follow-up Visit #3 will occur on Day 7 of the first week. Visit #3 can occur within the window of Day 6-10.

If the participant cannot return for Visit#3 within Week 1, and must reschedule, then the rescheduled Visit 3 should be scheduled as early as possible within the permissible visit window in order to increase the chances of rescheduled visits falling within the window. Visit #3 may be scheduled into Week 2 within the window of Day 8-10. The visit should be scheduled and completed before the first possible day of the next scheduled visit window. If this is not possible, it will be considered a "missed" visit.

Week Two (visits 4 & 5)

There are two follow-up visits scheduled in Week 2:

- Follow-up Visit #4 will occur in Week 2 within the visit window of Day 8-13.
- Follow-up Visit #5 will occur in Week 2 within the visit window of Day 11-17.

Each visit should be scheduled and completed before the first possible day of the next scheduled visit window. Therefore, Visit#4 will occur within Day 8-13 of Week 2, but if (as noted above) participant completion of Visit #3 Week 1-did not occur until Day 10 in Week 2 , then Visit #4 should be scheduled within a Day 11-13 window and Visit#5 should be scheduled within a Day 14-17 window.

Week Three (visit 6)

There is one follow-up visit scheduled in Week 3:

- Follow-up Visit #6 will occur in Week 3 within the visit window of Day 15-25.

This visit should be scheduled and completed before the first possible day of the next scheduled visit window.

Week Four (visit 7 – Primary Endpoint Visit

There is one follow-up visit scheduled in Week 4:

- Follow-up Visit #7 will occur in Week 4 within the visit window of Day 22-32

This visit should be scheduled and completed before the first possible day of the next scheduled visit window.

****Note:** Visit #7 unblinding cannot occur until day 29 or later. If possible, please consider scheduling the Primary Endpoint and Unblinding visit at the same visit (Day 29-32).

Weeks 5-24 (visit 8-12)

Follow up visits for Weeks 5-24 will be conducted on a monthly basis:

- Follow-up Visit #8, #10, and Visit #11 will each be conducted as a phone visit
- Follow-up Visit #9 and Final Follow-up Visit #12 will each be in-person clinic visits

Monthly visits will be scheduled within a visit window of +/- one week (7 days) for Month 2 (Visit #8) and Month 3 (Visit #9).

Monthly visits will be scheduled within a visit window of +/- 2 weeks (14 days) for Month 10 (Visit #10), Month 11 (Visit #11) and Month 12 (Visit #12).

5.C.2. Missed Visits:

If a follow-up visit cannot be completed within the permissible visit window, the visit should be scheduled and completed before the first possible day of the next scheduled visit window. If the visit cannot be completed before the first possible day of the next scheduled visit window, then it will be considered a "missed" visit, and the visit should be marked as missed in the database.

5.D. Follow-Up Visit Procedures

At each follow-up study visit, the following procedures will occur:

- The RC will review with the participant any new adverse events which may have occurred since the previous visit. The RC will also follow up with any previously reported adverse events until they have been resolved. Any change in pre-existing conditions will also need to be recorded. Example follow-up question for reviewing adverse events: *"Since your last visit, have you had any new symptoms, injuries, illness, or side effects?"* Example follow-up question for reviewing changes in pre-existing conditions: *"Since your last visit, have you had any worsening of pre-existing conditions?"* The Follow-up Visit **(VISIT)**, Medical Events **(EVENTS),** and Adverse Events **(AE)** forms will be completed at every study visit.
- At each study visit the participant will return the study medication bottle(s) to the RC, who will do a pill count to assess study medication compliance.
- The RC will update the Concomitant Medications **(CMED)** form at each visit** if there are any changes in the participant's medication use. **Note: CMED information is not collected at months 2, 4, & 5 telephone visits (during unblinded phase).
- The Dose Requisition (**DOSREQ)** information is updated and entered into the Data Management System (DMS) at each study visit during the dose initiation and dose revision period (Days 1-5). Dose Requistion **(DOSREQ2)** information is updated and entered into the DMS at the dose titration period (Days 6-28) and until stable/maintenance dose is reached.
- At each study visit and during any interim visit, the participant INR Log **(INRLOG)** is completed by the RC. The INRLOG is a continuous log and is updated with information from all available sources (inside or outside institutions or providers) where a check may have been made on the participant's INR value. The RC should routinely check with the participant or check participant's medical record to determine if a blood draw or point of care INR testing was done outside a scheduled visit.

5.D.1. Follow-up Procedures for Participant INRs

Patient INR values are an important component of the dosing algorithm. These INR values may be study visit scheduled INRs or INRs obtained between or outside scheduled patient study visits.

It is important that information on all reported INR values be recorded on the INR Log (see Section 8 INR Log).

In addition to recording the INR value on the INR Log, the RC must maintain source documentation of the INR report in the patient's study record. Documentation of the INR value should be obtained from the source where the patient's INR was checked such as clinical site laboratory or anticoagulation clinic or from an outside institution or healthcare provider. Such documentation can be an electronic record or paper record.

Besides the patient's identity details (full name, medical record number, date of birth), such INR documentation should include the date and time the INR was obtained, the type of test (conventional laboratory or point-of-care device), location, and the INR test result. This documentation should be kept in the patient's study record.

In the event that the RC cannot obtain written documentation of an INR from an outside provider or institution, the RC should make every effort to obtain verbal confirmation of the INR test result from the provider or institution and document a note in the patient's chart that states the INR result reported, date, time, who reported the INR to the RC, and the type of test (POC or conventional laboratory). If the patient is in the unblinded phase of the study, the RC should also document the change in warfarin dose associated with the particular INR result reported.

5.D.2. Forms Completion at each Follow-up

*****NOTE***** Please refer to MOP section 8 for case report form completion guidelines and instructions.

5.D.2.a) Week One (Day 4- visit 2)

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/DOSEREQ2	Dose Requisition Information
INRLOG	INR Log**
AE	Adverse Events
CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – completed on an as needed (PRN) basis
WSTOP	Early Warfarin Stop – completed on an as needed (PRN) basis
SSTOP	Study Stop - completed on an as needed (PRN) basis
UNBLIND	Unblinding - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

5.D.2.b) Week One (Day 7- visit 3)

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/DOSEREQ2	Dose Requisition Information
DIET/DIETUP	Diet Information and updates
INRLOG	INR Log**
AE	Adverse Events

CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – completed on an as needed (PRN) basis
DASS	Duke Anti-Coagulation Satisfaction Survey
WSTOP	Early Warfarin Stop – completed on an as needed (PRN) basis
SSTOP	Study Stop - completed on an as needed (PRN) basis
UNBLIND	Unblinding - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

5.D.2.c) Week Two (visit 4)

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/DOSEREQ2	Dose Requisition Information
INRLOG	INR Log**
AE	Adverse Events
CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – completed on an as needed (PRN) basis
WSTOP	Early Warfarin Stop – completed on an as needed (PRN) basis
SSTOP	Study Stop - completed on an as needed (PRN) basis
UNBLIND	Unblinding - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

5.D.3. Week Two (visit 5)

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/DOSEREQ2	Dose Requisition Information
DIET/DIETUP	Diet Information and updates
EUROQOL	Eq-5D Health Information Questionnaire
INRLOG	INR Log**
AE	Adverse Events
CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – completed on an as needed (PRN) basis
DASS	Duke Anti-Coagulation Satisfaction Survey
MMS	Modified Morisky scale
WSTOP	Early Warfarin Stop – completed on an as needed (PRN) basis
SSTOP	Study Stop - completed on an as needed (PRN) basis
UNBLIND	Unblinding - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

5.D.3.a) Week Three (visit 6)

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/DOSEREQ2	Dose Requisition Information
DIET/DIETUP	Diet Information and updates
INRLOG	INR Log**
AE	Adverse Events
CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – completed on an as needed (PRN) basis
WSTOP	Early Warfarin Stop – completed on an as needed (PRN) basis
SSTOP	Study Stop - completed on an as needed (PRN) basis
UNBLIND	Unblinding - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

5.D.3.b) Week Four (visit 7) – Primary Endpoint and Unblinding Visit

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/DOSEREQ2	Dose Requisition Information
DIET/DIETUP	Diet Information and updates
EUROQOL	Eq-5D Health Information Questionnaire
SF-36	Health Status Questionnaire
INRLOG	INR Log**
AE	Adverse Events
CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – completed on an as needed (PRN) basis
DASS	Duke Anti-Coagulation Satisfaction Survey
MMS	Modified Morisky scale
WSTOP	Early Warfarin Stop – completed on an as needed (PRN) basis
SSTOP	Study Stop - completed on an as needed (PRN) basis
UNBLIND	Unblinding - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

****Important Information for Week Four (4) -Study Visit #7 – Primary Endpoint Visit and Participant Unblinding ****

This visit is the primary endpoint visit and according to the study visit schedule, can occur within the visit day window of Day 22-32. **This is a clinic visit and an INR must be drawn on this visit.** Should the primary endpoint visit occur before Day 29, the patient dose will not be unblinded at that visit, but will continue on the blinded dose for that week until the Day 29 unblinding. If possible, please consider scheduling the Primary Endpoint and Unblinding visit at the same visit (Day 29-32).

5.D.3.b.(1) Participant Unblinding Procedure at Week Four

At Day 29 of the study, unblinding of warfarin dose for Day 29 will occur. The Day 29 pharmacy dosing module screen will now be available to the RC when the RC enters the Day 29 dose request, and the RC can now view the dose calculated for the patient at Day 29. The DMS will assist the Research Coordinator with the unblinding process. **See Section 9 O for RC instructions in operating the DMS screen module for unblinding at Day 29 and thereafter.**

The Research Pharmacist **will not** dispense blinded study drug on this day, nor will the patient continue to receive blinded study drug from the research pharmacy. The patient will now receive warfarin by written prescription from the clinical provider.

Research Coordinator Responsibilities For Conducting Unblinding

- On Day 29 for each enrolled patient, the pharmacy DMS module screen will be available to the Research Coordinator to view.
- The Research Coordinator will enter a dose request into the DMS and include in the dose request the INR results at Day 29.
- The DMS pharmacy module screen will reveal the Day 29 dose calculated for the patient and the patient's weekly dosing regimen.
- The RC will notify the Principal Investigator and/or Clinical Provider of the calculated Day 29 dose and weekly dosing regimen.
- The DMS module screen **WILL** indicate if the patient is at **maintenance dose. Maintenance dose is defined as the dose that leads to a therapeutic INR over two consecutive INR measurements, spanning a period of at least one week apart**. The RC must have entered the INR value from the previous week and enter the INR value for the current week Day 29 visit in order for this determination to be made.
- If maintenance dose is not achieved, the clinical provider dosing of the patient will continue to follow the dose-titration algorithm based on the INR and dose data inputted into the data management system (DMS) to identify any changes in dose needed, until the patient reaches stable/maintenance dose. The RC must use the current INR lab value (reported by site source or outside source) and enter that value into the DMS for the continued dosing at each scheduled visit until the patient reaches stable/maintenance dose.
- After the stable/maintenance dose is reached, dose titration will continue to be recommended as per the study titration algorithm, but the clinical provider will not be required to use the DMS algorithm for continued dosing.
- At the unblinding visit, the Research Coordinator will also be responsible for collecting and returning to the Research Pharmacy any previously dispensed blinded study drug given to the patient.

5.D.3.c) Month 2 (visit 8) - Telephone Visit

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/ DOSEREQ2	Dose Requisition Information - completed on an as needed (PRN) basis if participant remains on unblinded warfarin and has not reached stable/maintenance dose

INRLOG	INR Log**
AE	Adverse Events
CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – complete if participant remains on unblinded warfarin
WSTOP	Early Warfarin Stop – completed on an as needed (PRN) basis
SSTOP	Study Stop - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

5.D.3.d) Month 3 (visit 9)- In-person Visit:

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/ DOSEREQ2	Dose Requisition Information - completed on an as needed (PRN) basis if participant remains on unblinded warfarin and has not reached stable/maintenance dose
DIET/DIETUP	Diet Information and updates
EUROQOL	Eq-5D Health Information Questionnaire
SF-36	Health Status Questionnaire
INRLOG	INR Log**
AE	Adverse Events
CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – complete if participant remains on unblinded warfarin
DASS	Duke Anti-Coagulation Satisfaction Survey
MMS	Modified Morisky scale
WSTOP	Early Warfarin Stop – completed on an as needed (PRN) basis
SSTOP	Study Stop - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

5.D.3.e) Month 4 (visit 10) – Telephone Visit

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/ DOSEREQ2	Dose Requisition Information - completed on an as needed (PRN) basis if participant remains on unblinded warfarin and has not reached stable/maintenance dose
INRLOG	INR Log**
AE	Adverse Events
CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – complete if participant remains on unblinded warfarin
WSTOP	Early Warfarin Stop – completed on an as needed (PRN) basis

SSTOP	Study Stop - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

5.D.3.f) Month 5 (visit 11) – Telephone Visit

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/ DOSEREQ2	Dose Requisition Information - completed on an as needed (PRN) basis if participant remains on unblinded warfarin and has not reached stable/maintenance dose
INRLOG	INR Log**
AE	Adverse Events
CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – complete if participant remains on unblinded warfarin
WSTOP	Early Warfarin Stop – completed on an as needed (PRN) basis
SSTOP	Study Stop - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

5.D.3.g) Month 6 (visit 12) – In person Final Visit

Forms to be completed at this visit include:

PTCONT	Participant Contact Information and updates
DOSEREQ/ DOSEREQ2	Dose Requisition Information - completed on an as needed (PRN) basis if participant remains on unblinded warfarin and has not reached stable/maintenance dose
DIET/DIETUP	Diet Information and updates
EUROQOL	Eq-5D Health Information Questionnaire
SF-36	Health Status Questionnaire
INRLOG	INR Log**
AE	Adverse Events
CMED	Concomitant Medications
VISIT	Follow-up Visit Form
EVENTS	Medical Events
WARFLOG	Warfarin Log – complete if participant remains on unblinded warfarin
DASS	Duke Anti-Coagulation Satisfaction Survey
MMS	Modified Morisky scale
SSTOP	Study Stop - completed on an as needed (PRN) basis
DPCS	Data Processing Cover Sheet

5.E. Participant Retention

Retention generally refers to completion of follow-up visits and procedures as specified in the study protocol. To minimize bias and ensure the accuracy of study results, each study site will make every effort to retain enrolled study participants for the duration of study implementation, which is currently planned through June 2011.

5.E.1. Follow-Up Procedures for Participants Who Discontinue Study Drug

At whatever time point (blinded or unblinded phase) that the patient completes their warfarin treatment, they are expected to stay in the study and complete the remaining visits even if they are no longer on warfarin. Participants, who for medical or personal reasons discontinue use of study drug prior to the primary endpoint visit, will continue to be followed for all remaining study visits through to study completion at month 6. If a participant continues on unblinded warfarin after the primary endpoint visit and then discontinues use of warfarin before the month 6 visit, they will continue to be followed through to study completion at month 6 visit.

5.E.2. Participant Transfer

It is possible for a study participant to transfer to another COAG participating clinical center during the course of the study. However, it is preferred from a scientific as well as operational point of view that a participant completes the study at the same clinical center where they were originally enrolled. Upon identifying a need for a participant transfer to another clinical site, the transferring site will notify the receiving site as well as the Coordinating Center so that logistical details of the transfer can be discussed and agreed upon by the two sites.

5.F. Participant Withdrawal and Withdrawal of Consent

Participants are free to withdraw (or be withdrawn) from the study at any time. The withdrawal request can be made in person or during a phone contact. The various reasons for withdrawal may include:

- Adverse Event/Serious Adverse Event
- Significant concurrent illness
- Protocol noncompliance
- Investigator's discretion
- Withdrawn informed consent
- Relocation
- Dissatisfaction with treatment
- Loss of interest in the study
- Lost to follow-up

5.F.1. Voluntary Withdrawal

If a participant indicates that they no longer wish to participate in the study (withdraws consent), the RC will first alert the Principal Investigator who should then meet with the participant. The purpose of this meeting is to facilitate proper follow-up medical management of the participant.

If the participant wants to withdraw from the study while they are receiving blinded warfarin treatment, the PI will assess and discuss any issues of safety with the participant. The PI or clinician will also consult with the medical monitor to acquire the participant's unblinded dose information. The PI or clinician will then inform the participant and their follow-up medical provider of the warfarin dose the participant is currently receiving.

Following the decision of the participant to withdraw from the study, the clinical center RC should have the participant confirm their decision in writing. The RC will also follow local IRB guidelines for documenting/reporting participant withdrawal from the study.

The RC will complete the following case report forms at participant withdrawal:

SSTOP (Study Stop and Close-out) - select the representative reason(s) for withdrawal.

WSTOP (Early Warfarin Stop) – completed whenever participant discontinues warfarin treatment either in blinded or unblinded phase of study

UNBLIND – completed if warfarin dose unblinding occurs between Day 1 and Day 29 of study.

For those participants who withdraw (or are withdrawn) due to AE/SAE, the Adverse Event [AE] CRF must also be completed.

The participant study folder should be clearly marked to indicate study withdrawal and is maintained at the clinical center where the participant was recruited and followed. The RC should contact the CTCC Project Manager or Clinical Data Manager for any questions related to participant's withdrawal.

6. CONCOMITANT MEDICATIONS

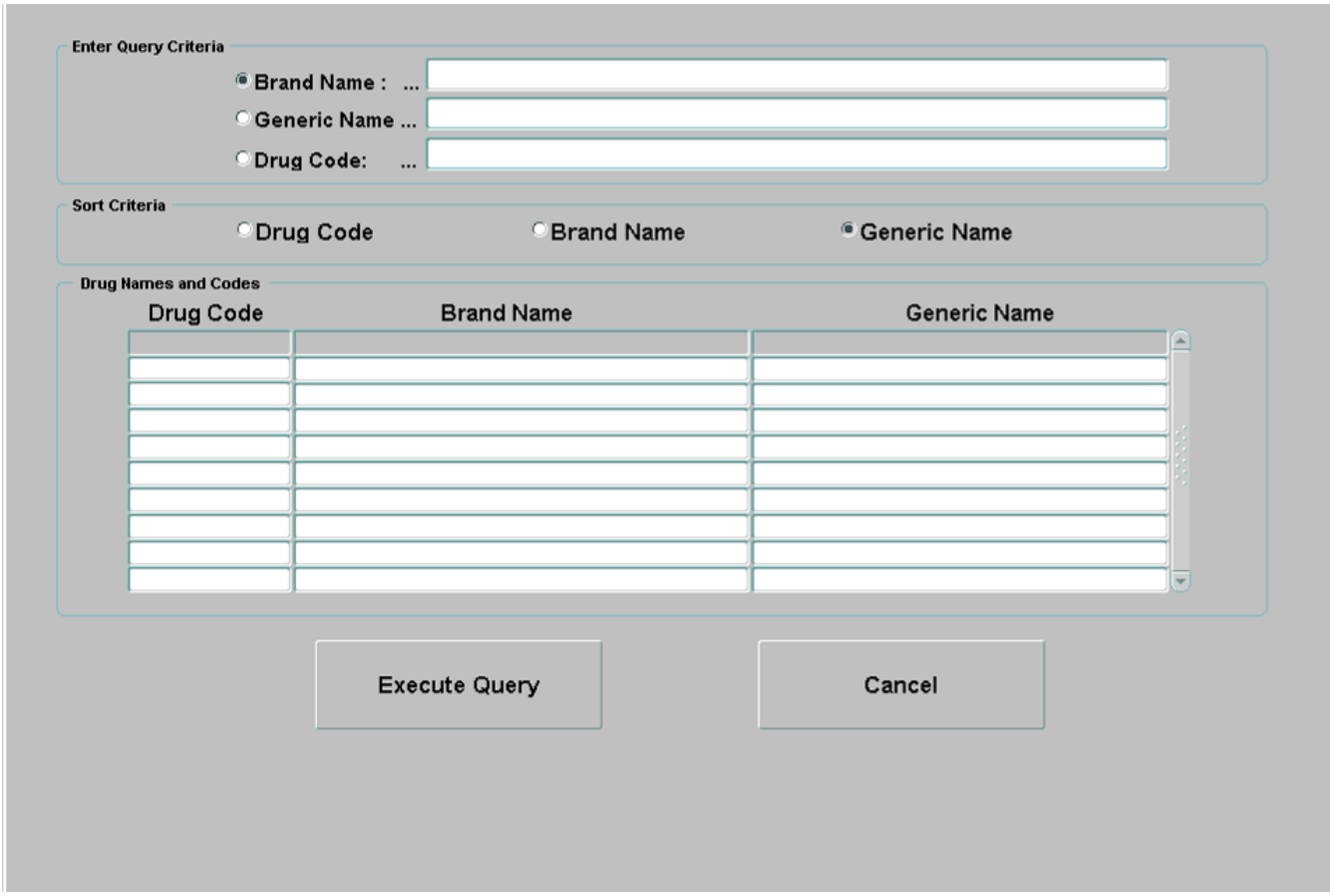
6.A. Collecting Concomitant Medication Data

At Visit 1, we will collect information from patients about the prescription and non-prescription medications they are currently taking. For a new enrollee who is an inpatient, this information should be available in the medical record. New enrollees who are outpatients can be asked to bring their medications with them to the first clinic visit. If the patient does not bring their medication with them, the RC will collect this information through participant interview. (A follow-up phone call to the participant may be necessary to confirm the accuracy of the interview results.) The information will be recorded on the CMED form for later entry into the data management system. This form is a log that will be reviewed and updated at each patient visit.

6.A.1. Using the Concomitant Medication Dictionary:

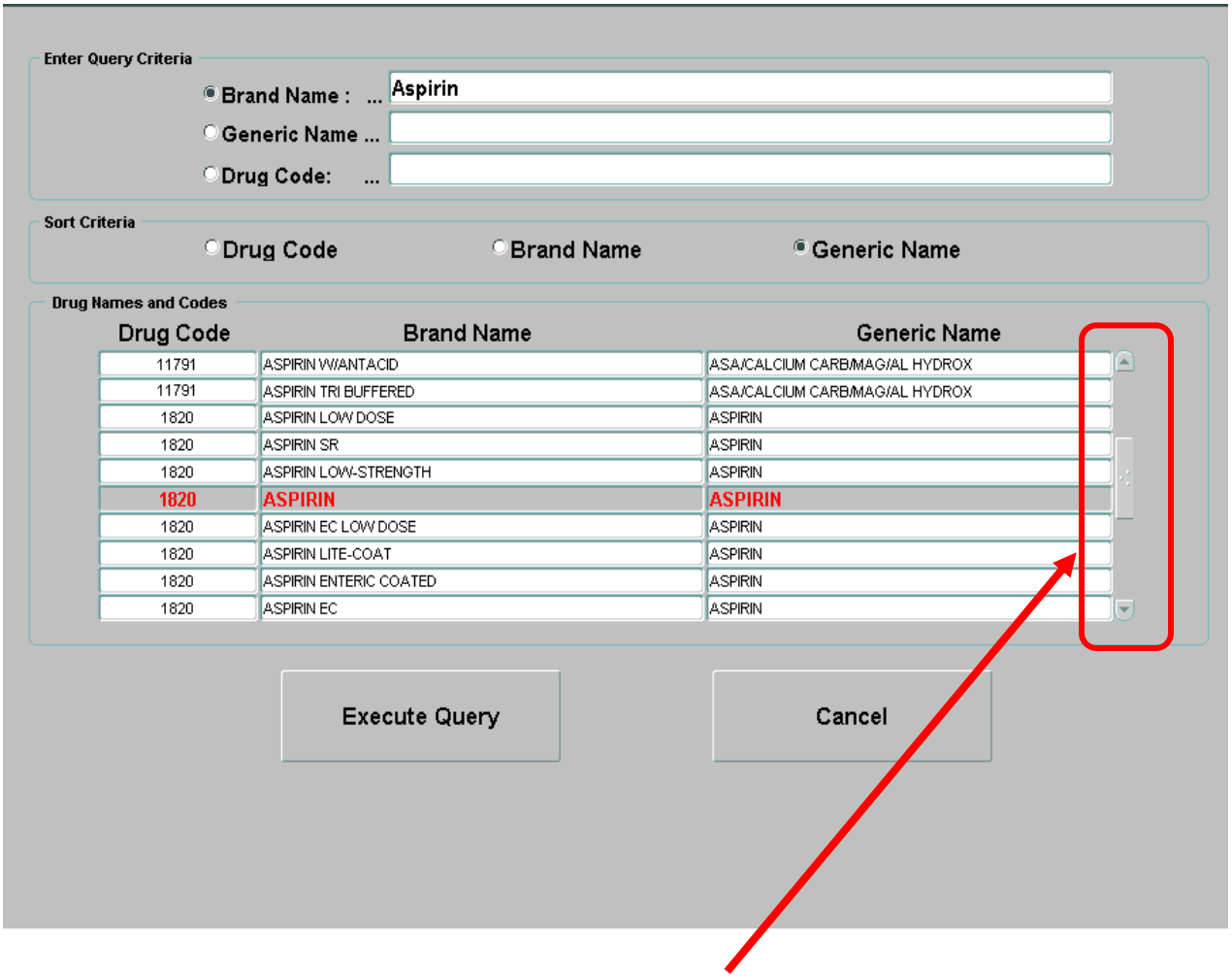
An electronic medication reference dictionary (National Drug Data File (NDDF) will be used to collect these data in a standardized fashion. This tool will be accessed through the main menu of the data management system.

After clicking on the Medication Tool Reference button, a search window will be displayed:



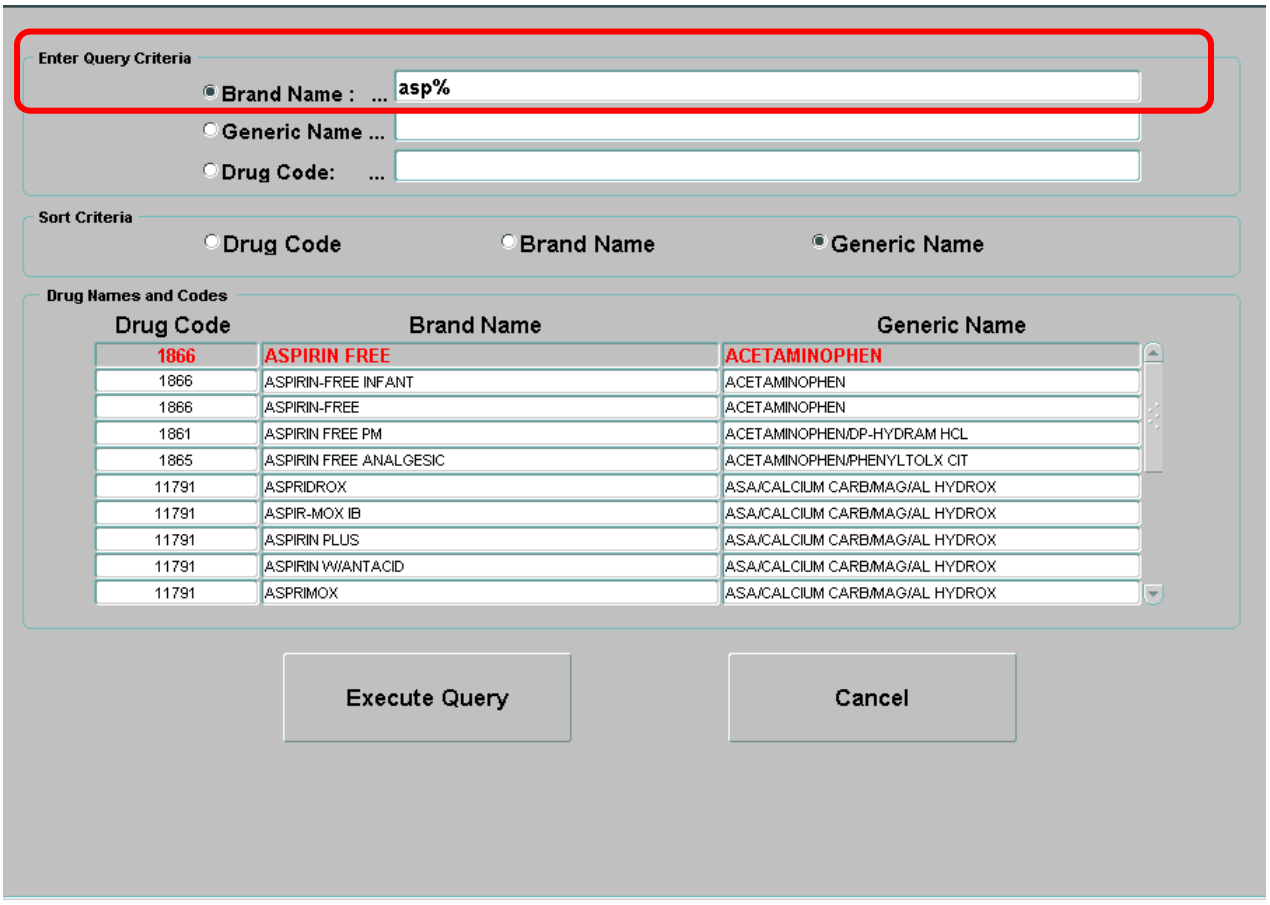
This window is divided by 3 sections:

- Enter Query Criteria – This section allows the user to enter and query for drugs based by Brand Name, Generic Name, or Drug Code.
- Sort Criteria – This section allows the user to sort their query entry by Drug Code, Brand Name, or Generic Name.
- Drug Names and Codes – This section displays the data queried and sorts it based on the criteria entered by the User.
- To search medications by Brand Name, make sure the radio button next to Brand Name has been selected, then enter the text of the drug to be searched for, and click on the button Execute Query. In the example below we are searching for aspirin:



- After the query has returned results, use the scroll bar to search the list for the most appropriate drug name.
- Then write the code down on the Concomitant Medication Log [CMED]. This information will then be used to enter the Medication code into COAG DMS.

- Repeat this search as need, based on the medications recorded during the clinic visit. If Brand Name is not working as query, try searching the term using the Generic Name query.
- If the complete spelling of a medication is unknown, the user can enter the first 2-3 characters and "%" to search for any term that begins with those characters:



- This type of search is referred to as a Wildcard Search, and will return any medication in the database that has "asp" in the Brand Name.
- Wildcard searches can be applied to the Generic Name and Drug Code search bars.

7. ADVERSE EVENTS

7.A. Identification of Adverse Events (AE)

It is important to remember in reporting adverse events that the warfarin dosing algorithm is the intervention in this research study, not warfarin itself. However, it is our obligation to monitor patients so that their participation is as safe as it can be, considering the underlying disease and risks inherent in warfarin treatment.

Adverse events will be recorded on the Adverse Event [AE] case report form at each clinic visit. This information may also be reported between scheduled study visits via participant phone calls or other unscheduled study visits or assessments if the patient reports health related problems or concerns.

Events will be categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) guide and corresponding MedDRA code, and documented on the AE case report form. These coding tools will be accessed via the study Data Management System (DMS).

The information recorded should be based on the signs or symptoms reported and detected during the study visit with the participant. In addition to the information obtained from the study visit evaluation, the participant should be asked a **standardized**, nonspecific question such as, "Have you had other health problems or concerns since your last clinic visit?"

Complete adverse event reporting includes the following information:

- Specific condition or event
- Whether a pre-existing condition has worsened (in severity and/or frequency)
- Abnormal laboratory value (if applicable)
- Grade (mild, moderate, etc.)
- Indication of seriousness of the event
- Outcome
- Relationship – relatedness to study
- Action taken
- Start and stop dates of the event

It is very important to identify, assess and code adverse events to achieve internal consistency within the clinical site and among the clinical sites. CTCC personnel will be available to assist clinical site personnel in the documentation required to appropriately describe and report events.

The data management system (DMS) will be utilized to manage the coding, reporting and analysis of adverse events and serious adverse events (SAE). Events will be coded by the clinical sites using current MedDRA terminology and will be available for assessment and review by the CTCC upon data entry.

After the baseline adverse event determination, a follow-up form [VISIT] will be completed to identify the following important medical events:

- Changes in warfarin use
- Hospitalization or emergency department visit
- Bleeding and clotting events

If any of the medical events above are identified, additional information will be collected on the [EVENT] form which will document the details about the incident(s).

7.B. Adverse Event (AE) Definitions

Definitions are per the January 2007 Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, Office on Human Research Protection (OHRP) Guidance. http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm. The requirements and processes for reporting adverse events are described in the corresponding NHLBI Guidelines.

Adverse Event (AE): An AE is any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's involvement in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE): An SAE is any AE that is:

a. fatal
b. life-threatening
c. requires or prolongs hospital stay
d. results in persistent or significant disability or incapacity
e. results in congenital anomalies or birth defects
f. an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance.

External adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, external adverse events are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

Internal adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, internal adverse events are those adverse events experienced by subjects enrolled by the investigator(s) at that institution.

7.C. Classifying Adverse Events

Adverse Events will be classified as to severity, potential relatedness, and expectedness to the study intervention and participation. The AE classification will determine the reporting requirements. The following definitions will be used to describe AEs:

7.C.1. Severity and Seriousness:

Level of severity (or grade) and the corresponding indicator of 'seriousness' for each event are defined below:

Severity	Seriousness
1. Mild AE; did not require treatment	Not serious
2. Moderate AE; resolved with treatment	Not serious
3. Severe AE; inability to perform normal activities; required professional medical attention	SAE if required or prolonged hospitalization
4. Life-threatening or permanently disabling	SAE
5. Death	SAE

7.C.2. Relatedness:

The potential event relationship to the study intervention, which is the dosing algorithm, is described below:

- Not related: event is clearly not related to the intervention
- Unlikely related: event is not likely related to the intervention
- Possibly related: event may be related to the intervention
- Related: event is clearly related to the intervention

7.C.3. Expectedness:

Unexpected Adverse Event: Any adverse event occurring in a research protocol, the nature, severity, or frequency of which is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are ***described in the protocol-related documents***, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and other relevant sources of information, such as product labeling and package inserts; or
    - the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Expected: Event that is known to be associated with the intervention or condition under study.

7.C.4. Known Events Associated with Warfarin Use:

Reports of side effects will be evaluated for changes and severity during each clinical visit. The following side effects are associated with warfarin use:

- Bleeding
- Allergic reactions
- Skin necrosis
- Purple toes syndrome
- Hepatic injury (based on liver function tests)
- Asthenia (loss of strength) or paresthesias (tingling, prickling sensation)

The following are reported, less serious, side effects of using warfarin:

- Bruising
- Bleeding gums when brushing teeth
- Nausea, abdominal pain, vomiting, diarrhea
- Alopecia (hair loss)
- Cold intolerance
- Fatigue
- Dysgeusia (impaired sense of taste)

7.C.4.a) Out-of-Range INR Values

It is expected that INR values will be out of the therapeutic range (2.0 – 3.0) during the dose-finding phase and periodically thereafter. Out-of-range INR values will not be reported as adverse events unless they require intervention.

For example, an INR value of 6.5 in and of itself should not be reported as an adverse event unless the clinician treats this patient by administering Vitamin K, admits them to the hospital for monitoring, and/or prolongs a hospital stay because of the INR. As another example, an INR of 1.5 in and of itself will not be considered an AE unless a clinician treats the patient with anticoagulants (e.g., low molecular weight heparin), admits them to the hospital for monitoring, and/or prolongs a hospital stay because of the INR.

All known INR results will be documented on the INR LOG form.

7.C.4.b) Bleeding Events

Bleeding is a common side-effect of taking warfarin. Depending on the INR level, it is not unusual for patients to experience some of the following signs: excessive bruising, bleeding from nose or gums, or blood in urine or stool. The list below serves as a guide to coding bleeding events.

Bleeding Events (Major bleeding events based on ISCOAT criteria)	**AE Coding Recommendations [Severity – Seriousness]**
Bleeding events that are self-limiting and require no intervention such as bruising, small ecchymoses (black and blue marks) or epistaxis (nose bleed), occasional hemorrhagic bleeding, bleeding resulting in decrease in hemoglobin decrease less than 2 g/dL without need for hospitalization or transfusion	Mild, Not serious
Bleeding resulting in decrease in hemoglobin of less than 2 g/dL and requiring transfusion of less than 2 units of blood, repetitive epistaxis for more than 5 minutes more than once in 24 hours, hematuria that occurs spontaneously or lasts more than 24 hours), hematemesis, and subcutaneous hematomas of more than 25 cm2 if spontaneous, or more than 100 cm2 if arising after trauma.	Moderate, Not Serious
Bleeding resulting in hemoglobin reduction of 2 g/dL or more and/or need for transfusion of two or more blood units but not meeting criteria for severe or fatal	Moderate, Serious
Intracranial hemorrhage (ICH), ocular bleeding with blindness, articular or retroperitoneal bleeding; bleeding requiring surgery or angiographic intervention	Severe, Serious
Death due to hemorrhage	Fatal, Serious

7.D. Adverse Event Reports

Clinical site personnel should follow the steps below to document adverse events:

- Collect AE information from patients in a consistent and standard manner by asking the same questions of patients each time.
- The AE form is a continuous log that will be updated at each visit. Review the last AE form to follow-up on unresolved AEs from the previous visit.
- Establish severity, relatedness and expectedness, in consultation with the PI if necessary.
- Access the online coding tool to categorize AE data.
- Enter AE data into the DMS as soon as possible (within one (1) week) after collecting AE data.

Routine reporting requirements to NIH and DSMB for AEs will be the responsibility of the CTCC. The CTCC will produce aggregate safety reports and distribute such reports to the appropriate parties. Each clinical site is responsible for reporting to their local IRB to meet their IRB reporting requirements.

7.D.1. Serious Adverse Events (SAE):

The clinical site is responsible for reporting SAEs to the CTCC within 24 hours of first knowledge of the event and to their local IRBs following their IRB's standard operating procedures. The CTCC will facilitate the timely reporting and distribution to regulatory authorities, NHLBI and the DSMB. SAE reporting guidelines are as follows:

a. SAEs will be documented on a form [SAEREPORT] that will assist the user in collecting complete information. This form should be completed and sent to the CTCC within 24 hours of first knowledge of the event.

b. Serious and unanticipated AEs that are ***fatal or life-threatening*** must be reported within 1 week to the local IRB and the NHLBI through the CTCC.

c. All other SAEs and unanticipated problems must be reported within 2 weeks to the NHLBI through the CTCC.

d. Clinical site personnel should notify the IRB of SAEs as per local requirements.

7.D.2. Unanticipated Problem Definition:

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- ***unexpected*** (in terms of nature, severity, or frequency) given the research procedures that are described in the IRB-approved research protocol and informed consent document;
- ***related or possibly related to participation in the research***; possibly related means that there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research.
- ***suggests that the research places subjects or others at a greater risk of harm*** (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

7.D.2.a) Unanticipated Problem Example

Medication errors and procedural mishaps are examples of Unanticipated Problems. The following is an example of an unanticipated problem (UP) that is <u>not</u> an adverse event but that must be reported to the IRB, appropriate institutional officials, and OHRP.

Example: As a result of a processing error at the medical center, a subject receives an incorrect dose of warfarin. While the dosing error increased the risk of bleeding and other adverse events, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation.

Nevertheless, this constitutes an unanticipated problem for the institution where the medication error occurred that must be reported to the IRB, appropriate institutional officials, and OHRP because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subject at a greater risk of physical harm than was previously known or recognized.

7.D.3. Filing an Unanticipated Problem Report:

An administrative form entitled Procedural and Unanticipated Problem [PUP] Report is used to describe the incident. Include all relevant details in this report. Send this report to the Clinical Trial Coordinating Center (CTCC) as soon as possible after first knowledge of the UP, within 48 hours. If the UP is also an Adverse Event, complete the AE form to document any corresponding adverse event information related to this UP.

SAEs that are also unanticipated problems must be reported within 7 days to the local IRB and CTCC for reporting to NHLBI.

7.E. Adverse Event Coding Using CTCAE and MedDRA

a. Descriptive adverse event information will be collected from the patient directly onto the paper AE form. Before entry of these data into the Data Management system, the user will access an external link to the Common Terminology Criteria for Adverse Events (CTCAE) guide provided by the NIH to code the event.

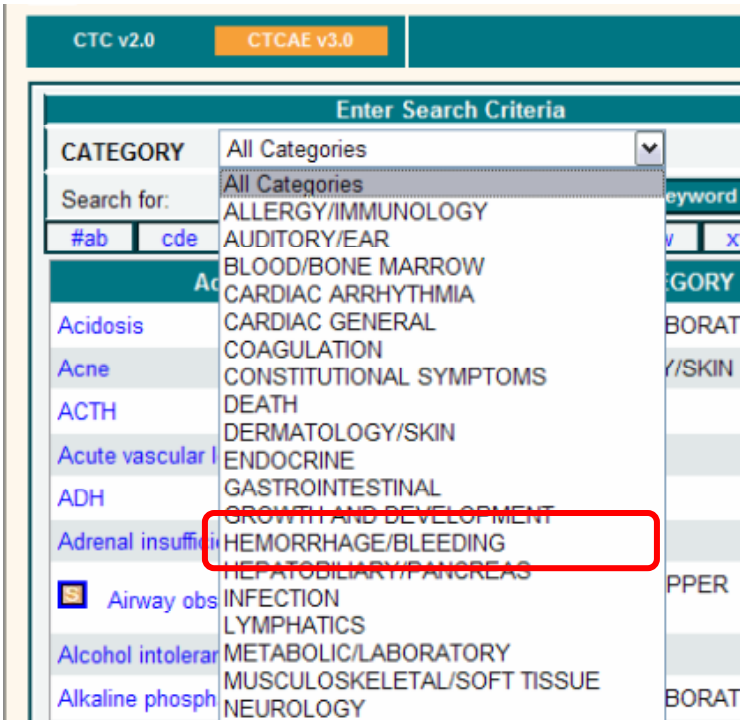
   http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

b. Select CTCAE Version 3.0 at the top left corner of the menu.

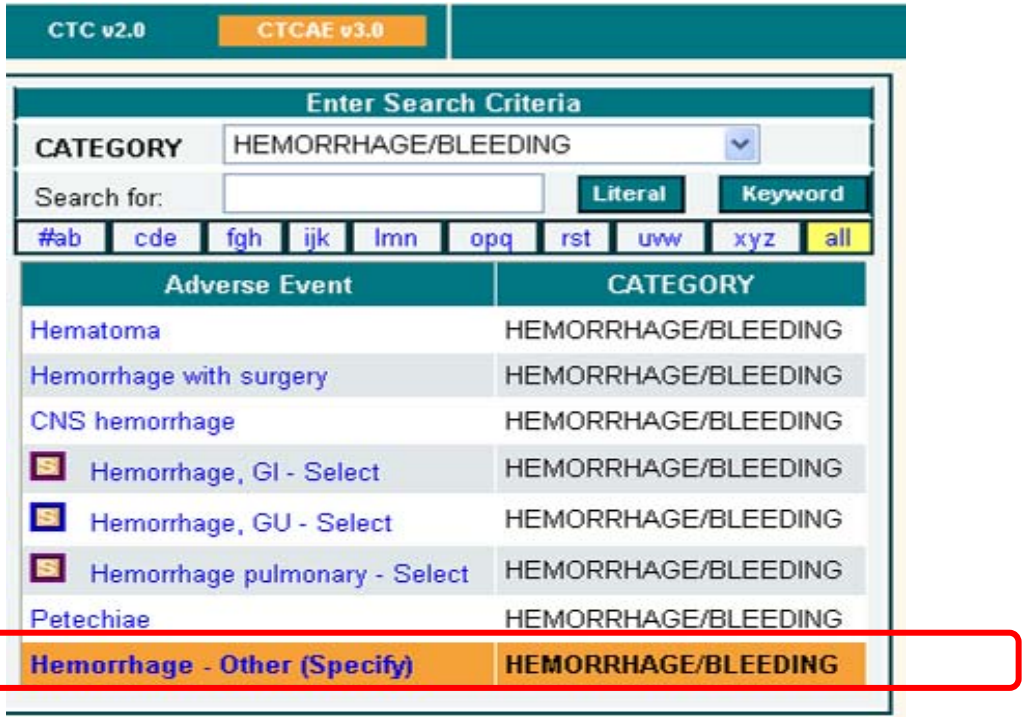
c. Category searches can be completed by clicking on the down arrow next to the word "All Categories". The user will be presented with a drop down list of body systems. If a body system is selected, the most common ailments will be presented and the user can scroll through the various conditions.

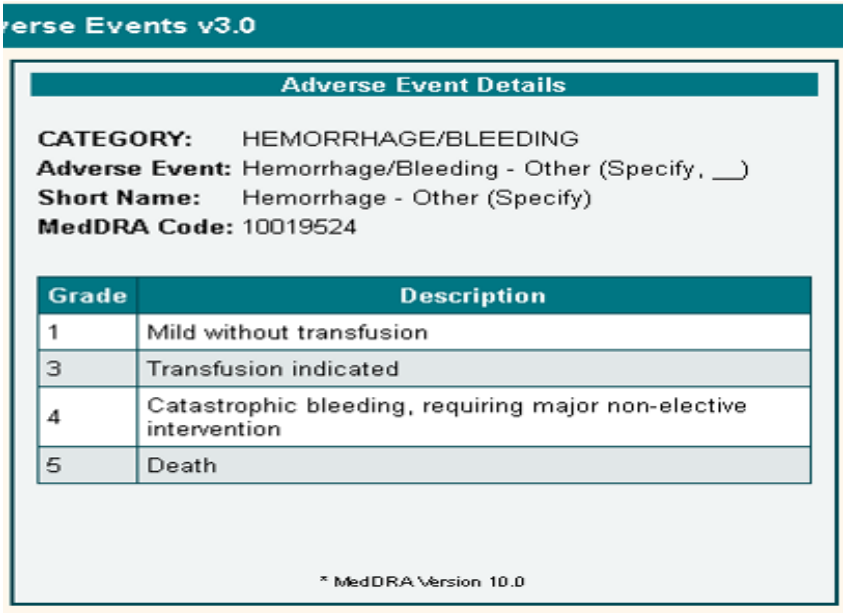
Adverse Event Example 1: A patient reports bleeding for 45 minutes after accidentally cutting herself with a bread knife.

- From the Category drop-down menu, select ***'Hemorrhage/Bleeding.'***



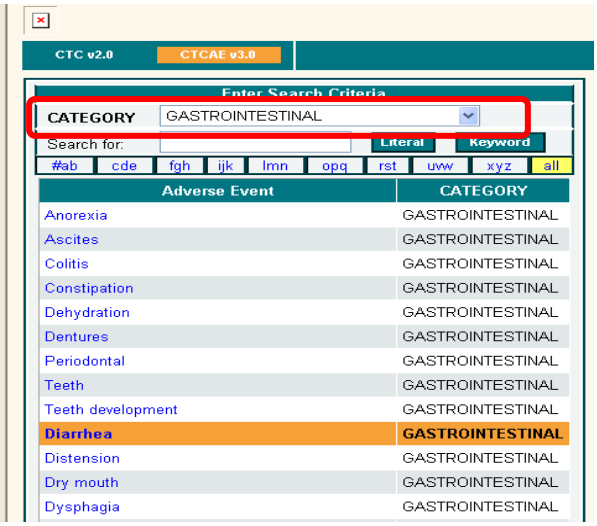
- From the list of adverse events on the left, select ***'Hemorrhage – Other (Specify).***' The following screens will be presented:



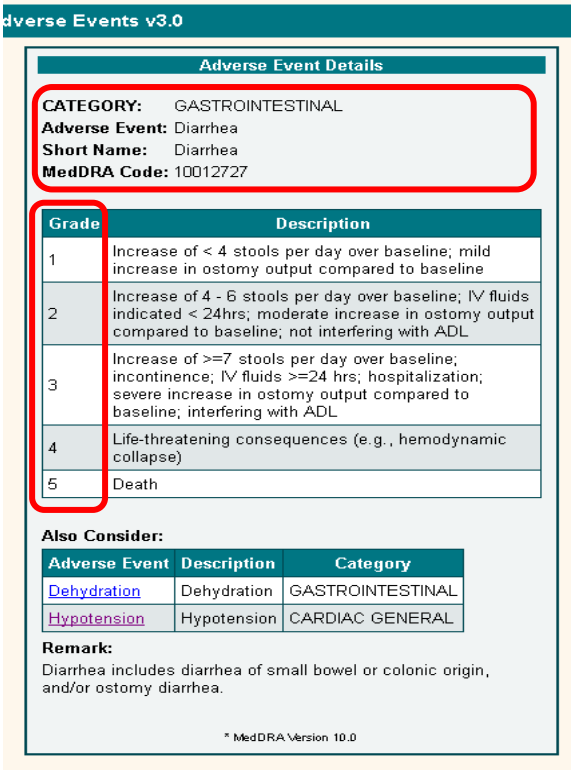


- Based on the description provide by the patient, the user will record the MedDRA Code number 10019524, and determine the grade based on the patient's description or intervention required. In this example, the grade would be 1 if the patient did not require a transfusion.
- Record this information on the AE form for entry into the DMS.

Adverse Event Example 2: A patient reports nausea and diarrhea that started shortly after he/she began warfarin and has remained problematic for the last 3 days.



- From the Category drop-down menu, select 'Gastrointestinal.'



- From the list of adverse events on the left, select 'Diarrhea.'
- Based on the description provide by the patient, the user will record the MedDRA Code number 10012727, and grade.

Record this information on the AE form for entry into the DMS.

7.F. Medical Monitor

The Medical Monitor, Dr. Scott Kasner, is a licensed physician and Vascular Neurologist associated with the Clinical Trial Coordinating Center (CTCC), and serves in an independent role. The Medical Monitor will be unblinded to study dose and treatment arm assignment for all patients enrolled in the study. The Medical Monitor is responsible for:

- Managing requests for warfarin dose adjustments
- Authorizing requests for dose unblinding
- Serving as a resource to investigators and coordinators for urgent concerns related to patient safety, particularly when such concerns might require interruption or cessation of the study intervention and /or any deviation from the study protocol.
- Reviewing SAE reports and major bleeding events

Dr. Kasner may be contacted by the clinical site investigator, the research coordinator, or research pharmacist. Patients are not to contact Dr. Kasner.

Contact information:

- Cell phone (preferred for urgent issues): (215) 593-6523
- Beeper number: (215) 452-4944
- Email (preferred for non-urgent issues): kasner@mail.med.upenn.edu

7.F.1. Patient Safety and Unblinding:

A clinical site PI may request dosing information in circumstances such as a medical emergency, or other situations in which the PI believes it is important to unblind the warfarin dose to medically manage the patient.

To initiate this request, the PI should contact the Medical Monitor. It will be the clinical site PI's responsibility to assess issues of patient safety and communicate them to the Medical Monitor. The Medical Monitor will make the final determination regarding unblinding a particular patient. The Medical Monitor will acquire dosing information from the local investigational pharmacist or the central IDS, depending on the situation. The clinical site PI will be responsible for communicating with the patient. Major Clinical Events

The Medical Monitor will review all SAEs that are considered by the PI to be probably or definitely related to treatment allocation. In addition, all acute thromboembolic events and major bleeding events will be reported to and reviewed by the Medical Monitor, regardless of the reported relationship between the event and the study intervention. This information will be provided to the Medical Monitor by the CTCC.

In cases in which there is disagreement on the classification of the SAE, thromboembolic event, or major bleeding events between the local investigator and the Medical Monitor, the determination by the Medical Monitor will be used as the final classification.

Consultation with the Medical Monitor will be documented by the CTCC on the MEDMONITOR case report form.

7.F.2. Warfarin Dosing Adjustments:

The Medical Monitor will be contacted by local investigators any time they are considering prescribing a warfarin dose other than the dose determined by the study algorithms.

During the blinded first 4 weeks, these changes would represent a “change in the percentage adjustment of warfarin dose” since investigators will not know the actual dose being given and/or a “change in plans to hold warfarin doses or give extra doses.” Such considerations should be made solely for patient safety, or when there is an issue not otherwise considered by the standard study algorithm such as:

- patient error with prior assigned dose,
- prescribing or dispensing error with prior assigned dose,
- recently instructed not to take anything by mouth, i.e., “NPO”, non-adherence,
- new medication addition or deletion,
- recent bleeding event,
- recent thromboembolic event

In these and other circumstances, a discussion between the site investigator and the Medical Monitor must occur, and an acceptable warfarin dose will be determined based on the relevant clinical issues. All deviations from the study algorithm dosing schedule must be approved and recorded by the Medical Monitor. If a dose override is approved, the Medical Monitor will contact the site Research Pharmacist to inform them of the change in dose. The change in dose information will be entered into the DMS by the site Research Pharmacist. Since subsequent INRs and dose adjustments will refer back to the override dose, this dose will replace the dose assigned by protocol in the database, and be identified as an override. The frequency of dose overrides will be monitored by the CTCC.

8. DATA COLLECTION AND ADMINISTRATIVE FORMS

8.A. Case Report Forms (CRFs):

A case report form is divided into 3 distinct sections:

- **Header:** The header is the top part of the CRF that includes the study logo/name, participant identifiers and CRF name.

  Generally the study name is an abbreviated name by which the study is identified; in this instance Clarification of Optimal Anticoagulation through Genetics will be referred to as ***COAG***.

  Participant identifiers in this study include Participant ID, Participant Initials, Clinical Center, Visit Date, Visit Number and CRC Initials. Occasionally a sequence number may be added to the header if a CRF needs to be completed more than once at a visit, e.g. **GENOTYPE**.

  The title clearly indicates the type of data that is collected on the case report form.

- **Questions/responses:** The questions and the space to record corresponding responses form the majority of the CRF. The responses could be in the form of spaces to record values, or checkboxes comprising of a list of applicable or relevant response categories to the question. The information could also be organized in the form of a log that collects data in a linear mode.
- **Footer:** The footer contains information about the most current version of the CRF used for data collection and the corresponding date, page number and the abbreviated name of the CRF.

  A version number and corresponding date is applied to track changes to the CRF from the start of the study. Date-based version number helps the biostatistician identify the availability of data for analysis based on the addition or deletion of questions. It is the responsibility of the Research Coordinator (RC) to maintain current versions of the CRFs at all times.

  Page numbers help track missing pages in case of printing errors or misplaced pages.

  The data table in the database is identified by the abbreviated name of the CRF in the lower right corner.

8.A.1. Types of Case Report Forms:

There are 2 types of case report forms – data and administrative CRFs.

- Data case report forms contain participant data and are entered in the database.
- Administrative case report forms are used for study organization and not entered in the database.

8.A.2. General Instructions:

- All CRFs should be completed in blue or black ink. Pencil, red ink, or other colored ink should not be used.
- WhiteOut™ or any other form of correction that distorts or hides the original data should not be used.
- Responses should not be left blank unless specific instructions on the CRF suggest that questions may be skipped.

- Only one response should be recorded per question unless instructions indicate to "Check all that apply".
- The latest versions of the CRFs should always be used. Please refer to the CRF Version Log (Appendix #) to confirm the version numbers in use.
- An original print should always be used when making copies; avoid making "copies of copies".
- Original copies are available for printing in the CRF module of the data management system.
- The RC should complete the header information prior to administering the CRFs at baseline and follow-up visits to ensure easy identification in case of separation of pages, or multiple participant visits in a day.
- The RC is responsible for reviewing all CRFs for completion and legibility at each visit to help minimize data errors.
- Personal identifiers should not be included on the CRFs used for data entry; study identifying information only (Participant ID, Participant Initials, CRF Completion Date, Visit Number, and Interviewer initials) should be recorded on the data entry CRFs.

8.A.3. Directions for Completing the Header Information:

The header of the CRF is the area at the very top that contains information to identify the participant, the study, and other data used to distinguish participants, CRFs and study visits from one another.

- Participant ID (PID): PID is a 6-digit number. The first digit is a hard-coded numerical value "1" representing the protocol number, the next 2 digits represent the Clinical Centers where the study is conducted. The last 3 digits are sequential numbers, starting with 001, of the participants screened and possibly enrolled at each Clinical Center. Hence the first participant screened in the study at Clinical Center 01 (University of Texas) is 001, and the PID is 101001.
- Participant Initials (Pt. initials): Participant initials are 3-character initials of the first, middle and last name of the participant, e.g. "CDE". If the middle name is not available, an "X" must be used.
- Clinical Center (CCID): CCID is as 2-digit code. The 12 Clinical Center IDs are:

01 - University of Texas
02 - Mount Sinai School of Medicine
03 - The University of California, San Francisco
04 - Washington University School of Medicine
05 - University of Maryland School of Medicine
06 - University of Florida
07 - Henry Ford Hospital
08 - Mayo Clinic College of Medicine
09 - Hospital of the University of Pennsylvania
10 - Vanderbilt University
11 - Intermountain Medical Center
12 - Marshfield Clinical Research Foundation
13 - Duke University Medical Center
14 - Georgia Health Sciences University
15 - University of Alabama at Birmingham
16 - University of Utah Health Care
17 - Tulane University
18 - Montefiore Medical Center

- Visit Date: This is the date when the visit occurs and the data (outlined in the protocol for the visit) is collected. Visit date must be entered in the mm/dd/yyyy format.
- Visit Number: This is a 2-digit code that represents the visit number (as outlined in the Visit Schedule – ***VSTSCH***) when different study processes occur.
- CRC Initials: This is a 3-letter ID for the Research Coordinator (RC) who collects the information and completes the CRF. This ID should be the RC's initials (first letter of the first, middle and last name).. If the middle name is not available, an "X" must be used.

8.A.4. Review of Completed Case Report Forms:

- The RC should review all CRFs for legibility, accuracy, and completeness in preparation for data entry.
- If the RC identifies an error while reviewing the CRFs, the error should be corrected on the completed CRF by crossing out the error with a single line in black ink, entering the correct information, initialing and dating the change; the RC may circle the correct answer for clarification, if needed.

Details on completion of the case report forms (CRFs) are available in section **8** of this manual.

Each form used in the study is displayed on the left with coding instructions and detailed CRF guidelines are included on the right-hand page. If you have further questions on the format of the Manual of Procedures (MOP), please contact CTCC personnel.

8.B. Case Report Form (CRF) Completion Guidelines:

Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

ENROLLMENT INFORMATION

1. Date of birth: ..... Computer will check age against birthdate. If they do not match, you will not be able to proceed with entry.	Record the date of birth in mm/dd/yyyy format. *Response cannot be left blank.*
a. Age:	Record age. Must be ≥18 years. *Response cannot be left blank*
2. Gender:	Check the appropriate box for question 2. "1=Male" or "2=Female" *Response cannot be left blank*
3. Ethnicity:	Check the appropriate box for question 3. "1=Hispanic/Latino" or "2=Non-Hispanic" *Response cannot be left blank*
4. Race (*check all that apply*)..... You must check at least one box in order to proceed with entry.	Check the appropriate box for question 4 CHECK ALL THAT APPLY" "1=American Indian or Alaska Native" "1=Asian" "1=Black or African American" "1=Native Hawaiian or Other Pacific Islander" "1=White" "1=Refused to respond"
PLEASE TRY AND GET A RACE CLASSIFICATION	
5. Height (*self-reported or most current available*):	Record height in feet and inches *Response cannot be left blank*
6. Weight (*self-reported or most current available*):	Record weight in pounds *Response cannot be left blank*
7. Diabetes (*include diet-controlled*):	Check appropriate boxes for questions 7 through 11. "1=Yes" or "0=No". *Responses cannot be left blank*
8. Is the primary indication for warfarin therapy treatment of a stroke:	
9. Currently on fluvastatin (*Lescol*):	
10. Currently on amiodarone (*Cordarone*):	
11. Current smoker:	
12. Record all current indications for warfarin therapy:	
a. Antiphospholipid antibody syndrome:	Check appropriate boxes for questions 12a through 12i. "1=Yes" or "0=No". *Responses cannot be left blank*
b. Aortic valve replacement:	
c. Atrial fibrillation:	
d. Atrial flutter:	
e. Cardiomyopathy:	
f. Cerebrovascular accident (*CVA*):	
g. Deep vein thrombosis (*DVT*):	
h. Mitral valve replacement	
i. Mural thrombus:	

V2.0.20100816 Page 1 of 2 ENROLL

[ENROLL] ENROLLMENT INFORMATION:

ENROLL is one of 5 CRFs needed to screen and randomize a potential participant in the study. The information collected on the ***ENROLL*** CRF is used towards the dosing algorithm. Each item of the ***ENROLL*** data is a required entry in the data management system (DMS); thus items should not be left unanswered. Cross check among items is built into the DMS to identify and allow correction of illogical responses, e.g. date of birth and age.

ENROLL is expected to be completed by the Research Coordinator on all potential participants, including screening failures, soon after the informed consent is signed. Data on the **ENROLL** CRF is completed by reviewing medical records and by querying the participant.

Q. 1-1a: When a participant reports his/her date of birth and age, the RC should check the reported date of birth against the age to verify the information. Participants have to be 18 years of age or older to participate in the study, hence this information will help make the determination for eligibility.

Q. 2: Gender is self-evident in most cases, but at times if it is unclear, the RC should use discretion and sensitivity in determining the gender.

Q. 3: Ethnicity is self-reported and it is required that the RC ask the participant their ethnic background and check the appropriate box.

Q. 4: Race is self-reported as well and the RC must record the response given by the participant. The participant may refuse to respond to the categories that are presented by the RC. Should this occur, the RC should explain the reason why collecting this information is important – the algorithm for determining the dose of warfarin that the participant is to receive requires that race be known and the RC should encourage the participant to provide this information. If after providing an explanation, the participant still refuses, then enrollment cannot proceed. If the participant's response is one of not knowing or uncertain of their race, the RC should ask the participant to make the best possible choice. If the participant reports race as a combination of African American and another race, then the African American category is checked.

Q. 5: Height may be recorded as a self-reported value or the most current measured value available in the medical records. It is reported in feet and inches.

Institutions that maintain height data in the metric system need to covert the value from centimeters (cm) to feet (ft) and inches (in) by multiplying the value in centimeters by .0328.

Q. 6: Weight too is recorded as a self-reported value. If the RC can find the most current measured value in the medical records, it is acceptable to record that value.

Institutions that maintain weight data in the metric system need to covert the value from kilograms (kg) to pounds (lbs) by multiplying the value in kilograms by 2.205.

Q. 7: Diagnosis of diabetes can be self-reported or recorded from the medical records. A potential participant who manages hyperglycemia diagnosed by a physician, through diet, oral medications or insulin is considered diabetic for this study.

If the information is gathered from the participant, the RC must ask pertinent health and medication-related questions to get the best possible information to confirm the diagnosis. If the RC is unsure of the information given by the participant, the RC can request the clinical center PI to make a determination of the diagnosis.

Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

ENROLLMENT INFORMATION

1. Date of birth:	Computer will check age against birthdate. If they do not match, you will not be able to proceed with entry. Record the date of birth in mm/dd/yyyy format. *Response cannot be left blank.*
a. Age:	Record age. Must be ≥18 years. *Response cannot be left blank*
2. Gender:	Check the appropriate box for question 2. "1=Male" or "2=Female" *Response cannot be left blank*
3. Ethnicity:	Check the appropriate box for question 3. "1=Hispanic/Latino" or "2=Non-Hispanic" *Response cannot be left blank*
4. Race (*check all that apply*).... You must check at least one box in order to proceed with entry.	Check the appropriate box for question 4 CHECK ALL THAT APPLY" "1=American Indian or Alaska Native" "1=Asian" "1=Black or African American" "1=Native Hawaiian or Other Pacific Islander" "1=White" "1=Refused to respond"
PLEASE TRY AND GET A RACE CLASSIFICATION	
5. Height (*self-reported or most current available*):	Record height in feet and inches *Response cannot be left blank*
6. Weight (*self-reported or most current available*):	Record weight in pounds *Response cannot be left blank*
7. Diabetes (*include diet-controlled*):	Check appropriate boxes for questions 7 through 11. "1=Yes" or "0=No". *Responses cannot be left blank*
8. Is the primary indication for warfarin therapy treatment of a stroke:	
9. Currently on fluvastatin (*Lescol*):	
10. Currently on amiodarone (*Cordarone*):	
11. Current smoker:	
12. Record all current indications for warfarin therapy:	
a. Antiphospholipid antibody syndrome:	Check appropriate boxes for questions 12a through 12i. "1=Yes" or "0=No". *Responses cannot be left blank*
b. Aortic valve replacement:	
c. Atrial fibrillation:	
d. Atrial flutter:	
e. Cardiomyopathy:	
f. Cerebrovascular accident (*CVA*):	
g. Deep vein thrombosis (*DVT*):	
h. Mitral valve replacement	
i. Mural thrombus:	

V2.0.20100816 Page 1 of 2 ENROLL

Q. 8: Item # 8 is updated in the current version to indicate if the primary indication for warfarin is for stroke. A Yes or No response is needed based on the available information in the participant's medcail records.

Q. 9: Use of fluvastatin for hypercholesterolemia is generally available in medical or pharmacy records or can be self-reported. If the RC is unsure of the self-report, he/she should make every attempt to get the best possible information.

If the participant is enrolled in the study, the use of fluvastatin is recorded on the Concomitant Medications (***CMED***) CRF.

Q. 10: Use of amiodarone, an anti-arrhythmic drug, is generally available in the participant's medical records or is self-reported. If the RC is unsure of the accuracy of the self-report, he/she should make every attempt to get the best possible information.

If the participant is enrolled in the study, the use of amiodarone is recorded on the Concomitant Medications (***CMED***) CRF.

Q. 11: A participant is considered a current smoker if he/she is a habitual smoker or has smoked within the past month (independent of the amount or the frequency). If a participant is considered a smoker, additional information on his/her smoking habits is collected on the Medical History (***MEDHX***) form.

Q. 12a-m: The RC must check "Yes" or "No" for each indication listed in items 12a-n. The information may be available in the medical records or self-reported. The RC must be able to explain the medical terminology to the potential participant to elicit the best possible response for these items.

Item 12n is checked as "Yes" only when the participant reports a condition not mentioned in items 12a through 12m. If "Yes" is checked in item 12n, space is provided to record specific text to clarify the response of "Other".

Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

ENROLLMENT INFORMATION

12. Record all current indications for warfarin therapy: .....*continued*	
j. Orthopedic surgery:	Check appropriate boxes for questions 12j through 12n. "1=Yes" or "0=No". *Responses cannot be left blank*
k. Post-cardiac ablation procedure:	
l. Post myocardial infarction (*MI*):	
m. Pulmonary embolism (*PE*):	
n. Other:	
n1. If yes, specify:	If yes to question 12n, record the other indication of warfarin therapy (maximum 500 characters)
13. Is the primary indication for warfarin therapy treatment of deep vein thrombosis (*DVT*) or pulmonary embolism (*PE*)?	Check the appropriate box for question 13. "1=Yes" or "0=No". *Response cannot be left blank*
14. Recruited during an inpatient stay or from an outpatient clinic:	Check the appropriate box for question 14 "1=Inpatient stay" or "2=Outpatient clinic" *Response cannot be left blank*
15. What is the planned duration of warfarin therapy?	Check at least one response 1 = at least 1 month 2 = >1 month, up to 2 months 3 = >2 months, up to 3 months 4 = >3 months, up to 4 months 5 = >4 months, up to 5 months 6 >5 months, up to 6 months 7 >6 months

Q. 13: The intent of the question is to determine if the current need to initiate warfarin therapy (and subsequently participation in the COAG study) is primarily due to a diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE). This information is either available in the medical records or from the participant's healthcare provider.

Q. 14: The RC must record an appropriate response to this question based on the participant's status at the time of recruitment for the study.

Q. 15: This is a newly added item due to an amendment to the .protocol. This item collects information on the planned duration of warfarin therapy. A range of time frames are provided as response categories and the Coordinator selects a category that best represents the duration.

ENROLL is a data CRF and must be double data entered in the data management system (DMS) prior to randomization

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Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

ELIGIBILITY CONFIRMATION

Inclusion criteria: *Responses to questions 1-6 must be "1 - Yes".*

1. Is the participant 18 years of age or older? .....
2. Is the participant able and willing to sign the informed consent? .....
3. Is the participant able to be followed in the outpatient anticoagulation clinic? .....
4. Is the expected duration of warfarin therapy at least one (1) month or longer? .....
5. Is the in-patient and/or outpatient clinician who is and will be managing the participant's anti-coagulation (AC) willing to adhere to the dosing algorithms and dose titration plans for this study? .....
6. Is the participant's target INR in the range of 2 to 3? .....

Check the appropriate box for questions 1 through 6;
1 = Yes or 0 = No

Questions 1 though 6 must be 1 = Yes for the participant to be eligible

RESPONSES TO QUESTIONS CANNOT BE LEFT BLANK

Exclusion criteria: *Responses to questions 7-20 must be "0 - No" or "99 - N/A".*

7. Is the participant currently taking warfarin? .....
8. Was the participant previously on warfarin therapy with known required stable dose? .....
9. In the clinician's opinion does warfarin dosing needs to be adjusted for reasons not accounted for by dosing algorithm? .....
10. Was the baseline INR (*prior to heparin or warfarin*) elevated? .....
11. Is warfarin treatment contraindicated for at least 3 months? .....
12. Is the participant's life expectancy less than 1 year? .....
13. Is the female participant pregnant? .....
    (*Must have a documented negative pregnancy test.*)
14. Is the female participant unwilling to use medically-approved method of birth control? .....
15. Is the participant unable to follow-up on a regular basis with anti-coagulation practitioners participating in the trial? .....

Check the appropriate box for questions 7 through 15;
1 = Yes, 0 = No or 99 = N/A

Questions 7 though 15 must be 0 = No or 99 = N/A for the participant to be eligible

RESPONSES TO QUESTIONS CANNOT BE LEFT BLANK

[ELIG] ELIGIBILITY CONFIRMATION:

Eligibility Confirmation (***ELIG***) is the most important case report form completed by the RC. It is a confirmation of the inclusion and exclusion criteria for enrollment of the participant in the study, based on the study protocol. This CRF is completed on all potential participants, including screening failures. Information for completing Question 4, 5, and 6 of the Inclusion Criteria and Question 9, 10 and 11 of the Exclusion Criteria must be confirmed with the healthcare provider/clinician.

Questions 1 through 6 are inclusion criteria with the expected response of "Yes", and questions 7 through 20 are exclusion criteria with the expected response of "No" or "N/A (not applicable)" to qualify for the study. Disqualifying responses are shaded in gray for inclusion and exclusion criteria.

Q. 1: Participant's age is available on the ***ENROLL*** CRF. The RC must confirm that the patient is 18 years or older of age to be recruited for the study.

Q. 2: The participant must consent to the study willingly and should not be coerced to participate. The RC should determine that the participant understands the responsibility associated with participation and signs the informed consent free of pressure.

Q. 3: A participant may be contacted for the study while hospitalized and the RC should determine if he/she is able to return to the outpatient anticoagulation clinic for follow-up care and study visits as outlined in the Visit Schedule (***VSTSCH***).

The first 5 days of the study are critical and the RC should determine the participant's availability for frequent dosing. The participant should additionally be available for the rest of the first 28 days for frequent assessments.

Q. 4: The RC should determine from the medical records and the healthcare provider if it is medically required for the participant to remain on warfarin therapy for at least one (1) month. Any time period less than that will disqualify the potential participant. This is an update from the previous version based on the recent amendment to the protocol.

Q. 5: The RC should check with the healthcare provider at the anticoagulation clinic that he/she is agreeable to the COAG study managing the participant's dosing based on the algorithm. If the healthcare provider determines that participation is not recommended, the participant is considered ineligible.

Q. 6: The RC must confirm with the healthcare provider/clinician that the target INR of 2-3 is planned for this participant's course of warfarin therapy.

Q. 7: The RC must confirm through self-reporting and by reviewing medical records that the participant is not taking warfarin at the time of enrollment. A "Yes" response will make the participant ineligible for participation.

Q. 8: If a review of medical or pharmacy records reveal that the participant was previously on a known and stable dose of warfarin, the participant is not eligible to participate in the study.

Q. 9: If a potential participant's dose may need to be adjusted outside of the dosing algorithm, the participant is not qualified to participate in the study. This information must be confirmed with the participant's clinician or health care provider.

Q. 10: This information is confirmed by reviewing the medical records and discussion with the healthcare provider at the time of recruitment.

Q. 11: This information is confirmed by reviewing the medical records and discussion with the healthcare provider at the time of recruitment.

Q. 12: It is confirmed by reviewing the medical records and discussion with the healthcare provider that the participant does not have a terminal illness with life expectancy of less than a year.

Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

ELIGIBILITY CONFIRMATION

16. Are there any factors likely to limit adherence to warfarin?

    a. Dementia (*unless minor problem*): .....
    b. Current alcohol or substance abuse: .....
    c. Plans to move in the next six months: .....
    d. History of unreliability in medication taking or appointment keeping: .....
    e. Significant concerns about participation in the study from spouse, significant other, or family members: .....
    f. Lack of support from primary health care provider: .....

17. Is the participant unable to provide consent or follow study procedures due to cognitive or other limitations? .....

18. Is the participant participating in another clinical trial in the next 6 months? .....

19. Has the participant had an estimated blood loss of >1000 cc requiring blood transfusions within 48 hours prior to randomization?

20. If the participant has received previous genetic testing, are the results of CYP2C9 or VKORC1 known? .....

Check the appropriate box for questions 16 through 20;
1 = Yes or 0 = No

Questions 16 though 20 must be 0 = No for the participant to be eligible

RESPONSES TO QUESTIONS CANNOT BE LEFT BLANK

21. Is the participant eligible for participation in the study? .....

Check the appropriate box for questions 21;
1 = Yes or 0 = No

V2.0.20100816 Page 2 of 2 ELIG

Q. 13: A female participant who is **capable of bearing children** must have current documentation of a negative pregnancy test to participate in the study. If the documentation is not available in the medical records, the research coordinator must order a pregnancy test. [This requirement does not apply to postmenopausal women and women who have had a hysterectomy].

- Medical Record documentation of a negative pregnancy test must be current documentation. Current documentation would include a documented negative pregnancy test that was performed since the patient's last menstrual period or a documented negative pregnancy test performed within the prior month to starting warfarin, whichever is shorter. Any documentation prior to this time point would not be acceptable proof of a negative pregnancy.
- If documentation is not available in the participant's medical records, the research coordinator must obtain a pregnancy test with negative pregnancy test results in order to confirm participant's eligibility.
- The research coordinator must follow the institutional standard for pregnancy testing. If the institutional standard requires serum testing for pregnancy, then a serum testing for pregnancy must be obtained.
- If outpatient point of care or hospital bedside urine testing for pregnancy is performed, it must be conducted according to the approved institutional practice guidelines (e.g. out-patient laboratory and hospital laboratory /JCAHO approved testing and quality control standards).

Nursing mothers are not excluded from participation in the study.

Check "N/A" for male participants or post menopausal females

Q. 14: A female participant of child-bearing age is expected to use medically-approved birth control methods and the research coordinator must confirm the use. If needed, the research coordinator must counsel the participant in the use of birth control for the duration of the study.

Check "N/A" for male participants or post menopausal females

Q. 15: Confirm with the potential participant if he or she has constraints that would prevent them from making frequent study visits and visits to the anti-coagulation clinic or the healthcare provider for warfarin therapy management

.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

ELIGIBILITY CONFIRMATION

16. Are there any factors likely to limit adherence to warfarin?
    a. Dementia (*unless minor problem*) .....
    b. Current alcohol or substance abuse.....
    c. Plans to move in the next six months.....
    d. History of unreliability in medication taking or appointment keeping .....
    e. Significant concerns about participation in the study from spouse, significant other, or family members.....
    f. Lack of support from primary health care provider.....
17. Is the participant unable to provide consent or follow study procedures due to cognitive or other limitations? .....
18. Is the participant participating in another clinical trial in the next 6 months?.....
19. Has the participant had an estimated blood loss of >1000 cc requiring blood transfusions within 48 hours prior to randomization?
20. If the participant has received previous genetic testing, are the results of CYP2C9 or VKORC1 known?.....

Check the appropriate box for questions 16 through 20.
"1=Yes" or
"0=No".

Questions 16 through 20 must be "0=No" for the participant to be eligible

NO RESPONSES CAN BE LEFT BLANK

21. Is the participant eligible for participation in the study? .....

Check the appropriate box for question 21.
"1=Yes" or
"0=No".

Questions 21 must be "1=Yes" for the participant to be eligible.

RESPONSE CANNOT BE LEFT BLANK

Q. 16a-f: The research coordinator needs to confirm by interviewing the participant if he or she has overt problems related to dementia or substance abuse that may interfere with warfarin therapy. If unsure, the research coordinator can seek assistance from the study PI to make the determination.

A participant may not be eligible for the study if the participant plans to move from a commutable distance to the institution, as this will affect the participant from being followed for the duration of the study.

The research coordinator may confirm with the participant's healthcare or other providers about the participant's reliability in making study visits. A participant known to skip health appointments may not be counted upon to complete study processes.

If family members express serious concerns about the participant's involvement in a research study, the research coordinator must evaluate the situation before enrolling the participant.

At times the primary care provider may express concerns about the participant receiving algorithm-based warfarin therapy. This may cause serious impediments for the research coordinator to maintain the enrolled participant in the study and should be taken into consideration during enrollment.

If the research coordinator has concerns about any of these issues, he or she can discuss the situation with the study PI to make a determination of eligibility.

Q. 17: The response in this item may be based on observations made by the RC, information available in medical records or information shared by the healthcare provider.

Q. 18: This information is confirmed with the participant or a care provider.

Q. 19: This information is confirmed by reviewing medical records and as a self-report, 48 hours prior to randomizing the participant.

Q. 20: This information may be available in the medical records or the participant may be able to provide the information.

Q. 21: This question summarizes the eligibility of the participant. A "Yes" response suggests that the participant met all the inclusion and exclusion criteria for the study and can proceed to randomization. A "No" response suggests that the participant did not meet one or more of the criteria.

During data entry in the data management system, built-in logic checks will display alerts to inform the RC of errors in responses between questions 1-20 and question 21. It will allow the RC to prevent him/her from saving the entered data and fix the error. Once the data is committed (saved) to the table, data edits have to be implemented by the CTCC. It is preferred that data once entered and committed to the DMS not be edited. Thus the CTCC recommends that the RC should review the **ELIG** data prior to data entry.

Q 21 is also a cross-check item for question 2 on the Randomization (***RAND***) CRF. Screening failures will not be allowed to proceed with randomization by the data management system.

ELIG is a data CRF and must be double data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

RANDOMIZATION

Blood sample should be collected for genotyping prior to randomization.

Responses are required for questions 1 through 3 to proceed with randomization.

1. Has the participant signed a written consent for the study?	Check the appropriate box. "1=Yes," or "0=No" This question cannot be left blank.
a. If yes, date participant signed the consent:	Record the date participant signed the consent form in mm/dd/yyyy format. This question cannot be left blank.
2. Based on the responses to the inclusion and exclusion criteria, is the participant eligible and ready for randomization in the study?.....	Check the appropriate box for questions 2 and 3..... "1=Yes" "0=No"
3. Did the healthcare provider order warfarin therapy for the participant?.....	This question cannot be left blank.

[RAND] RANDOMIZATION:

Randomization is a final process in enrollment for participants who qualify for the study, in that it assigns the willing and qualified participant to one of the two the study arms – genetics-guided dosing or clinical-guided dosing.

RAND errors cannot be edited; hence the RC has to review the data carefully prior to data entry. It is recommended that the RC randomize the participant..

Q. 1-1a: This is a confirmation that the potential participant has undergone the informed consent procedure and agrees to participation without duress. The expected response to this question is "Yes".

Date when the informed consent is signed is recorded in item 1a in the mm/dd/yyyy format.

Q. 2: The expected response is "Yes". Responses to question 2 on ***RAND*** and question 21 on ***ELIG*** are cross-checked by the data management system for the randomization to be successfully completed.

Q. 3: The intent of this question is to confirm that warfarin therapy is intended for this participant and the healthcare provider has ordered warfarin therapy in the participant's clinical chart.

RAND is a data CRF and is single data entered in the data management system.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**
Laboratory ID: Circle one Local/Central	**Genotype attempt:** Number of testing attempts	

GENOTYPING INFORMATION

Completed by the Research Coordinator:

1. Date and time specimen collected:.....	For questions 1 and 2, record the date in mm/dd/yyyy format and the time in military format.
2. Date and time specimen transferred/shipped to the genotyping laboratory:.....	

Completed by the genotyping laboratory personnel:

3. Date and time specimen received at the genotyping laboratory:	For questions 3 and 4, record the date in mm/dd/yyyy format and the time in military format.
4. Date and time specimen was analyzed:	
5. Check box if the specimen is not analyzable or the results are not available:.....	Check this box only if the results for VKORC1 **and** CYP2C9 are missing.
6. VKORC1 *(-1639 / 3673)*:.....	**ONLY** Check **ONE** response..... "0=GG" "1=AG" "2=AA" "88=Missing" *Only if VKORC1 test fails*
7. CYP2C9 (*check one*): ..... Place label here	**CYP2C9*2 CYP2C9*3** **ONLY** Check **ONE** response..... "1= *1*1/ CC/ AA" "2= *1*2/ CT/ AA" "3= *1*3/ CC/ AC" "4= *2*2/ TT/ AA" "5= *2*3/ CT/ AC" "6= *3*3/ CC/ CC" "7= Missing/Missing/Missing" *Only if CYP2C9 test fails*
8. DNA concentration:.....	Record the DNA concentration results
9. Total DNA:.....	Record total DNA results

Results entered in the DMS by (signature): _____

Test results confirmed by (signature): _____

Enter genotyping results in the data management system (DMS) immediately.

Fax completed case report form to the CTCC at (215) 573-4790.

[GENOTYPE] GENOTYPING INFORMATION:

Due to time constraints between recruitment and enrollment, ***GENOTYPE*** is completed soon after the RC determines that the participant is eligible and willing to participate in the study and genotyping blood specimen is drawn. This CRF tracks the specimen from collection to results. It is developed to meet the needs of the local laboratory and central laboratory.

Genotyping process for the RC involves collecting blood specimen from the participant, completing relevant information on the CRF and transporting the specimen and the CRF to the local genotyping laboratory. The RC is also responsible for shipping the specimen to the central laboratory at the earliest possible opportunity after the participant completes the visit. The RC must complete another copy of the CRF to include in the shipment.

The process at the local and central genotyping laboratory involves acknowledging the receipt of the specimen, analyzing the specimen and entering the results in the data management system. The completed CRFs must be held in a secure area of the laboratory and the copy faxed to the Clinical Trial Coordinating Center (CTCC) at regular time intervals.

In case of repeat analysis, results are recorded on a new CRF with each attempt. Copies of the CRF are available and can be printed from the COAG portal. It is important that header information be completed as well as the results if repeat analysis is warranted.

Genotyping results are confidential and not shared with the study research staff (RCs, PIs), health care providers or the Investigational Drug Service (research pharmacy) at the Clinical Center.

Laboratory ID: By circling the appropriate box at the top of the page, the RC identifies whether the CRF is intended for the institutional or central genotyping laboratory.

Genotype attempt: Space is provided in the header section of the CRF to record sequence numbers. It allows the genotyping laboratories (local and central) multiple attempts in the event of a genotyping failure.

Each genotyping laboratory (institutional and central) starts with sequence number "1" and continues sequentially with each additional attempt.

Items 1 and 2 are completed by the Research Coordinator prior to transferring the specimen to the local laboratory and shipping to the central laboratory.

Q. 1: This item refers to the date and time the specimen was collected from the participant.

Date is entered in the mm/dd/yyyy format and time is recorded in 24-hour clock (military time) format.

Q. 2: The date and time when the specimen is transferred to the institutional genotyping laboratory or shipped to the central laboratory is recorded in these items.

Date is entered in the mm/dd/yyyy format and time is recorded in 24-hour clock (military time) format.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**
Laboratory ID: Circle one Local/Central	**Genotype attempt:** Number of testing attempts	

GENOTYPING INFORMATION

Completed by the Research Coordinator:

1. Date and time specimen collected:.....	For questions 1 and 2, record the date in mm/dd/yyyy format and the time in military format.
2. Date and time specimen transferred/shipped to the genotyping laboratory:.....	

Completed by the genotyping laboratory personnel:

3. Date and time specimen received at the genotyping laboratory:	For questions 3 and 4, record the date in mm/dd/yyyy format and the time in military format.
4. Date and time specimen was analyzed:	
5. Check box if the specimen is not analyzable or the results are not available:.....	Check this box only if the results for VKORC1 **and** CYP2C9 are missing.
6. VKORC1 *(-1639 / 3673)*:.....	**ONLY** Check **ONE** response….. "0=GG" "1=AG" "2=AA" "88=Missing" *Only if VKORC1 test fails*
7. CYP2C9 (*check one*):	**CYP2C9*2 CYP2C9*3**
	ONLY Check **ONE** response….. "1= *1*1/ CC/ AA"
	"2= *1*2/ CT/ AA"
	"3= *1*3/ CC/ AC"
	"4= *2*2/ TT/ AA"
	"5= *2*3/ CT/ AC"
	"6= *3*3/ CC/ CC"
	"7= Missing/Missing/Missing" *Only if CYP2C9 test fails*
8. DNA concentration:.....	Record the DNA concentration results
9. Total DNA:.....	Record total DNA results

Place label here

Results entered in the DMS by (signature): _____

Test results confirmed by (signature): _____

Enter genotyping results in the data management system (DMS) immediately.

Fax completed case report form to the CTCC at (215) 573-4790.

Items 3 through 9 are completed by the genotyping laboratory personnel. The information recorded in the CRF at the laboratory is not shared with anyone associated with the study, with the exception of the CTCC and the study medical monitor.

Items 3 and 4 record administrative information:

Q. 3: Due to differences in genotyping processes at the Clinical Centers and a delayed receipt at the central laboratory, there may be a discernable lag when the laboratories process received specimens. This item requires the laboratory to acknowledge the receipt of the specimens by noting the date and time.

Date is entered in the mm/dd/yyyy format and time is recorded in 24-hour clock (military time) format.

Q. 4: This item notes the date and time the specimen is analyzed.

Date is entered in the mm/dd/yyyy format and time is recorded in 24-hour clock (military time) format.

Q. 5: When the specimen is analyzed, a check in the box in item 5 indicates that the laboratory could not generate reportable results for VKORC1 and CYP2C9 and genotyping analysis should be repeated.

If genotyping is incomplete at the first attempt, partial results may be recorded in items 6 and 7 by checking the appropriate response in one item and "Missing" response in the other item.

Q. 6: VKORC1 genetic information is recorded by checking the appropriate checkbox.

Q. 7: CYP2C9 genetic information is recorded by checking the appropriate checkbox.

The space under item 7 is provided to attach the label that corresponds to the label on the specimen transferred/shipped to the genotyping laboratories.

Q. 8: Space is provided for the genotyping laboratory to record DNA concentration.

Q. 9: Space is provided for the genotyping laboratory to record total DNA.

Signature 1: Space is provided for the Signature of the person who enters the data in the data management system.

Signature 2: Space is provided for the signature of the person who verifies that the data entered in the data management system is accurate.

FAX: CTCC contact information is available on the CRF.

GENOTYPE is a data CRF and must be double data entered in the data management system by the genotyping laboratory personnel as soon as possible.

Participant ID: **Participant Initials:** **Clinical Center:**

DOSE REQUISITION – INITIATION PERIOD

Study day	Date mm/dd/yyyy	Participant unavailable	INR to use for dose calculation	Participant location 1 = Inpatient 2 = Outpatient	Genetics data not available, calculate dose	# of days of additional capsules?*	Do not dispense calculated dose**
1	Record the date in mm/dd/yyyy format.	If the participant is not physically present when dose is requested, check this box.	Record the INR value. If it was not collected or a new INR value is not available, check this box. "99=No INR"	Record the location of the participant. "1=Inpatient" or "2=Outpatient"	If the genetics data is not available and a dose needs to be dispensed, check this box	If additional capsules are to be requested, record the number of days they are needed.	If the calculated dose should not be dispensed, check this box.
2							
3							
4							
5							

Check "No INR" box if INR value is not collected on that study day.

**Enter a value if additional capsules need to be requested from the pharmacy; leave blank if no additional capsules need to be requested.*

[DOSREQ] DOSE REQUISITION – INITIATION PERIOD:

DOSREQ is one of the most important CRFs to be completed during the dose initiation phase of the study, i.e. day 1 through day 5. It is completed by the RC and entered in the data management system daily, regardless of whether the participant is available for the visit.

If any of the conditions that are applied to dose revision during this phase change (e.g. participant is prescribed and takes Amiodarone after enrollment), the RC should note the changes on the **COMMENTS** CRF, attach the **COMMENTS** CRF to the **ENROLL** CRF and update the information on the DOSREQ screen in the DMS, immediately.

If the participant comes in for a clinical visit on days 1 through 5, the RC must update the **DOSREQ** information on the CRF and update the DMS prior to requesting the dose from the research pharmacy at his/her institution.

In case of drug overrides, the RC is responsible for communicating with the pharmacist and the study medical monitor.

The process of a drug override starts with the RC informing the research pharmacist of the need for intervention and to expect a call from the study medical monitor. The RC will contact the medical monitor and share pertinent details about the need for an override. He/she will also provide contact information for the pharmacist to the medical monitor. The medical monitor and the pharmacist will resolve the dose override issue and the medical monitor will inform the RC to proceed with the dose request.

The RC cannot request and the pharmacist cannot dispense a new dose unless the previous day's information is completed and entered in the DMS.

Study day: These are sequential values for each day of the dose initiation period (day 1 through 5) and have an administrative function in the data management system.

Study day 1, in most cases, is the day of randomization when the participant receives his/her first algorithm-generated dose. Follow-up days will be based on study day 1. In rare instances, study day 1 may be on the following day due to unexpected events (e.g. research pharmacy closes before the study processes are completed, participant cannot stay due to personal constraints).

Date: The date must correspond to the study day and is recorded in the mm/dd/yyyy format.

Participant unavailable: This box is checked if the participant is not available on a specific study day. This entry in the DMS informs the research pharmacist that a dose change is not expected. If the participant keeps a study visit, the box is left unchecked.

INR to use for dose calculation: This information is transferred from the INR Log (***INRLOG***). If the participant has his/her INR checked on days 2 through 5, the RC must also record the INR on the DOSREQ CRF for dose calculation.

By checking the "No INR" box, the RC indicates that an INR value is not available for the study day and cannot be applied to the dose algorithm.

Participant location: The research pharmacy dispenses warfarin capsules daily on days 1-5. Thus, each time the RC needs to request warfarin, by entering an appropriate code the RC indicates the participant's location to the research pharmacy.

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Participant ID: **Participant Initials:** **Clinical Center:**

DOSE REQUISITION – INITIATION PERIOD

Study day	Date mm/dd/yyyy	Participant unavailable	INR to use for dose calculation	Participant location 1 = Inpatient 2 = Outpatient	Genetics data not available, calculate dose	# of days of additional capsules?*	Do not dispense calculated dose**
1	Record the date in mm/dd/yyyy format.	If the participant is not physically present when dose is requested, check this box.	Record the INR value. If it was not collected or a new INR value is not available, check this box. "99=No INR"	Record the location of the participant. "1=Inpatient" or "2=Outpatient"	If the genetics data is not available and a dose needs to be dispensed, check this box	If additional capsules are to be requested, record the number of days they are needed.	If the calculated dose should not be dispensed, check this box.
2							
3							
4							
5							

Check "No INR" box if INR value is not collected on that study day.

**Enter a value if additional capsules need to be requested from the pharmacy; leave blank if no additional capsules need to be requested.*

Genetics data not available, calculate dose: The RC and the genotyping laboratory will develop a system at his/her institution to communicate the availability of genotyping data (without the laboratory revealing the data to the RC). When informed of the availability of the data, and by not checking the box, the DMS calculates the dose accordingly.

In rare instances when genotyping fails, the laboratory personnel will also communicate unavailability of the genotyping data to the RC. The RC then checks the box for missing genotyping data and proceeds with dose requisition. The DMS uses this information to calculate the dose for the specific day.

# of days of additional capsules: Study doses are provided on a daily basis for the first 4-5 days, but the participant may need to get additional capsules for various unforeseen reasons, e.g. their status change from inpatient to outpatient or a personal constraint or for weekend dosing. The RC can use his/her discretion and order additional capsules to cover the time period.

The RC should not enter a number in the space if he/she does not need to request additional capsules (other than the pre-determined number based on the participant's location).

Do not dispense calculated dose: An RC, at the request of the healthcare provider and in consultation with the clinical center PI and the study medical monitor, can request an override of the calculated dose. This is done by checking the box on the CRF. An override informs the research pharmacist of the change in the calculated dose. This could be in the form of a changed dose or holding off on dosing the participant on the specific study day.

A request to alter the calculated dose requires an intervention by the medical monitor. The process requires the RC to communicate the information to the pharmacist as well as consult with the medical monitor. A discussion between the research pharmacist and the medical monitor and a decision by the medical monitor conveyed directly to the pharmacist will determine the dose.

Dosed off-protocol: At times a participant may undergo medical or dental procedure and the medical care provider may decide to disregard the unknown calculated dose generated by the data management system and dose the participant based on clinical judgment. The RC must probe for this occurrence at each visit.

If the participant is dosed off-protocol, i.e. a dose that is not calculated by the data management system, the RC must check the box and contact the Medical Monitor.

DOSREQ is a data CRF in form of a log and is single data entered in the data management system daily by the RC.

Participant ID: **Participant Initials:** **Clinical Center:**

DOSE REQUISITION – TITRATION PERIOD

Study day	**Date** *mm/dd/yyyy*	**INR to use for dose calculation**	**Participant location** 1 = Inpatient 2 = Outpatient	**# of days of additional capsules?**	**Do not dispense calculated dose***	**Dosed off-protocol?****
Insert corresponding study day to maintain a unique Dose Requisition record in the data management system (DMS).	Record the date of the study day in mm/dd/yyyy format.	Record the INR to be used in the dose calculation.	Record location of the participant. "1=Inpatient" or "2=Outpatient "	If additional capsules are to be requested, record the number of days they are needed.	If the calculated dose should not be dispensed, check this box.	If participant received warfarin off protocol check this box.

**Check box if the medical monitor is contacted to resolve an override of a calculated dose.*

***Check box if the participant has received warfarin that is not a protocol-based calculated dose, contact the medical monitor and complete the UNBLIND CRF.*

[DOSREQ2] DOSE REQUISITION – TITRATION PERIOD:

DOSREQ2 is very similar to **DOSREQ** in content and function. **DOSREQ** is used for requesting study dose for days 1-5 (dose initiation and revision phases) and **DOSREQ2** is used for requesting study dose for days 6-28 (titration phase).

Titration phase does not require a genetics override. Typically a dose is requested using the **DOSREQ2** CRF on a study-based visit schedule (**VSTSCH**) when an INR result is available.

If a participant is seen outside of the study visit, an INR result is likely to be available as well. It is the responsibility of the RC to follow-up on the INR result and request a dose change.

A new calculated dose requires a new INR value and the dose requisition with a new INR is entered in the DMS. In the absence of a new INR the RC is not required to complete **DOSREQ2** to request study warfarin and he/she will call the research pharmacy directly to request the medication.

Study day: Study day is a numerical value and is defined as the day (counted from day 1 that corresponds to the participant's first dose) when the participant is seen for a study visit in the titration phase. Study day is written in on the CRF but is not entered in the DMS. The DMS calculates the study day when the RC logs in and selects DOSREQ2.

Date: Date corresponds to the study day calculated from the date of the first dose and is recorded in the mm/dd/yyyy format.

INR to use for dose calculation: This information is transferred from the INR Log (INRLOG). INR value is required for dose calculation during the titration phase. A participant cannot receive a new calculated dose unless INR value is available in the data management system.

Participant location: The research pharmacy dispenses a pre-determined number of capsules based on the participant's status as an inpatient or outpatient in the titration phase as well. Thus, each time the RC needs to request warfarin from the research pharmacy, the pharmacist should be aware of the participant's location to dispense the appropriate number of capsules.

# of days of additional capsules: Participant may need to get additional capsules because of their status change from inpatient to outpatient, or a personal constraint that may prevent them from a scheduled research visit. The RC can use his/her discretion and order additional capsules to cover the time period.

The RC should leave the cell "blank' if he/she does not need to request additional capsules (other than the pre-determined number based on the participant's location).

Do not dispense calculated dose: An RC, at the request of the healthcare provider and in consultation with the clinical center PI and the study medical monitor, can request an override of the calculated dose. This is done by checking the box on the CRF. An override informs the research pharmacist of the change in the calculated dose. This could be in the form of a changed dose or holding off on dosing the participant on the study day.

A request to alter the calculated dose requires an intervention by the medical monitor. The process requires the RC to communicate the information to the pharmacist as well as consult with the medical monitor. A discussion between the research pharmacist and the medical monitor and a decision by the medical monitor conveyed directly to the pharmacist will determine the dose.

Participant ID: **Participant Initials:** **Clinical Center:**

DOSE REQUISITION – TITRATION PERIOD

Study day	Date *mm/dd/yyyy*	INR to use for dose calculation	Participant location 1 = Inpatient 2 = Outpatient	# of days of additional capsules?	Do not dispense calculated dose*	Dosed off-protocol?**
Insert corresponding study day to maintain a unique Dose Requisition record in the data management system (DMS).	Record the date of the study day in mm/dd/yyyy format.	Record the INR to be used in the dose calculation.	Record location of the participant. "1=Inpatient" or "2=Outpatient "	If additional capsules are to be requested, record the number of days they are needed.	If the calculated dose should not be dispensed, check this box.	If participant received warfarin off protocol check this box.

**Check box if the medical monitor is contacted to resolve an override of a calculated dose.*

***Check box if the participant has received warfarin that is not a protocol-based calculated dose, contact the medical monitor and complete the UNBLIND CRF.*

Dosed off-protocol: At times a participant may undergo medical or dental procedure and the medical care provider may decide to disregard the unknown calculated dose generated by the data management system and dose the participant based on clinical judgment. The RC must probe for this occurrence at each visit.

If the participant is dosed off-protocol, i.e. a dose that is not calculated by the data management system, the RC must check the box and contact the Medical Monitor to initiate the unblinding procedure and complete the **UNBLIND** CRF.

DOSREQ2 is a data CRF in form of a log and is single data entered in the data management system daily by the RC.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

PERSONAL HISTORY FORM

Check one response for items 1 through 4.

1. What is your current marital status? ..... (*check one response*)	Record marital status. "1=Currently married" "2=Separated/divorced" "3=Widowed" "4=Never married" "5=Living with partner" "97=Refused to respond"
2. What is the highest education that you have ..... completed? (*check one response*)	Record highest level of education completed. "1=8th grade or less" "2=Did not complete high school" "3=Graduated from high school / completed GED" "4=Technical/vocational school degree" "5=Some college education/did not graduate" "6=College degree" "7=Graduate degree/professional degree" "97=Refused to respond"
3. What is your employment status?..... (*check one response*)	Record employment status. "1=Working" "2=Unemployed" "3=Retired" "4=Disabled" "97=Refused to respond"
4. What is your total annual household income?..... (*check one response*)	Record total annual household income. "1=$20,000 or under" "2=$20,001 – $50,000" "3=$50,001 – $100,000" "4=More than $100,000" "97=Refused to respond"
5. What type of health insurance do you have?..... (*check all that apply*)	Record type of health insurance. Check all applicable boxes. If "Other, specify" is checked, specify the insurance on the line provided. "1=No insurance" "1=Medicare benefits" "1=Medicaid benefits" "1=Private (*e.g. Blue Cross*)" "1=Group health plan (*e.g. HMO, PPO, POS*)" "1=Veteran Affairs (*VA*) benefits" "1=CHAMPUS or other military benefits" "1=Other, specify" "1=Don't know"

Research Coordinator: Please check the appropriate box to indicate who completed the CRF.

"1=Participant" "2=Interviewer" "3=Both"

[PERSHX] PERSONAL HISTORY FORM:

PERSHX CRF is given to the participant to complete at baseline, soon after the RC has completed randomization and is awaiting results from the genotyping laboratory. The information on the CRF is of a personal nature and participant should be allowed to complete the CRF in a quiet place. If the participant has questions, the RC must remain accessible to answer questions.

It is the RC's responsibility to check the CRF for legibility and completeness of the questionnaire when returned by the participant.

Questions 1 through 4 require 1 response per item. The participant is allowed to check more than one response in question 5.

Q. 1: The participant checks an appropriate response for the marital status item. The participant may decline to respond to the question.

Q. 2: The highest level of education is indicated by checking an appropriate response. The participant may refuse to provide a response by checking an appropriate box.

Q. 3: The participant checks an appropriate box to indicate employment status.

A participant who is employed part-time or full time is considered "working".

A participant, who is recently unemployed (e.g. lay offs) and who is capable of working and expected to return to work is considered "unemployed". A full time student who is not gainfully employed, or a mother who has chosen to stay at home to care for her family, is also considered "unemployed".

A participant is considered "retired" when he/she has ceased to be in the workforce and does not intend to be gainfully employed in the future.

A participant is considered disabled when he/she cannot seek employment because of a disability.

Q. 4: This information is sensitive and the participant may not wish to reveal his/her annual household income and can do so by checking the appropriate box.

Q. 5: A participant can check more than one response. Some of the response categories include examples to encourage the participant to select the most applicable response(s). If unsure, the participant can be encouraged to describe the health insurance and the RC can assist in selecting the response(s).

Interviewer type: The information in the shaded box is completed by the RC after the participant returns the CRF. PERSHX is a self-reported questionnaire and the participant is expected to complete the questionnaire. If it is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

PERHX is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL HISTORY

Does the participant have a history of the following?

1. Congestive heart failure:	Check the appropriate box for questions 1 through 3. "1=Yes" "0=No" "88=Don't know"
2. Heart attack or MI:	
3. Liver disease:	
If yes, was it….?	
a. Cirrhosis:	If yes in question 3, check the appropriate box for questions 3a through 3d. "1=Yes" "0=No" "88=Don't know"
b. Chronic or acute hepatitis: ..... (*exclude history of hepatitis*)	
c. Fatty liver or nonalcoholic steatohepatitis (*NASH*): ..	
d. Other:	
d1. If yes in question 3d, specify:	If yes in question 3d, specify the liver disease. (maximum 500 characters)
4. Hyperthyroidism:	Check the appropriate box for questions 4 through 6. "1=Yes" "0=No" "88=Don't know"
5. Hypothyroidism:	
6. Kidney disease:	
a. If yes, specify:	If yes in question 6, specify the kidney disease. (maximum 500 characters)
b. Is the participant on dialysis for this?	Check the appropriate box. "1=Yes" "0=No" "88=Don't know"
c. Most recent creatinine value:	Record the most recent creatinine value in mg/dl, and record the date that value was obtained in mm/dd/yyyy format.

[MEDHX] MEDICAL HISTORY FORM:

MEDHX is completed by the RC at the baseline visit.

ENROLL CRF records some of the current and historical medical information for the dosing algorithm. **MEDHX** CRF further investigates the medical information collected on **ENROLL**.

Information collected on the **MEHDHX** CRF is of historical nature and is recorded by reviewing the participant's medical charts and self-report.

Participant's healthcare provider can also be an important resource to consider when the medical information is unclear or missing.

The clinical center PI can also assist the RC to definitively determine the absence or presence of a diagnosis based on the available information in the medical charts.

Pharmacy can be used as a resource for gathering information. Medications taken by the participant help confirm the diagnoses.

Every attempt should be made to collect as much information as possible and to corroborate the self-reported information with the medical charts and other resources available within the clinical center.

If the participant is used as source the RC must employ probing techniques to elicit the best possible information.

A response of "Yes" indicates that the diagnosis can be confirmed based on the information that is available.

A response of "No" indicates that the diagnosis is absent based on the available information.

A response of "Don't know" suggests that the available information is inconclusive or cannot be corroborated with information in the medical records.

Space is provided to clarify "Other" responses in the form of text entry.

Q. 6c: Most recent creatinine value may be available in the participant's medical records and is recorded with the date when the results for creatinine were made available.

Date is recorded in the mm/dd/yyyy format.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL HISTORY

7. Diagnosis of cancer in the past 5 years:.....	Check the appropriate box. "1=Yes," "0=No," or "88=Don't know"
If yes, is/was it cancer of the....? a. Breast: ..... b. Prostate: ..... c. Melanoma:..... d. Lung:..... e. Stomach:..... f. Liver:..... g. Colon/rectal:..... h. Brain: ..... i. Throat/laryngeal:..... j. Blood/leukemia/lymphoma: ..... k. Other:.....	If yes in question 7, check the appropriate box for questions 7a through 7k. "1=Yes" "0=No" "88=Don't know"
k1. If yes in question 7k, specify:.....	If question 7k is yes, specify cancer. (maximum 500 characters)
8. Hypertension or high blood pressure:.....	Check the appropriate box for questions 8 and 9. "1=Yes" "0=No" "88=Don't know"
9. Diabetes:	
If yes, does the participant take....? a. Insulin: ..... b. Oral medications:..... c. Diet only:.....	If yes in question 9, check the appropriate box for questions 9a through 9c. "1=Yes" "0=No" "88=Don't know"
10. Peptic or stomach ulcer disease: ..... 11. Gastritis:..... 12. Malabsorption syndrome:..... 13. Current problem with diarrhea:	Check the appropriate box for questions 10 through 13. "1=Yes" "0=No" "88=Don't know"

No additional instructions given for this page. Please continue to the next page.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL HISTORY

Does the participant have a history of the following (*exclude current diagnoses for which participant is initiating warfarin use*).....?

14. Stroke:.....	Check the appropriate box for questions 14 through 17. "1=Yes" "0=No" "88=Don't know" If yes in questions 14 through 17, check the appropriate box. "1=Current" "2=Past" "88=Don't know"
a. If yes, is it current or past:	
15. TIA or mini stroke (*or infarct on brain imaging*):.....	
a. If yes, is it current or past:	
16. Pulmonary embolism:.....	
a. If yes, is it current or past:	
17. Deep vein thrombosis:	
a. If yes, is it current or past:	

18. Indicate the participant's smoking status: ..... [*Current = within 1 month of enrollment* *Recent = stopped between 1 month and 1 year prior to enrollment* *Former = stopped more than 1 year prior to enrollment* *Never = never smoked*]	Check the appropriate box. "1=Current smoker" "2=Recent smoker" "3=Former smoker" "4=Never smoked"
a. If current, recent or former smoker, how many years did/has the participant smoke(d)?	If the participant is a current, recent or former smoker, record the number of years participant smoked.
b. How often did/does the participant smoke?	Check the appropriate box to record how often the participant did/does smoke. "1=Every day" "2=Nearly every day" "3=3 to 4 times a week" "4=2 times a week" "5=Once a week" "6=Sporadic/less than once a week"
c. How much did/does the participant smoke on a typical smoking day?	Record the number of cigarettes participant did/does smoke on a typical day.

Qs. 14-17: The responses to these items are a confirmed against responses in ENROLL. If the participant is diagnosed with any of these conditions, the RC must confirm whether the diagnosis is current (i.e. based on recent/current hospitalization or healthcare visit) or past.

Q. 18: The response to this item is confirmed against the response in ENROLL, as well. These questions investigate the participant's smoking habits. Smoking status is defined in the CRF to record the most appropriate response in Q. 18.

Qs. 18a-c: If the response to Q. 18 is "Current smoker", additional responses in items 18a, 18b and 18c are required. These items refer to the frequency and amount related to the participant's smoking habit.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL HISTORY

19. Does the participant have a family history of venous thrombo-embolism (*VTE*):.....

20. Has the participant taken warfarin/Coumadin prior to the planned study use?.....

Check the appropriate box for questions 19 and 20.
"1=Yes"
"0=No"
"88=Don't know"

Research Coordinator: Please check the appropriate box to indicate the source of information.

"1=Participant" "2=Electronic medical records" "3=Both"

Q 19: This is a self-reported item and the participant is relied upon to provide the information.

Q. 20: This is an eligibility confirmation that the participant has not taken warfarin prior to enrollment in the study.

Data type: The information in the shaded box is completed by the RC The RC will check the appropriate box to indicate the source of the information.

MEDHX is a data CRF and must be single data entered in the data MANAGEMENT SYSTEM (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

DIET INFORMATION

1. Indicate if you consume any of the following foods on a regular basis:

   a. Avocado: .....
   b. Broccoli: .....
   c. Brussel sprouts: .....
   d. Cabbage: .....
   e. Chickpeas: .....
   f. Greens (*e.g. beet, collard, dandelion, mustard, turnip*): ..
   g. Green peas: .....
   h. Green tea: .....
   i. Kale: .....
   j. Lettuce: .....
   k. Spinach: .....
   l. Liver: .....

   Check the appropriate box for question 1a through 1l and question 2.
   "1=Yes"
   "0=No"
   If yes in question 2, go to questions 2a and 2b.

2. Do you drink coffee? .....

   If yes,

   a. What kind of coffee do you drink? .....
   If yes in question 2, check the appropriate box. "1=Caffeinated" "2=Decaffeinated" or "3=Both"

   b. When you drink coffee, what is the average amount? ....
   If yes in question 2, record the average number of cups consumed and check the appropriate box to specify frequency.
   "1=per day"
   "2=per week" or
   "3="occasionally/rarely"

3. Do you drink other caffeinated beverages (*e.g. iced tea, cola drinks*)? .....
   Check the appropriate box. "1=Yes" or "0=No." If yes in question 3," go to question 3a.

   If yes,

   a. When you drink other caffeinated beverages, what is..... the average amount?
   If yes in question 3, record the average number of cans/glasses consumed and check the appropriate box to specify frequency.
   "1=per day"
   "2=per week" or
   "3="occasionally/rarely"

[DIET] DIET INFORMATION:

DIET is completed by the participant and the RC should be available to answer any questions that the participant may have about the questionnaire.

Qs. 1a-l: This is a list of the top 12 vitamin K-rich foods and the participant checks "Yes" if he/she consumes these foods. The amount and frequency of use are not defined and the participant is allowed his/her judgment in responding to the question.

"Regular basis" is defined as consuming at least one serving per week.

Qs. 2-3: These 2 questions refer to the use of non-alcoholic beverages and the frequency and amount of use. Skip pattern instructions are included where applicable.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

DIET INFORMATION

4. Do you drink alcoholic beverages?.....	Check the appropriate box. "1=Yes" or "0=No." If yes in question 4, go to questions 4a, 4b, and 4c.
If yes,	
a. How often do you drink alcoholic beverages?.....	If yes in question 4, check the appropriate box. "1=Every day" "2=Nearly every day" "3=3 to 4 times a week" "4=2 times a week" "5=Once a week" "6=2 to 3 times per month" "7=Once a month" "8=Less than once a month"
b. How much do you drink on a typical drinking day? ..... *(1 drink = 10 oz can/bottle of beer or 4 oz glass of wine or 1 oz shot of hard liquor)*	If yes in question 4, record the total consumed on a typical drinking day. Response must be a whole number.
c. In the past 12 months, what is the highest number of drinks you can recall having on one occasion?.....	If yes in question 4, record highest number of drinks consumed on one occasion during the past 12 months. Response must be a whole number.

Research Coordinator: Please check the appropriate box to indicate who completed the CRF.

"1=Participant" "2=Interviewer" "3=Both"

Q 4: This question refers to the use, frequency and amount of alcoholic beverages that include beer, wine and hard liquor. A definition is included to help the participant determine what constitutes a drink.

Interviewer type: The information in the shaded box is completed by the RC after the participant returns the CRF. DIET is a self-reported questionnaire and the participant is expected to complete the questionnaire. If it is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

DIET is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

DIET INFORMATION – FOLLOW-UP

1. Since the last study visit, how many meals did you eat away from home (that is, at a restaurant or cafeteria, including at work?	Record the number of meals eaten away from home.
2. Have you been eating more than usual since your last study visit?.....	Check the appropriate box for each question, 2 through 6..... "1=Yes" "0=No" "88=Don't Know"
3. Have you been eating less than usual since your last study visit?.....	
4. Have you made any other changes in your diet since your last study visit?.....	
5. Have you had a weight gain since your last study visit?.	
6. Have you had a weight loss since your last study visit?.	

7. Indicate if any of the following foods were consumed in the past 7 days and if there was a change in the amount consumed compared with your usual diet:

	Not consumed	No change	Less than usual	Greater than usual
a. Avocado.....				
b. Broccoli				
c. Brussel sprouts.....				
d. Cabbage				
e. Chickpeas.....				
f. Greens (*e.g. beet, collard, dandelion, mustard, turnip*).....				
g. Green peas.....				
h. Green tea.....				
i. Kale.....				
j. Lettuce				
k. Spinach.....				
l. Liver.....				

Check only one box for each question, 7a through 7l.....
"0=Not consumed"
"1=No change"
"2="Less than usual"
"3=Greater than usual"

[DIETFUP] DIET INFORMATION FOLLOW-UP:

DIETFUP is completed by the participant as a self-report at follow-up visits as outlined in the Visit Schedule (**VSTSCH**). The participant should be encouraged to provide the best possible response to the questions. The questions are directed towards changes in the food intake pattern from the previous visit and the RC should instruct the participant accordingly.

Qs. 1-6: These questions refer to the eating pattern and possible changes in weight at follow-up. If the participant is unsure of the changes, he/she has a response option of "Don't know".

Qs. 7a-l: The participant should indicate by checking an appropriate box if he/she has consumed vitamin K-rich food and if there is a change in the eating pattern of these foods.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

DIET INFORMATION – FOLLOW-UP

8. Since the last study visit did you drink coffee?	Check the appropriate box..... "1=Yes" or "0=No"
If yes,	
a. Did you consume:.....	If yes in question 8, check the appropriate box for question 8a..... "1=Less than usual" "2=More than usual" or "3=About the same"
9. Since the last study visit did you drink other caffeinated beverages?.....	Check the appropriate box..... "1=Yes" or "0=No"
If yes,	
a. Did you consume:.....	If yes in question 9, check the appropriate box for question 9a..... "1=Less than usual" "2=More than usual" or "3=About the same"
10. Since the last study visit did you drink alcoholic beverages?.....	Check the appropriate box..... "1=Yes" or "0=No"
If yes,	
a. Did you consume:.....	If yes in question 10, check the appropriate box for question 10a..... "1=Less than usual" "2=More than usual" or "3=About the same"

Research Coordinator: Please check the appropriate box to indicate who completed the CRF.

"1=Participant" "2=Interviewer" "3=Both"

Qs. 8-9: These questions relate to the participant's intake of non-alcoholic beverages and if there is a change from the information provided at the previous visit.

Q. 10: This question refers to the participant's intake of alcoholic beverages and as in the previous 2 questions, the participant indicates with his/her response if there is a change in consumption from the previous visit.

Interviewer type: The information in the shaded box is completed by the RC after the participant returns the CRF. DIETFUP is a self-reported questionnaire and the participant is expected to complete the questionnaire. If it is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

DIETFUP is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

EQ-5D ™ HEALTH QUESTIONNAIRE (*EUROQOL*)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

1. Mobility:

Check the appropriate box. "1=I have no problems in walking about" "2=I have some problems in walking about" "3=I am confined to bed"

2. Self-Care:

Check the appropriate box. "1=I have no problems with self-care" "2=I have some problems washing or dressing myself" "3=I am unable to wash or dress myself"

3. Usual Activities (e.g. work, study, housework, family or leisure activities)

Check the appropriate box. "1=I have no problems with performing my usual activities" "2=I have some problems with performing my usual activities" "3=I am unable to perform my usual activities"

4. Pain/Discomfort:

Check the appropriate box. "1=I have no pain or discomfort" "2=I have some pain or discomfort" "3=I have extreme pain or discomfort"

5. Anxiety/Depression:

Check the appropriate box. "1=I am not anxious or depressed" "2=I am moderately anxious or depressed" "3=I am extremely anxious or depressed"

Please continue on the next page.....

[EUROQOL] EQ-5D HEALTH QUESTIONNAIRE:

EQ-5D is a standardized instrument for use as a measure of health outcome. **EQ-5D** is designed for self-completion by participants. It is completed at the baseline and follow-up visits as outlined in the Visit Schedule (**VSTSCH**).

Qs. 1-5: Instructions for completion are included on page 1 of the questionnaire. The participant should be encouraged to provide the best possible responses to these questions.

Page 2 of the questionnaire includes instructions for the participant, but the RC may wish to clarify the instructions for the participant as well. The participants are expected to indicate on the scale how they perceive their health on a scale of 0-100. The RC will record the score in the space provided, based on the mark made by the participant on the scale.

Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

EQ-5D ™ HEALTH QUESTIONNAIRE (*EUROQOL*)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Best imaginable health state

Your own health state today

Worst imaginable health state

6. Record the marked score.

Research Coordinator: Please check the appropriate box to indicate who completed the CRF.

"1=Participant" "2=Interviewer" "3=Both"

Interviewer type: The information in the shaded box is completed by the RC after the participant returns the CRF. EUROQOL is a self-reported questionnaire and the participant is expected to complete the questionnaire. If it is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

EUROQOL is a data CRF and must be single data entered in the data management system (DMS)

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Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

HEALTH STATUS QUESTIONNAIRE (*SF-36™*)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey.

	Excellent	Very Good	Good	Fair	Poor
1. In general, would you say your health is:.....	Check the appropriate box. "1=Excellent," "2=Very good," "3=Good," "4=Fair," or "5=Poor"				

	Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
2. Compared to one year ago, how would you rate your health in general now?.....	Check the appropriate box. "1=Much better now than one year ago," "2=Somewhat better now than one year ago," "3=About the same as one year ago," "4=Somewhat worse now than one year ago," or "5=Much worse now than one year ago"				

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.....	Check only one box for questions 3a through 3j. "1=Yes, limited a lot" "2=Yes, limited a little" "3=No, not limited at all"		
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
c. Lifting or carrying groceries			
d. Climbing several flights of stairs			
e. Climbing one flight of stairs			
f. Bending, kneeling, or stooping			
g. Walking more than a mile			
h. Walking several hundred yards			
i. Walking one hundred yards.....			
j. Bathing or dressing yourself			

[SF-36] HEALTH STATUS QUESTIONNAIRE (SF-36™):

SF-36 is a standardized, self-administered questionnaire, which is completed by the participant. Instructions for completion of the questionnaire are included but the RC may prefer review them with the participant to get the best possible responses. The participant should be encouraged to respond to the questions as best as he/she can. Some of the questions refer to time (e.g. past 4 weeks, typical day) and the participant must be instructed to read the questions carefully.

Interviewer type: The information in the shaded box is completed by the RC after the participant returns the CRF. SF-36 is a self-reported questionnaire and the participant is expected to complete the questionnaire. If it is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

SF-36 is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

HEALTH STATUS QUESTIONNAIRE (*SF-36™*)

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down the amount of time you spent on work or other activities.....					
b. Accomplished less than you would like.....	Check only one box for questions 4a through 4d. "1=All of the time" "2=Most of the time" "3=Some of the time" "4=A little of the time" "5=None of the time"				
c. Were limited in the kind of work or other activities.....					
d. Had difficulty performing the work or other activities (for example, it took extra effort).....					

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down the amount of time you spent on work or other activities.....					
b. Accomplished less than you would like.....	Check only one box for questions 5a through 5c. "1=All of the time" "2=Most of the time" "3=Some of the time" "4=A little of the time" "5=None of the time"				
c. Did work or other activities less carefully than usual.....					

	Not at all	Slightly	Moderately	Quite a bit	Extremely
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Check only one box. "1=Not at all", "2=Slightly," "3=Moderately," "4=Quite a bit," "5=Extremely"				

No additional instructions given for this page. Please continue to the next page.

Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

HEALTH STATUS QUESTIONNAIRE (*SF-36™*)

	None	Very Mild	Mild	Moderate	Severe	Very severe
7. How much bodily pain have you had during the past 4 weeks?.....	Check only one box. "1=None" "2=Very Mild" "3=Mild" "4=Moderate" "5=Severe" "6=Very Severe"					

	Not at all	A little bit	Moderately	Quite a bit	Extremely
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?.....	Check only one box. "1=Not at all" "2=A little bit, "3=Moderately, "4=Quite a bit" "5=Extremely"				

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	Check only one box for questions 9a through 9i. "1-All of the time" "2=Most of the time" "3=Some of the time" "4=A little of the time" "5=None of the time"				
b. Have you been very nervous?.					
c. Have you felt so down in the dumps nothing could cheer you up?.....					
d. Have you felt calm and peaceful?					
e. Did you have a lot of energy?..					
f. Have you felt downhearted and depressed?.....					
g. Did you feel worn out?.....					
h. Have you been happy?.....					
i. Did you feel tired?.....					

No additional instructions given for this page. Please continue to the next page.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

HEALTH STATUS QUESTIONNAIRE (*SF-36*™)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?.....	Check only one box. "1=All of the time" "2=Most of the time" "3=Some of the time" "4=A little of the time" "5=None of the time"				

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people.....	Check only one box for questions 11a through11d. "1=Definitely true" "2=Mostly true" "3=Don't know" "4=Mostly false" "5=Definitely false"				
b. I am as healthy as anybody I know					
c. I expect my health to get worse.....					
d. My health is excellent					

Thank you for completing these questions!

Research Coordinator: Please check the appropriate box to indicate who completed the CRF.

"1=Participant" "2=Interviewer" "3=Both"

No additional instructions given for this page. Please continue to the next page.

Participant ID: **Participant Initials:** **Clinical Center:**

INR LOG

INR #	INR date *mm/dd/yyyy*	Time INR drawn *military time*	INR value	Type of blood used 1 = Venous 2 = Capillary 88 = Unknown	Protocol-required INR? 1 = Yes 0 = No	INR source 1 = Study recognized lab. 2 = Other source(s)	INR used for dose titration? 1 = Yes 0 = No	*Heparin use? 1 = Yes 0 = No
Record sequential numbers for the INR Log to maintain a unique INR record in the data management system (DMS).	Record the date of the draw in mm/dd/yyyy format.	Record the time of the draw in military time, or if time is unknown, check the box "88=Unknown."	Record the INR value.	Record the type of blood used. "1=Venous" "2=Capillary" "88=Uknown"	Record whether the INR is protocol-required. "1=Yes" "2=No"	Indicate where the INR was processed. "1=Study recognized lab" "2=Other source(s)"	Record whether the INR was used for dose titration. "1=Yes" "0=No"	Record whether the participant has concurrently used any heparin products. "1=Yes" "2=No"

** If the participant has used heparin, complete the **CMED** form.*

[INRLOG] INR LOG:

INRLOG is a continuous log completed by the RC and its function in the study is to record all INR values. These INR values may be study protocol-based, e.g. outlined in the Visit Schedule (**VSTSCH**), AC clinic health management-based or they may be available from sources outside of the institution, e.g. the participant's healthcare provider. Thus the RC should routinely check with the participant if he/she had blood drawn for INR testing or check medical records and track the results.

The page number section in the footer allows the RC to track multiple pages of the CRF.

INR #: This is a sequential number starting with "1", and has an administrative function in the data management system.

Time INR drawn: If the time of the blood draw for INR is known, it is recorded in the 24-hour clock format. If the time is unknown, it is indicated by checking the "Unknown" box.

INR value: This is recorded directly from the source. A printout from the source should be maintained in the participant's chart for future reference.

Type of blood used: A coding legend is available within the CRF to record an appropriate code for the type of blood used for INR testing. "88"is recorded if this information is not available.

Protocol-required INR?: The RC is required to track all known INRs. Thus INRs may be recorded from various sources. A protocol-required INR is ordered at a study visit as outlined in the study protocol and the Visit Schedule (VSTSCH). Any INRs that are not protocol-based are recorded as "No".

INR source: INR testing done at the institution where the study is conducted is considered a study-recognized laboratory and INR results obtained from any source other than the institution is considered as non-study or "other" source.

The RC should use appropriate coding to indicate the INR source.

INR used for dose titration: An INR value should be available in the INRLOG and DOSREQ or DOSREQ2 CRF, if used for dose titration.

INRLOG tracks all available INRs. By using the appropriate coding, the RC indicates if a specific INR is used for dose titration.

Heparin use: If the participant is prescribed and taking heparin, the RC should record the use by coding "1".

Heparin use should be recorded on the **CMED** CRF as well.

INRLOG is a data CRF and must be single data entered in the data management system (DMS).

Participant ID: **Participant Initials:** **Clinical Center:**

ADVERSE EVENTS

Event #	Code*	AE description	Grade*	Serious event?	Outcome	Relationship	Action taken with study treatment	Start date *mm/dd/yyyy*	Stop date *mm/dd/yyyy*
Insert sequential numbers (1, 2, 3…) to maintain a unique adverse event record in the data management system (DMS)	Record MedDRA code which corresponds to selected Adverse Event " short name".	Record the Adverse Event "short name" as displayed in the Adverse Events Detail column.	Enter either 1,2, 3, 4 or 5.	Enter either Yes or No	Enter either 1, 2, 3, 4 5, or 88.	Enter either 1, 2, 3 or 4. .	Enter either 1,2,3,4, 88 or 99.	Enter date participant reports the start of symptoms. Must be recorded in mm/dd/yyyy format.	Insert date participant reports the cessation of event or change in grade from initial report. Must be recorded in mm/dd/yyyy format.

**Refer to the NIH/NCI website for MedDRA code, Event term and corresponding grade (http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx).*

AE codes table

Grade	Serious event?	Outcome	Relationship	Action taken with study treatment
1 = Mild 2 = Moderate 3 = Severe 4 = Life threatening/disabling 5 = Death	1 = Yes 0 = No	1 = Recovered/resolved with no sequelae 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 88 = Unknown	1 = Not related 2 = Unlikely related 3 = Possibly related 4 = Related	1 = Drug withdrawn 2 = Dose reduced 3 = Dose increased 4 = Dose not changed 88 = Unknown 99 = Not applicable

[AE] ADVERSE EVENTS:

When a participant reports a medical event to the RC, it is the RC's responsibility to record that event on the **AE** CRF as an adverse event. **AE** is a continuous log and is completed by the RC with the participant at each visit. Coding and URL information is available on the CRF to facilitate recording of adverse events. If the RC is unable to make a coding determination of the any of the items on AE, he/she should consult the study PI.

The page number section in the footer allows the RC to track multiple pages of the CRF.

Event #: This is sequential numbering of the events reported by the participant, starting with "1". One event per event # is recorded.

Code: The code that corresponds to the event is recorded from the MedDRA website. The url for the website is available on the CRF.

AE description: Record the Adverse Event "short name" as displayed in the Adverse Events Detail column.

Grade: Grade is determined by the description of the event as related by the participant and corresponds to the event description of the MedDRA code on the website. If grade is not available on the MedDRA website, the legend at the bottom of the page helps in coding the grade of the event.

Serious event: The study PI should use his/her medical judgment and the criteria in the protocol to determine if the event is considered "serious".

Outcome: The AE codes table at the bottom of the CRF provides guidance on assessing the outcome of the event.

Relationship: By assessing the details of the event, the study PI should determine the relationship of the event to the use of algorithm-generated dose of warfarin or participation in the study. Appropriate codes in the AE codes table should be recorded.

Action taken with study treatment: If changes are made in response to the event (e.g. dose override), the RC should note the change by using the appropriate code provided in the AE codes table at the bottom of the AE CRF.

Start date: This is the date of the onset of the event. It is recorded in the mm/dd/yyyy format.

Stop date: This is the date when the adverse event resolved. It is recorded in the mm/dd/yyyy format.

AE is a log and is single data entered in the data management system (DMS).

Participant ID: **Participant Initials:** **Clinical Center:**

CONCOMITANT MEDICATIONS

*Refer to the Concomitant Medications (**CMED**) guidelines in the Manual of Procedures (**MOP**) for completion instructions.*

Line #	Medication name	Medication code	Medication status	Visit number associated with status	Medication update	Visit number associated with update
Insert sequential numbers for each concomitant medications to maintain a unique record in the data management system (DMS)	Record the generic name of the medication displayed in the Medication Reference tool	Record the code number displayed in the Medication Reference tool	Enter either 1 or 2.	Record visit number associated with medication status in preceding column	Enter either 1 or 2	Record visit number associated with medication status in preceding column

Medication code	Medication status	Medication update
Refer to the Medication Reference Tool	1 = Reported at baseline 2 = New drug during the study	1 = Continued until study completion 2 = Stopped during study participation

[CMED] CONCOMITANT MEDICATIONS:

CMED is a continuous log and is completed by the RC with the participant at each visit. The RC continues to update information by attaching additional pages, as needed. Legend for coding is available within the CRF. The page number section in the footer allows the RC to track multiple pages of the CRF.

The RC should develop a system for collecting medication information from the participant. It could be in the form of a self-report, a written or printed list, or the participant may bring medication bottles to the visit. The RC may print a pharmacy list from the institution and check the medications with the participant, as well. The list at the start of the study should be comprehensive and should include all prescribed and over-the-counter drugs, including herbal supplements. **CMED** does not record specific information, e.g. dose or frequency of use, hence a medication is considered "continued", regardless of change in daily dose or frequency of use, until stopped.

Warfarin use outside of the protocol-generated dose on days 1-28 is recorded on the **WARFLOG** CRF.

At each visit (refer to **VSTSCH**), the RC should review the medications and update the list with the participant.

Line #: This is a sequential numbering of the medications taken by the participant, starting with "1". One medication per line is recorded.

Medication name: This information is provided by the participant. One medication per line is noted on CMED. The RC should ask the participant about all the medications he/she takes, including all prescription and over-the-counter medications. The RC may wish to name some of the commonly prescribed medications based on the participant's health history to elicit the best possible information. The medication name provided by the participant is noted in this column.

Medication code: The RC must look up medication code using the Medication Reference Tool. The Medication Tool allows the RC to look for codes by brand names or generic names.

Medication status: CMED is a continuous log; hence a new CRF does not get generated at each participant visit. In addition to reviewing and updating the existing list on the log, each new medication reported at a scheduled visit is recorded as well.

The status of the new medications is coded based on the visit schedule (**VSTSCH**). All medications reported at baseline are coded as "1". Medications started after the baseline visit are reported at a scheduled follow-up visit (**VSTSCH**) and are coded as "2".

Visit # at medication status: COAG study does not record specific information, e.g. dose, frequency, start and stop date for each medication. Additionally, CMED is designed as a continuous log. Therefore, visit number information is not recorded in the header or the DMS. The visit at which the participant first reports the medication provides approximation for the start date.

Medication update: At each study visit (VSTSCH) the RC reviews the medication list with the participant to determine changes in medications. If the participant informs the RC that he/she stopped taking study medication, the RC should use "2" to code stopping of the medication. If at the last study visit (Visit 12 or early termination) the participant is known to have continued with the medication, the RC uses "1" to code this information.

Visit # at medication update: The follow-up visit at which the participant reports stopping the medication is recorded in this space.

CMED is a log and is single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

FOLLOW-UP VISIT FORM

Type of follow-up:	Check the appropriate box for type of visit. "1=In-person" "2=Phone" "3=Missed visit (*stop here*)"

This form is not applicable for a missed participant visit.

Questions 1 though 9 completed by interviewing the participant.

1. Since your last study visit, have you had your warfarin/Coumadin stopped for any reason?	Check one response; check "N/A" if participant is not on warfarin therapy.

If yes, complete EVENTS form, Section I.

2. Since your last visit, have you taken any warfarin that was not given to you by the study?	Check the appropriate box "1=Yes" "0=No"
a. How many days did you take the non-study warfarin?	If yes to question 2, record number of days on non-study warfarin

If off-protocol dosing for 2 or more days on days 1 through 28, contact the Medical Monitor.

3. Since your last study visit, have you been seen in an emergency room or were you hospitalized?	Check the appropriate box. "1=Yes" "0=No"

If yes,

a. Was it for bleeding, a stroke or TIA (mini-stroke) or a blood clot?	Check the appropriate box. "1=Yes" "0=No"
b. Did you experience bleeding, a stroke, or TIA (mini-stroke) or a blood clot during hospitalization?	Check one response; check "N/A" if participant is not hospitalized.

If yes in question 3a, complete EVENTS form Section II and AE form. If no in question 3a, complete AE form.
If yes in question 3b, complete EVENTS form Section IV and AE form. If no in question 3b, complete AE form.

4. Since your last visit have you seen your healthcare provider for [any other] bleeding or a blood clot, not as an inpatient and not in the emergency room?	Check the appropriate box. "1=Yes" "0=No"

If yes, complete EVENTS form Section III and AE form.

5. Since your last visit have you experienced any other bleeding or any bruising that did not require you to see your healthcare provider?	Check the appropriate box. "1=Yes" "0=No"
a. Was this a new bleeding or bruising event?	Check the appropriate box. "1=Yes" "0=No"
b. Since its occurrence, is it...?	Check one appropriate response.
6. Since the last study visit, have you experienced any other serious health problems that required you to be hospitalized?	Check the appropriate box. "1=Yes" "0=No"

If yes, complete AE form.

[VISIT] FOLLOW-UP VISIT FORM:

This form is completed at each subsequent study visit after the baseline visit, as indicated on the visit schedule. It is completed by the RC through participant interview and medical record review as indicated. The intent of this form is to collect all incidences of adverse events, including primary endpoint events such as bleeding or blood clots. It is also intended to help measure warfarin compliance. Based on the participant's responses, you may need to complete additional CRFs, specifically, the Adverse Event form and the Medical Events form. Follow the CRF instructions carefully.

Indicate whether information for this form is being collected in a face to face interview, over the phone or if the participant is not available for the visit. If participant is unavailable, indicate that the visit is "missed" and stop.

The questions refer to the time period between the last visit and the current visit.

Q l: Indicate if participant stopped taking their warfarin for any reason. Follow additional form instructions. If the participant stopped warfarin therapy in the time period between the last visit and the current visit, the response should be "No". If warfarin was stopped prior to this period, the expected response should be "N/A"

Q2: Indicate if participant took any warfarin that was not provided by the study and how many days this occurred. Follow additional form instructions.

Q 3: Indicate if participant was seen in an emergency room or hospitalized since last visit. Follow additional form instructions.

Q.3b: This question refers to events that may occur while hospitalized. Indicate if the participant is not hospitalized by checking an "N/A" response.

Q4: Indicate if participant had an outpatient visit with their healthcare provider since last study visit. Follow additional form instructions.

Q 5: Indicate if participant experienced any other bleeding or bruising event not already described in questions 3 or 4.

Q 6: Indicate if participant was hospitalized for any other event not already described in question 3. Follow additional form instructions.

Questions 7, 8 and 9 refer to participant compliance when on warfarin therapy; indicate discontinuation of warfarin therapy in previous visit windows, by checking "N/A".

By checking the appropriate box in Qs 7 and 8, indicate if the participant has adhered to the prescribed dosing in the time period since the last visit.

Q 7: Indicate if participant missed any doses of warfarin in the last seven days. If yes, record number of days missed. Follow additional form instructions.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

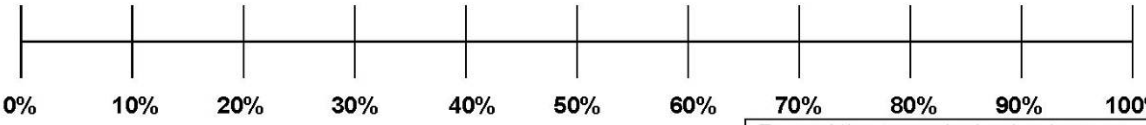
FOLLOW-UP VISIT FORM

Check "N/A / 99"if the participant discontinued warfarin more than 7 days ago for questions 7 and 8.

7. Did you skip taking any warfarin capsules in the past 7 days?.....	Check one response; check "N/A" if participant is not on warfarin therapy.
a. How many days did you skip taking warfarin capsules?.....	If yes to question 7, record number of days warfarin was skip
8. Did you take extra warfarin capsules in the past 7 days?.....	Check one response; check "N/A" if participant is not on warfarin therapy.
a. How many days did you take extra warfarin capsules?	If yes to question 7, record number of days warfarin was skip

If the participant missed 2 or more days or took 2 or more extra doses, contact the Medical Monitor.

Put a cross on the line below at the point showing your best guess about how much of your warfarin you have taken since your last study visit. For example, 0% means you have taken no dose, 50% means you have taken half of your prescribed doses, and 100% means you have taken all of your prescribed doses.



9. Score:.....	Record the numerical value here or check N/A if participant not on warfarin.

Complete the following questions based on the warfarin capsules dispensed, as noted on the returned bottle(s).

Questions 10 through 13 are completed during visits 2 through 7 only; for all other visits check N/A and go to question 14:.....	Check box if this is not Visit 2-7 and skip to Q. 14.
10. Did the participant return the bottles from the previous visit?.....	Check one response; check "N/A" if participant is inpatient at Visits 1-7.

If yes, continue. If no or N/A, go to question 14.

11. # of warfarin capsules dispensed:.....	Record the number of capsules dispensed from Bottle A and Bottle B. If no B bottle check "99=N/A".
12. # of warfarin capsules returned:.....	Record the number of capsules returned from Bottle A and Bottle B. If no B bottle check "99=N/A".
13. # of warfarin capsules lost/unusable:.....	Record the number of capsules lost/unusable from Bottle A and Bottle B. If no B bottle check "99=N/a"

Data for questions 14 is obtained through medical chart review.

14. Has the participant's target INR changed since the last study visit?..	Check the appropriate box. "1=Yes" "0=No"
a. New range:	If yes to Q 14, record the new range; if range is not known check "88=Unknown"
b. Date range changed:.....	Record date in the *mm/dd/yyyy format*

Q 8: Indicate if participant took any additional doses of warfarin in the last seven days. If yes, record number of additional days. Follow additional form instructions.

Q9: Write the number that best represents the cross inserted on the line by the participant after reading the question instructions to them.

If the participant discontinued warfarin therapy prior to the current visit time frame, check "N/A" response.

The participant interview portion of this form is now complete.

Qs 10-13 Complete these questions for visits 2 through 7 For all other visits, check "NA".

If the participant received algorithm generated warfarin during inpatient stay at visits 1-7, check "N/A in Q. 10.

If participant has returned study pill bottles, count the number of pills returned and complete questions 11- 13, otherwise skip to question 14.

Q 14: Indicate if participant's INR range has been adjusted since the last visit and the date when the adjustment occurred. Obtain this information by reviewing the participant's medical record.

VISIT is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL EVENTS

Section I: Warfarin/Coumadin

Check N/A if warfarin/Coumadin was <u>not</u> stopped:	Check box if warfarin is not stopped in the current visit window.
1. Date your warfarin/Coumadin was stopped:	Date of discontinuation of warfarin if in the current visit window if known or check "Unknown" box.
2. Were you hospitalized for a procedure at the time?	Check one response; if "No" response, skip to Q 3; if "Yes", continue.
If yes in question 2, what type of procedure was it…?	
a. Cardioversion:	Check one response "Yes" or "No" for each item in Qs 2a-2e.
b. Cardiac catheterization or angioplasty:	
c. Cardiac surgery:	
d. Other surgery:	
e. Other procedure:	
e1. If yes in question 2e, specify:	If "Yes" in Q 2e, provide additional information.
3. If no in question 2, was it prior to an outpatient procedure?	Check one response; if "No" response, skip to Q 4; if "Yes", continue.
If yes in question 3, what type of procedure was it…?	
a. Cardioversion:	Check one response "Yes" or "No" for each item in Qs 3a-3d.
b. Cardiac catheterization:	
c. Dental procedure:	
d. Other procedure:	
d1. If yes in question 3d, specify:	If "Yes" in Q 3d, provide additional information.
4. Was your warfarin/Coumadin stopped because of bleeding?	Check one response – "Yes" or "No".
5. Was it due to other reasons?	Check one response; if "No" response, skip to Q 6; if "Yes", continue.
a. If yes in question 5, specify:	If "Yes" in Q 5, provide additional information.
6. Was your warfarin/Coumadin restarted?	Check one response; if "No" response, skip to Section II; if "Yes", continue.
a. When was your warfarin/Coumadin restarted?	If warfarin is restarted in the current visit window, enter date if known or check "Unknown" box.
b. Total number of days warfarin/Coumadin stopped:	If known, enter # of days warfarin discontinued or check "Unknown" box.

If warfarin/Coumadin is stopped for 2 or more days during dose initiation, revision or titration period (day 1 through 28), contact the Medical Monitor.

[EVENTS] MEDICAL EVENTS:

This form is only completed based on positive responses to questions on the VISIT form related to warfarin interruptions, bleeding and clotting events. Sections I, II or III may be skipped based on those responses. Follow skip pattern instructions carefully.

This CRF is administered by the Research Coordinator to the participant.

Section I:

If participant stopped their warfarin for any reason since last visit, complete this section, otherwise skip to section II.

Q l: Record date participant stopped taking warfarin. Check unknown if participant can not recall.

Q2: If participant was hospitalized for a procedure at the time of warfarin discontinuation, complete questions 2a-2e, otherwise skip to question 3.

Q 3: If participant stopped their warfarin in anticipation of an outpatient procedure, complete questions 3a – 3d, otherwise skip to question 4.

Qs 4- 5: Relates to warfarin discontinuation prompted by bleeding or other reasons not described elsewhere

Q 6: Record date warfarinn was restarted and total number of days the warfarin was stopped if participant can provide/recall this information, otherwise mark the questions as “unknown”.

Note: If warfarin is stopped for 2 or more days, for any reason during days 1-28 of the study, the Medical Monitor must be contacted.

Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

MEDICAL EVENTS

Section II: Emergency Room Visit or Hospitalization

Check N/A if participant was not seen in the emergency room or hospitalized:	Check box if participant was seen in ER or hospitalized in the current visit window.
7. Was the emergency room visit or hospitalization for bleeding?	Check one response; if "No" response, skip to Q 18; if "Yes", continue.
If yes in question 7, what type of bleeding was it…?	
8. Nose bleed:	Check one response; if "No" response, skip to Q 9; if "Yes", continue.
a. Were you seen in an emergency room only or were you hospitalized?	Check one response to indicate if ER visit or hospitalization in the current visit window for nose bleed.
9. Blood in stool:	Check one response; if "No" response, skip to Q 10; if "Yes", continue.
a. Was the blood in stool the result of a procedure (e.g. colonoscopy)?	Check one response in Qs 9a-9f.
b. Were you seen in an emergency room only or were you hospitalized?	
c. Did you see the red blood in the stool?	
d. Did you see black tarry stools?	
e. Was the blood invisible to you and only detected by a routine screening test?	
f. Did you have endoscopy, colonoscopy, upper GI or lower GI series for the blood in stool?	
10. Vomiting blood:	Check one response; if "No" response, skip to Q 11; if "Yes", continue.
a. Were you vomiting blood as a result of a procedure (e.g. endoscopy)?	Check one response in Qs 10a-10f.
b. Were you seen in an emergency room only or were you hospitalized?	
c. Did you vomit red blood?	
d. Did you vomit coffee ground material?	
e. Did you have endoscopy, colonoscopy, upper GI or lower GI series for the vomiting blood?	
11. Coughing up blood:	Check one response; if "No" response, skip to Q 12; if "Yes", continue.
a. Were you seen in an emergency room only or were you hospitalized?	Check one response in Qs 11a and 11b; indicate in Q 11a if seen in ER or hospitalized for coughing up blood.
b. Did you have a bronchoscopy for coughing up blood?	

Section II:

If participant was seen in an emergency room or hospitalized since last visit, complete this section, otherwise skip to section III.

Q 7: If participant was seen in an emergency room or hospitalized for bleeding, complete questions 8-17, otherwise skip to question 18

Qs 8 – 15 Record responses to possible bleeding events which could result in a person requiring a visit to an emergency room or a hospitalization. Follow the skip patterns as indicated.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL EVENTS

Section II: Emergency Room Visit or Hospitalization.....*continued*

12. Bleeding after cut or blood draw:	Check one response; if "No" response, skip to Q 13; if "Yes", continue.
a. Were you seen in an emergency room only or were you hospitalized?	Check one response to indicate if ER visit or hospitalization in the current visit window for bleeding after cut.
13. Blood in urine:	Check one response; if "No" response, skip to Q 14; if "Yes", continue.
a. Were you seen in an emergency room only or were you hospitalized?	Check one response in Qs 13a-13e; indicate in Q 13a if seen in ER or hospitalized for blood in urine.
b. Did you see bright red blood?	
c. Was the blood invisible to you and only detected by a urine test?	
d. Was the bleeding the result of a procedure i.e. a catheter insertion or cystoscopy?	
e. Did you have a cystoscopy for blood in urine?	
14. Bleeding in head:	Check one response; if "No" response, skip to Q 15; if "Yes", continue.
a. Were you seen in an emergency room only or were you hospitalized?	Check one response to indicate if ER visit or hospitalization in the current visit window for bleeding in head.
15. Other type of bleeding:	Check one response; if "No" response, skip to Q 16; if "Yes", continue.
a. If yes in question 15, specify:	If "Yes" in Q 15, provide additional information.
b. Were you seen in an emergency room only or were you hospitalized?	Check one response to indicate if ER visit or hospitalization in the current visit window for other type of bleeding.
16. Was your warfarin/Coumadin held 3 or more days because of any of the bleeding events?	Check one response.
17. For any of the bleeding events described, did you require...?	
a. Blood transfusion:	Check one response in Qs 17a-17e.
b. Surgery:	
c. Nasal packing:	
d. Cauterization:	
e. Other procedure:	
e1. If yes in question 17e, specify:	If "Yes" in Q 17e, provide additional information.

Qs 8 – 15: Record responses to possible bleeding events which could result in a person requiring a visit to an emergency room or a hospitalization. Follow the skip patterns as indicated.

Q 16: Indicate if warfarin was interrupted as a result of the bleeding event

Q 17: Record if participant required any interventions to control/stop the bleeding event.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL EVENTS

Section II: Emergency Room Visit or Hospitalization.....*continued*

18. Was the emergency room visit or hospitalization for a stroke or TIA (*mini-stroke*)?	Check one response; if "No" response, skip to Q 19; if "Yes", continue.
a. If yes, were you seen in emergency room only or were you hospitalized?	Check one response to indicate if ER visit or hospitalization in the current visit window for stroke or TIA.
19. Was the emergency room visit or hospitalization for a blood clot?	Check one response; if "Yes" in Q 19 continue; if "No" skip to Q 24.

If yes in question 19, ask questions 20 through 25. If no, go to question 24.

20. Was it for a clot in the veins of your legs?	Check one response; if "Yes" in Q 20 continue; if "No" skip to Q 21.
a. If yes, were you seen in emergency room only or were you hospitalized?	Check one response to indicate if ER visit or hospitalization in the current visit window for a clot in vein of legs.
21. Was it for a clot in your lungs?	Check one response; if "Yes" in Q 21 continue; if "No" skip to Q 22.
a. If yes, were you seen in emergency room only or were you hospitalized?	Check one response to indicate if ER visit or hospitalization in the current visit window for a clot in lungs.
22. Was it for a clot in your hands or feet?	Check one response; if "Yes" in Q 22 continue; if "No" skip to Q 23.
a. If yes, were you seen in emergency room only or were you hospitalized?	Check one response to indicate if ER visit or hospitalization in the current visit window for a clot in hands or feet.
23. Was it for a clot in your kidney?	Check one response; if "Yes" in Q 23 continue; if "No" skip to Q 24.
a. If yes, were you seen in emergency room only or were you hospitalized?	Check one response to indicate if ER visit or hospitalization in the current visit window for a clot in the kidney.
24. Were you hospitalized for any other bleeding or blood clot event?	Check one response; if "Yes" in Q 24 continue; if "No" skip to Q 25.
a. If yes in question 24, specify:	If "Yes" in Q 24, provide additional information.
25. Were you seen in the emergency room for any other bleeding or blood clot event?	Check one response; if "Yes" in Q 25 continue; if "No" skip to Section III.
a. If yes in question 25, specify:	If "Yes" in Q 25, provide additional information.

Q 18: Indicate if the participant's emergency room visit or hospitalization was related to a stroke or TIA, otherwise skip to question 19.

Q 19: If participant was seen in an emergency room or hospitalized for a blood clot, complete questions 20-25, otherwise skip to question 24.

Qs 20-25 Record responses to possible blood clot events which could result in a person requiring a visit to an emergency room or a hospitalization.

Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

MEDICAL EVENTS

Section III: Out-patient Care

Check N/A if participant did not receive outpatient care:	Check box if participant was not seen as an outpatient in the current visit window and skip to Section IV.
26. Since your last visit, have you seen a healthcare provider for bleeding, not as an inpatient and not in the emergency room?.....	Check one response if received outpatient care only; if "No" response, skip to Q 39; if "Yes", continue.
a. If yes, how many visits?.....	Enter number of visits for outpatient care in the current visit window.
If yes, what type of bleeding was it…?	
27. Nose bleed:	Check one response.
28. Blood in stool:.....	Check one response; if "No" response, skip to Q 29; if "Yes", continue.
a. Was the blood in stool the result of a procedure (e.g. colonoscopy)?.....	Check one response in Qs 28a-28e.
b. Did you see the red blood in the stool?.....	
c. Did you see black tarry stools?.....	
d. Was the blood invisible to you and only detected by a routine screening test?	
e. Did you have endoscopy, colonoscopy, upper GI or lower GI series for the blood in stool?.....	
29. Vomiting blood:	Check one response; if "No" response, skip to Q 30; if "Yes", continue.
a. Were you vomiting blood as a result of a procedure (e.g. endoscopy)?	Check one response in Qs 29a-29d.
b. Did you vomit red blood?.....	
c. Did you vomit coffee ground material?.....	
d. Did you have endoscopy, colonoscopy, upper GI or lower GI series for the vomiting blood?.....	
30. Coughing up blood:.....	Check one response; if "No" response, skip to Q 31; if "Yes", continue.
a. Did you have a bronchoscopy for coughing up blood?	Check one response to indicate if bronchoscopy administered in the current visit window for a coughing up blood.
31. Bleeding after a cut or blood draw:	Check one response; if "No" response, skip to Q 32; if "Yes", continue.

Section III:

If participant was seen by their healthcare provider for a bleeding or clotting event since last visit, that did not require an emergency room visit or hospitalization, complete this section, otherwise check "N/A" and move to the next section.

Q 26: If participant was seen on an outpatient basis by their healthcare provider for a bleeding event, indicate total number of visits and complete questions 27-36, otherwise skip to question 39

Qs 27-36 Record responses to possible bleeding events which could result in a person requiring an outpatient visit to their healthcare provider. Follow the skip patterns as indicated.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL EVENTS

Section III: Out-patient Care.....*continued*

32. Blood in urine:	Check one response; if "No" response, skip to Q 33; if "Yes", continue.
a. Did you see red blood?	Check one response in Qs 32a-32d.
b. Was the blood invisible to you and only detected by a routine urine test?	
c. Was the bleeding the result of a procedure i.e a catheter insertion or cystoscopy?	
d. Did you have a cystoscopy for blood in urine?	
33. Bleeding in head:	Check one response in Qs 33-35.
34. Was it for bruising?	
35. Vaginal or menstrual bleeding:	
36. Any other type of bleeding?	Check one response; if "No" response, skip to Q 37; if "Yes", continue.
a. If yes in question 36, specify:	If "Yes" in Q 36, provide additional information.
37. Was your warfarin/Coumadin held 3 or more days because of any of the bleeding events?	Check one response in Q 37.
38. For any of the bleeding events described did you require...?	
a. Blood transfusion:	Check one response in Qs 38a-38e.
b. Surgery:	
c. Nasal packing:	
d. Cauterization:	
e. Other procedure:	
e1. If yes in question 38e, specify:	If "Yes" in Q 38e, provide additional information.

Qs 27 – 36: Record responses to possible bleeding events which could result in a person requiring a visit to an emergency room or a hospitalization. Follow the skip patterns as indicated.

Q 37: Indicate if warfarin was interrupted as a result of the bleeding event

Q 38: Record if participant required any interventions to control/stop the bleeding event.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL EVENTS

Section III: Out-patient Care.....*continued*

39. Since your last visit, have you seen a healthcare provider for a <u>new</u> clot, not as an inpatient and not in the emergency room?.....	Check one response; if "No" response, skip to Q 40; if "Yes", continue.
a. If yes, how many visits?.....	Enter number of visits for outpatient care for a new clot in the current visit window.
b. Was it for a clot in the veins of your legs?.....	Check one response in Qs 39a-39f.
c. Was it for a clot in your lungs?	
d. Was it for a clot in your hands or feet?.....	
e. Was it for a clot in your kidney?.....	
f. Were you seen for any other bleeding or blood clot event?.....	
f1. If yes in question 39f, specify:.....	If "Yes" in Q 39f, provide additional information.
40. Was the visit with your healthcare provider for a <u>new</u> stroke or TIA (*mini-stroke*)?	Check one response and go to Section Iv.

Q 39: If participant was seen on an outpatient basis by their healthcare provider for a NEW blood event, indicate total number of visits and complete questions 39 a-f, otherwise skip to question 40

Q 40 Indicate if the participant's outpatient visit with their healthcare provider was for a NEW stroke or TIA.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL EVENTS

Section IV: Stroke, TIA (mini stroke) or Bleeding during Hospitalization

Check N/A if participant did not have stroke, TIA (mini stroke) or bleeding during hospitalization:	Check box if participant was not hospitalized or did not experience stroke, TIA or bleeding episodes in the current visit window and stop here.
41. Did you experience bleeding during hospitalization?	Check one response; if "No" response, skip to Q 52; if "Yes", continue.
If yes in question 41, what type of bleeding was it…?	
42. Nose bleed:	Check one response; if "No" response, skip to Q 43; if "Yes", continue.
a. If yes, did the nose bleed prolong your hospitalization?	Check one response in Q 42a.
43. Blood in stool:	Check one response; if "No" response, skip to Q 44; if "Yes", continue.
If yes,	
a. Was the blood in stool the result of a procedure (e.g. colonoscopy)?	Check one response in Qs 43a-43f.
b. Did the blood in your stool prolong your hospitalization?	
c. Did you see the red blood in the stool?	
d. Did you see black tarry stools?	
e. Was the blood invisible to you and only detected by a routine screening test?	
f. Did you have endoscopy, colonoscopy, upper GI or lower GI series for the blood in stool?	
44. Vomiting blood:	Check one response; if "No" response, skip to Q 45; if "Yes", continue.
If yes,	
a. Were you vomiting blood as a result of a procedure (e.g. endoscopy)?	Check one response in Qs 44a-44e.
b. Did vomiting blood prolong your hospitalization?	
c. Did you vomit red blood?	
d. Did you vomit coffee ground material?	
e. Did you have endoscopy, colonoscopy, upper GI or lower GI series for the vomiting blood?	

Section IV captures data on participants who relate events that occurred while hospitalized; this section mirrors Section II, which records events that leads to hospitalization.

In some instances these events may lead to prolonged hospitalization. Appropriate questions and responses to these questions will provide information to indicate the outcome of these events.

Skip patterns are introduced similar to other sections based on responses to the lead-in questions.

EVENTS is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL EVENTS

Section IV: Stroke, TIA (mini stroke) or Bleeding during Hospitalization……*continued*

45. Coughing up blood:.....	Check one response; if "No" response, skip to Q 46; if "Yes", continue.
If yes,	
a. Did coughing up blood prolong your hospitalization?.....	Check one response in Qs 45a and 45b.
b. Did you have a bronchoscopy for coughing up blood?	
46. Bleeding after cut or blood draw:	Check one response; if "No" response, skip to Q 47; if "Yes", continue.
a. If yes, did bleeding after a cut or the blood draw prolong your hospitalization?.....	Check one response, if Q 46 is "Yes".
47. Blood in urine:	Check one response; if "No" response, skip to Q 48; if "Yes", continue.
If yes,	
a. Did the blood in your urine prolong your hospitalization?	Check one response in Qs 45a and 45b.
b. Did you see bright red blood?.....	
c. Was the blood invisible to you and only detected by a urine test?.....	
d. Was the bleeding the result of a procedure i.e. a catheter insertion or cystoscopy?.....	
e. Did you have a cystoscopy for blood in urine?.....	
48. Bleeding in head:	Check one response; if "No" response, skip to Q 49; if "Yes", continue.
a. If yes, did the bleeding in your head prolong your hospitalization?.....	Check one response, if Q 48 is "Yes".
49. Other type of bleeding:.....	Check one response; if "No" response, skip to Q 50; if "Yes", continue.
If yes,	
a. Specify:.....	If "Yes" in Q 49a, provide additional information.
b. Did this bleeding prolong your hospitalization?.....	Check one response.
50. Was your warfarin/Coumadin held 3 or more days because of any of the bleeding events?.....	Check one response; check "N/A" if not on warfarin therapy.

No additional instructions given for this page. Please continue to the next page.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MEDICAL EVENTS

Section IV: Stroke, TIA (mini stroke) or Bleeding during Hospitalization……*continued*

51. For any of the bleeding events described, did you require…?	
a. Blood transfusion:……	For any "Yes" responses in Qs 41, 42, 43, 44, 45, 46, 47, 48, or 49, check one response in Qs 51a-51e.
b. Surgery:……	
c. Nasal packing:……	
d. Cauterization:……	
e. Other procedure:……	
e1. If yes in question 51e, specify:……	If "Yes" in Q 49a, provide additional information.
52. Did you experience stroke or TIA (mini-stroke) during your hospitalization?……	Check one response; if "No" response, skip to Q 53; if "Yes", continue.
a. If yes, did the stroke or TIA (mini-stroke) prolong your hospitalization?……	Check one response, if Q 52 is "Yes".
53. Did you experience blood clots during your hospitalization?……	Check one response; if "No" response, stop here; if "Yes", continue.

If yes in question 53, ask questions 54 through 58. If no, stop here.

54. Was it for a clot in the veins of your legs?……	Check one response.
a. If yes, did the clot in the veins of your legs prolong your hospitalization?……	Check one response, if Q 54 is "Yes".
55. Was it for a clot in your lungs?……	Check one response.
a. If yes, did the clot in your lungs prolong your hospitalization?…	Check one response, if Q 55 is "Yes".
56. Was it for a clot in your hands or feet?……	Check one response.
a. If yes, did the clot in your hands or feet prolong your hospitalization?……	Check one response, if Q 56 is "Yes".
57. Was it for a clot in your kidney?……	Check one response.
a. If yes, did the clot in your kidney prolong your hospitalization?.	Check one response, if Q 57 is "Yes".
58. Did you experience any other bleeding or blood clot events during your hospitalization?……	Check one response.
If yes,	
a. Specify:……	If "Yes" in Q 58, provide additional information.
b. Did the bleeding or blood clot event(s) prolong your hospitalization?……	Check one response, if Q 58 is "Yes".

No additional instructions given for this page. Please continue to the next page.

Participant ID: **Participant Initials:** **Clinical Center:**

WARFARIN LOG

(Completed between Visits 8 and 12 or if participant takes off-protocol dose between Visits 1 and 7)

Line #	Start date mm/dd/yyyy	Stop date mm/dd/yyyy	Weekly dose (in mg)	Frequency 1 = Daily 2 = Once a week 3 = 2 X/week 4 = 3 X/week 5 = 4 X/week 6= 5 X/week 7= 6 X/week
Insert sequential numbers for the Warfarin Log to maintain a unique Warfarin record in the data management system (DMS)	Record the start date in mm/dd/yyyy format.	Record the stop date in mm/dd/yyyy format.	Record the current weekly dose in mg.	Indicate the frequency of the dose. "1=Daily", "2=Once a week", "3=2 X/week", "4=3 X/week" "5=4 X/week" "6=5 X/week", or "7=6 X/week"

V2.0.20100209 Page __ of __ WARFLOG

[WARFLOG] WARFARIN LOG:

WARFLOG, maintained by the RC, is typically completed after the participant completes the titration phase (days 1 through 28) and goes into the maintenance phase of the study.

A blinded dose is recorded by the pharmacist in the data management system day 1 through 28. In an instance when the participant is dosed off-protocol but continues participation in the study, the RC records the off-protocol dose on WARFLOG.

During the maintenance phase of the study (months 2 through 6) the Research Coordinator will record off-study warfarin dose information.

WARFLOG is a log and is single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

DUKE ANTICOAGULATION SATISFACTION SURVEY (DASS)

We would like to know how your anti-clot treatment (warfarin/Coumadin) affects you, and what you know and feel about your anti-clot treatment. Please check the answer that best fits your situation. If a question does not apply to you, then check "Not at all".

	Not at all	A little	Some-what	Moder-ately	Quite a bit	A lot	Very much
1a. How much does the possibility of bleeding or bruising limit you from taking part in physical activities (*for example, housework, gardening, dancing, sports, or anything else you would usually do*)?..							
1b. How much does the possibility of bleeding or bruising limit you from traveling?							
1c. How much does the possibility of bleeding or bruising limit you from getting the medical care you need (*for example, visiting a dentist, chiropractor, or doctor of your choice*)?							
1d. How much does the possibility of bleeding or bruising limit your ability to work for pay?							
1e. Overall, how much does the possibility of bleeding or bruising affect your daily life?							

Check the appropriate box for questions 1a through 1e.

"1=Not at all"
"2=A little"
"3=Somewhat"
"4=Moderately"
"5=Quite a bit"
"6=A lot" or
"7=Very much"

Only check one response for each question

Being on anti-clot treatment may mean changing some of your other habits as well.

2a. How much does anti-clot treatment limit your choice of food (*diet*)?	
2b. How much does anti-clot treatment limit the alcoholic beverages you might wish to drink?	
2c. How much does anti-clot treatment limit the over-the-counter medications (*for example, aspirin, ibuprofen, vitamins*) you might wish to take?	
2d. Overall, how much does anti-clot treatment affect your daily life?.....	

Check the appropriate box for questions 2a through 2d.

"1=Not at all"
"2=A little"
"3=Somewhat"
"4=Moderately"
"5=Quite a bit"
"6=A lot" or
"7=Very much"

Only check one response for each question

[DASS] DUKE ANTICOAGULATION SATISFACTION SURVEY (DASS):

DASS is a standardized self-reported instrument to assess quality of life in patients on anticoagulation therapy. The RC must review completion instructions with the participant and have the participant complete the questionnaire.

It is expected that the participant completes this interview if he/she has been maintained on warfarin therapy in the time period since the last visit. If the participant discontinues warfarin prior to the current visit, in that instance, DASS can be skipped.

Interviewer type: The information in the shaded box is completed by the RC after the participant returns the CRF. DASS is a self-reported questionnaire and the participant is expected to complete the questionnaire. If it is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

DASS is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

DUKE ANTICOAGULATION SATISFACTION SURVEY (DASS)

Being on anti-clot treatment means doing a lot of things, some every day and some less often.

Daily tasks could include: remembering to take your medicine at a certain time, taking the correct doses of your medicine, not drinking much alcohol, following a moderate diet, avoiding bruising and bleeding, and so forth.

Occasional tasks could include: traveling to the clinic for blood check-ups, contacting the clinic in case of bleeding or other important events, and so forth.

	Not at all	A little	Some-what	Moder-ately	Quite a bit	A lot	Very much
3a. How much of a hassle (*inconvenience*) are the daily tasks of anti-clot treatment?	Check the appropriate box for questions 3a and 3b. "1=Not at all" "2=A little" "3=Somewhat" "4=Moderately" "5=Quite a bit" "6=A lot" or "7=Very much" Only check one response for each question.						
3b. How much of a hassle (*inconvenience*) are the occasional tasks of anti-clot treatment?.....							

Considering anti-clot treatment as a whole (that is, both the daily and occasional tasks), please consider the following.

3c. How complicated do you find your anti-clot treatment to be?.....	Check the appropriate box for questions 3c and 3h. "1=Not at all" "2=A little" "3=Somewhat" "4=Moderately" "5=Quite a bit" "6=A lot" or "7=Very much" Only check one response for each question.
3d. How time-consuming do you find your anti-clot treatment to be?.....	
3e. How frustrating do you find your anti-clot treatment to be?.....	
3f. How painful do you find your anti-clot treatment to be?.....	
3g. Overall, how much of a burden do you find your anti-clot treatment to be?.....	
3h. Overall, how confident are you about handling your anti-clot treatment?.....	

No additional instructions given for this page. Please continue to the next page.

Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

DUKE ANTICOAGULATION SATISFACTION SURVEY (DASS)

These last questions ask what you know and feel about your anti-clot treatment.

		Not at all	A little	Some-what	Moder-ately	Quite a bit	A lot	Very much
4a.	How well do you feel that you understand the medical reason for your anti-clot treatment?							
4b.	How much do you feel reassured because of your anti-clot treatment?							
4c.	How much do you worry about bleeding and bruising?							
4d.	Overall, how much has anti-clot treatment had a positive impact on your life?							
4e.	Overall, how much has anti-clot treatment had a negative impact on your life?							
4f.	Overall, how satisfied are you with your anti-clot treatment?							
4g.	Compared with other treatments you have had, how difficult is your anti-clot treatment to manage?							
4h.	How likely would you be to recommend this form of anti-clot treatment to someone else with your disease or medical condition?							

Check the appropriate box for questions 4a and 4h based on the participant's response.

"1=Not at all"
"2=A little"
"3=Somewhat"
"4=Moderately"
"5=Quite a bit"
"6=A lot" or
"7=Very much"

Only check one response for each question.

Research Coordinator: Please check the appropriate box to indicate who completed the CRF.

☐1 Participant ☐2 Interviewer ☐3 Both

No additional instructions given for this page. Please continue to the next page.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

MODIFIED MORISKY SCALE (*MMS*)

1. Do you ever forget to take your medicine? .....
2. Are you careless at times about taking your medicine? .....
3. When you feel better do you sometimes stop taking your medicine? .....
4. Sometimes if you feel worse when you take your medicine, do you stop taking it? .....
5. Do you know the long-term benefit of taking your medicine as told to you by your doctor or pharmacist? .....
6. Sometimes do you forget to refill your prescription medicine on time? .....

Check the appropriate box for questions 1 through 6.
"1=Yes" or
"0=No"

Research Coordinator: Please check the appropriate box to indicate who completed the CRF.

"1=Participant" "2=Interviewer" "3=Both"

[MMS] MODIFIED MORISKY SCALE (MMS):

MMS is a brief, self-reported, 6-item adherence scale questionnaire. It is completed by the participant and is an indicator of motivation and knowledge. Each item requires a "Yes" or "No" response.

In rare instances when the participant is not on any concomitant medication, MMS can be skipped.

Interviewer type: The information in the shaded box is completed by the RC after the participant returns the CRF. MMS is a self-reported questionnaire and the participant is expected to complete the questionnaire. If it is completed with significant assistance from the interviewer, the RC will check the appropriate box at the end of the questionnaire.

MMS is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

EARLY WARFARIN STOP

[Completed by the Clinical Center Principal Investigator]

1. Did the participant permanently discontinue warfarin treatment (*prior to Visit 12*)?

Check the appropriate box "1=Yes" or "0=No"

2. Date when last took warfarin:

Record date in format mm/dd/yyyy

3. Indicate last COAG study visit completed:

Record last visit completed

4. Check reason(s) for permanently discontinuing warfarin treatment prior to week 12 visit (*check all that apply*):

Indicate all reasons a participant did not complete protocol as specified

- If AE indicated, record the number associated with the AE from the AE form
- If "Specify" indicated, record reason (maximum 500 characters)

5. Did the participant stop warfarin treatment due to participation in the blinded dosing trial?

Check the appropriate box "1=Yes" or "0=No"

a. If yes, specify: Record reason (maximum 500 characters)

6. Is the participant willing to continue with study visits without warfarin treatment?

Check the appropriate box "1=Yes" or "0=No"

*If no, complete the Study Stop and Close-Out (**SSTOP**) CRF.*

Additional Comments: _____

_____Record additional comments (maximum 500 characters)

[WSTOP] EARLY WARFARIN STOP:

Early Warfarin Stop (**WSTOP**) CRF is used to obtain pertinent data in the event the participant chooses to discontinue warfarin therapy prior to the 6 month visit (visit 12). The CRF is completed by the clinical center Principal Investigator (PI).

This discontinuation may occur due to a personal choice or a clinical determination. The participant may choose to terminate the use of warfarin during the initiation, titration or maintenance phase of the study. It may also be a judgment made by the participant's healthcare provider upon assessing his/her health, e.g. an adverse event, medical condition that makes taking warfarin prohibitive.

WSTOP is completed on an as-needed basis (PRN).

Q. 1: This question confirms that a decision has been made to terminate warfarin therapy for the participant prior to the last visit of the study at 6 months/Visit 12 and the "Yes" box is checked. As a "PRN" CRF, the expected response in question 1 is "Yes".

Q. 2: The participant should provide the date when he/she last took the study generated dose of warfarin during the initiation or titration phase or a clinician prescribed dose during the maintenance phase.

A completed visit is one in which more than 50 percent of the expected study data for the visit was obtained from the participant. The date is entered in the mm/dd/yyyy format.

Q. 3: This item refers to the last study visit completed by the participant prior to discontinuing warfarin therapy.

Q. 4: This item provides reasons for stopping warfarin use and multiple responses are acceptable. Clarification is required with each response in the form of space provided for text entries. If an adverse event is the reason for stopping warfarin, space is provided for an AE number which proves a cross-reference to the Adverse Events (AE) CRF.

Q 5: Response to this item in terms of early termination may provide an insight into the use of blinded dosing and how well the clinicians and the participants accept the concept, and if blinded dosing can interfere in maintaining participant interest.

Q. 6: A participant may discontinue warfarin therapy but may choose to continue with study visits. The information provided by the participant by continuing to the end is vital and without being coercive, participants must be encouraged to keep up with the scheduled visits.

If the participant decides not to continue with the study visits, the RC must complete the Study Stop and Close-Out (**SSTOP**) CRF.

Space is provided at the bottom of the page to add comments on the termination of warfarin therapy.

WSTOP is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	Participant Initials:	Clinical Center:
Visit Date:	Visit Number:	CRC Initials:

STUDY STOP AND CLOSE-OUT

1. Did the participant successfully complete the COAG study (*through Visit 12*)?

Check the appropriate box "1=Yes" or "0=No"

a. If no, check reason(s) for early withdrawal (*check all that apply*):

Indicate all reasons a participant did not complete protocol as specified

- If AE indicated, record the number associated with the AE from the AE form
- If "Specify" indicated, record reason (maximum 500 characters)

b. Indicate last COAG study visit completed:

Record last visit completed

c. Date last COAG study visit completed:

Record date in format mm/dd/yyyy

2. Principal Investigator comments (*optional*):

Enter Principal Investigator comments (maximum 500 characters)

[SSTOP] STUDY STOP:

By completing the Study Stop and Close-Out (**SSTOP**) CRF, the RC indicates that the participant is no longer actively participating in the study. This CRF can be completed at the end of the study, Visit 12 or if a participant decides to terminate participation prematurely, at any point in the study. The decision can be made by the participant or his/her healthcare provider to terminate the participant permanently. Unlike WSTOP, this CRF is completed on all participants.

This CRF is completed by the Clinical Center Principal Investigator (PI) and the Research Coordinator (RC). A signature by the PI and the RC additionally signifies that the study was conducted per the protocol and the established guidelines provided in the Manual of Procedures (MOP).

An early termination may be a personal choice or a clinical judgment and the decision must be respected by the study personnel.

Q. 1: The response to this item may be a "Yes" for a participant who completed the scheduled visits to the end of the study (Visit 12). The response may be "No" if the participant decides to end participation prior to the end of the study.

Q. 1a: This item provides reasons for ending participation. The reasons are identical to the ones on the WSTOP form. Clarification is required with each response in the form of space provided for text entries. If an adverse event is the reason for stopping warfarin, space is provided for an AE number which proves a cross-reference to the Adverse Events (AE) CRF.

Q. 1b: This item refers to the last study visit completed by the participant prior to termination.

Q. 1c: The participant should provide the date when he/she completed the last study visit.

A completed visit is one in which more than 50 percent of the expected study data for the visit was obtained from the participant. The date is entered in the mm/dd/yyyy format.

Comments: Space is provided at the bottom of the page for the Clinical Center PI to add comments.

SSTOP is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

STUDY STOP AND CLOSE-OUT

SIGNATURES:

I verify that all information collected on the ***COAG*** study CRFs for this participant is correct to the best of my knowledge and was collected in accordance with the procedures outlined in the COAG study protocol and Manual of Procedures (***MOP***).

3. Principal Investigator signature:

Check the appropriate box "1=Yes" or "0=No"
Principal Investigator sign here to verify all data are accurate _____ Enter date in the mm/dd/yyyy format

4. Research Coordinator signature:

Check the appropriate box "1=Yes" or "0=No"
Research Coordinator sign here to verify all data are accurate _____ Enter date in the mm/dd/yyyy format

No additional instructions given for this page. Please continue to the next page.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

UNBLINDING

*If unblinding involves discontinuation of warfarin treatment, complete Early Warfarin Stop (**WSTOP**) CRF.*

1. Type of unblinding:

   a. Dose

   Check the appropriate box "1=Yes" or "0=No"

   b. Randomization

   Check the appropriate box "1=Yes" or "0=No"

2. Date of unblinding:

   Record the date in mm/dd/yyyy format

3. Reason(s) for unblinding (*check all that apply*):

   Indicate all reasons a participant was unblended:

   - If AE indicated, record the number associated with the AE from the AE form
   - If "Specify" indicated, record reason (maximum 500 characters)

4. Person requesting unblinding:

   Check **only** one response

   Enter either 1,2,3 or 98
   If "Other, specify " Record reason (maximum 500 characters)

   a. If someone other than the Principal Investigator (*PI*) requested unblinding, was the PI contacted prior to unblinding?

   Check the appropriate box "1=Yes" or "0=No"

[UNBLIND] UNBLINDING:

Request for unblinding in the COAG study may be for the blinded warfarin dose or the randomization to one of the 2 treatment arms. A request is not expected for unblinding of the randomization since the information that is revealed is not likely to reverse a potentially serious medical condition, whereas it is expected that the Medical Monitor will receive requests for unblinding of the blinded dose in the event of a reported serious medical condition.

Unblinding may be requested when a clinician cannot effectively assess or treat a participant's medical condition. Unblinding can be initiated by the AC clinician who contacts the Clinical Center RC and/or the PI. It may also be requested by a healthcare provider outside of the research environment when the participant provides contact information. It requires the RC to contact the Medical Monitor who would have access to the last calculated dose generated by the data management system and the last blinded dose dispensed by the research pharmacy. The Medical Monitor will evaluate the request and make the determination if unblinding is warranted.

Typically, the Medical Monitor will reveal the dose to the site PI, who then contacts the treating clinician. If the request is from a non-study source, the Medical Monitor will also inform the Clinical Center RC and PI of the blinded dose. It is the responsibility of the RC to complete the **UNBLIND** CRF once the unblinding process is completed.

The participant may continue on warfarin therapy after the unblinding and maintain the scheduled study visits and all study processes are reinstated, except blinded dosing. If warfarin therapy is discontinued and the participant maintains his/her study visits, the RC must complete **WSTOP**. If the participant chooses to terminate participation in the study, the RC must complete the **SSTOP** form.

Q. 1a-b: This item identifies the type of unblinding that is requested when contacting the Medical Monitor.

Q. 2: The date when the process of unblinding is initiated and the medical monitor is contacted is recorded in the mm/dd/yyyy format.

Q. 3: The reasons for unblinding are indicated by checking the appropriate boxes. Multiple reasons may be checked for this item. Space is provided to note additional information related to the reason(s) for unblinding. If an adverse event is the reason for unblinding, the AE number provides a cross-reference to the information on the Adverse Events (AE) CRF.

Q. 4: Unblinding is expected to be a team effort involving communication between the Medical Monitor and the person(s) requesting the unblinding. If the request is from a source other than the RC or the PI, they should soon be drawn into the process to make it smooth and efficient. If the "Other" box is checked, the person should be identified.

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

UNBLINDING

5. Was the medical monitor (*or designee*) contacted?

Check the appropriate box "1=Yes", "0=No", or "99=N/A (*if medical monitor requests unblinding*)

a. If no, specify reason for not contacting the medical monitor:

Record reason (maximum 500 characters)

b. If no, the person who assisted with unblinding:

Record name (maximum 500 characters)

6. Person contacted at the site's Investigation Drug Service (*IDS*):

Record name (maximum 500 characters)

7. Additional comments on the event that led to the unblinding request:

Record comments (maximum 500 characters)

8. Principal Investigator signature and date:

Principal Investigator signs here

Enter date in the mm/dd/yyyy format

Q. 5: Most unblindings will occur with the involvement of the Medical Monitor. Occasionally, in an emergent situation, the Medical Monitor may not be contacted and an appropriate box should be checked and additional information should be included in the space that is provided and the person assisiting in the unblinding should be identified.

Q. 6: The space is provided to write in the name of the research pharmacist or designee who is contacted to assist with the unblinding.

Q. 7: Any additional information that is relevant to understand the process leading up to unblinding may be noted in the space that is available.

PI signature: The Clinical Center PI is ultimately responsible for the unblinding process and should attest to the veracity of the information that is provided in the CRF by signing the document.

UNBLIND is a data CRF and must be single data entered in the data management system (DMS).

Participant ID:	**Participant Initials:**	**Clinical Center:**
Visit Date:	**Visit Number:**	**CRC Initials:**

COAG CONSENT

Agreement to participate in the COAG study:

1. Participant agrees to participate in the COAG study, which includes the use of genetics data and measurements of other factors in the blood to study response to warfarin dosing:	Check the appropriate box for question 1. "1=Yes" or "0=No". This question must be "1=Yes" for the participant to be eligible.
2. Participant agrees to allow the COAG study to notify the participant about genetic conditions that may have potentially important meaning for his/her health and treatment:	Check the appropriate box for questions 2 through 4. "1=Yes" or "0=No".
3. Participant agrees to allow the COAG study to notify the participant's physician about genetic conditions that may have potentially important meaning for the participant's health and treatment:	
4. Participant gives permission to study genetics and other biological factors for other health conditions:	

Agreement for future use of COAG blood sample and information collected in the COAG study:

5. Participant agrees to give permission to study his/her genetics and other biological factors for other health conditions besides response to warfarin therapy:	Check the appropriate box for questions 5 through 8. "1=Yes" or "0=No".
6. Participant agrees to allow future studies to make genetic and other information available on a controlled access website to approved researchers: ..... [*Such information cannot be used to identify the participant; permission is given to have coded genetic information and coded medical information placed in a special database for use only by approved researchers.*]	
7. Participant agrees to allow researchers from private companies to have access to DNA and genetic data which may be used to develop laboratory tests or pharmaceutical therapies that could benefit other people:	
8. Participant gives permission to be contacted in the future to see if he/she is willing to provide additional biological samples or follow-up information about his/her health or medical care:	

[COAGCONS] COAG CONSENT:

COAGCONS is completed by the RC. It is based on the participant's responses on the informed consent to the use of specimen for genotyping for the study and other current and future uses. This form is completed on participants who agree to participate in the study, are randomized and have their blood drawn.

Items 1-4 refer to the agreement to participate in the COAG study. Items 5-8 refer to the agreement for future use of COAG blood specimen and information collected in the COAG study.

Q. 1: As an enrolled participant, the response to this item is expected to be "Yes".

Qs. 2-8: The participant may or may not wish to consent to these items; therefore responses may be "Yes" or "No".

COAGCONS is a data CRF and must be single data entered in the data management system (DMS).

PARTICIPANT ID LOG

ADD CCID – CLINICAL CENTER

PID #	Participant name (first, middle, last)	Medical records number	Recruitment site 1 = Inpatient 0 = Outpatient	Participant status 1 = Eligible 2 = Ineligible 3 = Refused	If eligible, randomized? 1 = Yes 0 = No
101001					
101002					
101003					
101004					
101005					
101006					
101007					
101008					
101009					
101010					
101011					
101012					
101013					
101014					
101015					

[PIDLOG] PARTICIPANT ID LOG:

Each Clinical Center is provided with a Participant ID LOG (**PIDLOG**) with 500 Clinical Center-specific PIDs that are generated by the CTCC. If additional PIDs are needed, the RC may add the PIDs or contact the CTCC. The information on the PILOG identifies the participant by connecting the name with the numerical research identifier in the form of a PID, hence a system must be put in place at the Clinical Center to secure and protect the information.

The information on the document is maintained in the form of a log with each line representing one participant. In addition to the name, the participant's institution-based medical record number is registered. The location of recruitment (inpatient or outpatient), eligibility information (eligible, ineligible or refused participation) and randomization information is coded as well. This helps the RC track each potential participant in the study. Legend is provided at the top of each column to assist with coding the information.

Each consented participant is assigned a PID and a PID once assigned cannot be re-used. A consented participant may not qualify or though eligible and randomized, may subsequently refuse participation, yet the information is maintained for the participant on the PIDLOG.

PIDLOG is an administrative log and the data is not entered in the data management system.

Participant ID: _____ **Participant Initials:** _____ **Clinical Center:** ____

Visit Date: _____ **Visit Number:** ____ **CRC Initials:** _____

PARTICIPANT CONTACT INFORMATION

[Administrative CRF]

Name: _____

Known by any other names: _____

Address: _____

_____

Daytime phone: (_____) _____ _____ ☐ Work ☐ Home

Evening phone: (_____) _____ _____ ☐ Work ☐ Home

Permission given to call at work: ☐ Yes ☐ No

Cell phone: (_____) _____ _____

Email address: _____

Mailing Address, if different: _____

_____

Other Contacts (name and address of relatives/friends in the event the participant cannot be contacted directly):

Name 1: _____

Address: _____

_____

Phone number: (_____) _____ _____ ☐ Work ☐ Home ☐ Cell

Preferred time to call: __ __ : __ __ ☐ am ☐ pm

Relationship to you: _____

Name 2: _____

Address: _____

_____

Phone number: (_____) _____ _____ ☐ Work ☐ Home ☐ Cell

Preferred time to call: __ __ : __ __ ☐ am ☐ pm

Relationship to you: _____

[PTCONT] PARTICIPANT CONTACT INFORMATION:

This is an administrative CRF that is completed by the Research Coordinator at the baseline visit and updated at each subsequent visit. As an administrative CRF, the information on this CRF is not data entered in the data management system.

The information obtained from the participant for **PTCONT** is of a personal nature connecting the Participant ID to a name and should be maintained separately from the research chart.

The information collected for this CRF will help locate the participant through more than one mode (e.g. home and cell phone, e-mail) and more than one contact person (friends or relatives).

PTCONT is an administrative CRF and is not entered in the data management system (DMS).

Participant ID: _____ Participant Initials: _____ Clinical Center: ____

Visit Date: _____ Visit Number: ____ CRC Initials: _____

DATA PROCESSING COVER SHEET

[Administrative CRF]

Visits	Data review / initials	First entry / initials	Second entry / initials
Visit 1 - Screening and baseline visit.....	☐ _____	☐ _____	☐ _____
Visit 2 – Day 4 / month 1, week 1.....	☐ _____	☐ _____	
Visit 3 – Day 7 / month 1, week 1.....	☐ _____	☐ _____	
Visit 4 – Day A / month 1, week 2.....	☐ _____	☐ _____	
Visit 5 – Day B / month 1, week 2.....	☐ _____	☐ _____	
Visit 6 – Month 1, week 3.....	☐ _____	☐ _____	
Visit 7 – Month 1, week 4.....	☐ _____	☐ _____	
Visit 8 – Month 2.....	☐ _____	☐ _____	
Visit 9 – Month 3.....	☐ _____	☐ _____	
Visit 10 – Month 4.....	☐ _____	☐ _____	
Visit 11 – Month 5.....	☐ _____	☐ _____	
Visit 12 - Month 6.....	☐ _____	☐ _____	

Comments:

V1.0.20090720 Page 1 of 1 DPCS

[DPCS] DATA PROCESSING COVER SHEET:

The Data Processing Cover Sheet (**DPCS**) is an administrative tool to organize the process of data review and entry after the RC completes a visit. It may be visit-specific or it may be participant-specific.

To assure the quality of the data that is collected at a visit, each Clinical Center should introduce a process to review the data. Once reviewed, a check in the box and initials in the space that is provided, indicates that the data is ready for data entry. The same process is applied to data entry.

Majority of the CRFs are single entry but the 5 critical CRFs at the baseline visit are double data entered and the columns reflect the entry status.

DPCS is an administrative CRF and is not entered in the data management system (DMS).

Participant ID: _____ Participant Initials: _____ Clinical Center: ____

Visit Date: _____ Visit Number: ____ CRC Initials: _____

COMMENTS SHEET

[Administrative CRF]

Visit #/CRF Question	Comment

[COMMENT] COMMENTS SHEET:

COMM is an administrative CRF with multiple uses. As an administrative CRF, the information on this CRF is not data entered in the data management system.

When attached to a CRF, it may be used to explain certain participant responses that are likely to be queried by the SDCC, or when attached to a visit packet, may provide explanation for circumstances outside of the standard flow of a visit.

COMM may be additionally used to note contact with the medical monitor and the outcome of the contact.

COMM is an administrative CRF and is not entered in the data management system (DMS).

8.C. Submission of Case Report Forms to the CTCC

The Clinical Data Management (CDM) division of the CTCC is responsible for monitoring all data associated processes. CDM may request copies of any completed case report form or visit packets for any COAG study participants at any time during the course of the study. Copies of case report forms could be requested for several reasons, including data auditing and case report form completion review.

If a request is made:

- The Clinical Center RC is responsible for making photocopies of all requested case report forms
- The original case report forms should remain in the participant's COAG study binder and the photocopies are sent to the CTCC
- All personal identifiers should be removed from the copies sent to the CTCC
- All multi-page case report forms should be stapled and the visit packet should be paper-clipped together
- Preferably, copies should be sent to the CTCC via overnight mail
- It is very important that response to requests be made as soon as possible, to ensure data quality

8.D. Data Quality Management Procedures

8.D.1. Queries:

Queries will be sent to the Research Coordinators in response to errors logged by the Data Management System when it views the verified data in the application against a set of rules written to validate the data. A query can also be generated by a manual review of the verified data against an expected set of data standards by the Data Management staff and the study biostatisticians at the CTCC.

8.D.2. Types of Queries Generated by the Database:

There are several types of queries that are generated by the Data Management System and sent to the Clinical Centers.

8.D.2.a) Missing Fields

Collected data should be reviewed for completeness at the Clinical Centers prior to entry and verification. A data field on a case report form that is left blank in the data table is logged as an error by the Data Management System and will be queried; e.g., if a medical history question was left blank, the Research Coordinator may inform the CTCC (in the same format as the query is sent by the CTCC) by e-mail of the missing field soon after the data is entered and verified or a query will be sent by the CTCC requesting the information.

If a query is sent to the Clinical Center, the Research Coordinator must attempt to find the correct response or provide an explanation for the missing data. An explanation is acceptable when a response is left blank for a reason. For example, the participant may have chosen to not respond to a question.

8.D.2.b) Skip Patterns

Skip patterns account for fields that should or should not be answered, depending on the response to the first question in the series. For example, "types of cancer" on **MEDHX** case report form should only be answered if participant was diagnosed with cancer. If "types of cancer" is coded and the participant has not been diagnosed with cancer, a query is sent because the field should be left blank. Conversely, if the participant was diagnosed with cancer and "types of cancer" has not been checked, a query is generated because the field should not be blank.

If a skip pattern query is sent to the Research Coordinator, and a change is warranted, the case report form should be updated with the correction, using the standard correction technique outlined earlier.

8.D.2.c) Range Checks

Many fields have a specific range of expected responses, which is designed to include approximately 95% of the population. For example, a participant's height has both a low range and a high range, and anything outside of those ranges may generate a query. The range check query is sent to confirm the value entered because it is higher/lower than the expected range.

The Research Coordinator should confirm data that is queried in his/her response to the CTCC or provide a correction to the data.

8.D.2.d) Logic Checks

These checks review the data to ensure the data is logical, e.g., men should respond "N/A" to female-oriented questions, and women should respond "N/A" to male oriented questions.

8.D.3. Types of Queries Generated by Manual Monitoring:

8.D.3.a) Monitoring Checks

These checks monitor the data for completeness and accuracy. Biostatisticians and Data Management staff at the CTCC manually view the data and queries are sent for data that look incomplete or appear to conflict with the design of the COAG study. The Research Coordinators should manage these queries in a similar manner as outlined above for the database-generated queries. If changes are necessary, a faxed or e-mailed response is expected. An explanation without data change, can be sent by e-mail. Types of monitoring queries include:

- Safety issues –**AE**, **CMED**, **EVENT**
- COAG Study Procedures – Withdrawals, Unblinding, Data Entry and Verification Status.

8.D.4. Managing Queries:

8.D.4.a) Receiving Queries from CDM

Queries are sent in an EXCEL spreadsheet via email, and contain the following information:

CC ID	CRF Date
Clinical Center	RC ID
Participant ID	Date Queried
Participant Initials	Description of the Problem
Visit Number	Resolution column
CRF Name	

8.D.5. Making Corrections Based on Queries:

- The Research Coordinator should print the spreadsheet e-mailed by the CTCC. At Clinical Centers with more than one Research Coordinator, the lead Research Coordinator will inform the CTCC at the start of the COAG study how they would like to receive the queries – whether one Research Coordinator at the Clinical Center receives all queries or the RC ID on the case report form determines who receives the queries.
- The Research Coordinator(s) is responsible for identifying the correction to be made or providing an explanation. CTCC Data Management staff is available to assist the Research Coordinators in resolution of the queries, if needed.
- If a query results in a correction, the correction must be included on the query and documented on the original case report form (initialed and dated).
- If it is determined that a correction is not needed, an explanation (e.g. participant's height is correct), should be documented on the query.
- All queries should be initialed, dated and filed with the participant's data binder.
- Any questions related to the queries should be directed to the originator of the query at the CTCC.

8.D.6. Query Response to the CTCC:

- Queries can be returned to the CTCC via email or fax. A copy of the response e-mailed or faxed to the CTCC is retained in the participant's COAG study binder.
- Explanations that do not require changes to the database are e-mailed to the CTCC, as well.
- The response to the query should be directed to the originator of the query at the CTCC.
- Original text must be "quoted" if responding to the query by email.
- A dedicated fax line [(215) 573-4790] is available at the CTCC to accept query responses and data sent from the Clinical Centers.

Responses to safety-related queries are expected at the CTCC in 3 working days. Responses to all other queries are expected at the CTCC in 5 working days.

9. DATA MANAGEMENT SYSTEM USERS GUIDE

9.A. Introduction

The data management system (***DMS***) is developed in accordance with the requirements of the **COAG** Project. The DMS is an Oracle-based application that utilizes java script. In order for users to connect to and run the DMS, it will be necessary to install the Oracle Jinitiator plug-in and security certificate. Updates are available at the following website: rt4.cceb.med.upenn.edu/crcu_html/jinit/jinit_download.htm.

This manual is developed as a reference guide for the data entry person on the project. To access the DMS, the user will need a computer with access to the internet through an internet browser. The DMS is used for entry of the data that is collected on the COAG CRFs. The data tables within the DMS are collectively labeled as the production database.

9.B. Oracle JInitiator

Before the data management system (DMS) is installed on a personal computer, two components need to be downloaded onto the computer first - Oracle JInitiator ver.1.3.1.22 and the SSL Certificate. The following instructions will guide the user through installation of these add-ons.

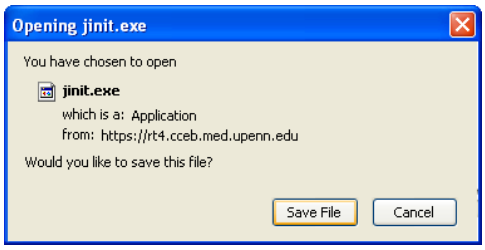
- Open a web browser: Internet Explorer (IE) 6.0 or FireFox 2.0 or higher or Netscape.
- Type in the following url:

https://rt4.cceb.med.upenn.edu/crcu_html/jinit/jinit_download.htm

The Oracle JInitiator version 1.3.1.22 must be loaded first.

- Click the highlighted link, “Download Oracle JInitiator 1.3.1.22”

A prompt will next confirm the file name and the location of the executable.



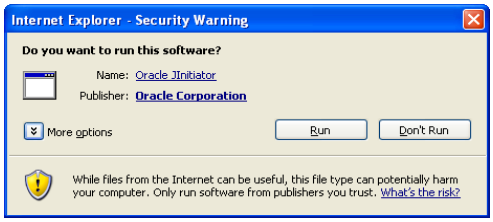
- Click the “Save File” button

The user will be prompted to run or save the self-extracting jinit.exe file.

- Click the “Save” button to save the file to the PC

Once this is done, JInitiator will begin the download.

The next window is a security warning about the download that is about to be loaded.



- Click the “Run” button

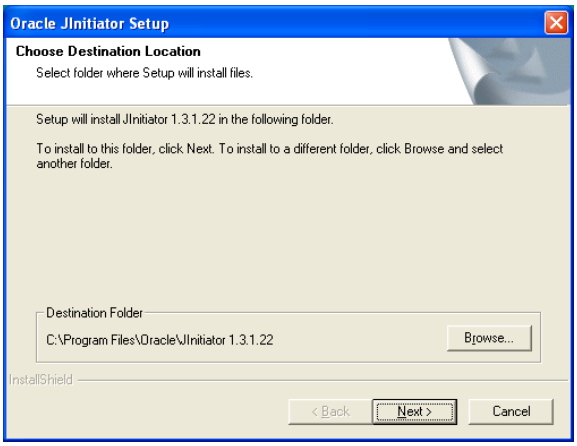
The installer will prompt the user for a destination location to save the file.

The default location the executable points to is C:\Program files\Oracle\JInitiator, on the hard drive of the PC.

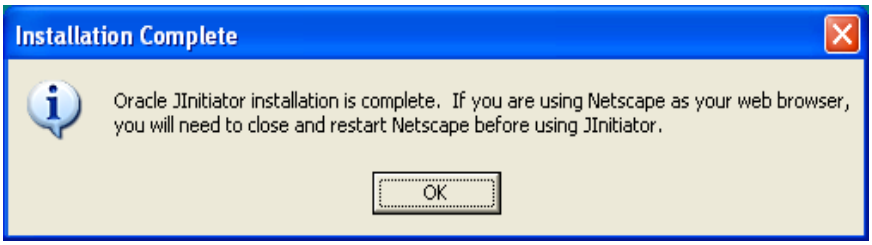
If this is the incorrect desired location for this file:

- Click the “Browse” button to choose a desired location to save this file on the PC.

If correct, click the “Next” button to continue the installation.



Once the installation is complete, the following window will appear:

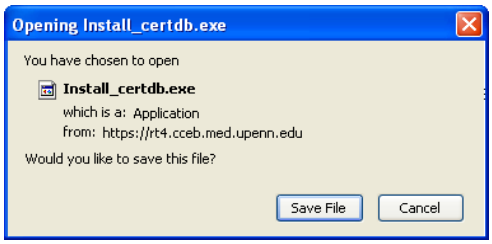


Note: If using the Internet Explorer browser or FireFox browser, it is not necessary to close and restart the browser, but if using the Netscape web browser, the user will need to close and restart the browser before using JInitiator.

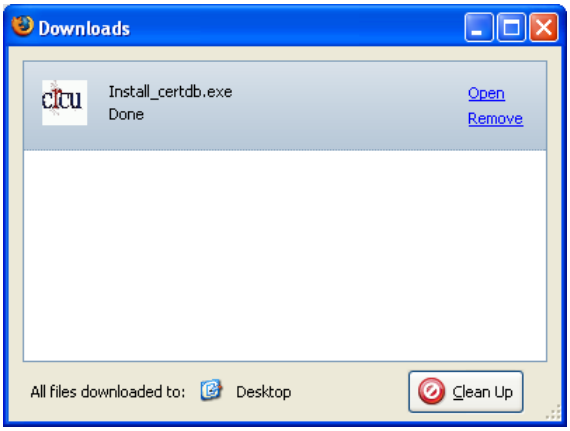
9.C. SSL Certificate:

Once the Oracle JInitiator executable is loaded onto the PC:

- Click the second plug-in, the SSL Certificate called, ”Certificate Installer”
- Once the link is chosen, the following window will appear:

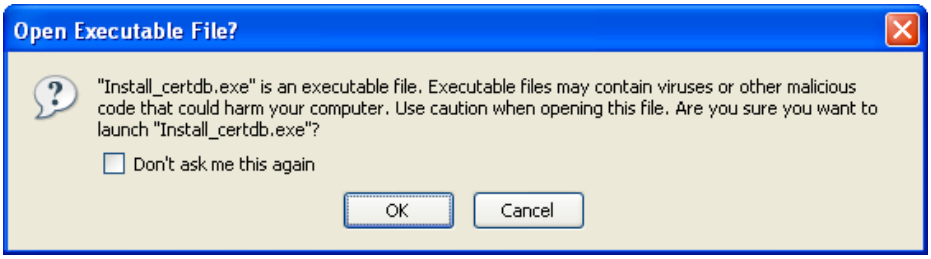


- When downloading this or any file, a separate window will open exclusive to download content.



- Select “Open” to begin the downloading process.

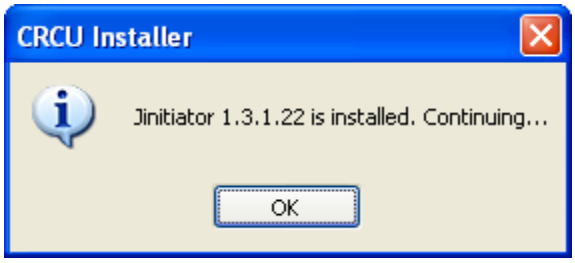
The next screen illustrates a security function that provides caution to downloading executable files that may contain viruses or other malicious code(s) that could harm the computer.



- Click “OK” to proceed with the installation

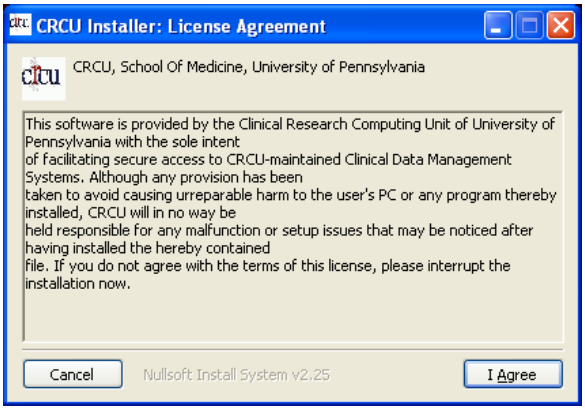
This window advises the user that the installation of the CERTDB.TXT file will begin.

- Click “Yes” to continue



- Click “OK” to continue with the installation

Once the License agreement is reviewed:



- Click “I Agree” to continue installation

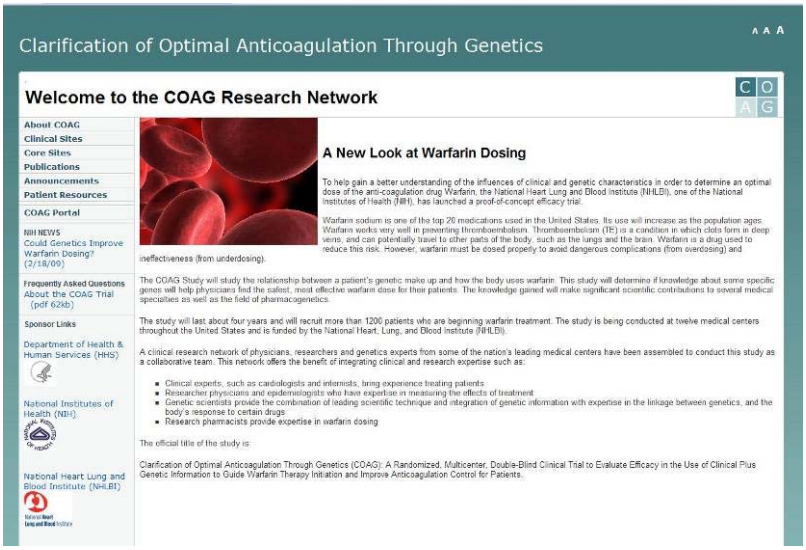
Setup will provide a prompt that indicates the location for the installation to be downloaded. There is an option to choose a different location to save the certificate.

9.D. Data Management System Web Site:

Connect to the Internet, run a web browser (Internet Explorer 6-8 and Mozilla Firefox 2-3 are supported at this time) and connect to COAG study portal

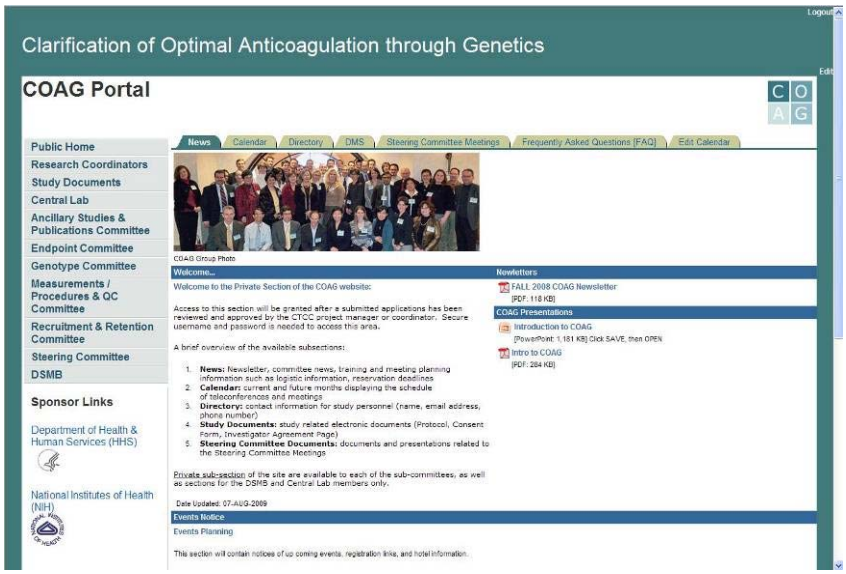
http://www.coagstudy.org

The portal main page will be displayed



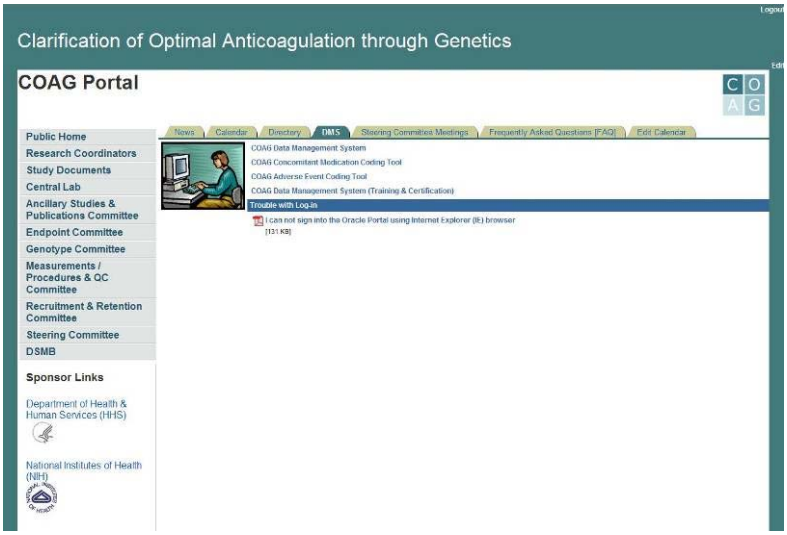
Click on the "**COAG Portal**" link and you'll be prompted to enter your portal credentials (emailed to you by the COAG study coordinator)

Click "**Login**" and the portal main internal page will be displayed



Click on the "**DMS**" tab

The DMS page will be displayed.



To access the Production DMS, click on the "**COAG Data Management System**" link.

To access the Training DMS, click on the "**COAG Data Management System (Training & Certification)**".

In both cases, if you have correctly installed all the software described in section 9.B and 9.C, you should get the DMS login screen.

In case you have trouble logging to the DMS through the portal, and the solutions provided by the COAG coordinator in the email containing your account credentials do not work, you can access the production DMS directly, via the following web address:

https://rt4.cceb.med.upenn.edu/crcu_html/COAG1.htm.

We do not recommend you save the above address in your browser's "Favorites" or Bookmarks, since it is non-published address, and could be subject to changes during the study.

Should you have problem executing and of the above steps, please contact COAG Help Desk Support. See section 10.A for details on how to contact the Help Desk.

9.E. COAG -- MAIN MENU

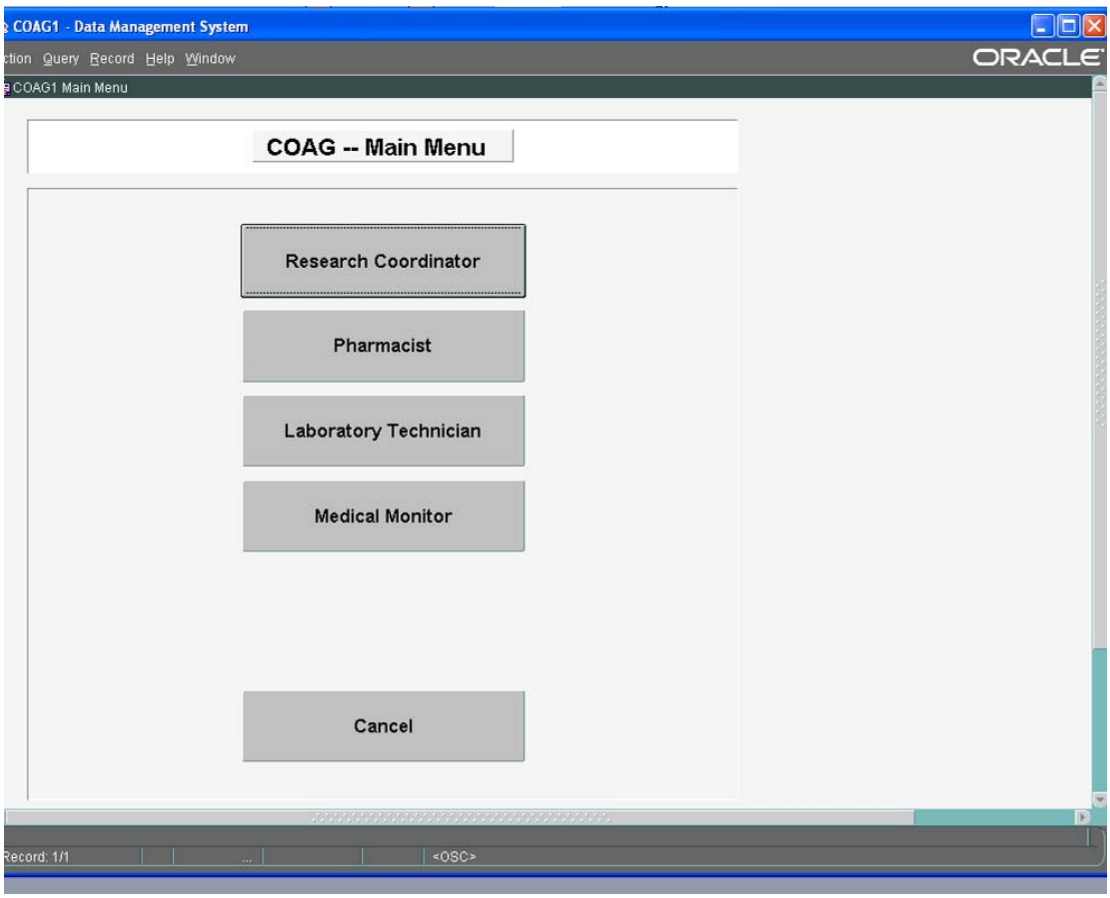
Once you have successfully navigated to the Data Management System (DMS) web site, you will first be presented with the Main Menu screen. The Main Menu is used to navigate to the appropriate module of the DMS.

The COAG main menu contains a set of buttons that will provide the user access to data entry modules. The privileges provided to the user will determine the functions available in the DMS.

The function buttons available are:

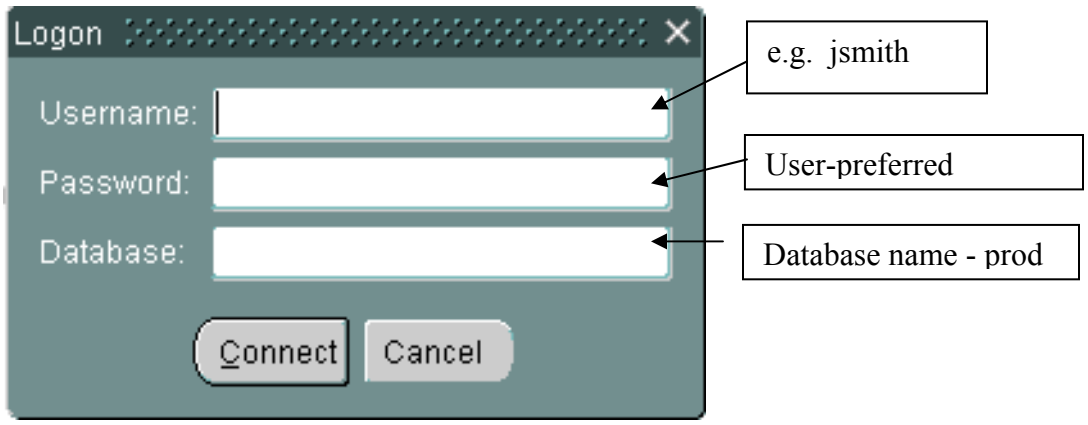
- Research Coordinator: data entry of visit forms, continuous logs, and dosing requests
- Pharmacist: view calculated dose and enter dispensed dose
- Laboratory Technician: data enter genotyping data at the local and central laboratories
- Medical Monitor: accesses all modules

Click on the button that represents your position on the study.



9.F. Data Management System log in:

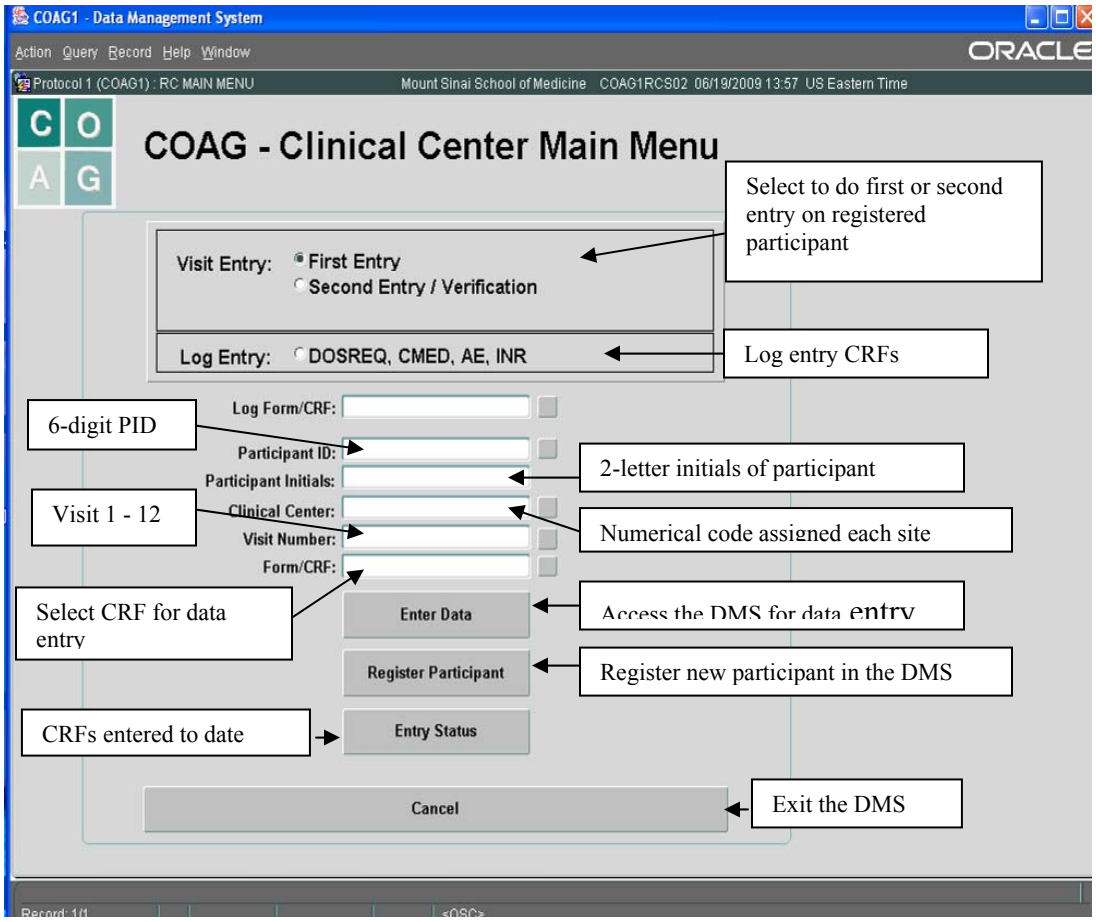
- Enter requested log-in information in the dialog box
  - Username - the first initial and last name, limited to 8 characters
  - Password - for the first time user a temporary password – "temp01" - is provided; a prompt will request the user to create a new password that is easily remembered for future log-ins
  - Database - 'PROD'; will give the user access to the COAG database



- Click on the "Connect" button to access the main menu of the Data Management System

9.G. COAG – Clinical Center Main Menu – For Research Coordinators

- Click on the RESEARCH COORDINATOR button
- The COAG Clinical Center Main Menu appears



The Clinical Center Main Menu allows the Research Coordinator to access different functions within their module.

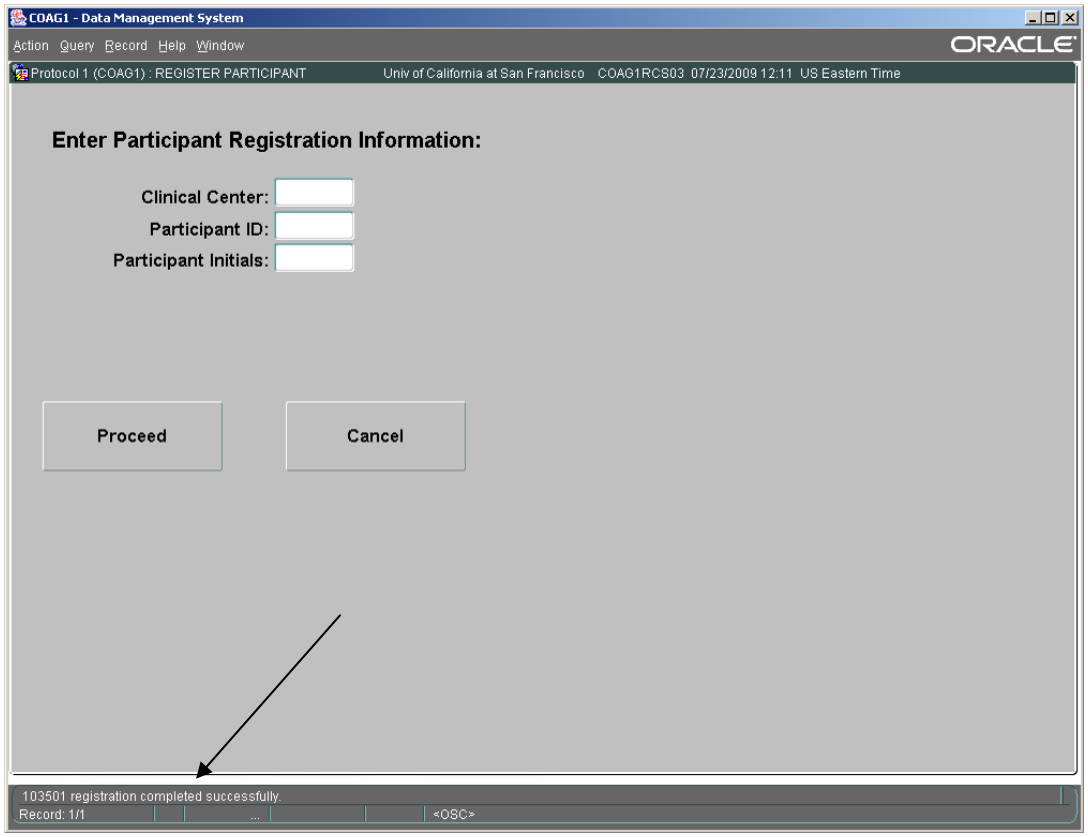
The following are functions available:

- Register Patient - new patients must be registered in the DMS before any data entry can proceed
- Enter Data – selection of CRF-related data screen for data entry
- Entry Status - view all data that has been entered to-date

9.H. Participant Registration:

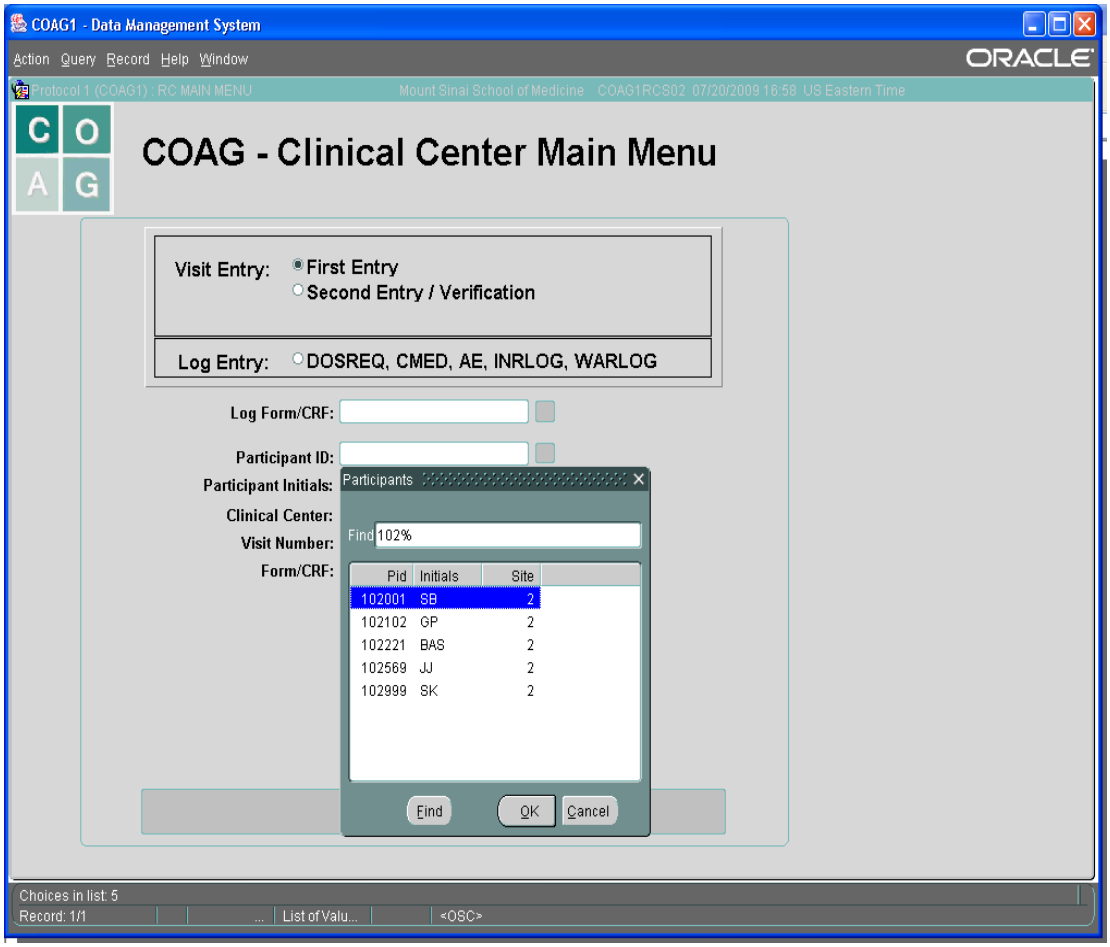
To begin data entry, a participant's information must be registered into the database. The "Register Patient" button provides access to this module. The data management system requires re-entry (verification) of the registration to ensure accuracy of the information entered.

- From the COAG Clinical Center Main Menu, select "Register Patient"
- Type in the Clinical Center, the Participant ID and the Participant Initials in the appropriate spaces
- Click "Proceed" to save the data
- Retype the above information on the verify screen (second registration screen). Information that is re-typed must match the original input in order to register the participant. If it does not match, the user will get an error message that takes him/her back to the first registration screen so any changes can be made.
- Click the Register button and a message will appear in the lower left corner of the screen stating that the PID you just registered was registered successfully.
- Multiple participants can be registered
- When registration of participants is complete, click "Cancel" to return to the COAG Clinical Center Main Menu.

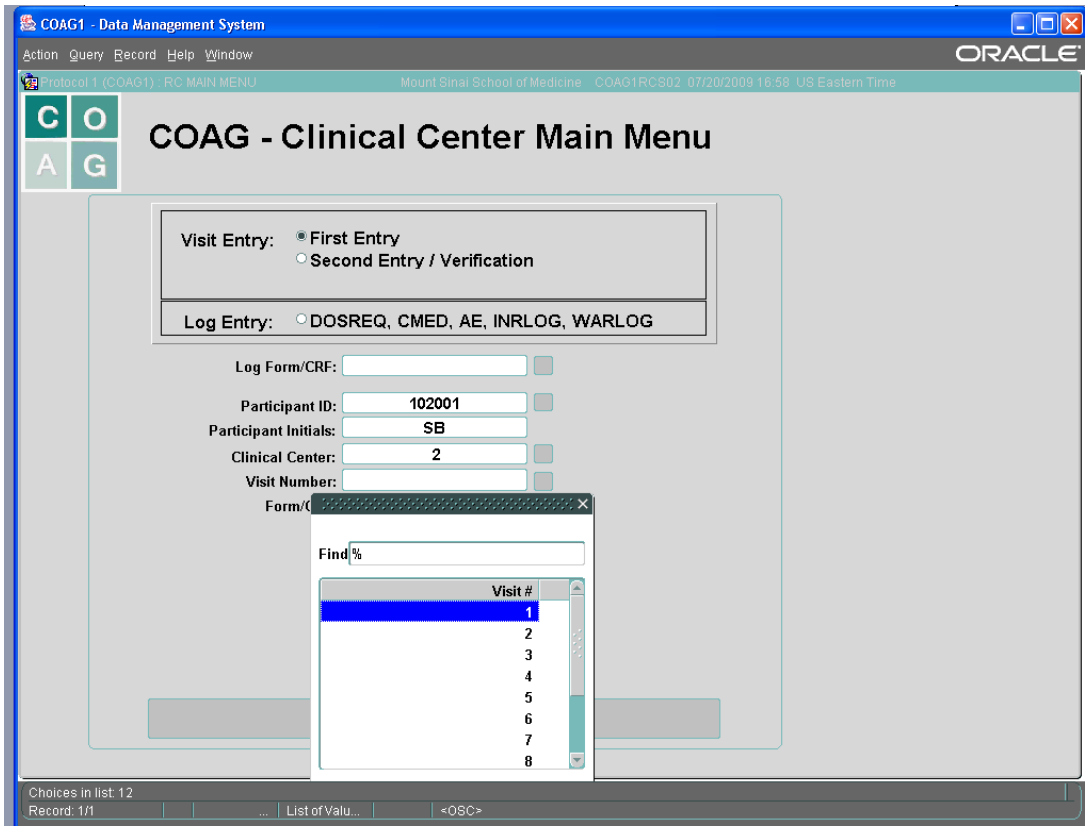


9.I. Visit Entry – First Entry

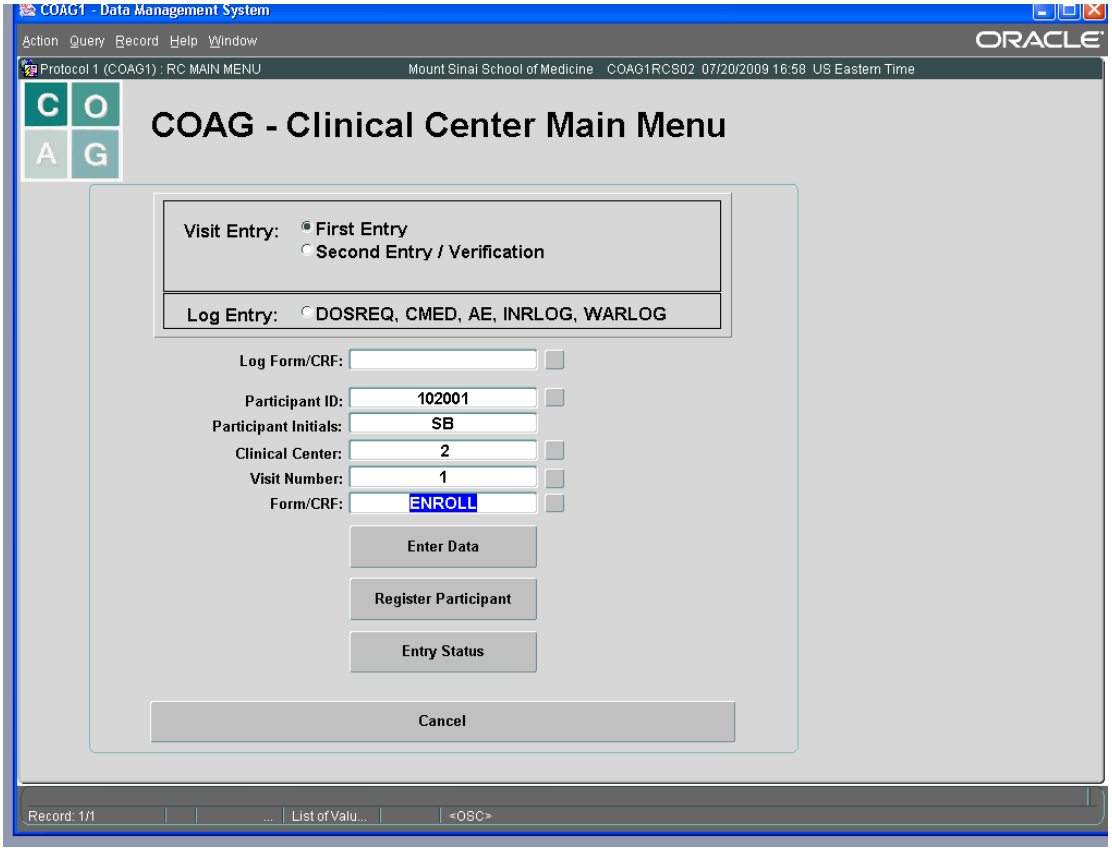
- Select "First Entry"
- Select the PID from the drop box or type it in. The Participant Initials and Clinical Center will automatically populate if you select from the drop box.
- If you type in the Participant ID, you will have to type in the Participant initials and Clinical Center. This is to ensure that you enter data on the correct participant.



- Select the visit number from the drop box or type it in

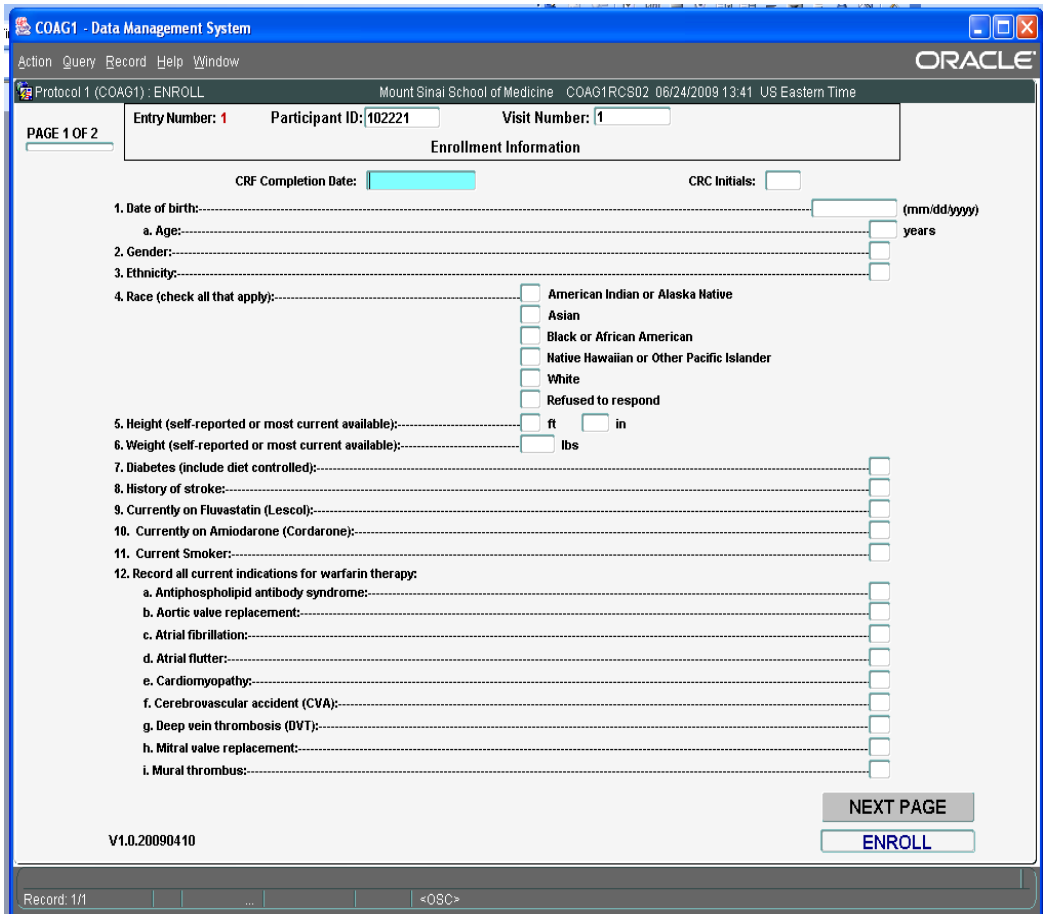


- Select the CRF name from the drop box or type it in. The CRF name is the abbreviated name located in the lower right corner of every form.
- Click “Enter Data” button

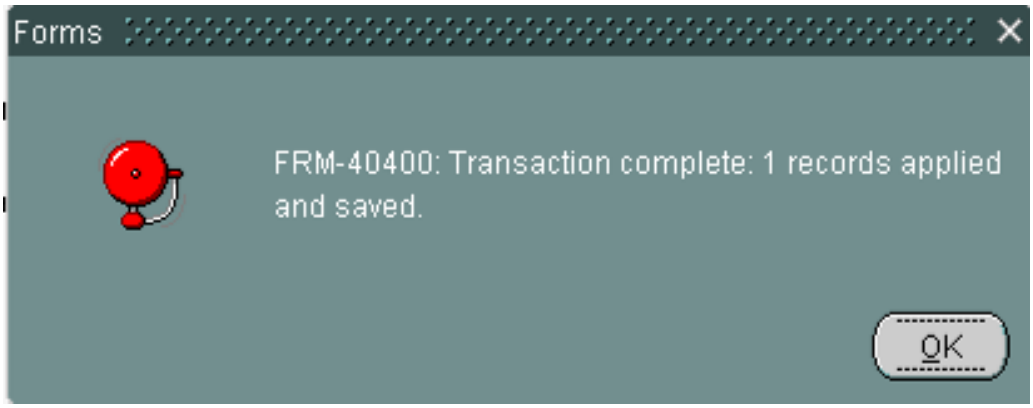


When entering a CRF:

- PID and Visit number will automatically populate
- Type in the CRF Completion Date (Visit Date from the CRF) in mm/dd/yyyy format
- Type in the CRC initials – these are the initials of the person who conducted the interview
- Enter data as collected on the COAG CRF using the tab or enter key to navigate through the screen. For the ENROLL, ELIG, and RAND forms, all fields must have a value in order to continue to the next field.
- For CRFs with multiple pages, click on “Next Page” or when the cursor is in the last field on the data entry screen hit tab or enter.



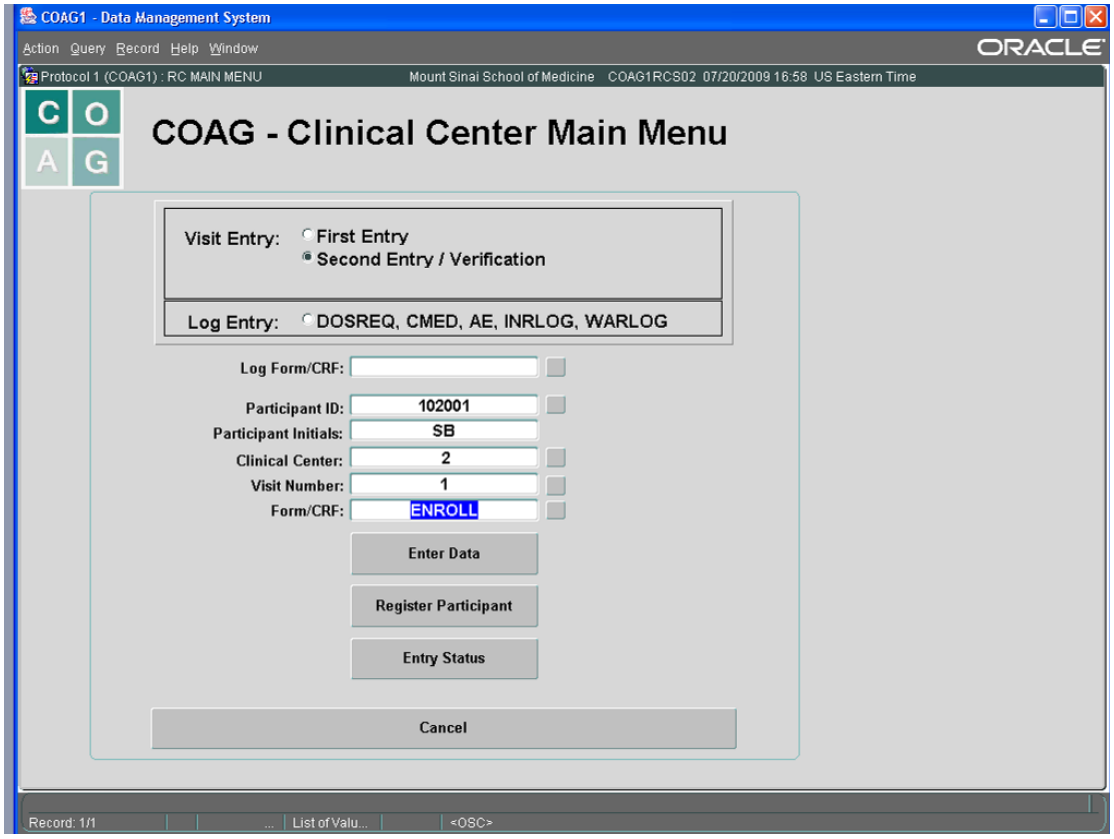
- When data entry is complete, click on “Save Data”
- A dialog box informs the user that the data is successfully saved



- Click the “Ok” button to return to the COAG Clinical Center Main Menu
- Second entry on the ENROLL and ELIG forms must be completed immediately before continuing any data entry.

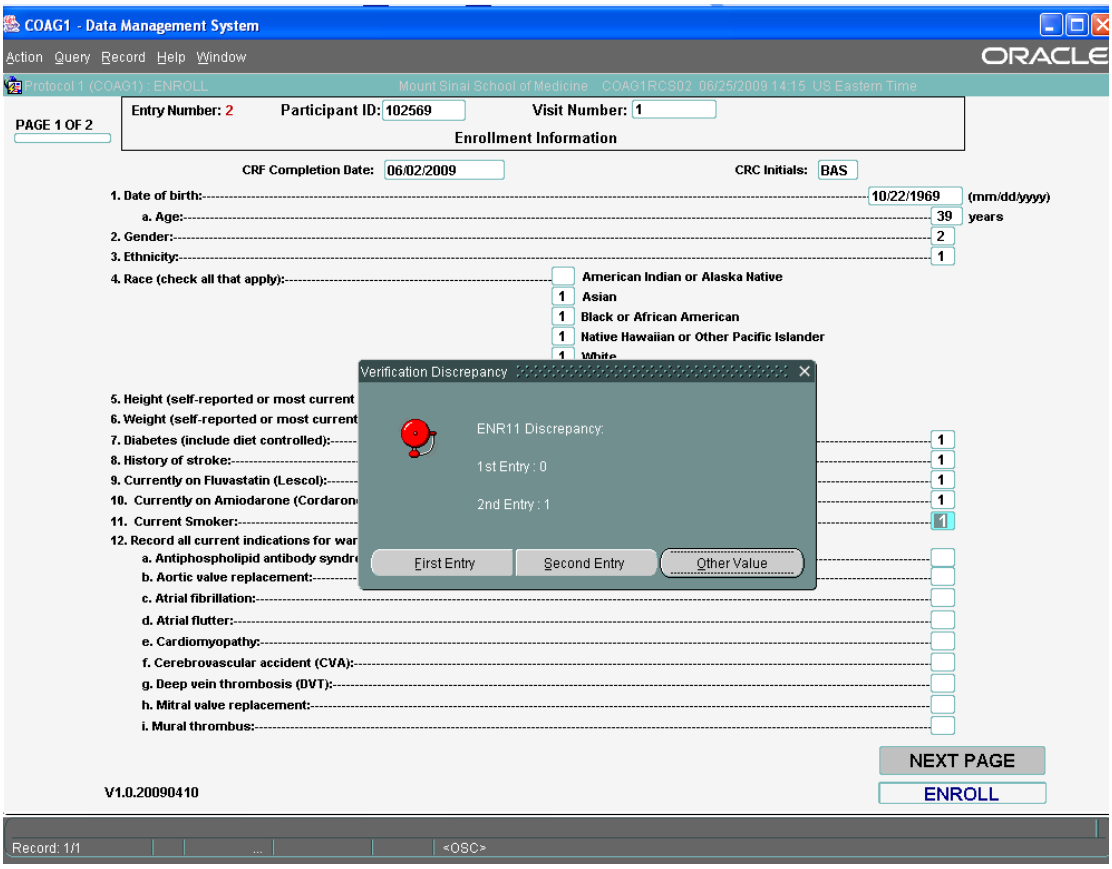
9.J. Second entry for ENROLL and ELIG only

- From the COAG Clinical Center Main Menu, select “Second Entry/Verification”
- Select the PID, the visit number, and the CRF name from the drop box or type them in
- Click “Enter Data”



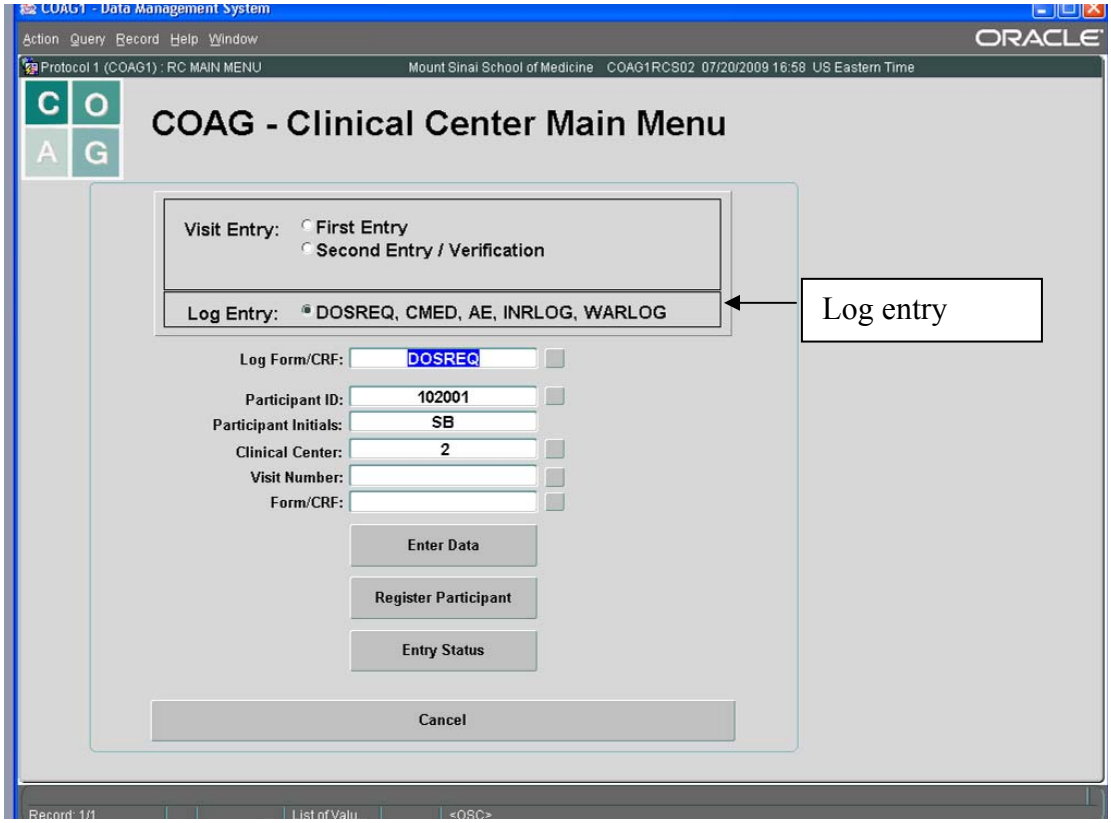
- Enter the data according to first entry instructions.
- During the “Second Entry/Verification” process, a “Verification Discrepancy” box may appear as you try to go through the fields.
- The box appears if you enter a value under second entry that differs from first entry.
- The box contains the following: the question number where the discrepancy occurred; the value that was entered under first and second; and three options to rectify the discrepancy. They are:
  - First Entry: value entered under first entry
  - Second Entry: value entered under second entry
  - Other Value: allows you to change the value if both first and second entry are incorrect

- Select First Entry or Second Entry, or, if both are incorrect, enter the correct value and proceed with data entry



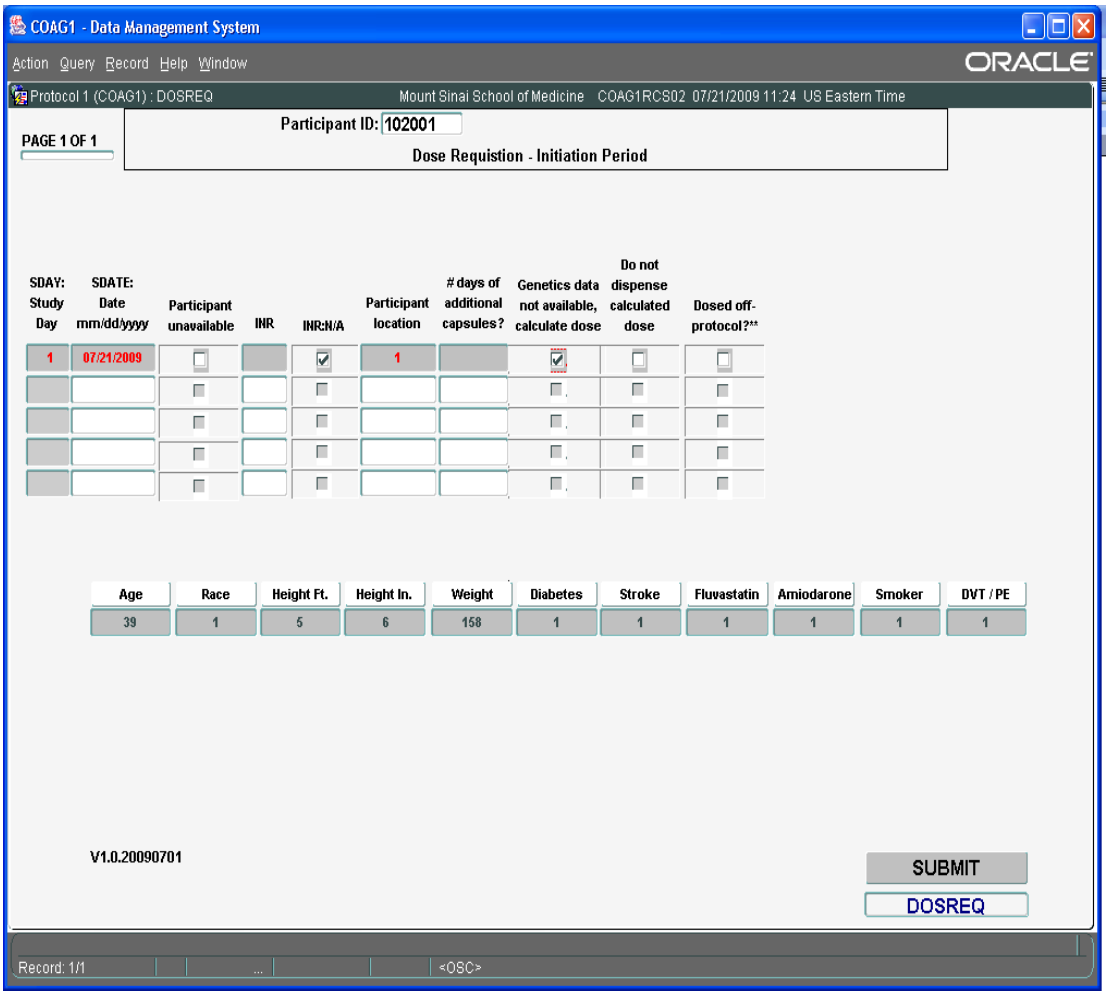
9.K. Data entry – Dose Requisition:

- Click on DOSREQ from the list of log entry forms
- Select the PID from the drop box or type it in
- Click “Enter Data” button

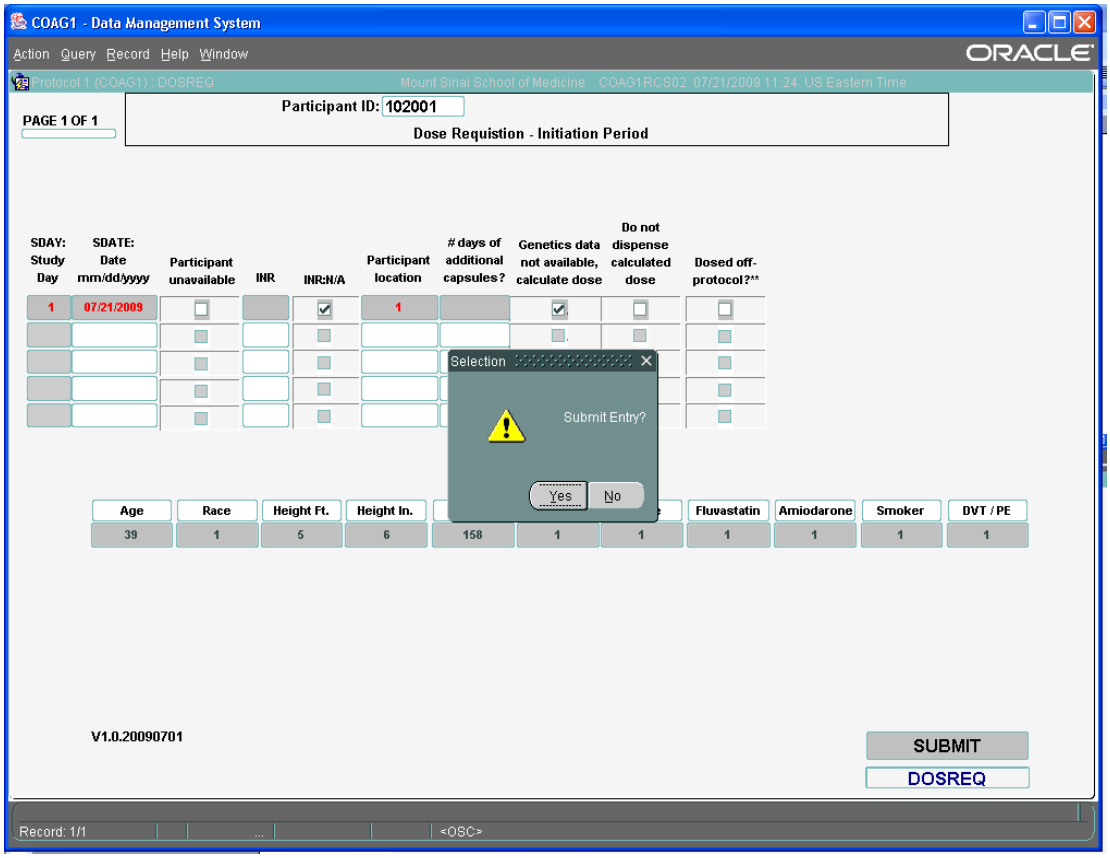


From this screen you will request (order) dosing for the first five (5) days

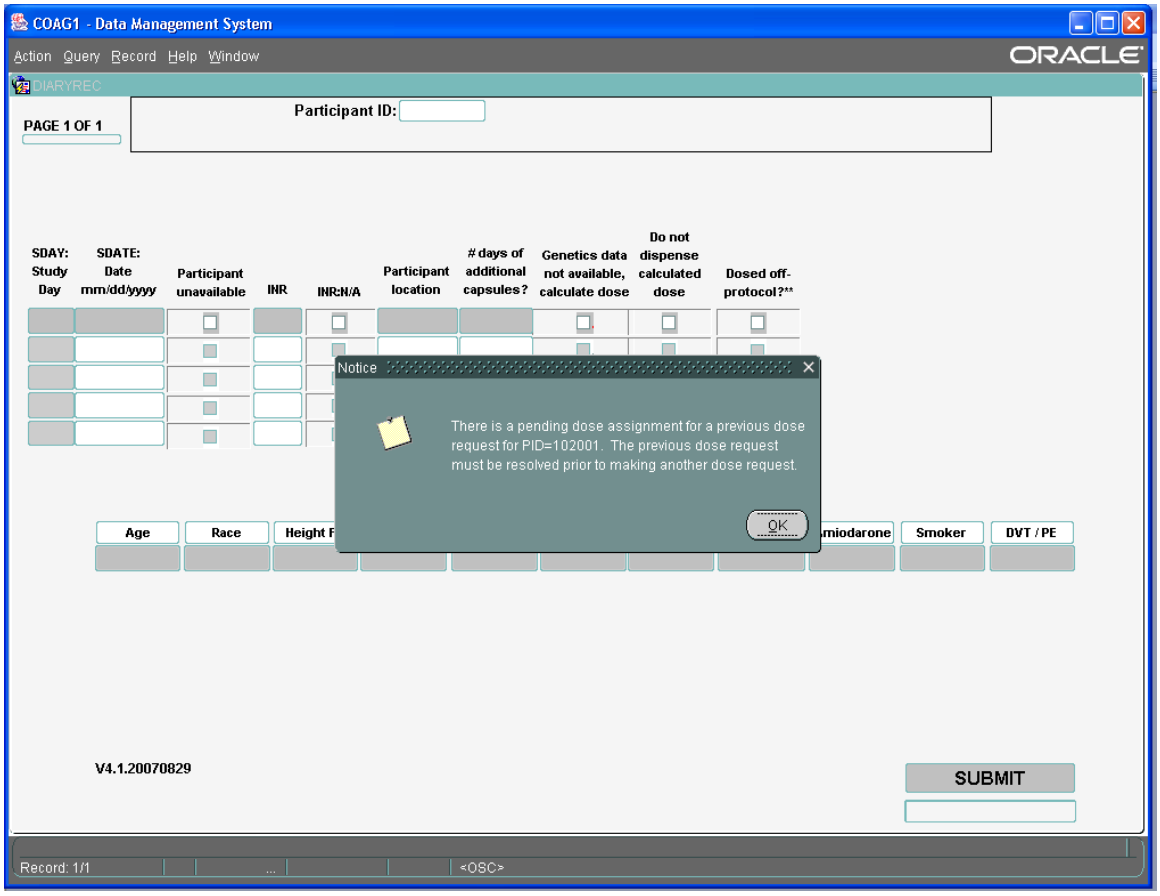
- Enter the required information from the DOSREQ CRF for that day
- Click the “Submit” button to save the data



- A pop up box will ask if you want to submit the entry
- If data entry is complete and accurate, click “Yes”

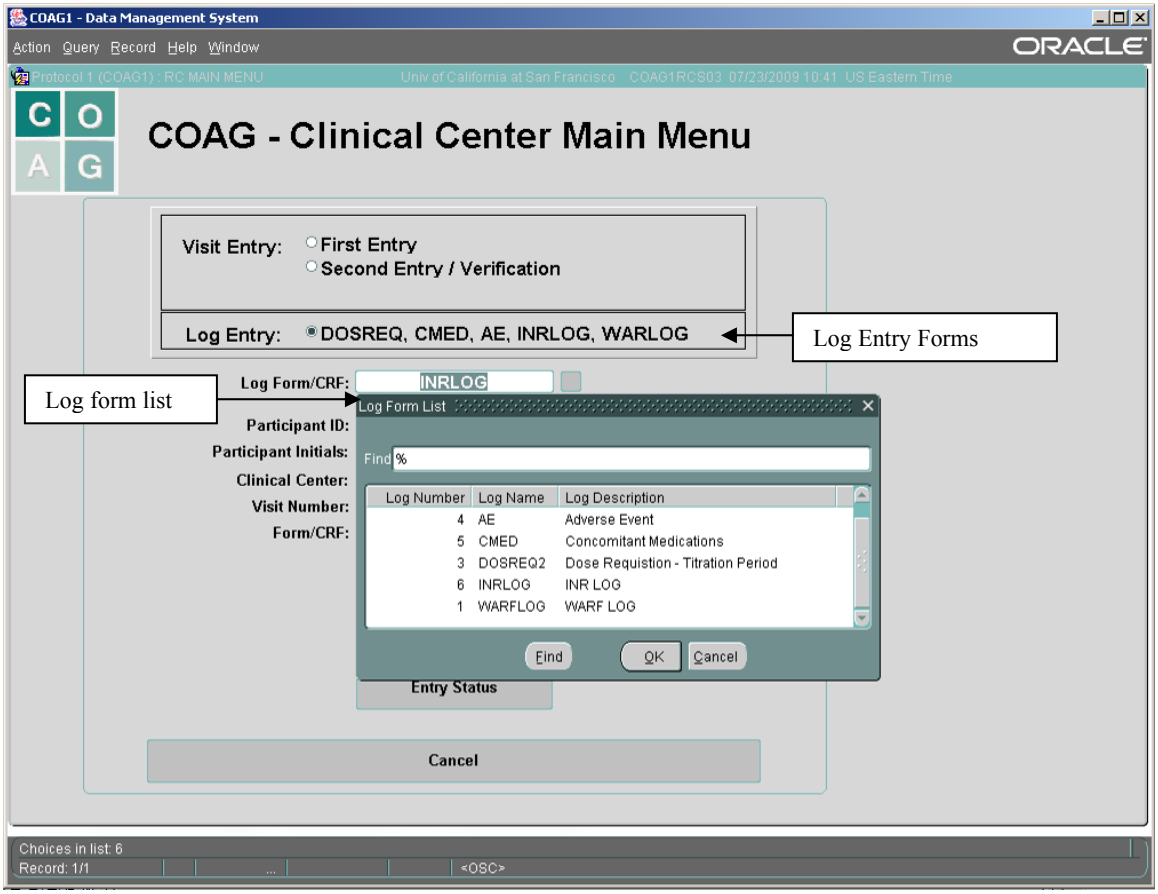


If you request a dose before the pharmacy has a chance to dispense a previous request, you will receive an error message stating that there is a pending dose assignment for a previous dose request for PID #XXX. The previous dose request must be resolved prior to making another dose request.



9.L. Data entry – Other Log Forms

- Click on DOSREQ from the log entry forms
- From the Log Form/CRF drop box select the desired form and click “Ok”
- Click “Enter Data” button
- Screen for the selected form will appear and data may be entered

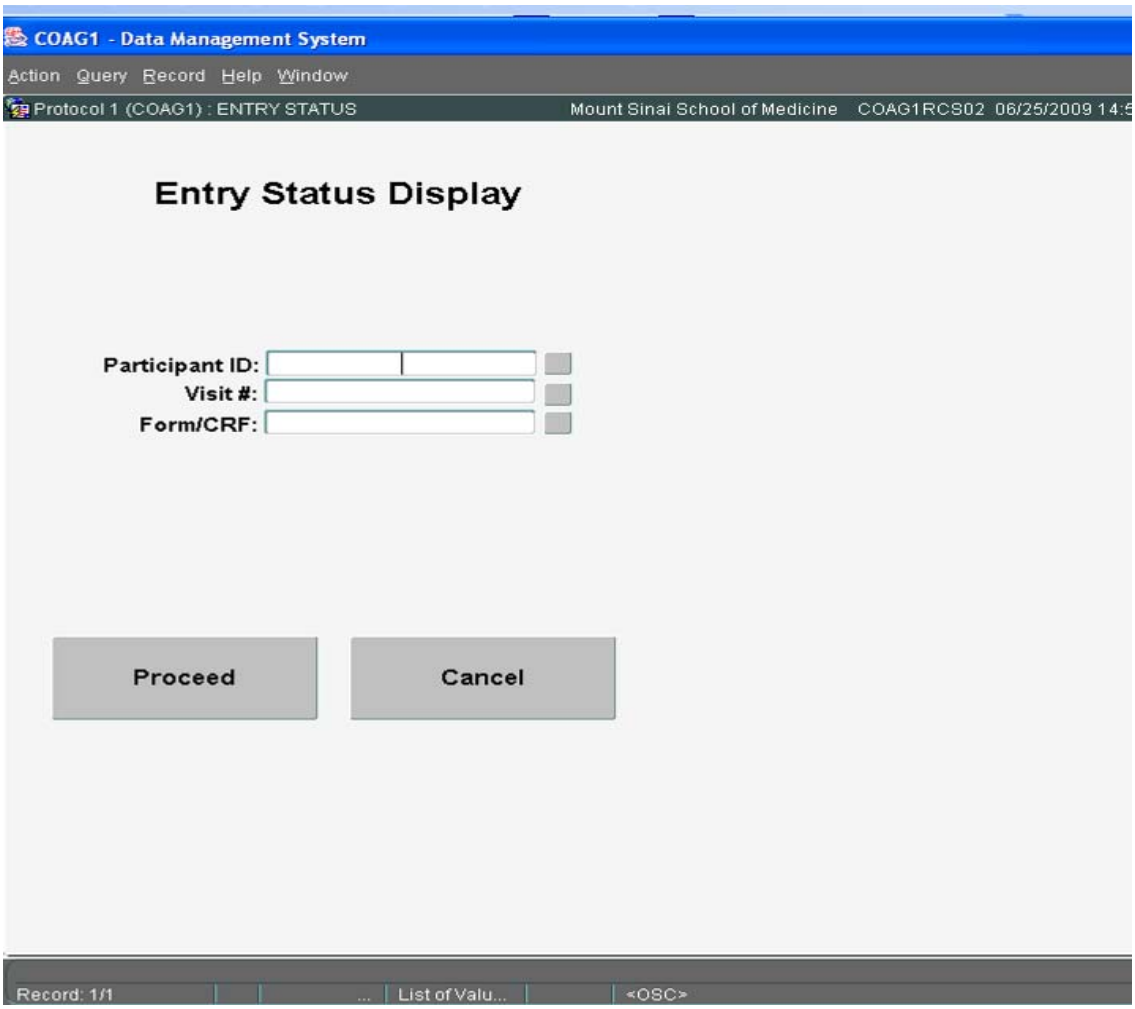


9.M. Entry Status

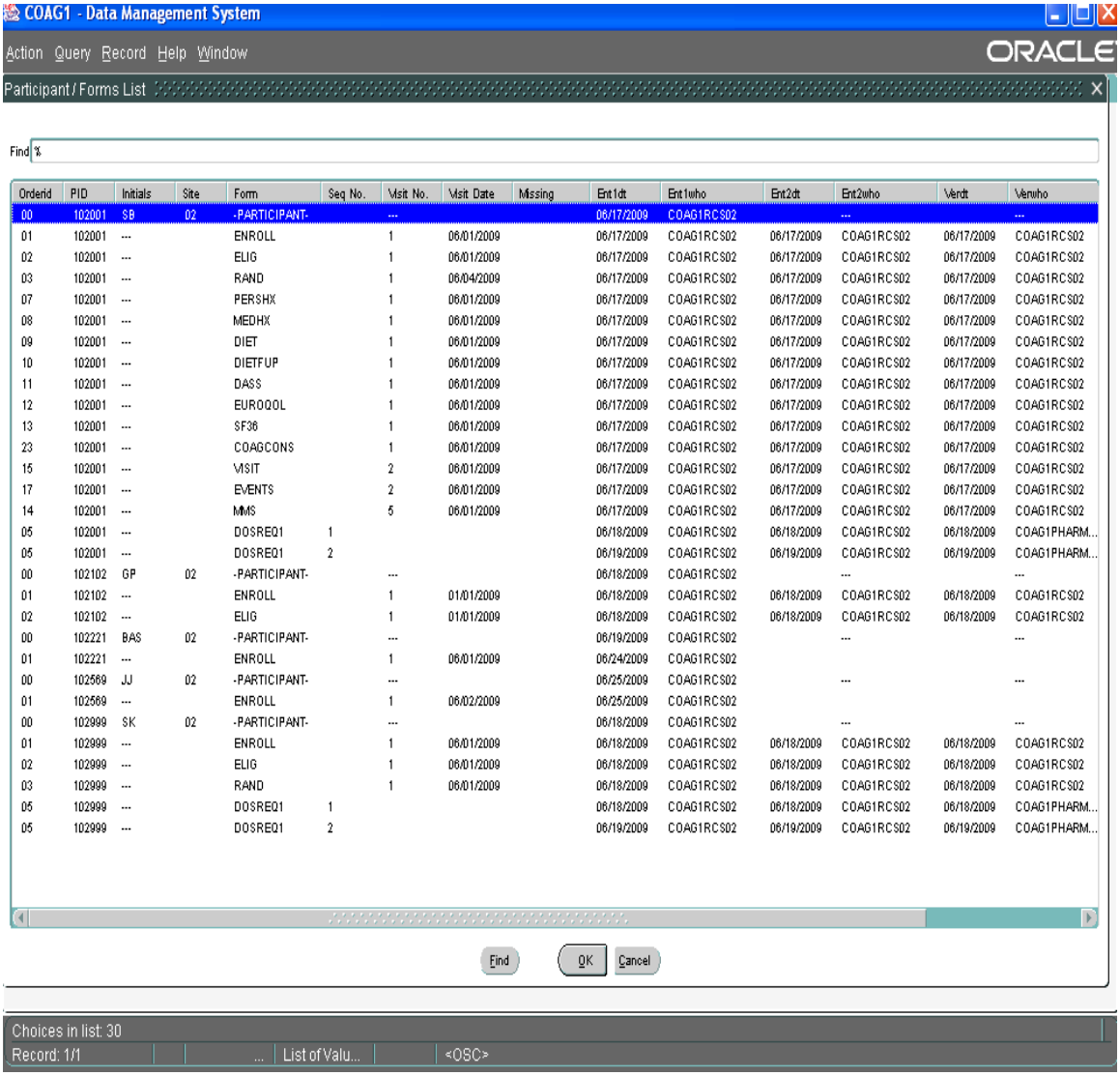
This function allows the user to view a list of CRFs that have been entered for either one participant or all participants to-date.

To view all the data entered to-date for a site:

- From the COAG Clinical Center Main Menu, click Entry Status
- Click the "Proceed" button on the "Entry Status Display" screen (ignore the required information in the dialogue box)



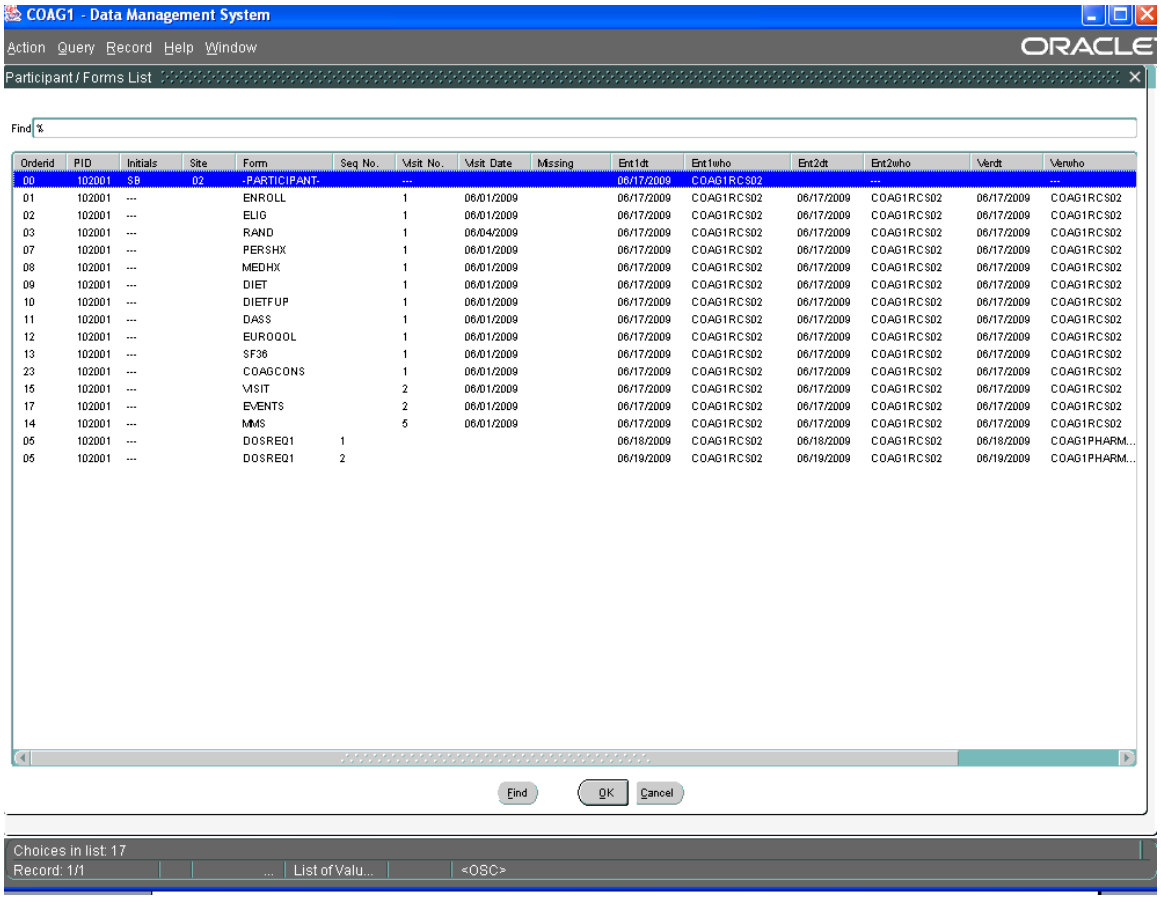
A list of all participants with all the CRFs that have been entered to-date appears, as well as any CRFs that have been marked as missing.



Orderid	PID	Initials	Site	Form	Seq No.	Visit No.	Visit Date	Missing	Ent1dt	Ent1who	Ent2dt	Ent2who	Verdt	Verwho
00	102001	SB	02	-PARTICIPANT-		---			06/17/2009	COAG1RCS02		---		---
01	102001	---		ENROLL		1	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
02	102001	---		ELIG		1	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
03	102001	---		RAND		1	06/04/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
07	102001	---		PERSHX		1	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
08	102001	---		MEDHX		1	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
09	102001	---		DIET		1	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
10	102001	---		DIETFUP		1	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
11	102001	---		DASS		1	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
12	102001	---		EUROQOL		1	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
13	102001	---		SF36		1	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
23	102001	---		COAGCONS		1	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
15	102001	---		VISIT		2	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
17	102001	---		EVENTS		2	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
14	102001	---		MMS		5	06/01/2009		06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02	06/17/2009	COAG1RCS02
05	102001	---		DOSREQ1	1				06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02	06/18/2009	COAG1PHARM...
05	102001	---		DOSREQ1	2				06/19/2009	COAG1RCS02	06/19/2009	COAG1RCS02	06/19/2009	COAG1PHARM...
00	102102	GP	02	-PARTICIPANT-		---			06/18/2009	COAG1RCS02		---		---
01	102102	---		ENROLL		1	01/01/2009		06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02
02	102102	---		ELIG		1	01/01/2009		06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02
00	102221	BAS	02	-PARTICIPANT-		---			06/19/2009	COAG1RCS02		---		---
01	102221	---		ENROLL		1	06/01/2009		06/24/2009	COAG1RCS02				
00	102569	JJ	02	-PARTICIPANT-		---			06/25/2009	COAG1RCS02		---		---
01	102569	---		ENROLL		1	06/02/2009		06/25/2009	COAG1RCS02				
00	102999	SK	02	-PARTICIPANT-		---			06/18/2009	COAG1RCS02		---		---
01	102999	---		ENROLL		1	06/01/2009		06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02
02	102999	---		ELIG		1	06/01/2009		06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02
03	102999	---		RAND		1	06/01/2009		06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02
05	102999	---		DOSREQ1	1				06/18/2009	COAG1RCS02	06/18/2009	COAG1RCS02	06/18/2009	COAG1PHARM...
05	102999	---		DOSREQ1	2				06/19/2009	COAG1RCS02	06/19/2009	COAG1RCS02	06/19/2009	COAG1PHARM...

To narrow your search for a particular participant, CRF, or Visit:

- Enter the PID, CRF, or visit number on the “Entry Status Display” screen
- Click on “Proceed”
- A list of your search appears.



9.N. Editing

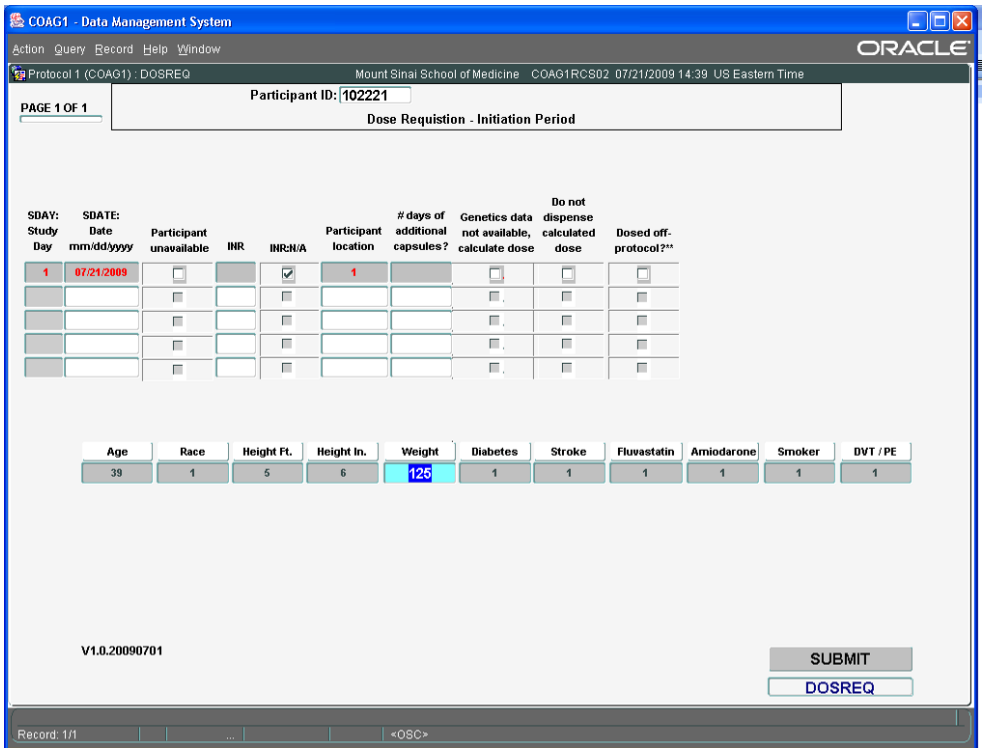
You have the ability to edit selected fields from the ENROLL form through the DOSREQ module. You must edit the data before you submit the request for dose. The editable fields are:

- Age
- Race
- Height
- Weight
- Diabetes
- Stroke
- Fluvastatin
- Amiodarone
- Smoker
- DVT/PE.

Please be sure the change you make in the DOSREQ module is noted on the COMM CRF. You do not need to edit ENROLL.

To edit:

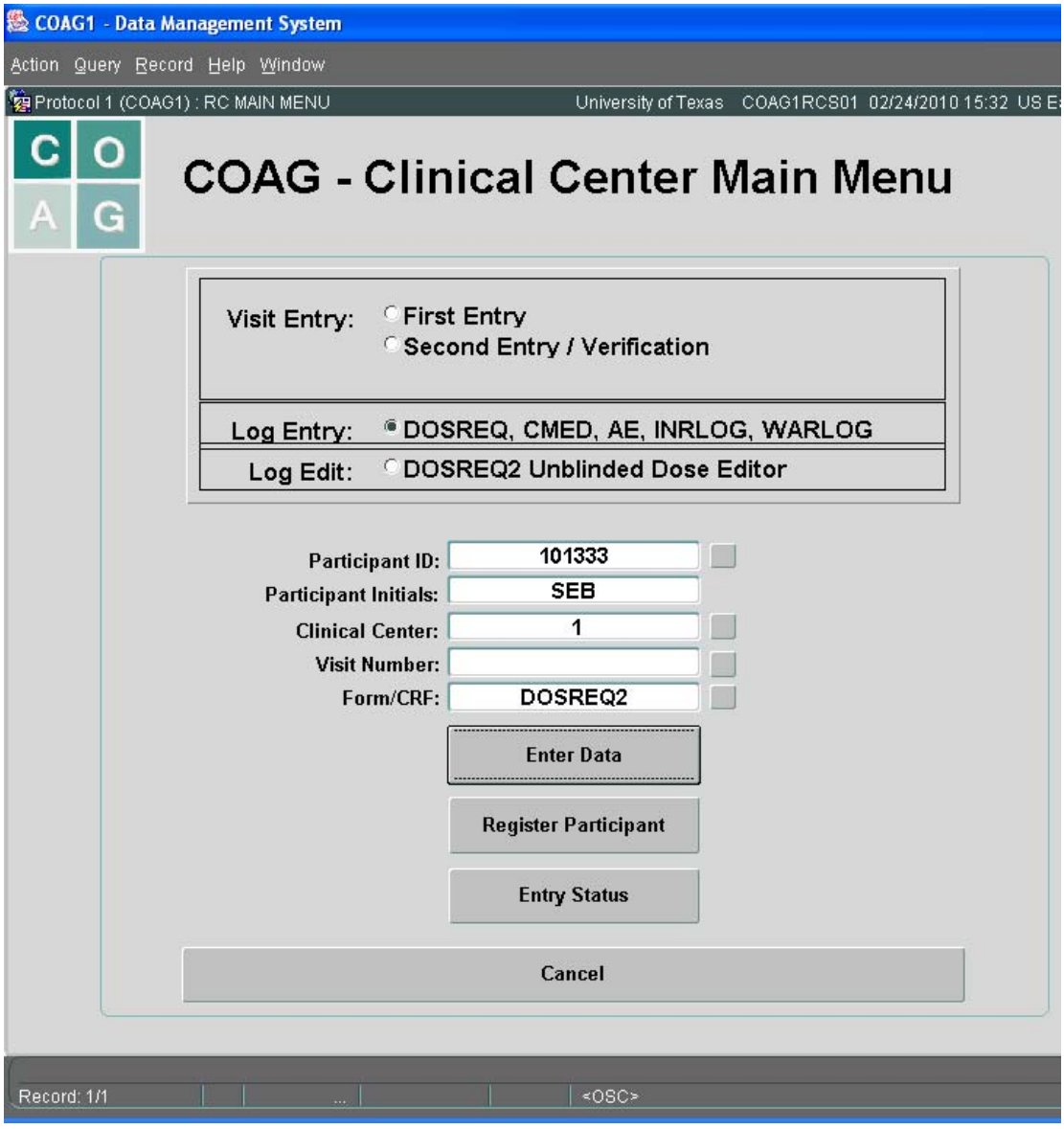
- You must enter the study day date in order for the cursor to go to the field to be edited.
- You can enter all study day data and then edit the field or just enter the study day date, edit the field and then continue with the study day entry.
- Click on the appropriate button representing the field you want to change
- The field value will be highlighted
- Enter the correct information
- Click "submit" button.



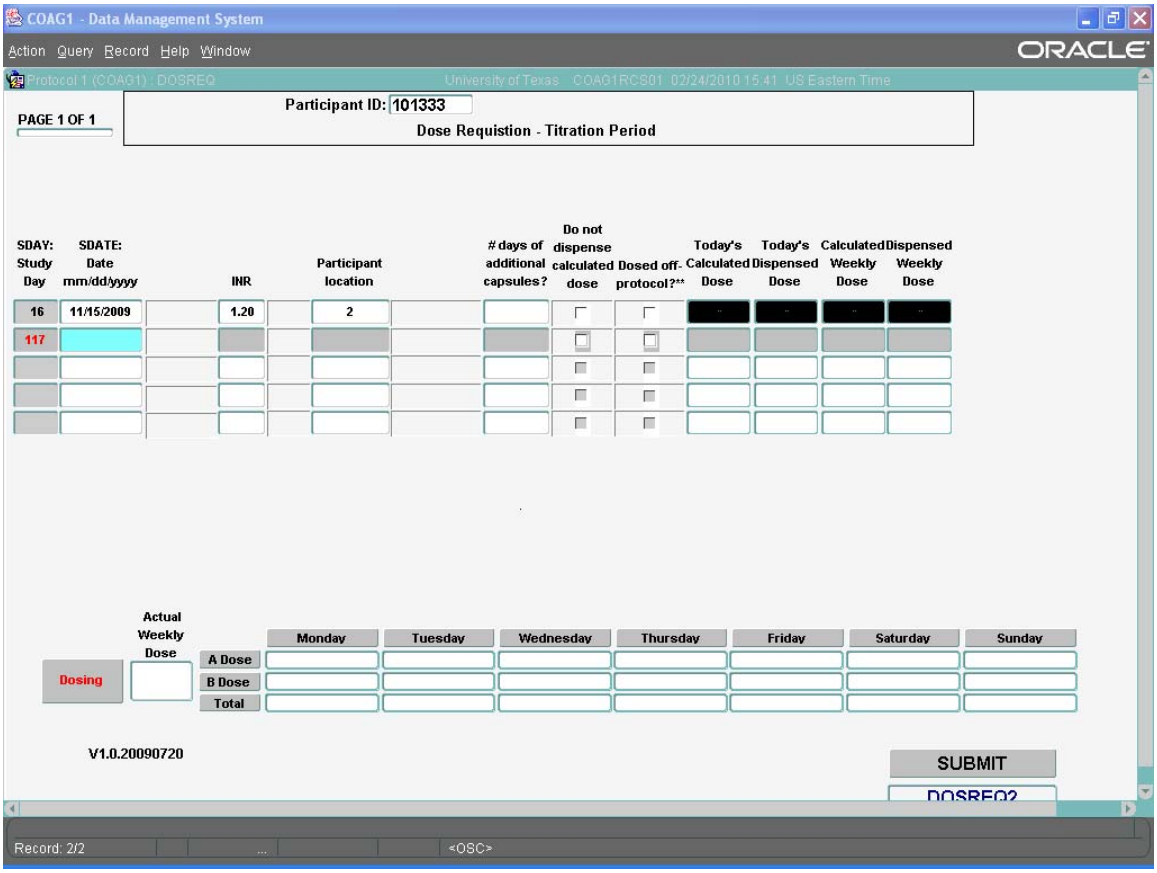
9.O. Data Management System (DMS) Screen Module for Unblinding

The following screens will demonstrate the use of the DMS pharmacy module screen that the Research Coordinator will utilize to initiate unblinded warfarin doses for the participant:

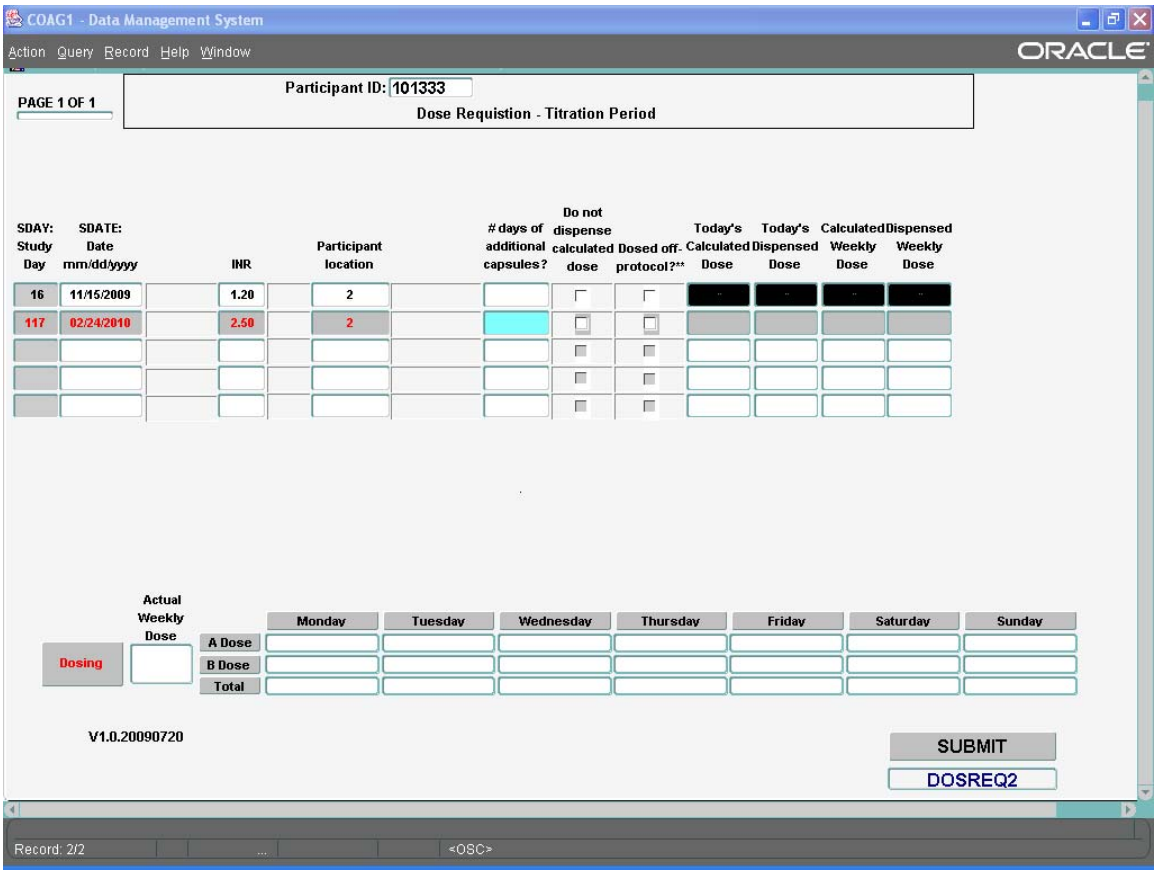
1. From the main menu choose Log Entry: DOSREQ, CMED, AE,…
and choose Form/CRF: DOSREQ2 as below:



2. When the screen opens, the user will be able to see the Today's Calculated Dose, Today's Dispensed Dose, Weekly Calculated Dose, and Weekly dispensed dose fields. Values for these fields for study days prior to day 29 will be blacked out to maintain blinding.

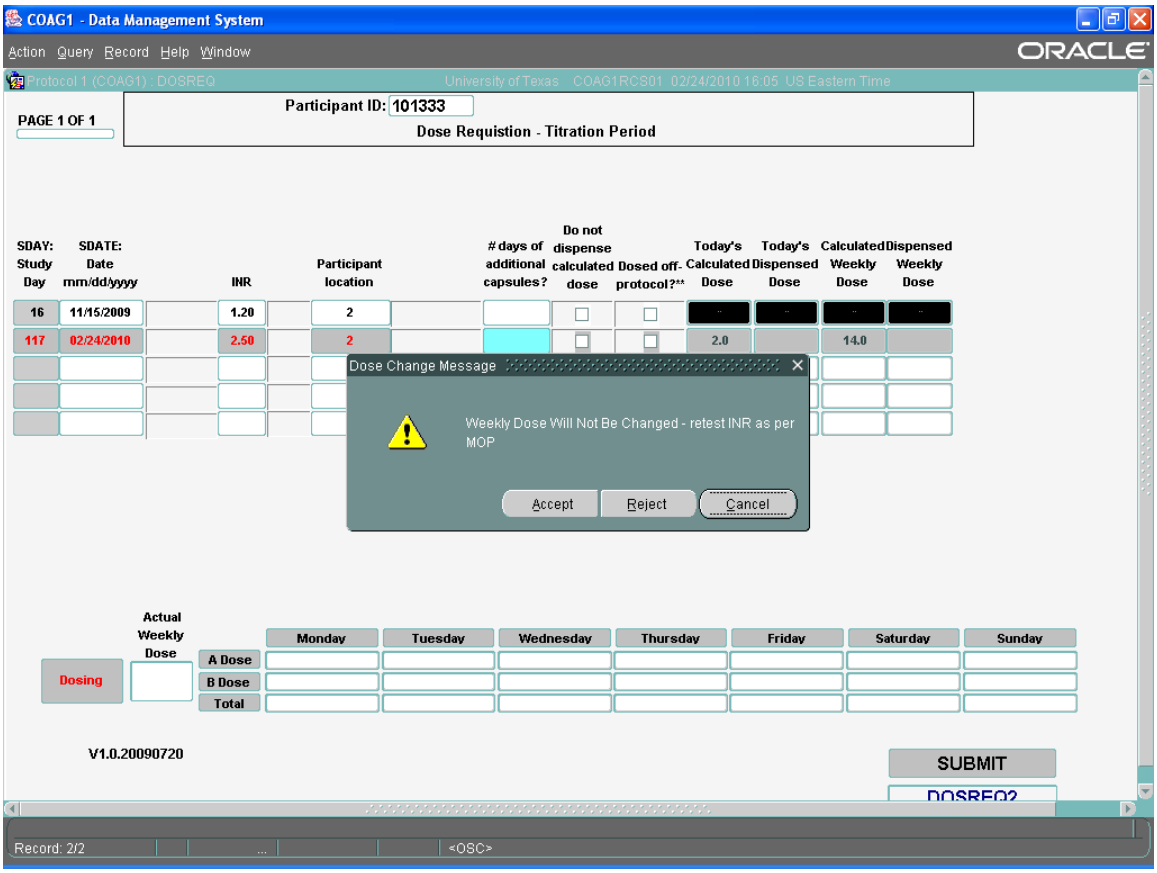


3. A new row will be created and the appropriate study day calculated in the Study Day column. At a minimum, the user will then enter the Date (today's date), INR and Participant location. User can also enter, **if necessary**, # days additional capsules, the do not dispense calculated dose check box, and the dosed off-protocol checkbox.

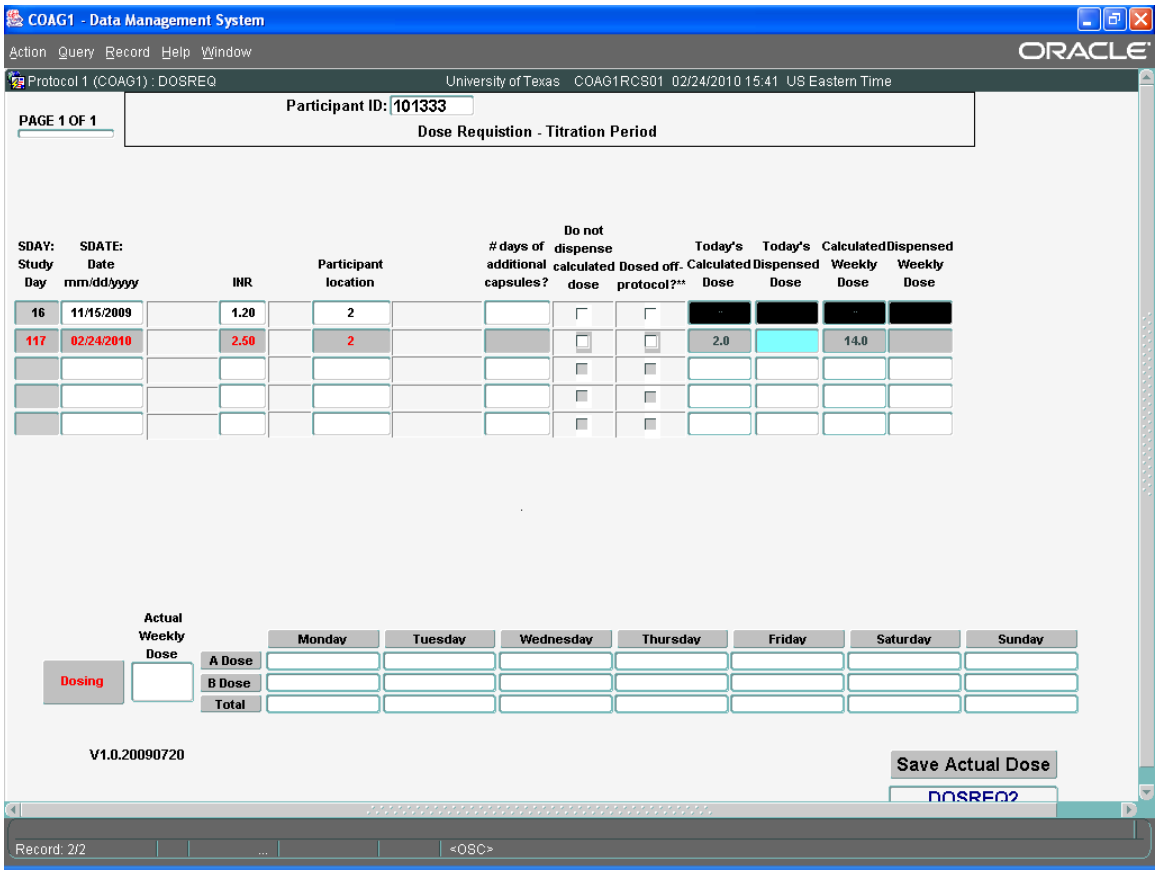


4. After entering those items, press the "Submit" button to calculate Today's dose and the Weekly Dose. After pressing the "Submit" button, the dose values will be calculated and a message will appear indicating how the dose will be changed from the prior dose. Press "Accept" to accept this change (even if you are going to override the calculations), and view the "Today's Calculated Dose" and "Calculated Weekly Dose" values. You will then be able to enter the actual "Today's Dispensed Dose" and "Dispensed Weekly Dose" doses.

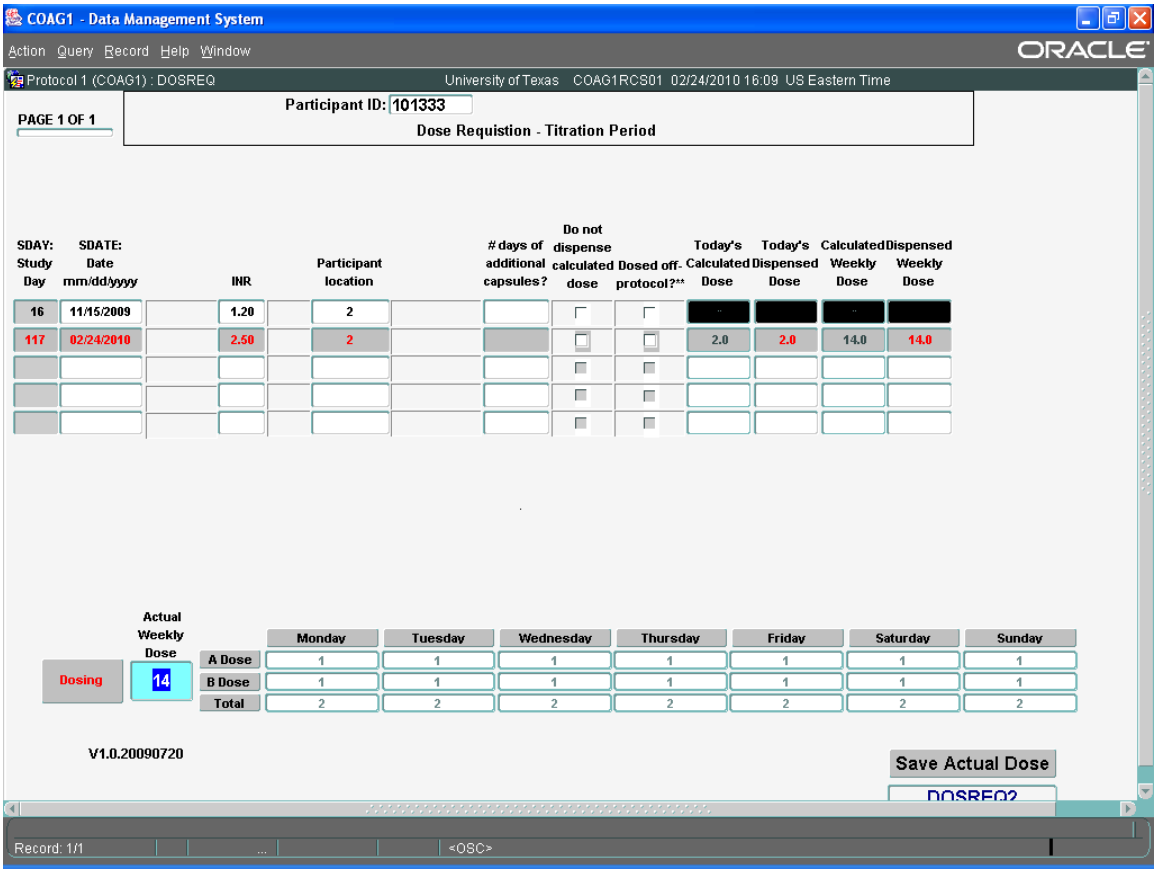
   If you wish to exit the dose request screen without saving the calculated doses and entering the dispensed doses, for any reason, press the "Reject" or "Cancel" buttons to exit. If "Reject" or "Cancel" is pressed, you will need to re-submit the dose request for that day. Do not press the "Reject" or "Cancel" button if you are intending to override the calculated dose. Only pressing the "Accept" button will save the calculated dose to the database and allow you to enter dispensed doses, even if the dispensed doses are going to be different than what was calculated.



5. After pressing the “Accept” button, the User will be able to update “today’s dispensed dose” and “dispensed weekly dose”.

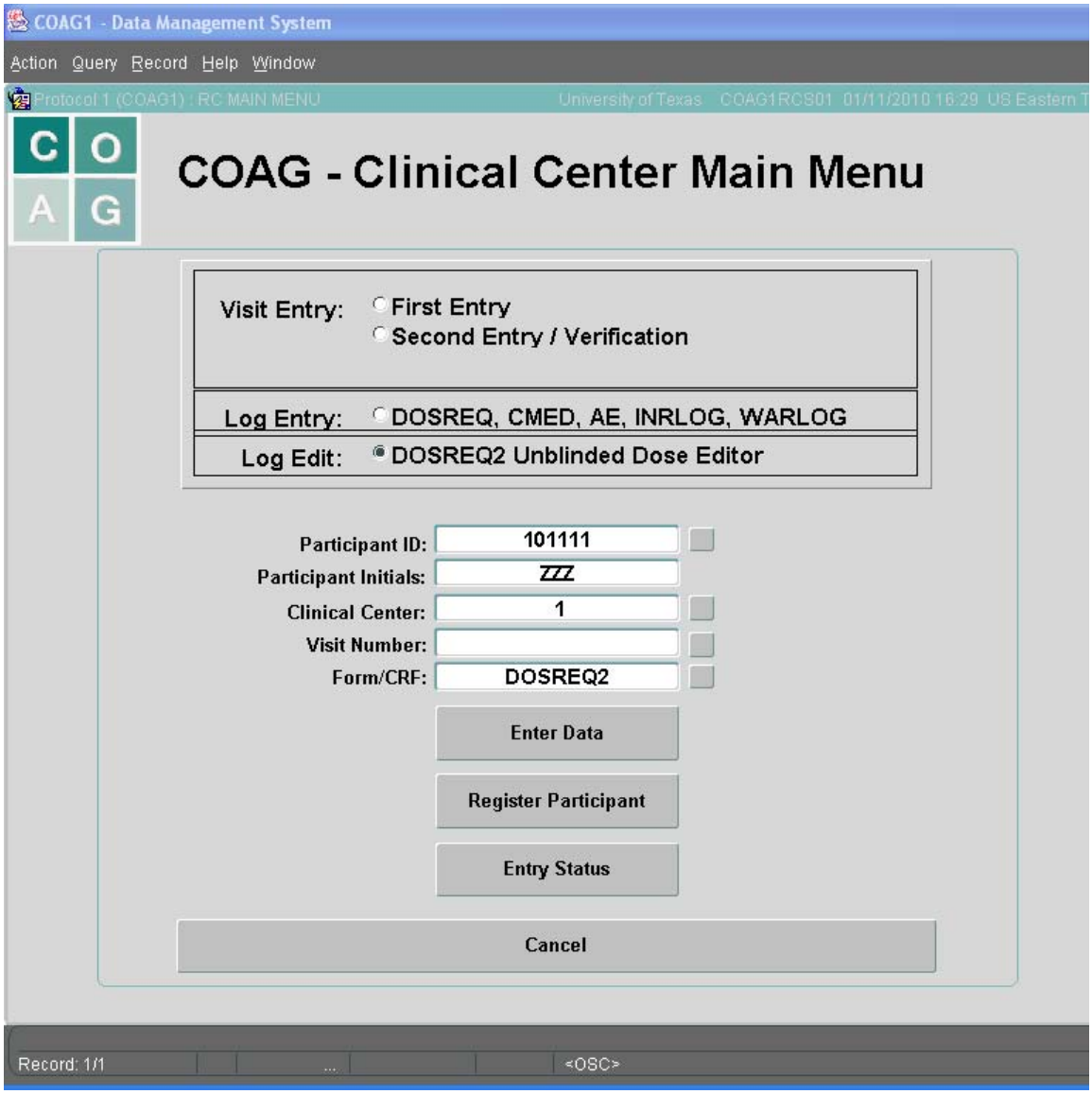


6. After entering “today’s dispensed dose” and “weekly dispensed dose” (shown below in red), press the “Tab” key, and the weekly dosing schedule will be populated at the bottom of the screen.

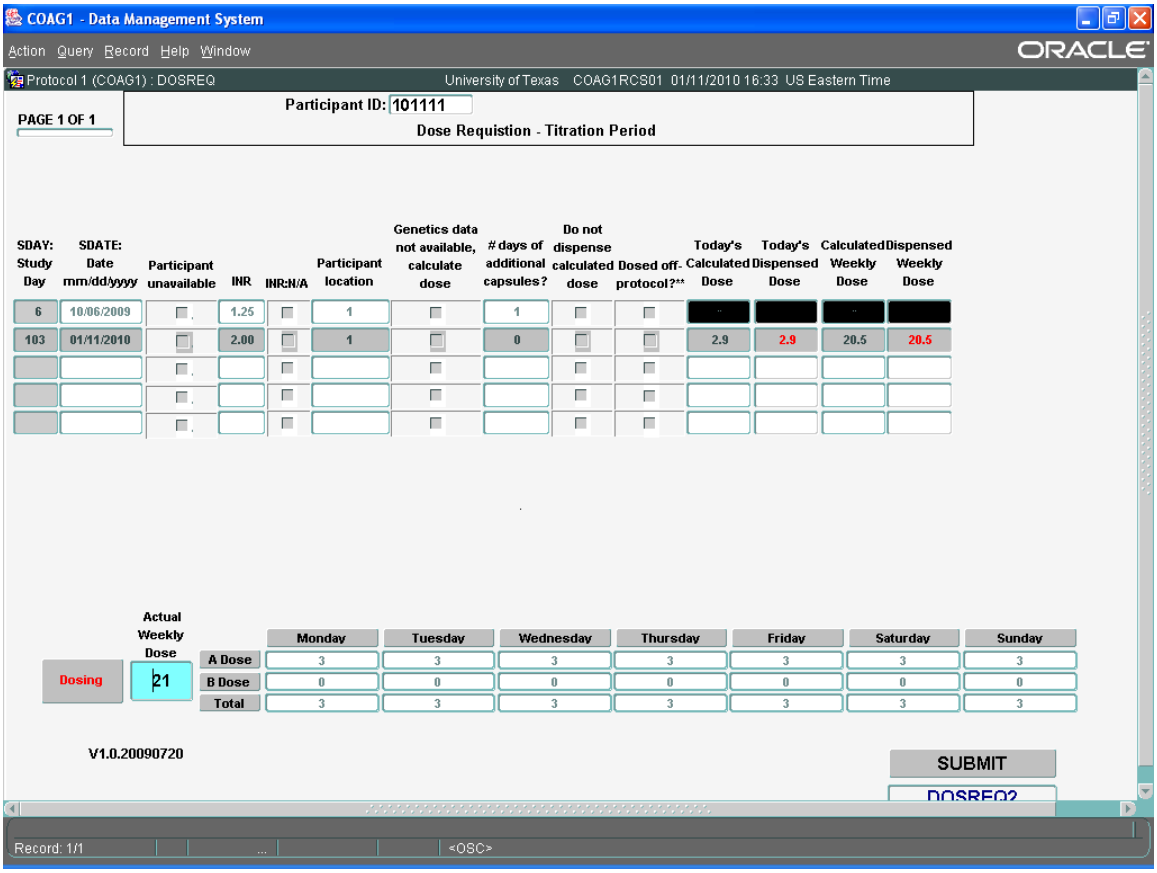


After reviewing the weekly dosing schedule, press the “Save Actual Dose” button to save the dosing information to the database. The dispensed dose information will then be saved and the user will be taken back to the main menu.

7. A dose can be edited up until the point in time in which the next dose is calculated. To edit an unblinded dose, choose the "Log Edit: DOSEREQ2 Unblinded dose editor" as shown below:



8. The dosreq2 form will open and the user will be able to change the daily/weekly calculated doses.

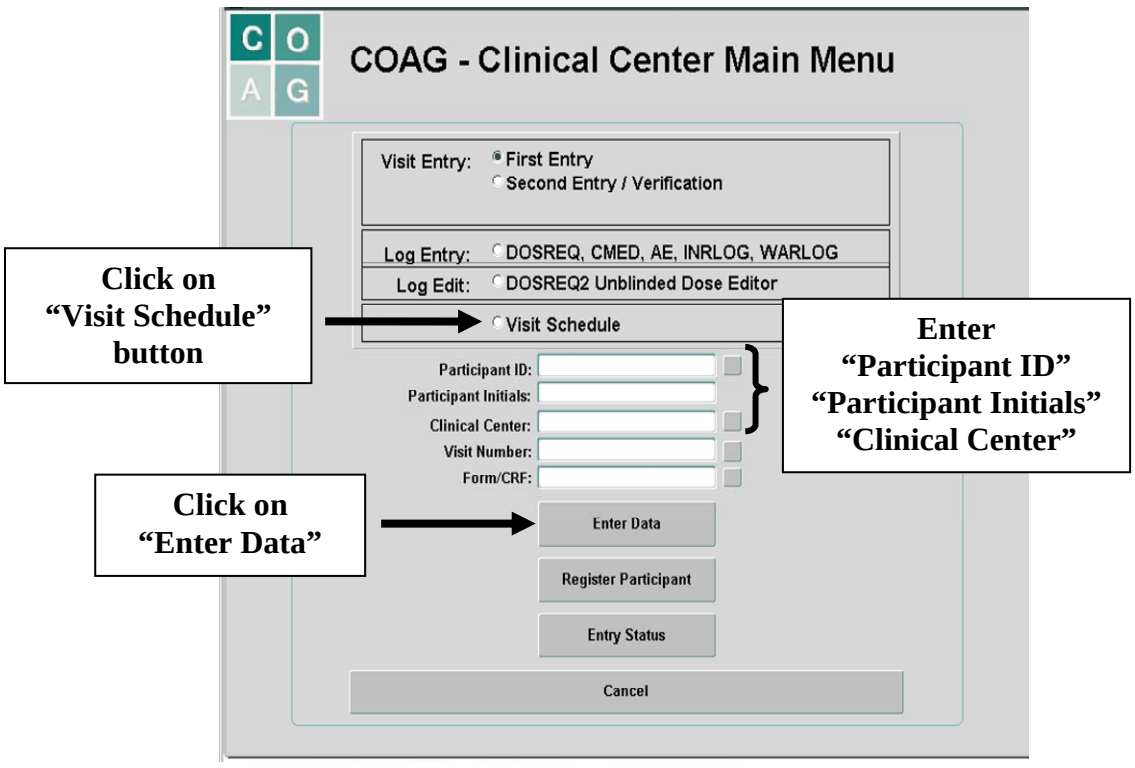


9. After completing the update, press the “submit” button to save the changes to the database.

9.P. Visit Schedule Report DMS Instructions

- On the DMS Main Menu screen select the "Research Coordinator" module
- When prompted log-in with your username and password
- On the Clinical Center Main Menu screen, click on the "Visit Schedule" button
- Enter "Participant ID", "Participant Initials", and "Clinical Center" ID
- Select the "Enter Data" module
- Print the schedule that appears in the .pdf format
- Obliterate Participant ID with a black magic marker and write in the participant's name on his/her copy

Note: Highlighted row is Visit 7 (primary endpoint visit) and "Target Date" is Day 29 – unblinding date for algorithm-based dosing



10. SPONSORED PROJECT HELP DESK

The sponsored project help desk will answer questions concerning the operation of the Data Management System (DMS) and will assist in resolving any issues that hinder the effective use of the software.

10.A. Technical Support

The Help Desk will provide technical support related to problems and issues that may arise when working with the application provided by the CTCC.

The Help Desk will not be responsible for providing technical support for hardware and/or software that are not provided by the CTCC (e.g. word processors, spreadsheets, modems, printers, and hardware) and has direct local institutional support.

Helpdesk Phone Number: 215.573.4623

Helpdesk E-mail: crcuhelp@mail.med.upenn.edu

The COAG helpdesk will be available at the CTCC from 9am – 5pm EST Monday through Friday. The helpdesk can be reached via telephone or e-mail using the contact information above. If contacting helpdesk via telephone, you will be prompted to leave a message indicating the nature of your support requested. Your message will be saved electronically and forwarded to helpdesk support personnel, who will review your message and contact you as soon as possible (typically within an hour). E-mails will be handled in a similar fashion. Each helpdesk support staff member will receive a copy of e-mails sent to the helpdesk e-mail address, and will respond as soon as possible. Support requests that are submitted after 5pm EST will be addressed the following business day.

Requests to the helpdesk should be limited to technical support of the COAG Data Management System (DMS) as it pertains to the COAG study. This would include any issues involving connectivity / access to the COAG DMS, installation on your computer, Error Messages, etc. Questions related to general study operations or the protocol, or other technical issues that are not directly related to the COAG DMS should be directed to Project Management (PJM) or Clinical Data Management (CDM) at the CTCC.

10.B. Assignment of Data Management System (DMS) Accounts

A DMS account consists of a username and password that uniquely identifies a user. DMS accounts are required for a user to gain access to the data entry area, and are the primary means for ensuring data security and confidentiality. Therefore, it is critically important that all DMS accounts are kept secure and confidential and are not shared with anyone.

NOTE: The username and password used to individually access your project Web site (http://www.coagstudy.org/) is **not** your DMS username and password. Access to the project Web site infers no access to the project DMS. You may reach the project DMS through a link from within the project Web site but will then be prompted for a specific DMS account username and password.

In addition to providing data security and confidentiality, DMS accounts provide a means to trace all database activities to individual user accounts.

To obtain DMS accounts, a Clinical Center or Site representative will notify the CTCC project manager of the requested user's name and provide a description of what functions the user will be performing in the DMS. The CTCC Project Manager will in turn notify the Sponsored Project Help Desk of the new user request.

*****Important*****

When a DMS account has been created, the Sponsored Project Help Desk will contact the user with his/her account information.

When personnel leave the project, a representative from the Clinical Center or Site should promptly contact the CTCC Project Manager. The Sponsored Project Help Desk will then take the necessary actions to deactivate that user's database account.

11. APPENDICES

11.A. Appendix 1 – Warfarin Dosing Instructions

WARFARIN DOSING INSTRUCTIONS

Date: _____ Participant Name: _____

Instructions given by: _____

If you have any questions, please call : _____ at _____
Research Coordinator Telephone

BOTTLE A	BOTTLE B	Single Dose Bottle
Take _____ pill(s) on the following days	Take _____ pill(s) on the following days	Take on these days
☐ Monday	☐ Monday	Day / Pill
☐ Tuesday	☐ Tuesday	Day / Pill
☐ Wednesday	☐ Wednesday	Day / Pill
☐ Thursday	☐ Thursday	Day / Pill
☐ Friday	☐ Friday	Day / Pill
☐ Saturday	☐ Saturday	Day / Pill
☐ Sunday	☐ Sunday	Day / Pill

- ✓ Always take your pills as directed at the same time each day.
- ✓ Never skip a dose, and never take a double dose unless instructed to do so by the research doctor or study personnel.
- ✓ If you do forget to take a dose, take it as soon as you remember unless it is the next day. If it is the next day, then skip the missed dose and resume your normal dosing schedule for that day.
- ✓ For your next clinic visit, bring back all your study pill bottles and any pills not taken
- ✓ DO NOT destroy any pills not taken
- ✓ DO NOT share your medication with anyone

Data Quality Management Procedures

Queries:

Queries will be sent to the Research Coordinators in response to errors logged by the Data Management System when it views the verified data in the application against a set of rules written to validate the data. A query can also be generated by a manual review of the verified data against an expected set of data standards by the Data Management staff and the study biostatisticians at the CTCC.

Types of Queries Generated by the Database:

There are several types of queries that are generated by the Data Management System and sent to the Clinical Centers.

Missing Fields

Collected data should be reviewed for completeness at the Clinical Centers prior to entry and verification. A data field on a case report form that is left blank in the data table is logged as an error by the Data Management System and will be queried; e.g., if a medical history question was left blank, the Research Coordinator may inform the CTCC (in the same format as the query is sent by the CTCC) by e-mail of the missing field soon after the data is entered and verified or a query will be sent by the CTCC requesting the information.

If a query is sent to the Clinical Center, the Research Coordinator must attempt to find the correct response or provide an explanation for the missing data. An explanation is acceptable when a response is left blank for a reason. For example, the participant may have chosen to not respond to a question.

Skip Patterns

Skip patterns account for fields that should or should not be answered, depending on the response to the first question in the series. For example, “types of cancer” on **MEDHX** case report form should only be answered if participant was diagnosed with cancer. If “types of cancer” is coded and the participant has not been diagnosed with cancer, a query is sent because the field should be left blank. Conversely, if the participant was diagnosed with cancer and “types of cancer” has not been checked, a query is generated because the field should not be blank.

If a skip pattern query is sent to the Research Coordinator, and a change is warranted, the case report form should be updated with the correction, using the standard correction technique outlined earlier.

Range Checks

Many fields have a specific range of expected responses, which is designed to include approximately 95% of the population. For example, a participant’s height has both a low range and a high range, and anything outside of those ranges may generate a query. The range check query is sent to confirm the value entered because it is higher/lower than the expected range.

The Research Coordinator should confirm data that is queried in his/her response to the CTCC or provide a correction to the data.

Logic Checks

These checks review the data to ensure the data is logical, e.g., men should respond "N/A" to female-oriented questions, and women should respond "N/A" to male oriented questions.

Types of Queries Generated by Manual Monitoring:

Monitoring Checks

These checks monitor the data for completeness and accuracy. Biostatisticians and Data Management staff at the CTCC manually view the data and queries are sent for data that look incomplete or appear to conflict with the design of the COAG study. The Research Coordinators should manage these queries in a similar manner as outlined above for the database-generated queries. If changes are necessary, a faxed or e-mailed response is expected. An explanation without data change, can be sent by e-mail. Types of monitoring queries include:

- Safety issues –**AE**, **CMED**, **EVENT**
- COAG Study Procedures – Withdrawals, Unblinding, Data Entry and Verification Status.

Managing Queries:

Receiving Queries from CDM

Queries are sent in an EXCEL spreadsheet via email, and contain the following information:

CC ID	CRF Date
Clinical Center	RC ID
Participant ID	Date Queried
Participant Initials	Description of the Problem
Visit Number	Resolution column
CRF Name	

Making Corrections Based on Queries:

- The Research Coordinator should print the spreadsheet e-mailed by the CTCC. At Clinical Centers with more than one Research Coordinator, the lead Research Coordinator will inform the CTCC at the start of the COAG study how they would like to receive the queries – whether one Research Coordinator at the Clinical Center receives all queries or the RC ID on the case report form determines who receives the queries.
- The Research Coordinator(s) is responsible for identifying the correction to be made or providing an explanation. CTCC Data Management staff is available to assist the Research Coordinators in resolution of the queries, if needed.
- If a query results in a correction, the correction must be included on the query and documented on the original case report form (initialed and dated).
- If it is determined that a correction is not needed, an explanation (e.g. participant's height is correct), should be documented on the query.
- All queries should be initialed, dated and filed with the participant's data binder.
- Any questions related to the queries should be directed to the originator of the query at the CTCC.

Query Response to the CTCC:

- Queries can be returned to the CTCC via email or fax. A copy of the response e-mailed or faxed to the CTCC is retained in the participant's COAG study binder.
- Explanations that do not require changes to the database are e-mailed to the CTCC, as well.
- The response to the query should be directed to the originator of the query at the CTCC.
- Original text must be "quoted" if responding to the query by email.
- A dedicated fax line [(215) 573-4790] is available at the CTCC to accept query responses and data sent from the Clinical Centers.

Responses to safety-related queries are expected at the CTCC in 3 working days. Responses to all other queries are expected at the CTCC in 5 working days.

Clarification of Optimal Anticoagulation Through Genetics (COAG):
A Randomized, Multicenter, Double-Blind Clinical Trial to Evaluate Efficacy in the Use of Clinical Plus Genetic Information to Guide Warfarin Therapy Initiation and Improve Anticoagulation Control for Patients.

http://www.coagstudy.org

COAG Data Management System Manual for Research Pharmacy

Version 1.1 - November 2009

Prepared by:
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Contents

1. Overview of Study Design and Dosing Interventions 1
   1.A. Study Design, Objectives, and Primary Endpoint 1
   1.B. Study Flow 1
   1.C. Method of Blinding 3
   1.D. Dosing Interventions 3
      1.D.1. Genotype-guided Dosing 3
      1.D.2. Clinical-guided Dosing 5
      1.D.3. Medical Monitor 5
      1.D.4. Warfarin Dose Adjustments (Dose Over-ride) 6
      1.D.5. Unblinding Procedures at Week Four (4): 7
      1.D.6. Patient Safety and Unblinding: 7
2. Clinical Site Research Pharmacy responsibilities in the COAG Clinical Trial 8
   2.A. Summary of Responsibilities for Research Pharmacy 8
3. Data Management System Dose Calculation 8
   3.A. Overview 8
   3.B. Pharmacy Module 9
4. Data Management System Users Guide 9
   4.A. Introduction 9
   4.B. Oracle JInitiator 10
   4.C. SSL Certificate 12
   4.D. Data Management System Web Site 15
      4.D.1. COAG-MAIN MENU: 17
      4.D.2. Data Management System Log In: 18
   4.E. COAG –Clinical Center Menu for Research Pharmacists 19
   4.F. Viewing Calculated Dose and Entering Dose Dispensed 20
      4.F.1. Dose Initiation Days 1 through 3: 20
      24
      4.F.2. Dose Revision Phase – Day 4 and Day 5 25
      4.F.3. Dose Titration Phase (After Day 5): 26
      4.F.4. Dose Over-ride Notification: 27
5. Sponsored Project Help Desk 28
   5.A. Technical Support 28
   5.B. Assignment of Data Management System Account 28

1. Overview of Study Design and Dosing Interventions

1.A. Study Design, Objectives, and Primary Endpoint

This Clarification of Optimal Anticoagualtion through Genetics (COAG) study is a randomized, multicenter, double-blind trial comparing two approaches to guiding warfarin therapy initiation. Prior to initiating warfarin therapy, participants will be recruited from up to 12 US academically-affiliated clinical sites from both the inpatient and outpatient level of care.

Clinical and genotype data will be collected on all participants. All participants who meet eligibility criteria at baseline screening will then be randomized to one of the two study dosing intervention arms: the genotype-guided dosing arm or the clinical-guided dosing arm, which will test the effects of algorithm guided dosing over the first 4-5 days of therapy.

The primary objective of the study is to compare the two strategies with respect to the time participants spend within the therapeutic INR range (PTTR) during the first 4 weeks of therapy:

- initiation of warfarin therapy based on algorithms using clinical information and an individual's genotype using genes known to influence warfarin response ("genotype-guided dosing"), and
- initiation of warfarin therapy based on algorithms using only clinical information ("clinical-guided dosing").

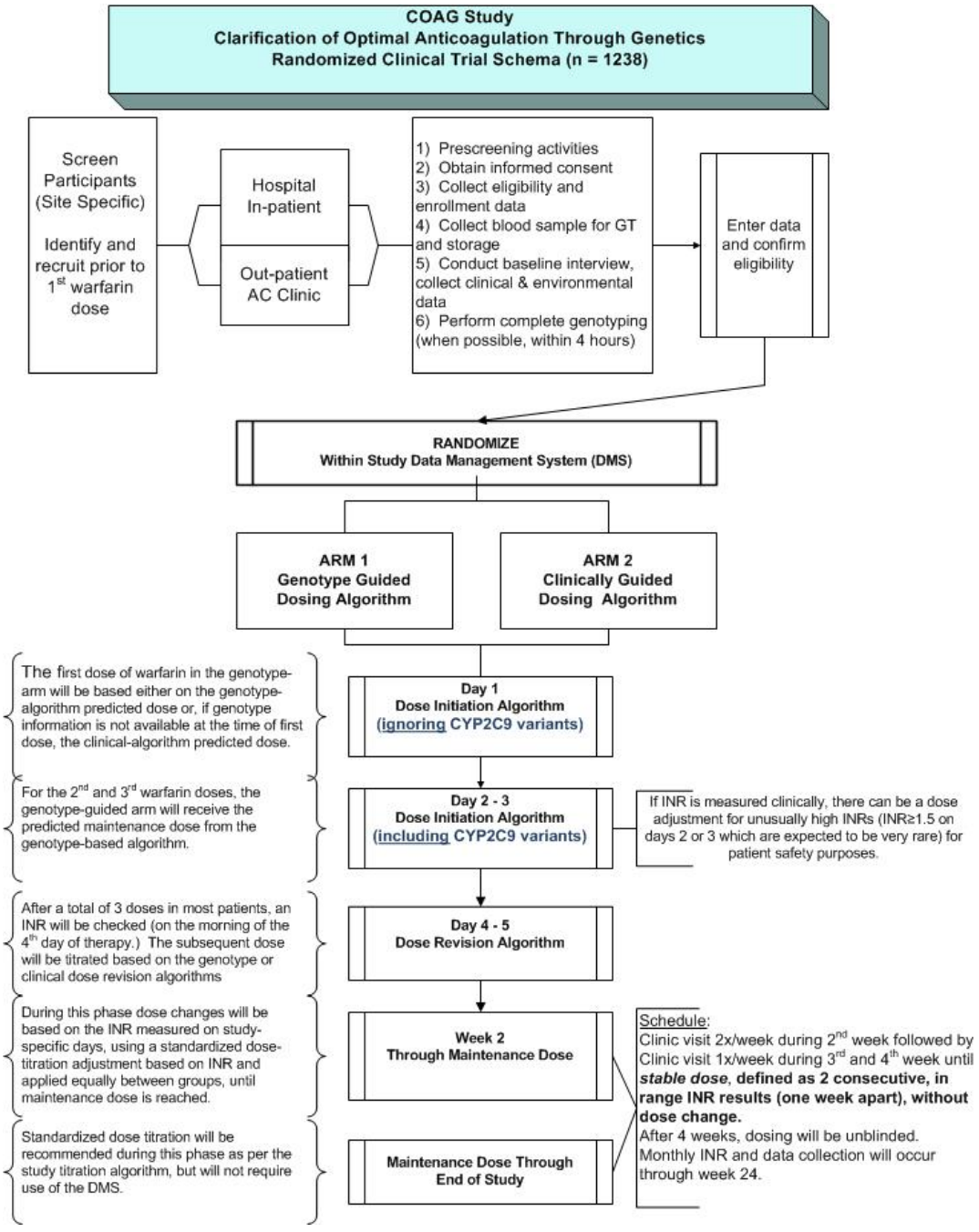
Each arm will include a baseline dose initiation algorithm and a dose revision algorithm applied over the first 4-5 doses of warfarin therapy. Thus, the intervention will be applied over these first 4-5 days. Following this period, dose titration will be the same between arms and blinded treatment assignment and warfarin dose will continue for the first 4 weeks of the trial (up to the primary endpoint). By comparing the two strategies in this trial, the study will be able to determine if genetic information provides added benefit above and beyond what can be done simply with clinical information.

Secondary objectives of the study are to compare the two strategies with respect to the PTTR during the first 2 weeks and 3 and 6 months of therapy; other outcomes at 2 and 4 weeks and 3 and 6 months, including time to stable warfarin dosing and INR above range (>4.0); number of dose changes required; and major clinical outcomes, including major bleeds, combination of major and minor bleeds, combination of major bleeds and thromboembolic complications, cost, and quality of life.

The primary endpoint of this study is the percentage of time participants spend within the therapeutic INR range (PTTR) during the first four weeks of therapy. This will be calculated from the INR values using the standard method that assumes a linear change in INR from one measurement to the next using the method of Rosendaal et al.[78]

1.B. Study Flow

The study will be conducted over a period of 36 months. Study visits will be followed according to the protocol visit schedule for the duration of 24 weeks. The first 4 weeks of treatment duration is a blinded study phase with 20 weeks of unblinded follow-up. The following is a diagram of the study flow:


COAG Study
Clarification of Optimal Anticoagulation Through Genetics
Randomized Clinical Trial Schema (n = 1238)
Screen Participants (Site Specific)
Identify and recruit prior to 1st warfarin dose
Hospital In-patient
Out-patient AC Clinic
1) Prescreening activities
2) Obtain informed consent
3) Collect eligibility and enrollment data
4) Collect blood sample for GT and storage
5) Conduct baseline interview, collect clinical & environmental data
6) Perform complete genotyping (when possible, within 4 hours)
Enter data and confirm eligibility
RANDOMIZE
Within Study Data Management System (DMS)
ARM 1
Genotype Guided
Dosing Algorithm
ARM 2
Clinically Guided
Dosing Algorithm
The first dose of warfarin in the genotype-arm will be based either on the genotype-algorithm predicted dose or, if genotype information is not available at the time of first dose, the clinical-algorithm predicted dose.
Day 1
Dose Initiation Algorithm
(ignoring CYP2C9 variants)
For the 2nd and 3rd warfarin doses, the genotype-guided arm will receive the predicted maintenance dose from the genotype-based algorithm.
Day 2 - 3
Dose Initiation Algorithm
(including CYP2C9 variants)
If INR is measured clinically, there can be a dose adjustment for unusually high INRs (INR≥1.5 on days 2 or 3 which are expected to be very rare) for patient safety purposes.
After a total of 3 doses in most patients, an INR will be checked (on the morning of the 4th day of therapy.) The subsequent dose will be titrated based on the genotype or clinical dose revision algorithms
Day 4 - 5
Dose Revision Algorithm
During this phase dose changes will be based on the INR measured on study-specific days, using a standardized dose-titration adjustment based on INR and applied equally between groups, until maintenance dose is reached.
Week 2
Through Maintenance Dose
Schedule:
Clinic visit 2x/week during 2nd week followed by
Clinic visit 1x/week during 3rd and 4th week until stable dose, defined as 2 consecutive, in range INR results (one week apart), without dose change.
After 4 weeks, dosing will be unblinded.
Monthly INR and data collection will occur through week 24.
Standardized dose titration will be recommended during this phase as per the study titration algorithm, but will not require use of the DMS.
Maintenance Dose Through End of Study

1.C. Method of Blinding

In order to blind participants, investigators and clinical site personnel to warfarin dose, and thus blind to study arm and genotype, all warfarin tablets will be blinded for the first 4 weeks for each study participant (i.e., up until the primary study endpoint). In order to do this and to replicate as closely as possible the usual way in which warfarin is prescribed and taken in practice, doses of warfarin will be encapsulated in hard gelatin capsules. There is NO placebo capsules used in this trial. All capsules will look the same regardless of warfarin dose. After 4 weeks (the primary outcome duration), clinicians will be informed of the actual dose that the patient is taking and patients will then receive their warfarin through their usual pharmaceutical outlet. The research pharmacy will no longer provide study drug.

1.D. Dosing Interventions

Patients will be randomized to one of the two dosing intervention arms: genotype-guided dosing OR clinical-guided dosing that will test the effects of algorithm-guided dosing over the first 4-5 days of therapy.

1.D.1. Genotype-guided Dosing

Dose Initiation Phase

Patients in this arm will have their initial dose based on an **"**initiation algorithm**"** that uses both clinical and genetic data (Days 1-3**).** The dose will be calculated by the data management system (DMS) using the regression coefficients from the dosing algorithm (sites will not need to do any calculations). The clinical and genotype data will be input into the central database: The clinical information will be input by the research coordinator, who will not know the genotype information and will not have access to that information in the DMS. The genetic information will be input by laboratory personnel who will not know the clinical information and will not have access to that information in the DMS. This information will then be used by the DMS to calculate the patient's initial dose. The calculated dose information in the DMS will then be accessed by the site Research Pharmacist who will not be blinded to dose but will be blinded to clinical information, genotype, and study arm. The Research Pharmacy will then dispense the blinded warfarin dose for the patient. Routinely for hospital in-patients, dosing will occur on a daily basis during the dose initiation phase. The research coordinator enters a dose requisition for each day and the Research Pharmacist logs on to the pharmacy module of the data management system (DMS) to see the assigned dose for that day and dispenses a single dose accordingly.

Dose Dispensing on Day 1 and Day 2 –Dose Initiation Phase

For patients randomized to the genotype-guided dosing arm, the "initiation algorithm" incorporates the CYP2C9 variant on Day 2 of the dose initiation phase. As a result, the dose dispensed on Day 2 of the study may be different for those patients assigned to this arm. In order to blind investigators and patients from observing this change in dose from Day 1 to Day 2, some participants in both the genotype arm and clinical arm will receive 2 pills on Day 1 and 2 pills on Day 2 based on a selected dose assignment for those days. This dosing scheme will be applied as follows:

- If the assigned dose is 4 mg on Day 1, the patient will receive two - 2mg capsules. This dosing scheme applies ONLY to Day 1 when a 4mg dose is assigned. Then give single capsule amount for dose assigned on Day 2.

- ❖ If the assigned dose is 6 mg on Day 2, the patient will receive two – 3 mg capsules. This dosing scheme applies ONLY to Day 2 when a 6mg dose is assigned. Then give single capsule amount on Day 3.

(Please also refer to instructions in Pharmacy Manual Medication Dispensing and Accountability and Data Management System for Manual for Research Pharmacy - Section 3 and Section 4.

Predicted Doses for Day 2 and Day 3 – Dose Initiation Phase

A feature in the Pharmacy Module of the COAG Data Management System (DMS) will permit the Research Pharmacist to view the predicted dose for Day 2 and Day 3 of the Dose Initiation Phase for the purpose of pre-dispensing doses for Day 2 and Day 3. This predicted dose is calculated by the DMS using the Day 2 algorithm of incorporating the CYP2C9 variant. Use of the predicted dose feature to pre-dispense Day 2 & Day 3 dose is to be used in the following circumstances:

- For the **outpatient** whose next scheduled clinic visit is Day 4 or Day 5
- For the hospital **in-patient** whose Day 2 and Day 3 dosing schedule will occur over a **weekend or holiday period**

IMPORTANT NOTE: There are times when the actual dose the patient is to receive for Day 2 and Day 3 (and Day 4 if needed) may be different than the predicted dose viewed in the DMS. This will occur in the following situations:

- o **When genetic data is entered into the DMS after Day 1.** Genetic data entered at Day 2 or thereafter will result in the DMS calculating a change in dose for patients assigned to the genotype dosing arm.
- o **When genetic data is not available on Day 1** (for either inpatients or outpatients), then the pre-dispense dose feature should not be used.
- o **An INR is entered into the DMS on Day 2, 3, or 4 and the INR is greater than or equal to 1.5** - This will most likely occur with hospital inpatients, who then will require a new dose to be dispensed by pharmacy and a recall of any pre-dispensed dose issued.

Dose Revision Phase (Day 4 and/or Day 5)

After three doses of warfarin, each patient's INR on day 4 of therapy will be input into the DMS by the Research Coordinator. This information, along with clinical and genetic information already in the system, will be used to calculate a new estimated dose (dose revision). If patients are unable to have an INR on day 4 (e.g., because they are outpatients and the fourth day falls on a Sunday), they will continue on their initial dosing and the dose revision algorithm (which includes a variable for the 5th day of dosing along with one for the fourth day of dosing) will be applied on day 5. Although the protocol specifies that only a day 4 or a day 5 INR will be drawn, some patients at the inpatient level of care will have INRs drawn on both days. For these patients the dose revision algorithm will be applied on both of those days.

IMPORTANT NOTE - What to do if there is a calculated dose of zero (0) mg: There may instances when the DMS algorithm will calculate a dose of zero (0) mg for a participant. This may occur when a reported INR is greater than 3.0. Therefore, **if the calculated dose is zero (0) mg. during Days 1-5 the medical monitor must be contacted** to verify the reason for a dose of zero (0) mg and to determine what dose is to be dispensed to the patient. (Refer to Section 1.D.3 for Medical Monitor contact information).

Dose Titration Phase

Following the dose initiation and dose revision phases, patients will enter the dose titration phase (day 6 – week 4). In order to make the subsequent management of participants as equivalent as possible for all participants in both arms, all dose adjustments in the dose titration phase and until stable maintenance dose is reached will be based on INR measurements according to a standardized protocol. During this phase dose changes will be based on the INR measured on study-specific days, using a standardized dose-titration adjustment based on INR and applied equally between groups. Participants will be instructed to contact the research coordinator at the site if they start any new medications or stop any current medications. If these medications interact with warfarin, the participant will return in 5-7 days for an INR check and adjustments will be made accordingly, again maintaining blinding of dosing during the first 4 weeks of therapy.

The dose revision and titration calculations will generate a weekly dose. Weekly dosing may require two different doses of warfarin on different days of the week (e.g., a 27 mg weekly dose requirement would be given as: 5 mg Mon/Wed/Fri and 3 mg Tues/Thurs/Sat/Sun Dosing). Weekly dosing will be rounded to the nearest integer (e.g., if the weekly dose is 35 mg/week and the dose titration calls for a 5% increase in dose, the new dose of 36.75 mg will be rounded to 37 mg/week). These dose titrations are both typical of available standardized dose adjustments and allow for titration to be standardized across arms, during the blinded phase of the trial and beyond.

After 4 weeks, dosing will be unblinded and the patient will not long received blinded study drug. **(See Section 1.D.5)**. Patient dosing will continue to follow the dose-titration algorithm based on the INR and dose data inputted into the data management system (DMS) to identify any changes in dose needed, until each patient reaches stable/maintenance dose (defined as the dose that leads to a therapeutic INR over two consecutive INR measurements, spanning a period of at least one week apart). After that, dose titration will continue to be recommended as per the study titration algorithm, but will not require the use of the DMS

1.D.2. Clinical-guided Dosing

Patients in this arm will have their initial dose based on an initial dose algorithm that uses only clinical data but not genotype information, again deriving dose from regression coefficients. Criteria for choosing this algorithm are the same as those for choosing the genotype-guided algorithm. The clinical information input by the research coordinator into the data management system will calculate the patient's dose. The research coordinator will not know if genetic information is also being used to calculate dose or if the patient is in the clinical-guided dosing arm. The dosing scheme for Dose Dispensing on Day 1 and Day 2 -Dose Initiation Phase as described in Section 1.D.1 will also be applied in this arm. Following the dose initiation phase (Days 1-3), a clinical dose revision algorithm will be used to modify dose (similar to the genetic dose revision algorithm, but not utilizing genetic information). After Day 5, patients will have subsequent dose adjustments based on standardized titration, similar to the genotype-guided arm as discussed in Section 1.D.1.-Dose Titration.

1.D.3. Medical Monitor

The Medical Monitor, Dr. Scott Kasner, is a licensed physician and Vascular Neurologist associated with the Clinical Trial Coordinating Center (CTCC), and serves in an independent

role. The Medical Monitor will be unblinded to study dose and treatment arm assignment for all patients enrolled in the study. The Medical Monitor is responsible for:

- Managing requests for warfarin dose adjustments
- Authorizing requests for dose unblinding
- Serving as a resource to investigators and coordinators for urgent concerns related to patient safety, particularly when such concerns might require interruption or cessation of the study intervention and /or any deviation from the study protocol. The medical monitor is also available to Research Pharmacists for questions or concerns related to dose dispensing.
- Reviewing SAE reports and major bleeding events

Dr. Kasner may be contacted by the clinical site investigator, the research coordinator, or research pharmacist. Patients are not to contact Dr. Kasner.

Medical Monitor Contact Information:

- Cell phone (preferred for urgent issues): 215-593-6523
- Beeper number: 215-452-4944

1.D.4. Warfarin Dose Adjustments (Dose Over-ride)

The Medical Monitor will be contacted by site investigator any time they want to prescribe a warfarin dose other than the dose determined by the study algorithms (dose over-ride). During the blinded first 4 weeks, these changes would represent a “change in the percentage adjustment of warfarin dose” since investigators will not know the actual dose being given and/or a “change in plans to hold warfarin doses or give extra doses.” Such considerations should be made solely for patient safety, or when there is an issue not otherwise considered by the standard study algorithm such as:

- patient error with prior assigned dose,
- prescribing or dispensing error with prior assigned dose,
- recently instructed not to take anything by mouth, i.e., “NPO”, non-adherence,
- new medication addition or deletion,
- recent bleeding event,
- recent thromboembolic event

In these and other circumstances, a discussion between the site investigator and the Medical Monitor should occur, and an acceptable warfarin dose will be determined based on the relevant clinical issues. All deviations from the study algorithm dosing schedule must be approved by the Medical Monitor. If a request for dose over-ride is approved, the Medical Monitor will contact the site Research Pharmacist to inform them of the change in dose. The change in dose information will be entered into the DMS by the site Research Pharmacist. Since subsequent INRs and dose adjustments will refer back to the over-ride dose, it is important that the Research Pharmacist enter the dose change correctly into the DMS as this dose will replace the dose assigned by protocol in the database, and be identified as an over-ride. The frequency of dose over-rides will be monitored by the CTCC.

Only the Medical Monitor will inform the Research Pharmacist of patient dose changes outside of the assigned algorithm.

1.D.5. Unblinding Procedures at Week Four (4):

****

At Day 29 of the study, unblinding of warfarin dose will occur. The Research Pharmacist **will not** dispense blinded study drug on this day, nor will the patient continue to receive blinded study drug from the research pharmacy. The patient will now receive warfarin by written prescription from the clinical provider.

On Day 29 for each enrolled patient, the pharmacy DMS module screen will be available to the Research Coordinator to view. The Research Coordinator will enter a dose request into the DMS and include in the dose request the INR results at Day 29. The DMS pharmacy module screen will reveal the Day 29 dose calculated for the patient and the patient's weekly dosing regimen. The RC will notify the Principal Investigator of the calculated Day 29 dose and weekly dosing regimen. The Research Coordinator will also be responsible for collecting and returning to Research Pharmacy any blinded study drug dispensed to the patient.

NOTE: Clarification of the Research Coordinator view of the DMS Pharmacy Module: The Research Coordinator view of the DMS pharmacy module will be such that the Research Coordinator cannot view any doses dispensed to the patient before Day 29 . The DMS module screen will also inform the RC as to whether or not the patient is at maintenance dose

*****Important to Note: The Research Pharmacist must NOT REVEAL any doses dispensed before Day 29)**. If an Investigator requests information about doses dispensed to the patient before Day 29, please instruct the Research Coordinator to contact the Medical Monitor for this information

Clinical provider dosing of the patient will continue to follow the dose-titration algorithm based on the INR and dose data inputted into the data management system (DMS) to identify any changes in dose needed, until each patient reaches stable/maintenance dose (defined as the dose that leads to a therapeutic INR over two consecutive INR measurements, spanning a period of at least one week apart). After that, dose titration will continue to be recommended as per the study titration algorithm, but the clinical provider will not be required to use the DMS algorithm for continued dosing.

1.D.6. Patient Safety and Unblinding:

A clinical site PI may request dosing information in circumstances such as a medical emergency or in a rare situation in which the PI believes it is important to unblind the warfarin dose to medically manage the patient.

To initiate this request, the PI should contact the Medical Monitor. It will be the clinical site PI's responsibility to assess issues of patient safety and communicate them to the Medical Monitor. The Medical Monitor will make the final determination regarding unblinding the dose of a particular patient. The Medical Monitor may request dosing information from the research pharmacist or the central IDS, depending on the situation. The clinical site PI will be responsible for communicating with the patient.

Only in the event of a medical emergency wherein the Medical Monitor cannot be reached by the PI and the warfarin dose must be revealed in order to act for patient safety, the site Research Pharmacist is permitted to reveal patient dose to the site PI or clinician.

2. Clinical Site Research Pharmacy responsibilities in the COAG Clinical Trial

2.A. Summary of Responsibilities for Research Pharmacy

In the COAG clinical trial, the Research Pharmacist is responsible for activities related to dispensing of study drug, entering study drug information into the COAG data management system, maintaining the integrity of blinded study dose information. Specific responsibilities include:

- Maintaining study drug supply, receipt, storage, preparation, dispensation, and disposal or return according to procedures outlined in the Investigation Drug Service Pharmacy Manual.
- Accountability of pharmacy drug records and record security
- Dispensing dose and quantity as assigned in the COAG data management system dose calculation module
- Accurately entering the dose dispensed for each patient into the data management system
- Not dispensing study drug if the "do not dispense calculated dose" flag is present in the data management system.
- When a dose "over-ride" is requested, discussing dose changes only with COAG Medical Monitor and dispensing over-ride dose ordered by the Medical Monitor
- Maintaining the integrity of the blinded study dose and will not reveal participant dose information to site PI, other investigators, or Research Coordinator.

3. Data Management System Dose Calculation

3.A. Overview

The Data Management System (DMS) is programmed to calculate the dose of warfarin that each patient is to receive. The DMS will include several modules to calculate the daily dose of study medication for randomized subjects based on algorithms defined in the protocol. These modules will check for the availability of specific data elements that are required by the algorithms and will prevent a dose calculation from occurring if mandatory data are missing. Medication dosing will be calculated for the following dosing phases of the protocol:

1. Initial dose algorithm - The initial dose algorithm will be used if the subject is at day one, day two, or day three of the intervention According to the protocol, a value for INR is not expected for days 1 through 3. However, if an INR is obtained for any reason on day 2 or 3, it will be used to modify the dose calculation.
2. Dose revision algorithm - The revision dose algorithm will be used if the subject is at day four or day five of the intervention. The dose calculated on days four and/or five will be calculated as a weekly dose for study participants.
3. Dose titration - During this dose titration phase, dose changes will be based on the INR measured on study-specific days, using a standardized dose-titration adjustment based on INR and applied equally between groups, day 6 through week 4.

For each of these phases, the research coordinator will complete a dose request form and enter that data into the DMS. Depending on where the subject is in the visit schedule, one of the dose calculations will be selected by the DMS and used to determine the optimum medication dose and that value will be recorded in the DMS. The research coordinator will notify the Research Pharmacist (by phone) that a dose request has been submitted for the patient. The dose calculated for the patient will be displayed to the Research Pharmacist in the pharmacy module. Once the dose has been successfully submitted, the dose calculation cannot be attempted again for that study day. The results of the dose calculation will not be displayed to the research coordinator.

The research coordinator has the capability of submitting a dose request when the genetics data is unavailable if it is necessary to obtain the study medication due to time constraints.

3.B. Pharmacy Module

Because the research pharmacist in this study is not blinded to study dose, the DMS will allow a pharmacist at a clinical site to view the warfarin dose calculated for dispensing to the patient. The calculated dose may be for a single day or may represent several days. Initial dose calculations will result in a single dose recommendation.

Please refer to above Section 1.D.1-Predicted Doses for Day 2 and Day 3 Dose Initiation Phase and please refer to Section 4.F-Viewing Calculated Dose and Entering Dose for viewing predicted doses and instructions about pre-dispensing predicted doses**.**

The pharmacy module will contain entry fields to allow the Pharmacist to record the actual dose dispensed for the patient. In cases of clinician over-ride, the actual dose dispensed that you record into the entry field will be different from the viewed DMS-calculated dose. The module will also allow the Pharmacist to view all previously calculated and dispensed doses.

If research pharmacy is required to enter a record of the study medication into the in-patient hospital electronic medical records system, this information is enter as: “Warfarin Blinded Dose” so as to preserve the blinding of the study dose dispensed for the patient.

Weekly Dosing Regimens

It is important to ensure that medication regimens are not so complex as to lead to patient errors. Thus, no weekly dosing regimen will require the use of more than 2 bottles of warfarin. ***Please refer to the Investigational Drug Pharmacy Manual*** for instructions on dispensing for weekly dosing.

The clinical dose revision and titration calculations will generate a weekly dose and the module will show the weekly dosing schedule displayed in daily doses that the patient is to receive.

4. Data Management System Users Guide

4.A. Introduction

The data management system (***DMS***) is developed in accordance with the requirements of the **COAG** Project. The DMS is an Oracle-based application that utilizes java script. In order for users to connect to and run the DMS, it will be necessary to install the Oracle Jinitiator plug-in and security certificate. Updates are available at the following website: rt4.cceb.med.upenn.edu/crcu_html/jinit/jinit_download.htm.

This manual is developed as a reference guide for the data entry person on the project. To access the DMS, the user will need a computer with access to the internet through an internet browser.

The DMS is used for entry of the data that is collected on the COAG CRFs. The data tables within the DMS are collectively labeled as the production database.

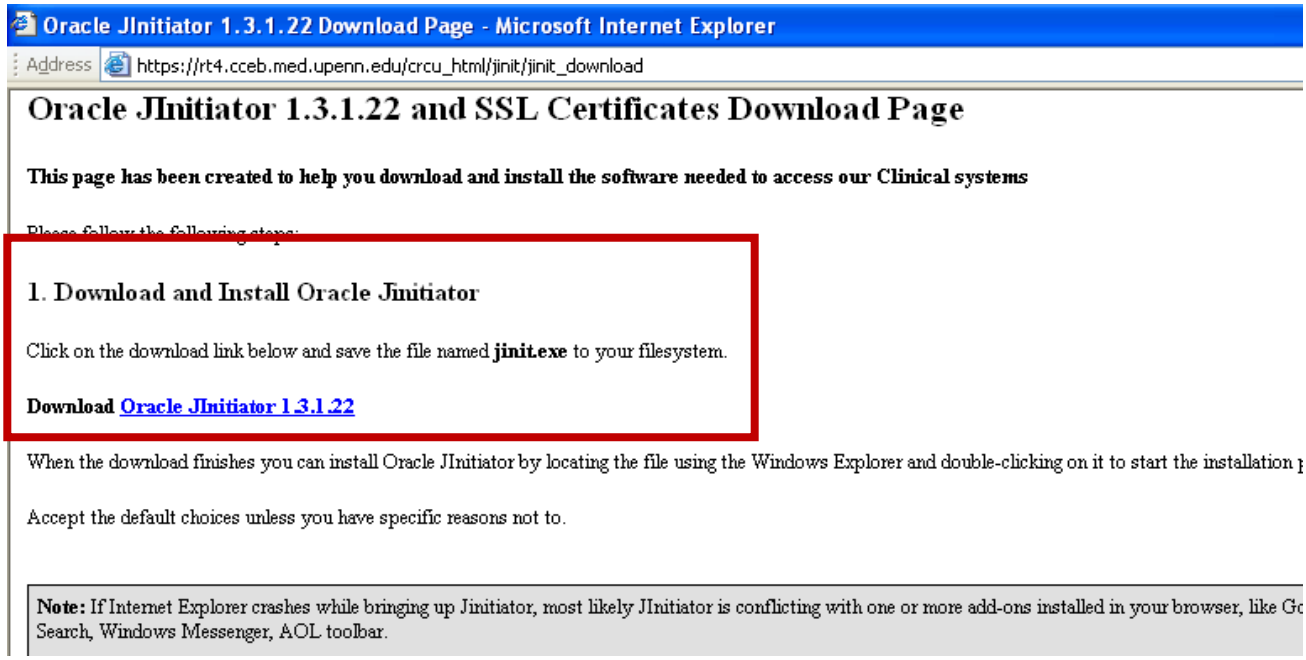
4.B. Oracle JInitiator

Before the data management system (DMS) is installed on a personal computer, two components need to be downloaded onto the computer first - Oracle JInitiator ver.1.3.1.22 and the SSL Certificate. The following instructions will guide the user through installation of these add-ons.

- Open a web browser: Internet Explorer (IE) 6.0 or FireFox 2.0 or higher or Netscape.
- Type in the following url:

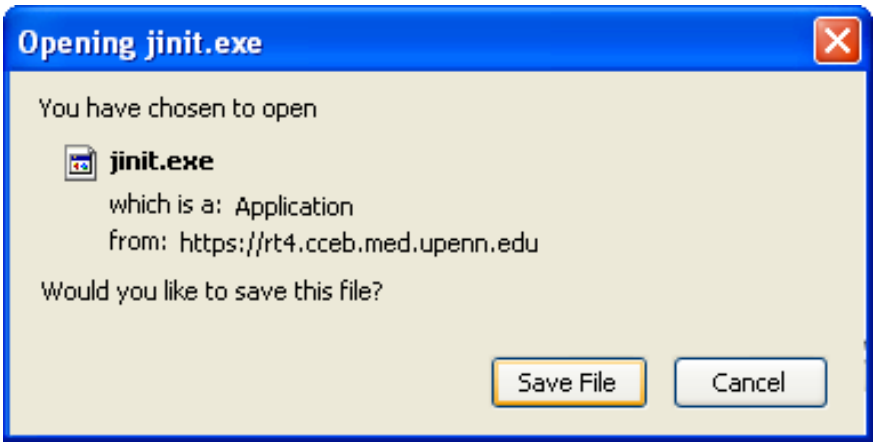
https://rt4.cceb.med.upenn.edu/crcu_html/jinit/jinit_download

The Oracle JInitiator version 1.3.1.22 must be loaded first.



- Click the highlighted link, “Download Oracle JInitiator 1.3.1.22”

A prompt will next confirm the file name and the location of the executable.



- Click the “Save File” button

The user will be prompted to run or save the self-extracting jinit.exe file.

- Click the “Save” button to save the file to the PC

Once this is done, JInitiator will begin the download.

The next window is a security warning about the download that is about to be loaded.

- Click the “Run” button

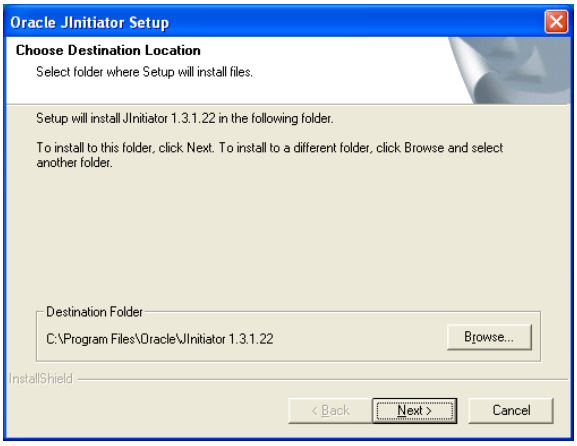
The installer will prompt the user for a destination location to save the file.

The default location the executable points to is C:\Program files\Oracle\JInitiator, on the hard drive of the PC.

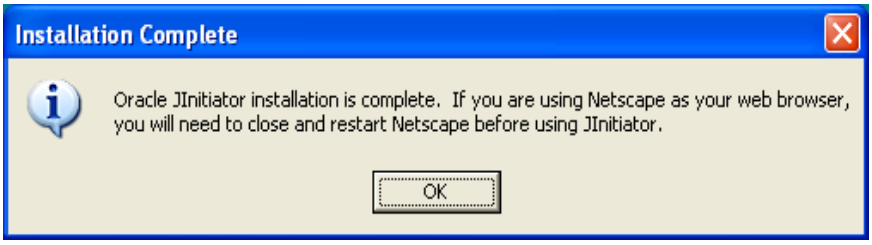
If this is the incorrect desired location for this file:

- Click the “Browse” button to choose a desired location to save this file on the PC.

If correct, click the “Next” button to continue the installation.



Once the installation is complete, the following window will appear:

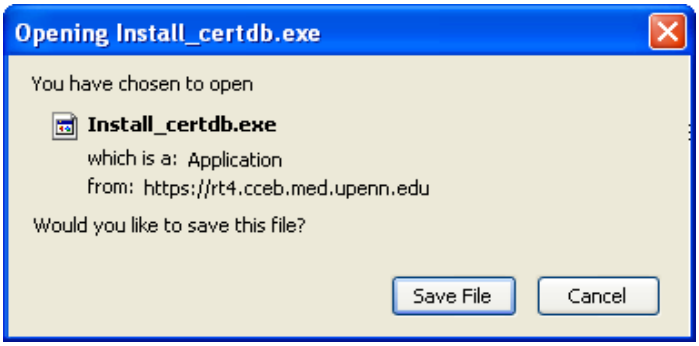


Note: If using the Internet Explorer browser or FireFox browser, it is not necessary to close and restart the browser, but if using the Netscape web browser, the user will need to close and restart the browser before using JInitiator.

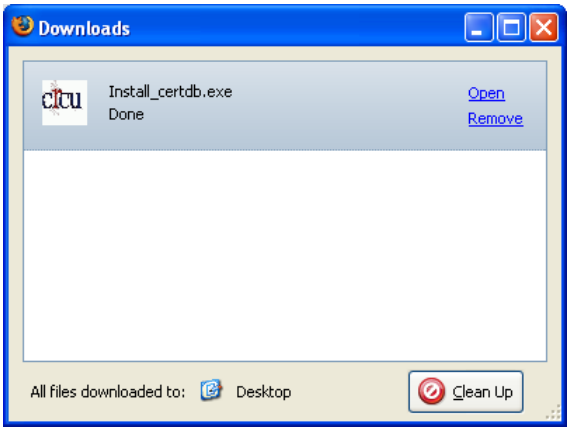
4.C. SSL Certificate

Once the Oracle JInitiator executable is loaded onto the PC:

- Click the second plug-in, the SSL Certificate called, ”Certificate Installer”
- Once the link is chosen, the following window will appear:

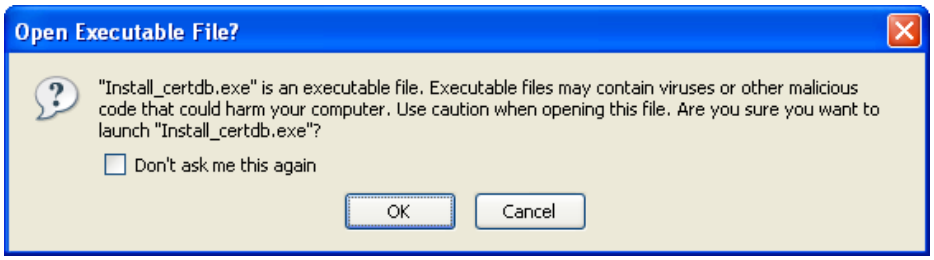


When downloading this or any file, a separate window will open exclusive to download content.



- Select “Open” to begin the downloading process.

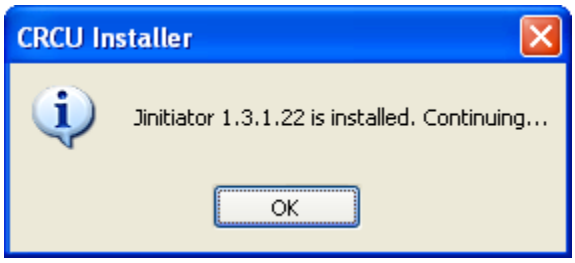
The next screen illustrates a security function that provides caution to downloading executable files that may contain viruses or other malicious code(s) that could harm the computer.



- Click “OK” to proceed with the installation

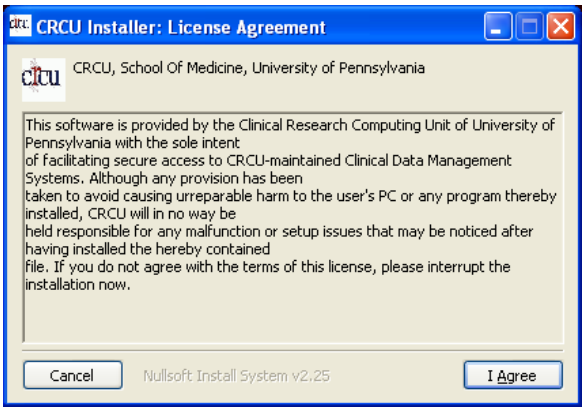
This window advises the user that the installation of the CERTDB.TXT file will begin.

- Click “Yes” to continue



- Click “OK” to continue with the installation

Once the License agreement is reviewed:



- Click “I Agree” to continue installation

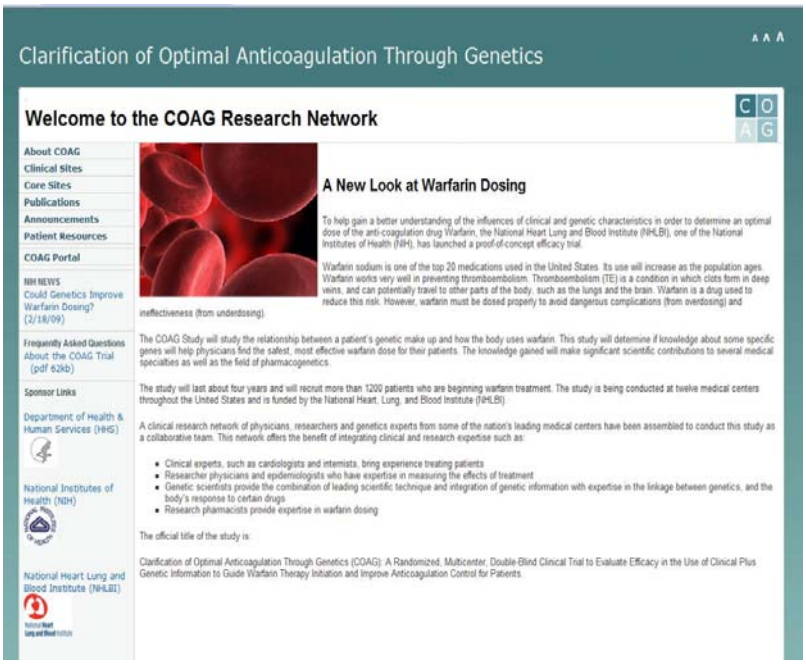
Setup will provide a prompt that indicates the location for the installation to be downloaded. There is an option to choose a different location to save the certificate.

4.D. Data Management System Web Site

Connect to the Internet, run a web browser (Internet Explorer 6-8 and Mozilla Firefox 2-3 are supported at this time) and connect to COAG study portal

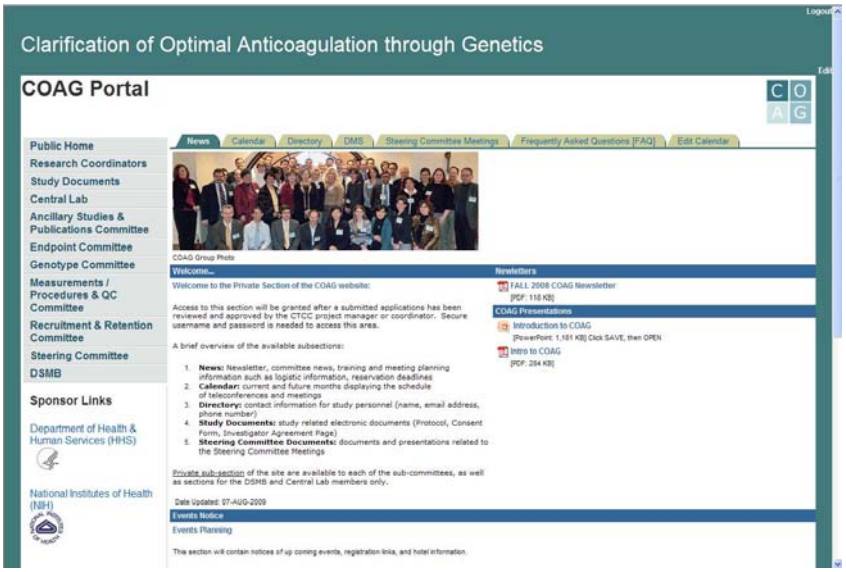
http://www.coagstudy.org

The portal main page will be displayed



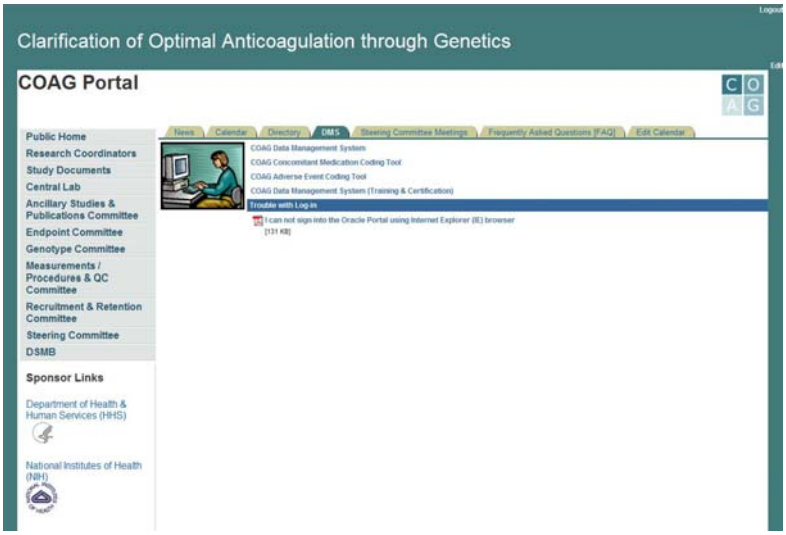
Click on the "**COAG Portal**" link and you'll be prompted to enter your portal website user name and password.

Click "**Login**" and the portal main internal page will be displayed



Click on the "**DMS**" tab

The DMS page will be displayed.



To access the Production ("Live") DMS, click on the "**COAG Data Management System**" link.

To access the Training DMS, click on the "**COAG Data Management System (Training & Certification)**".

In both cases, if you have correctly installed all the software described in section 9.B and 9.C, you should get the DMS login screen.

In case you have trouble logging to the DMS through the portal, and the solutions provided by the COAG coordinator in the email containing your account credentials do not work, you can access the production DMS directly, via the following web address:

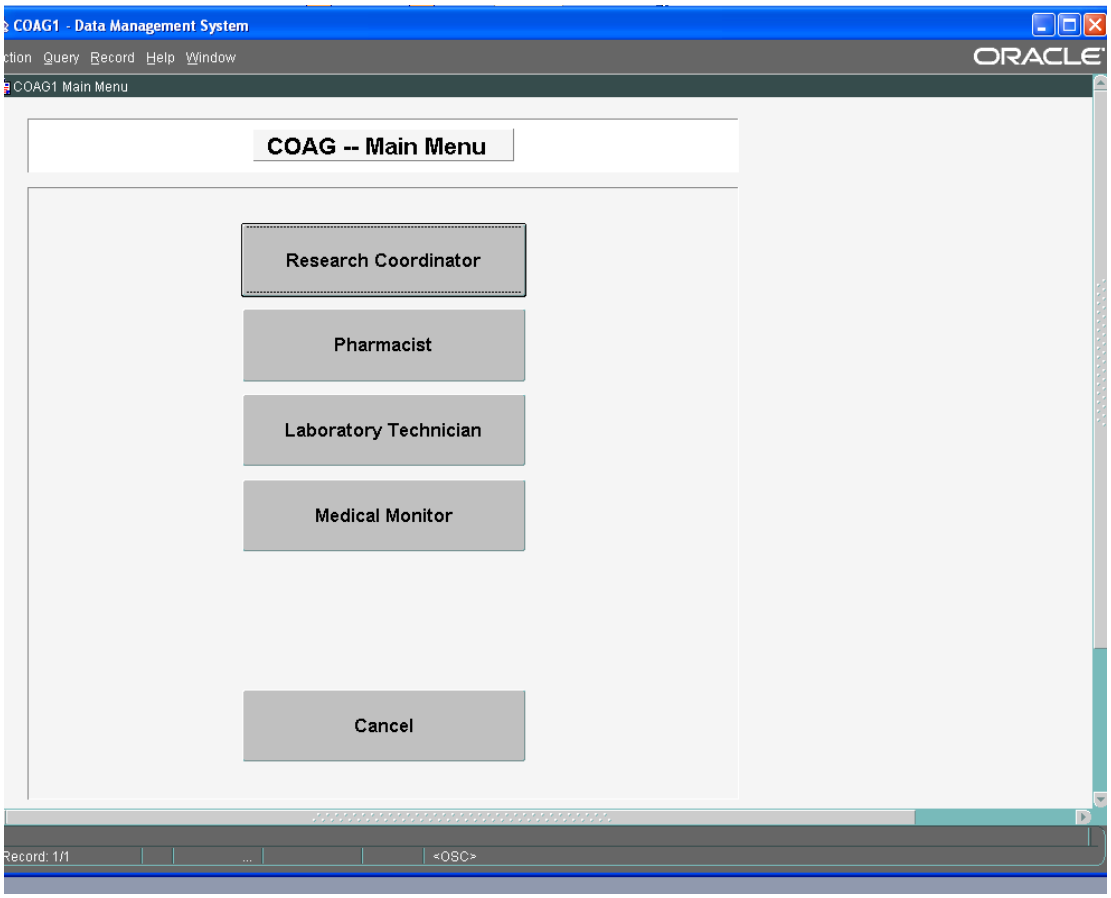
https://rt4.cceb.med.upenn.edu/crcu_html/COAG1.htm.

We do not recommend you save the above address in your browser's "Favorites" or Bookmarks, since it is non-published address, and could be subject to changes during the study.

Should you have problem executing and of the above steps, please contact COAG Help Desk Support. See section 6.A for details on how to contact the Help Desk.

4.D.1. COAG-MAIN MENU:

Once you have successfully navigated to the Data Management System (DMS) web site, you will first be presented with the Main Menu screen. The Main Menu is used to navigate to the appropriate module of the DMS. The COAG Main menu contains a set of buttons that will provide the user access to data entry modules. The privileges provided to the user will determine the functions available in the DMS. The Pharmacist view is the calculated dose and enter dispensed dose. Locate the Pharmacist button that represents your position on the study.

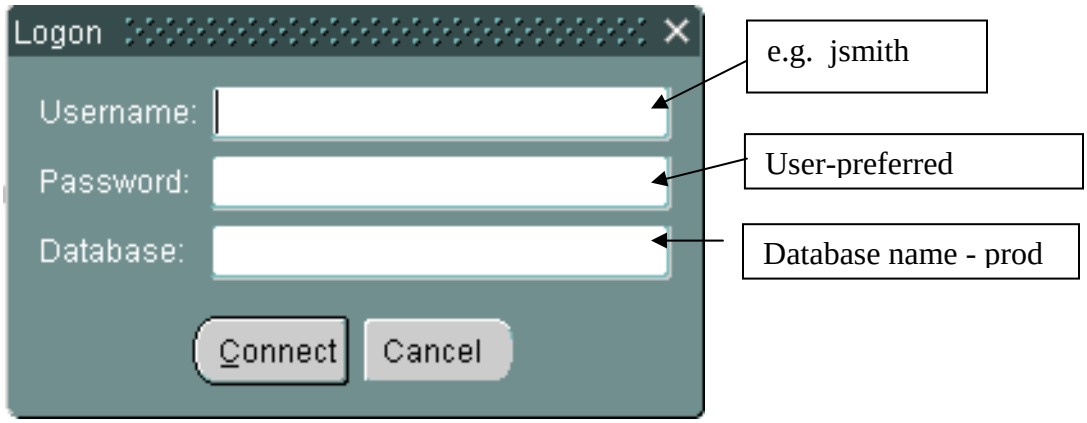


- Click on the Pharmacist button.

4.D.2. Data Management System Log In:

You will now be prompted to log into the database with your user name and password.

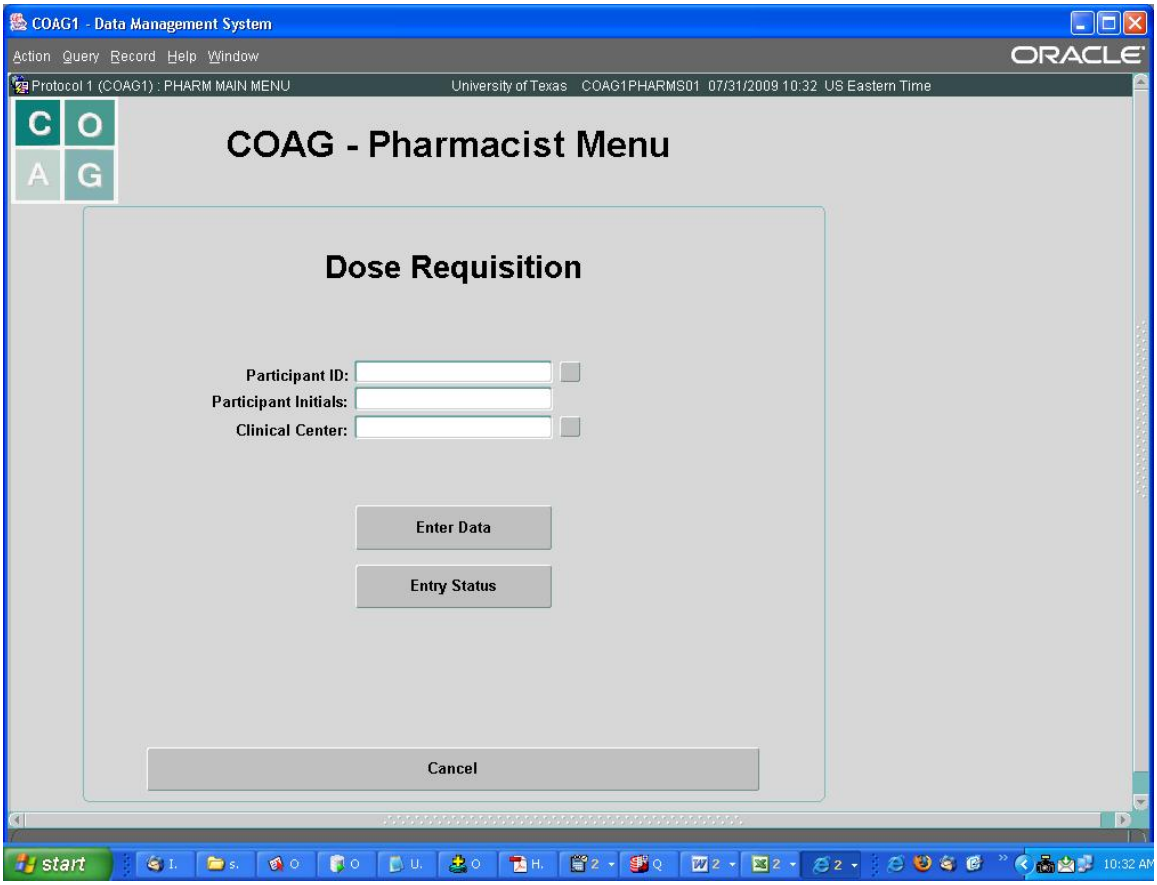
- Enter requested log-in information in the dialog box
  - Username - the first initial and last name, limited to 8 characters
  - Password - for the first time user a temporary password – “temp01” - is provided; a prompt will request the user to create a new password that is easily remembered for future log-ins
  - Database - ‘PROD’; will give the user access to the COAG database



- Click on the “Connect” button to access the Pharmacist menu of the Data Management System

4.E. COAG –Clinical Center Menu for Research Pharmacists

- Select the Participant ID (PID) from the drop box or type it in. The Participant Initials and Clinical Center will automatically populate if you select from the drop box.
- If you type in the Participant ID, you will have to type in the Participant initials and Clinical Center.

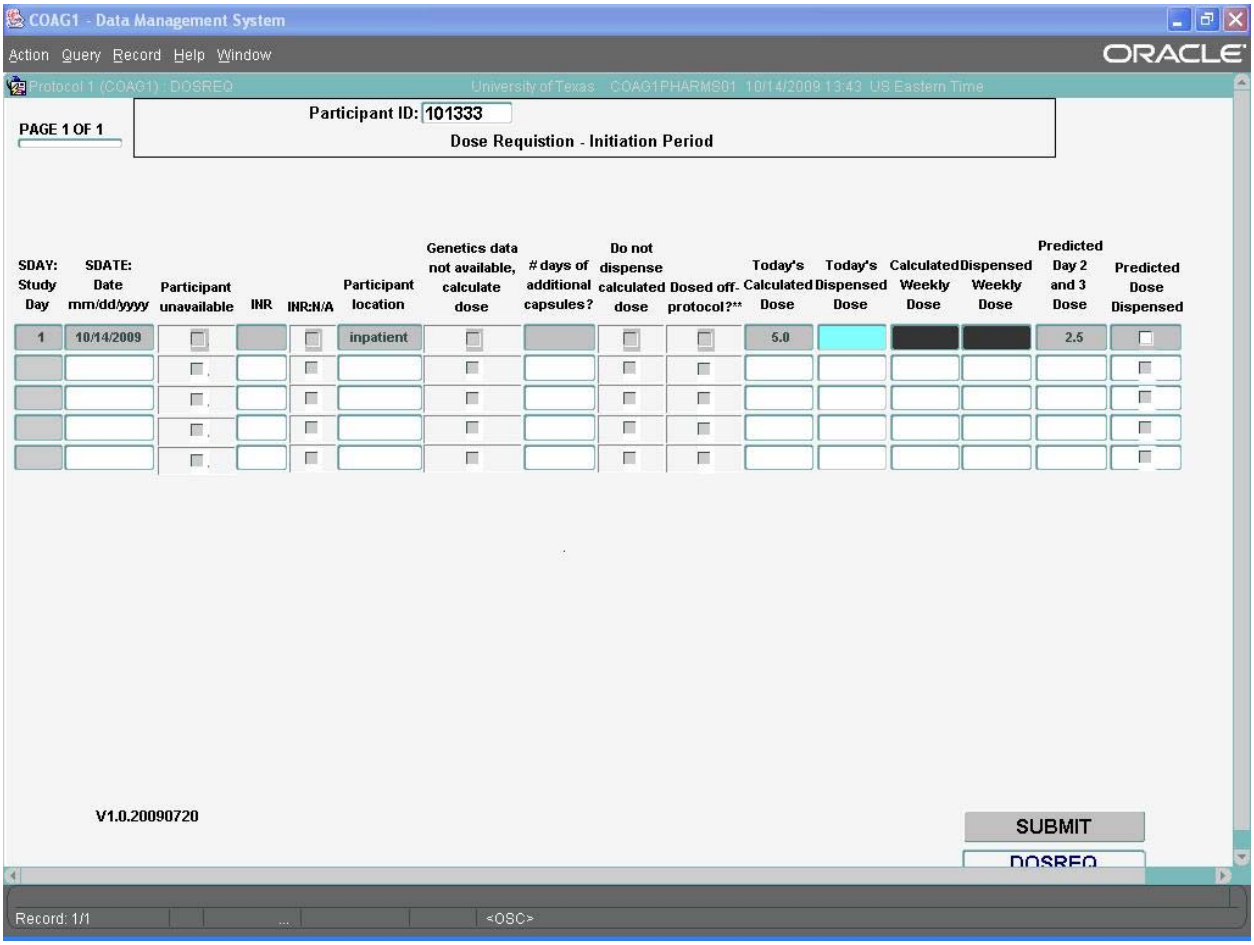


4.F. Viewing Calculated Dose and Entering Dose Dispensed

4.F.1. Dose Initiation Days 1 through 3:

As shown below, from this screen you can view the dose requested in the initiation period. The screen will display the participant ID, study day and date and participant location. It will indicate if an INR is available or not available (Note: An INR will not be entered into the dose requisition by the Research Coordinator (RC) on Day 1 – box darkened on screen). It will also indicate if genetic data is available or not available. It will display today's calculated dose.

The below screen informs you that this is the first dose requested for an in-patient participant in the dose initiation phase. An 5.0 (mg) dose has been calculated for today's warfarin dose.

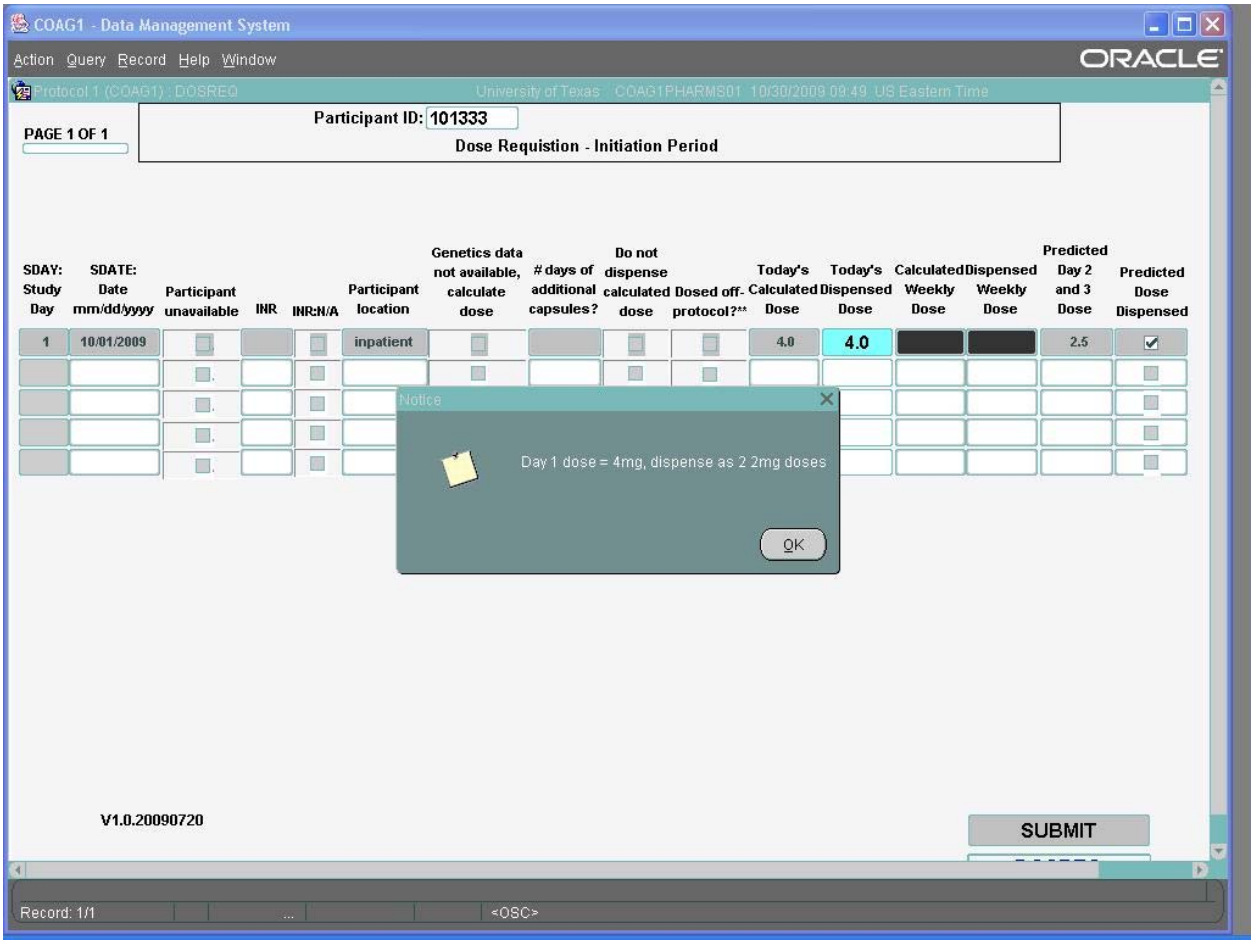


The pharmacist will record the dose dispensed in the "Today's Dispensed Dose" box of the screen. After completing this entry, click on the SUBMIT button on the bottom right of the screen.

Dose Dispensing on Day 1 and Day 2 –Dose Initiation Phase

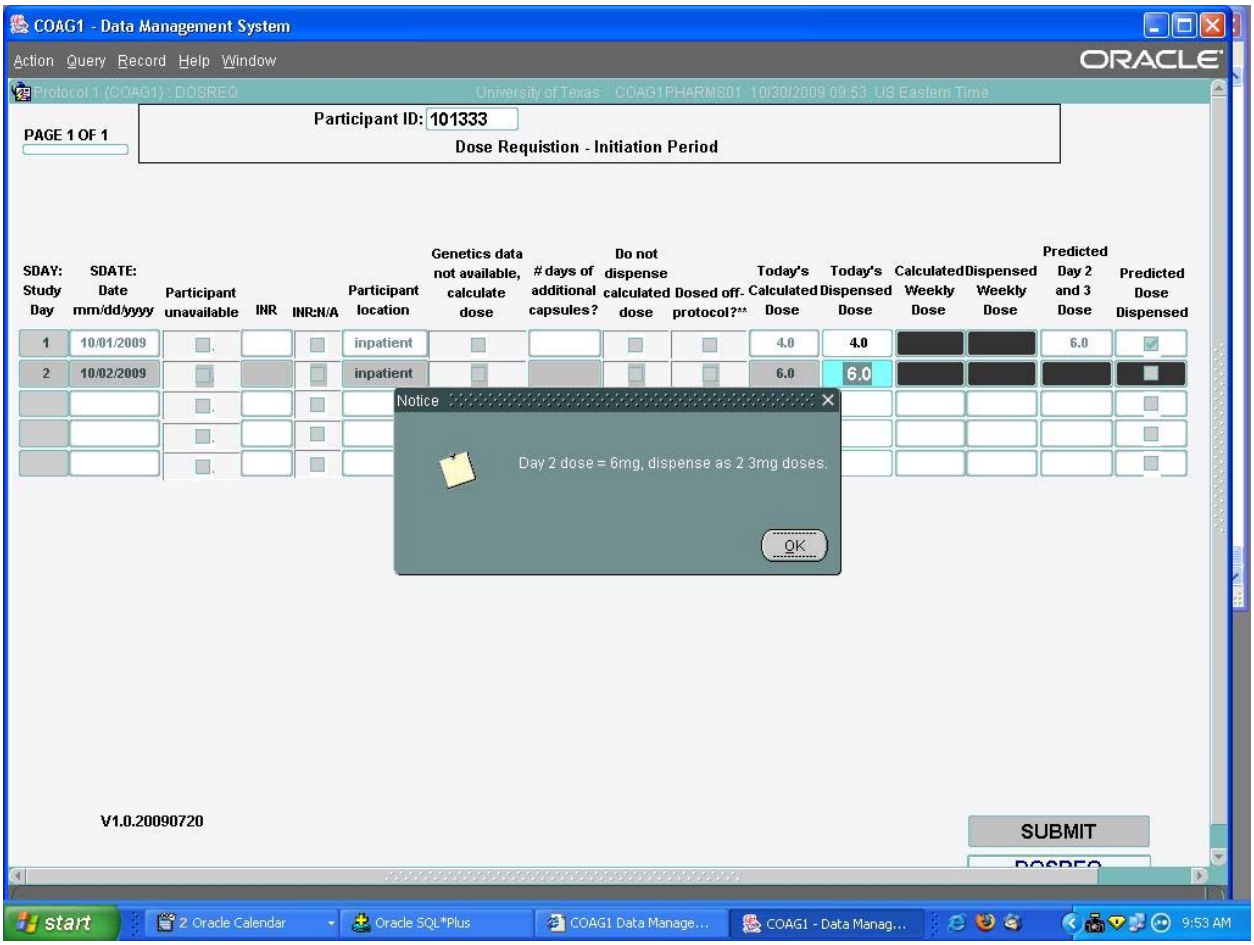
For patients randomized to the genotype-guided dosing arm, the "initiation algorithm" incorporates the CYP2C9 variant on Day 2 of the dose initiation phase. As a result, the dose dispensed on Day 2 of the study may be different for those patients assigned to this arm. In order to blind investigators and patients from observing this change in dose from Day 1 to Day 2, some participants in both the genotype arm and clinical arm will receive 2 pills on Day 1 and 2 pills on Day 2 based on a selected dose assignment for those days.

The DMS will notify you of what to give on Day 1 for patients whose dose is 4 mg. as shown on the below screen pop-up reminder.



The above screen applies only to Day 1. Then give regular capsule amount for day 2.

Likewise, for Dosing on Day 2, the DMS will notify you of what to give on Day 2 for patients whose dose is 6 mg as shown on the below screen pop-up reminder.

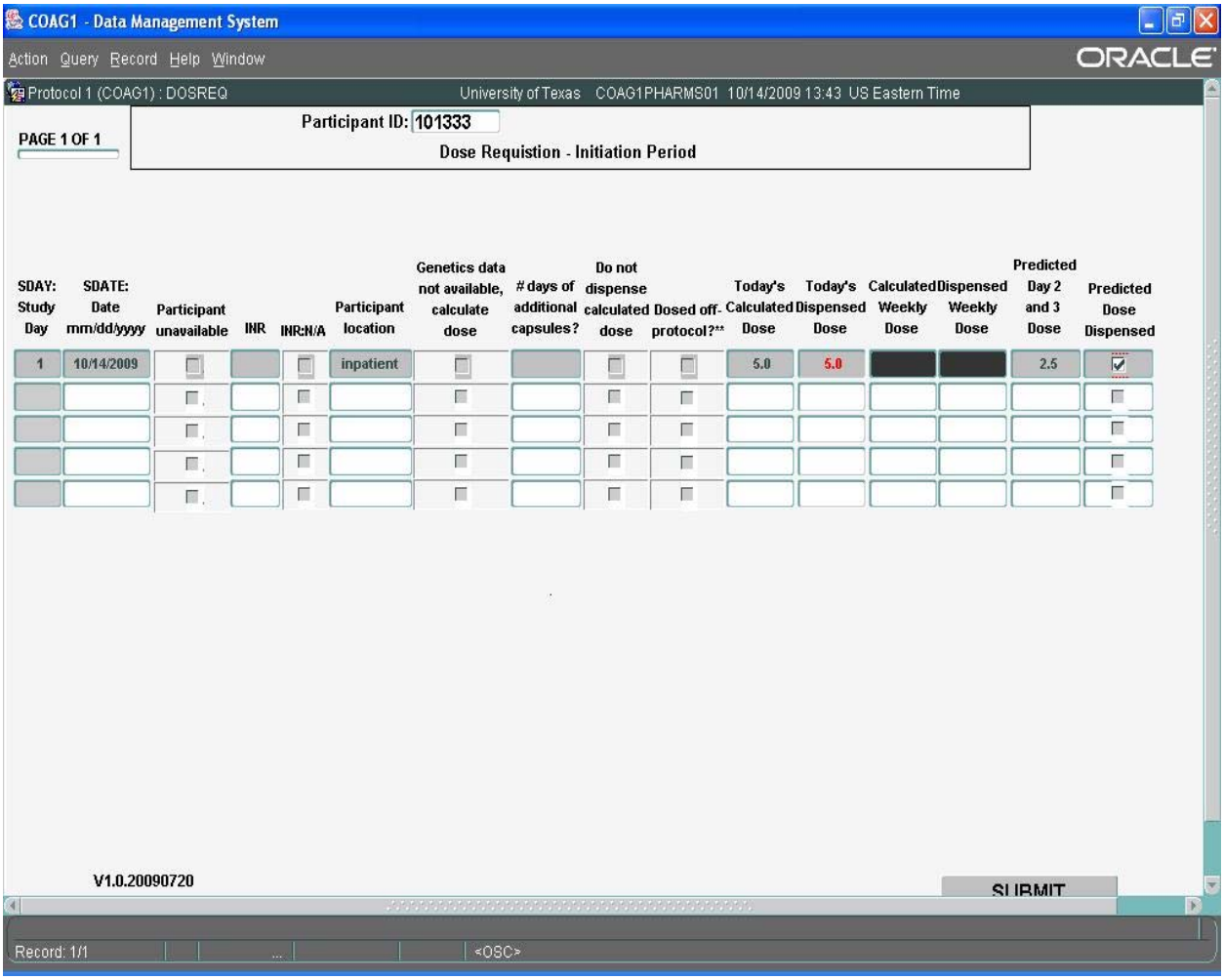


The above screen applies only to Day 2. Give regular capsule amount from day 3 on.

Predicted Day 2 and Day 3 Dose

The screen below shows that the pharmacist can also view the predicted Day 2 and Day 3 dose of 2.5 mg for the participant. If the pharmacist dispenses the predicted dose in advance, check the "Predicated Dose dispensed" box as shown on the screen above. (Also refer to instructions in Section 1.D.1 Predicted Doses for Day 2 and Day 3 – Dose Initiation Phase)

After completing this entry, click on the SUBMIT button on the bottom right of the screen.

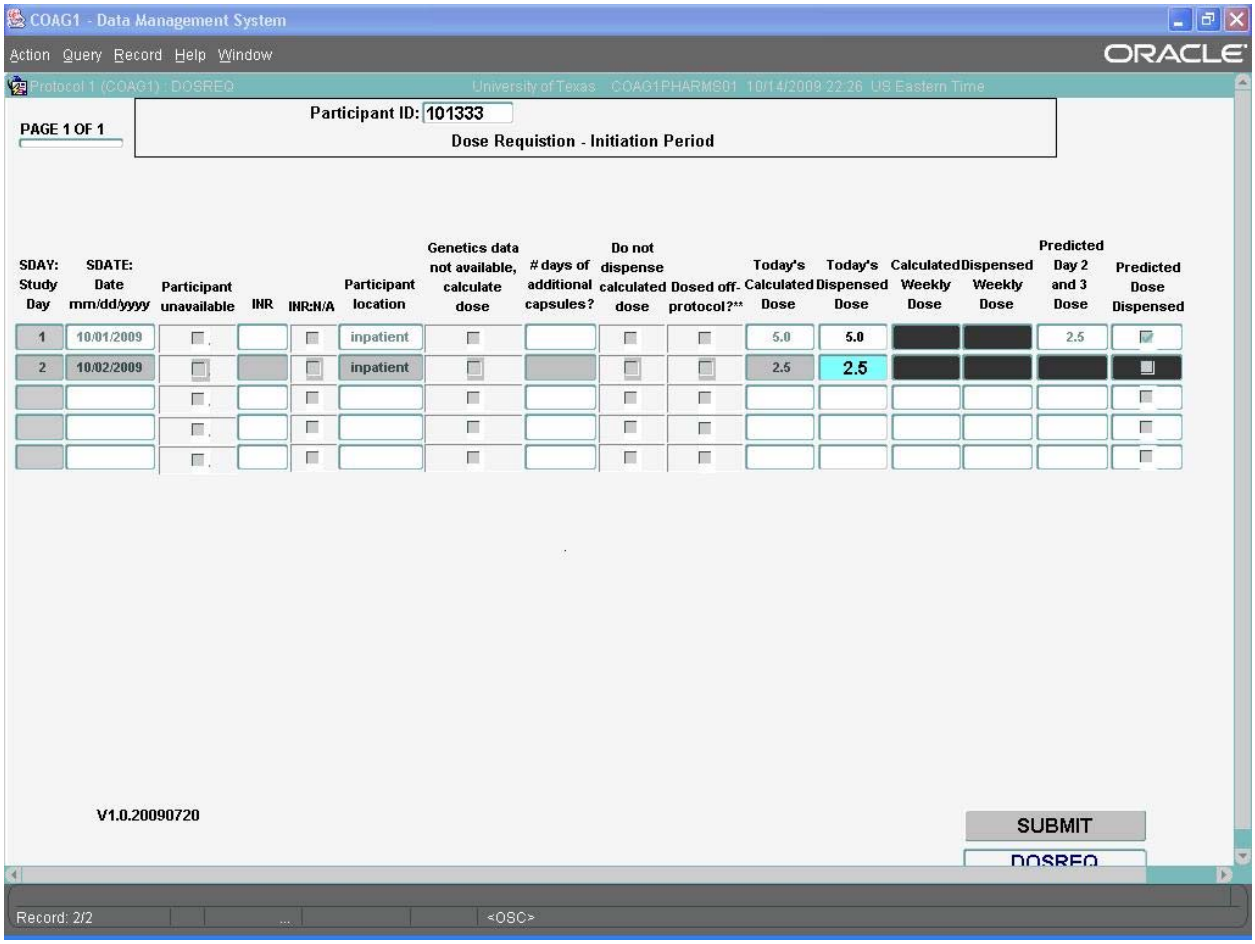


Use of the predicted dose feature to pre-dispense Day 2 & Day 3 dose is to be used in the following circumstances:

- For the **outpatient** whose next scheduled clinic visit is Day 4 or Day 5
- For the hospital **in-patient** whose Day 2 and Day 3 dosing schedule will occur over a **weekend or holiday period**

Entering of advanced dispensed dose for Day 2 and Day 3 into the DMS

Entering of advanced dispensed dose for days 2, 3 (and 4 if needed) into the DMS can be completed by the pharmacist only after the RC (retrospectively) enters a dose request for days 2 and 3 (and 4 if needed). See below screen.

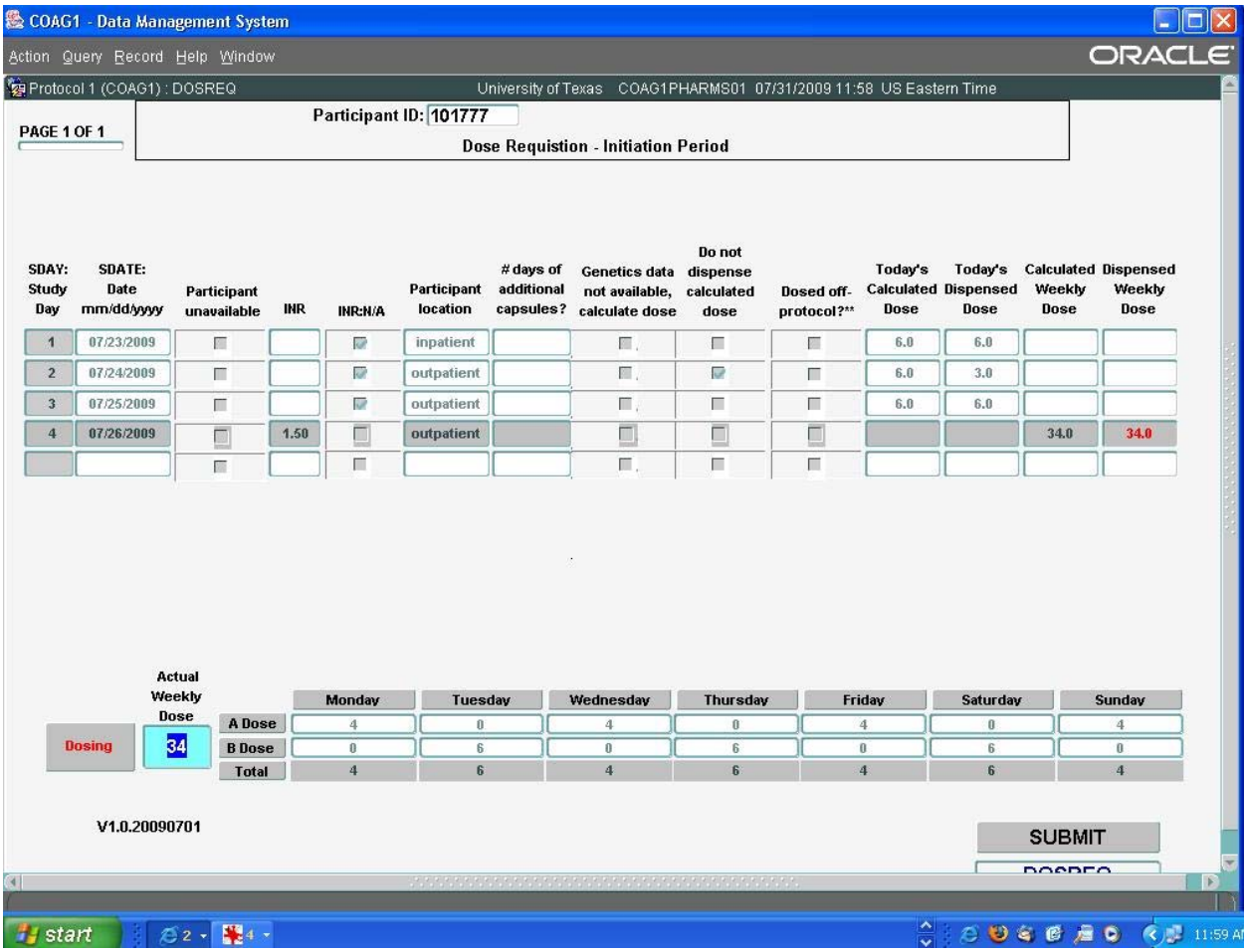


The predicted Day 2 and Day 3 dose allows the Research Pharmacist to dispense study drug for these days in advance, but the Research Coordinator cannot enter a dose request for Day 2 and Day 3 in advance. Therefore, the Research Coordinator will need to enter a dose request for days 2 and 3 (and 4 if needed), retrospectively.

4.F.2. Dose Revision Phase – Day 4 and Day 5

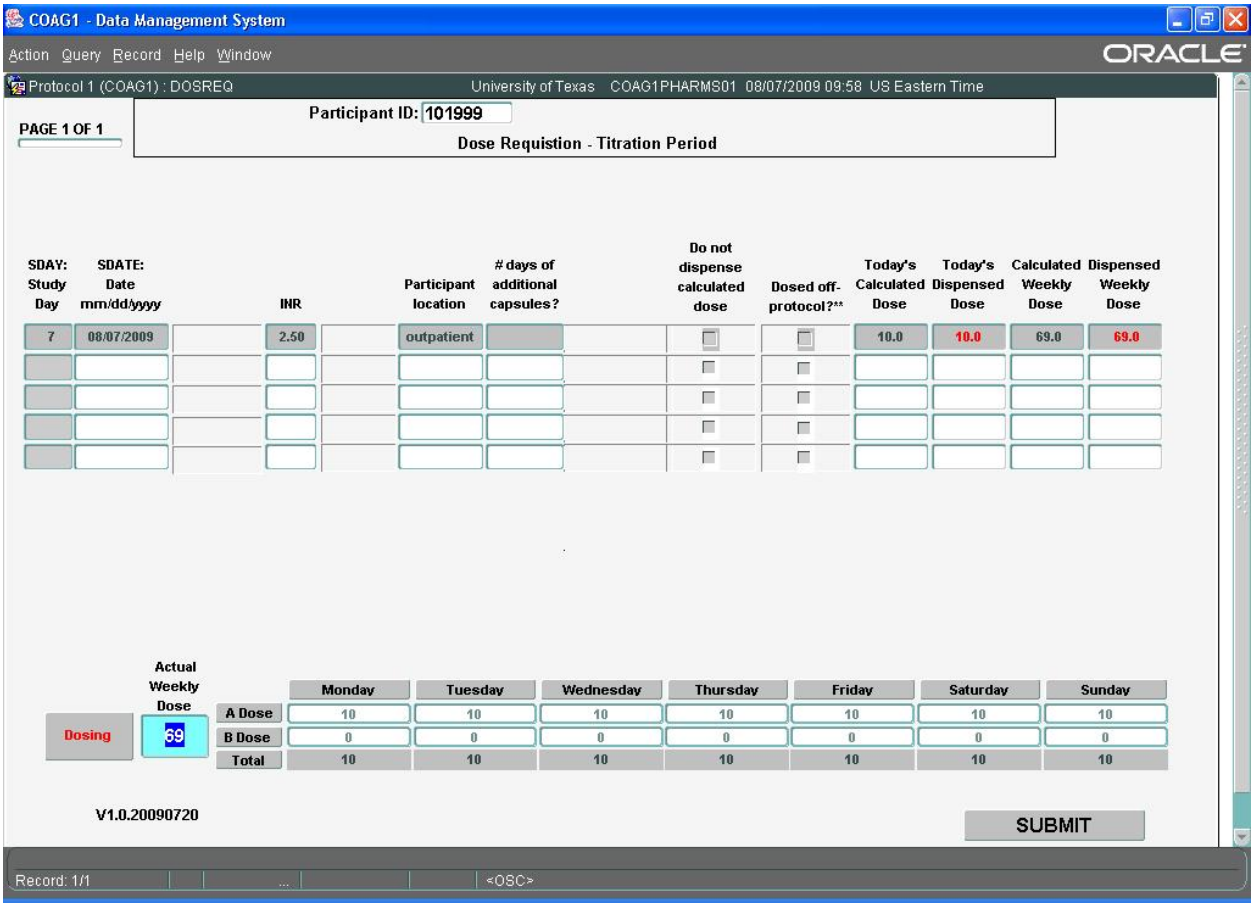
The below screen informs you of the request for the participant in day 4 dose revision phase. The participant is at out-patient status. A calculated weekly dose is displayed (34.0).

The pharmacist records the dose dispensed in the "Dispensed Weekly Dose" box of the screen. After completing this entry, click on the SUBMIT button on the bottom right of the screen. A schedule of daily dosing for the week is displayed in the lower screen.



4.F.3. Dose Titration Phase (After Day 5):

The below screen informs you of the request for the participant in day seven dose titration phase.



For the titration period there is a **daily** and **weekly** dose shown. **Dispense the DAILY dose today only and then the WEEKLY dose to begin the next day.**

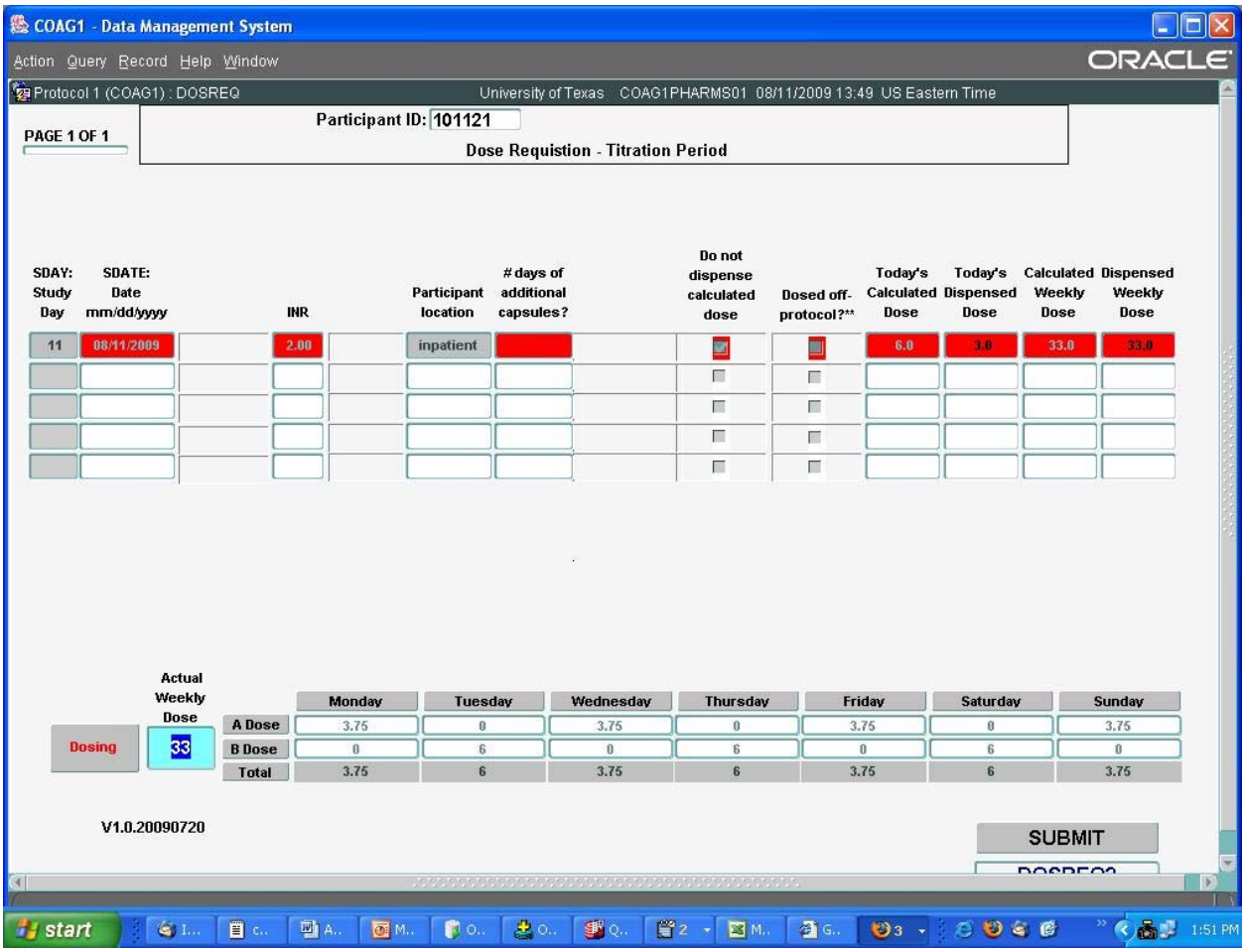
The pharmacist records the dose dispensed in the "Today's Dispensed Dose" and records the dose dispensed in the "Dispensed Weekly Dose" box of the screen. After completing this entry, click on the SUBMIT button on the bottom right of the screen. A schedule of daily dosing for the week is displayed in the lower screen.

Note: Based on the patient's clinic visit schedule, additional capsules may be requested to ensure dosing till the next clinic visit. The box "# days of additional capsules" will indicate a number for the days that additional capsules are requested.

4.F.4. Dose Over-ride Notification:

The site research coordinator will contact you by phone to alert you when a "dose over-ride" (over-ride of calculated dose) has been requested by the clinician.

As displayed in the below screen, information on this study day is highlighted in red, and the "Do not dispense calculated dose" has been flagged by the research coordinator. The calculated dose for today 6.0 (mg) is displayed.



In this situation, you **will not** dispense the calculated dose. You will wait to be contacted by the Medical Monitor (via telephone contact). The Medical Monitor will ask you to tell him the DMS calculated dose for today. The Medical Monitor will then instruct you on what dose to dispense, or may instruct you to hold the dose.

You will record the dose dispensed (1.0) in the "Today's Dispensed Dose" box of the screen and record the dose dispensed (33.0) in the "Dispensed Weekly Dose" box of the screen. After completing this entry, click on the SUBMIT button on the bottom right of the screen. A schedule of daily dosing for the week is displayed in the lower screen.

Similarly, the "Dosed off Protocol" is flagged by the research coordinator when warfarin dosing is stopped on a patient or if the patient received warfarin treatment outside of protocol regimen. When "Dosed off Protocol" is flagged, the pharmacist will not dispense the calculated dose as the patient is no longer receiving dosing according to protocol.

5. Sponsored Project Help Desk

The sponsored project help desk will answer questions concerning the operation of the Data Management System (DMS) and will assist in resolving any issues that hinder the effective use of the software.

5.A. Technical Support

The Help Desk will provide technical support related to problems and issues that may arise when working with the application provided by the CTCC.

The Help Desk will not be responsible for providing technical support for hardware and/or software that are not provided by the CTCC (e.g. word processors, spreadsheets, modems, printers, and hardware) and has direct local institutional support.

Helpdesk Phone Number: 215.573.4623

Helpdesk E-mail: crcuhelp@mail.med.upenn.edu

The COAG helpdesk will be available at the CTCC from 9am – 5pm EST Monday through Friday. The helpdesk can be reached via telephone or e-mail using the contact information above. If contacting helpdesk via telephone, you will be prompted to leave a message indicating the nature of your support requested. Your message will be saved electronically and forwarded to helpdesk support personnel, who will review your message and contact you as soon as possible (typically within an hour). E-mails will be handled in a similar fashion. Each helpdesk support staff member will receive a copy of e-mails sent to the helpdesk e-mail address, and will respond as soon as possible. Support requests that are submitted after 5pm EST will be addressed the following business day.

Requests to the helpdesk should be limited to technical support of the COAG Data Management System (DMS) as it pertains to the COAG study. This would include any issues involving connectivity / access to the COAG DMS, installation on your computer, Error Messages, etc. Questions related to general study operations or the protocol, or other technical issues that are not directly related to the COAG DMS should be directed to Project Management (PJM) or Clinical Data Management (CDM) at the CTCC.

5.B. Assignment of Data Management System Account

A DMS account consists of a username and password that uniquely identifies a user. DMS accounts are required for a user to gain access to the data entry area, and are the primary means for ensuring data security and confidentiality. Therefore, it is critically important that all DMS accounts are kept secure and confidential and are not shared with anyone.

NOTE: The username and password used to individually access your project Web site (http://www.coagstudy.org/) is **not** your DMS username and password. Access to the project Web site infers no access to the project DMS. You may reach the project DMS through a link

from within the project Web site but will then be prompted for a specific DMS account username and password.

In addition to providing data security and confidentiality, DMS accounts provide a means to trace all database activities to individual user accounts.

To obtain DMS accounts, a Clinical Center or Site representative will notify the CTCC project manager of the requested user's name and provide a description of what functions the user will be performing in the DMS. The CTCC Project Manager will in turn notify the Sponsored Project Help Desk of the new user request.

*****Important*****

When a DMS account has been created, the Sponsored Project Help Desk will contact the user with his/her account information.

When personnel leave the project, a representative from the Clinical Center or Site should promptly contact the CTCC Project Manager. The Sponsored Project Help Desk will then take the necessary actions to deactivate that user's database account.

Clarification of Optimal Anticoagulation Through Genetics (COAG): A Randomized, Multicenter, Double-Blind Clinical Trial to Evaluate Efficacy in the Use of Clinical Plus Genetic Information to Guide Warfarin Therapy Initiation and Improve Anticoagulation Control for Patients.

http://www.coagstudy.org

Pharmacy Manual

Version 1.1 - November 2009

Coordinating Center Pharmacy:

University of Pennsylvania School of Medicine
Investigational Drug Service
3600 Spruce St
Ground Maloney Bldg
Philadelphia, PA 19104
215-349-8817 fax 215-349-5132 http://www.itmat.upenn.edu/ctsa/ids

Contents:

Introduction 3
Medication Description 4
Packaging and Labeling 4
IMPORTANT! 5
Medication Dispensing and Accountability 5
Inventory Records 5
Inpatient Dispensing 6
Outpatient Dispensing 8
Medication Storage 9
Reordering 10
Medication Returns 10
Medications Returned by Patients 10
Expired or Damaged Bottles (Undispened) 11
Expired or Damaged Capsules (from an opened bottle, Undispensed) 11
Outpatient (Weekly) Dosing Chart 12
Resupply Request Fax 16
Patient-Specific Worksheet 17
Inventory Record for Partial Bottles 18
Perpetual Inventory Record 19
Drug Destruction Record 20

Introduction

The objective of the Clarification of Optimal Anticoagulation through Genetics (COAG) trial is to conduct a multicenter, double-blind, randomized trial comparing two approaches to guiding warfarin therapy initiation: 1) initiation of warfarin therapy based on algorithms using clinical information and an individuals genotype using genes known to influence warfarin response (genotype-guided dosing), and 2) initiation of warfarin therapy based on algorithms using only clinical information (clinical-guided dosing).

Each arm will include a baseline dose initiation algorithm and a dose revision algorithm applied over the first 4-5 doses of warfarin therapy. Thus, the intervention will be applied over these first 4-5 days (the intervention period). Following this period, dose titration will be the same between arms. By comparing the two strategies in this trial, the study will be able to determine if genetic information provides added benefit above and beyond what can be done simply with clinical information. The primary objective of the study is to compare the two strategies with respect to the time participants spend within the therapeutic INR range (PTTR) during the first 4 weeks of therapy. Secondary objectives of the study are to compare the two strategies with respect to the PTTR during the first 2 weeks and 3 and 6 months of therapy; other outcomes at 2 and 4 weeks and 3 and 6 months, including time to stable warfarin dosing and INR above range (4.0); number of dose changes required; and major clinical outcomes, including major bleeds, combination of major and minor bleeds, combination of major bleeds and thromboembolic complications, cost and quality of life.

Subject Enrolled and Randomized: Genetic Dosing vs INR Dosing

↓

INITIAL TITRATION PERIOD (DAILY):

- Coordinator logs on to COAG portal, enters requested information, selects “REQUEST DOSE”
- Site pharmacist logs on to COAG portal to see ASSIGNED DOSE for that day
- A SINGLE DAILY DOSE is dispensed and recorded on patient-specific worksheet
  - *Note: as of 11/2009, coordinators may request Days 2 and 3 in advance if necessary.*

↓

OUTPATIENT:

- Coordinator notifies site pharmacist of visit and how long until the next visit *(method of notification per site pharmacy’s typical practices)*
- Site pharmacist then:
  - Logs on to COAG portal to see the ASSIGNED WEEKLY DOSE
  - Checks the Dosing Chart in the Pharmacy Manual for assistance in determining the dosing directions for each weekday AND what strengths of warfarin to dispense
  - Signs out bottles on perpetual inventory AND affixes labels onto patient-specific worksheet

Medication Description

For this trial, Coumadin® brand of warfarin tablets, has been donated and will be converted into blinded doses in opaque two-tone blue gelatin Size 1 capsule shells. There are NO placebo capsules used in this trial. Instead, there are (13) different strengths of medication used, in order to ensure that every possible dose can be administered using one or in some cases two capsules.

The process used in this trial mirrors the process used by AstraZeneca in a previous clinical trial and reported in Johansson S, Ohlsson L, Steinhoff H, Wahlander K, Cullberg M: No effect of encapsulation on the pharmacokinetics of warfarin, *Biopharm. Drug Dispos*. 26: 121–127 (2005).

Capsules have been prepared in the following strengths, which include some not commercially available, in order to accommodate as many possible dose assignments using a single capsule per dose:

0.5mg	**1mg**	**1.25mg**	**1.5mg**	**2mg**	**2.5mg**	**3mg**
3.75mg	**4mg**	**5mg**	**6mg**	**7.5mg**	**10mg**	

Packaging and Labeling

Finished capsules are packaged into white opaque tamper-evident bottles (2 ounce size) with child-resistant caps.

Each bottle will contain (10) blinded capsules.

A two-part label is affixed to each bottle.

NOTE that this label by itself, is not sufficient for dispensing. For outpatient use (including at discharge from the hospital) it is necessary for the site to apply a regular medication label as well, with directions, prescriber name, subject and date of dispensing, etc. For the medication label, each site has the option to either:

- Use its own labels if it has a system to print medication labels, or
- Create its own labels on a printer, or
- The central pharmacy can print and provide sheets of labels pre-printed with various directions.

The two-part labels already affixed to each bottle, contain information that identifies the study and bottle contents.

Left side (remains on bottle):

- ‘COAG Study’
- ‘Warfarin (blinded dose) #10 capsules’
- ‘For Investigational use Only’
- Unique serial number

Right side (removed in the pharmacy):
- 'COAG Study'
- Actual strength (MG), lot number and use-by date for the capsules inside the bottle
- Unique serial number

The unique serial number is identical on both label halves for one bottle. The intent of the number is to allow the SITE PHARMACY to identify the bottle, if the label is removed inadvertently, or before a prescription label can be placed on the bottle.

IMPORTANT!

- **The right side (removable) portion of the label, MUST be removed and remain in the site pharmacy. Dispensing the bottle with the removable label attached, will UNBLIND anyone who sees the bottle.**
- **If the bottle is dispensed directly to a study subject, that label is affixed to the patient-specific worksheet.**
- **If the bottle is used to prepare individual doses for inpatient use, the label should remain on the bottle and the bottle must remain in the pharmacy.**

Medication Dispensing and Accountability

For this trial there will be a combination of inpatient and outpatient dispensing over approximately 30 days for each subject. **There is a 'computer' component to this as well, which will be covered in separate instructions provided by the Data Coordinating Center.**

Inventory Records

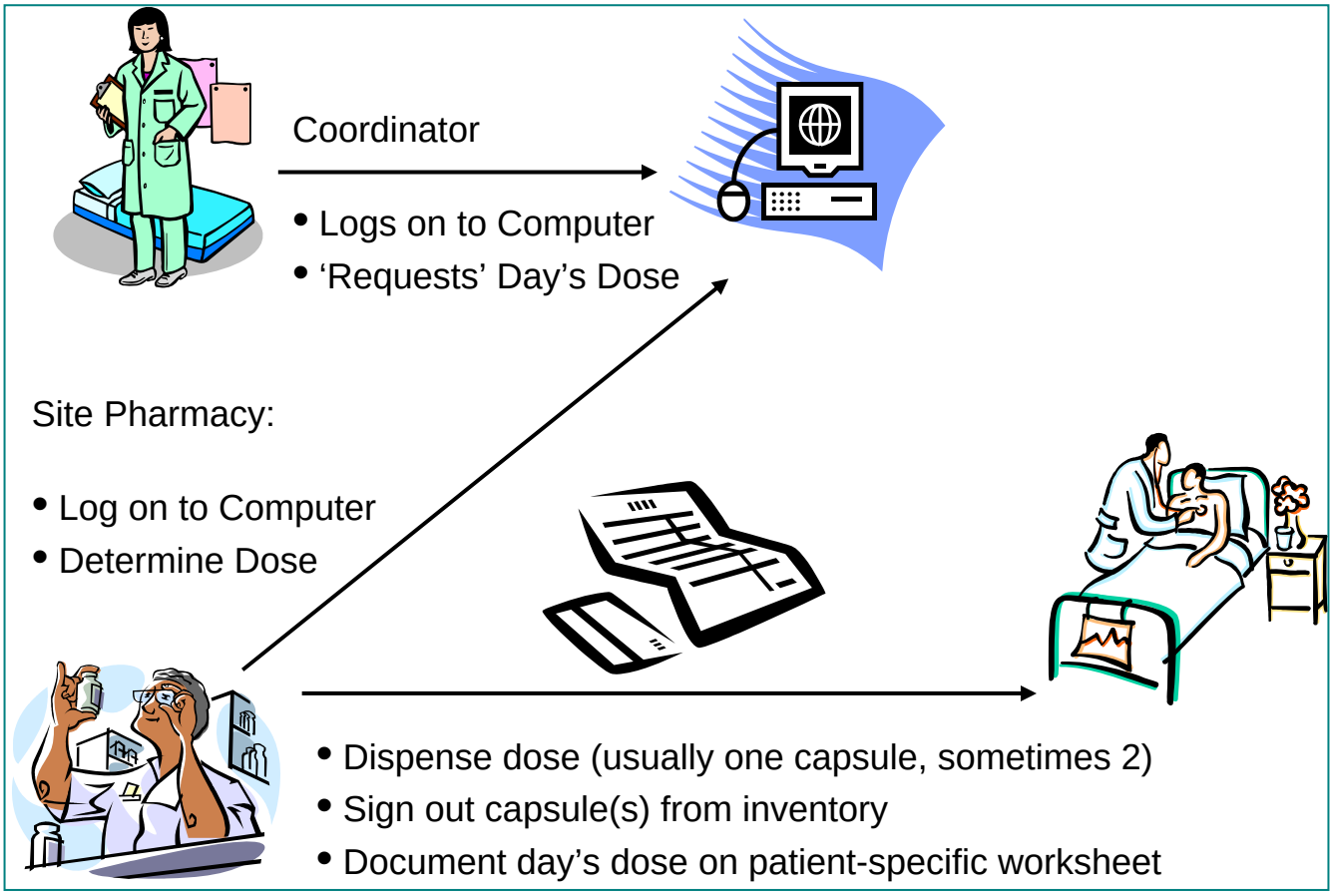
There are three inventory records provided for this study. Two of these are optional IF the site prefers to substitute its own records.

- **Perpetual Inventory (Bottles):**
  - This is an inventory for each strength of medication. The IDS will prepare inventory logs that track three strengths at a time (in separate columns) in order to help reduce the number of pages.
  - Sites may SUBSTITUTE their own perpetual inventory records as long as they contain (at least) an ongoing balance of bottles on hand for each strength, when new bottles were received and when bottles were dispensed.

- **Inventory for Inpatient Dispensing:**
  - This is a simple inventory record for bottles that you open to dispense to inpatients. Since inpatients will require only one capsule per day, this record was created to help with keeping track of who the individual capsules were dispensed to.
  - Sites may SUBSTITUTE their own perpetual inventory records as long as they contain (at least) a record of where the capsules went to for each bottle opened.

- **Patient-Specific Worksheet:**
  - This worksheet is unique for each new subject. The first few lines are intended for documenting individual doses given to inpatients, while the remainder of the page is intended for outpatient dispensing.
  - For inpatients, the date and dose are most important, as this record will show what dose was actually dispensed each day. This information is not available in the investigator's records and the computer system will only show the 'assigned' dose, so this record is the only place where the actual dose on each individual day, is captured.
  - For outpatients, visits are several days to a week apart. At each visit, the 'weekly' dose is looked up in the computer system. The bottles and directions needed, are shown in the 'outpatient dosing chart' below. The tear-off label for each bottle, is pasted onto a box on he worksheet (in some cases you will need two bottles per dispense, thus there are 2 boxes per row).
  - All doses destroyed once the patient completes the blinded 30 day course, are documented on this sheet as well. The sheet is then faxed back to the central pharmacy so that the information can be used for quality assurance and so that the data center will have a record of all dispensing for each subject once it begins to analyze the study data. The central pharmacy will hold these sheets securely until that time.

Initial (Titration) Dispensing



During the initial (titration) dispensing period, someone must log onto the computer each day to see what the computer has determined should be the patient's dose for that day. In situations where the subject is an outpatient and cannot return to clinic the next day, or for inpatients when the pharmacy is closed, the coordinator has the option to request additional doses (eg. on Day 1, the Day 2 and Day 3 doses can be requested early, as long as the genetic information has been entered in the system by the laboratory first).

Sites may use one of these methods for inpatient dispensing:

- Sites may unit-dose medication out of a bottle.
  - If this is done, make sure that there is a clear mechanism to be able to tell what capsule contains what strength, WITHOUT listing that strength on the package itself. Options might include using the original drug lot number, since this is unique to one strength; using a lot number created at your institution; or assigning a code for each strength (if doing this, we recommend something besides a sequential letter or number for each strength!) Feel free to call the central pharmacy to discuss what options may work best in your situation.

- Repackage a single dose at a time into a prescription bottle at the site, using your own prescription labels or labels generated by your inpatient pharmacy system.

- Repackage a single dose at a time, into a pre-labeled bottle provided by the central pharmacy. The central pharmacy will provide bottles pre-labeled, specifically for use in the inpatient setting. Sites may request these initially or by marking the correct box on the drug resupply request form.

Maintenance Dispensing (eg. beyond the initial 3-5 days of titration)

Site Pharmacy:

- Log on to Computer
- Determine WEEKLY Dose

Check bottom of screen (or Dosing Chart in this manual) to see directions and which bottle strengths are needed

- Dispense 1 or 2 bottles to patient, investigator or coordinator (may vary by institutional practice)
- Sign out bottle(s) from perpetual inventory log
- Paste bottle LABELS onto patient-specific worksheet and document the dose and dispense date

When dispensing outpatient bottles, the site has two options for labeling. The directions are not pre-printed on each bottle because they may change depending on the assigned dose. Directions may include:

- Take one capsule once daily.
- Take one capsule on Mon-Wed-Fri
- Take one capsule on Tue-Thur-Sat-Sun
- Take one capsule only on this day: _____
- Etc

Because of this variation, the prescription label needs to be affixed at time of dispensing. Sites may choose one of these two options:

- Use pre-printed labels provided by the central pharmacy, with varying instructions. The site would need to fill in the patient, ID number and date, on the label before dispensing.

- Generate prescription labels at the site pharmacy. If choosing this option, make sure that you are able to generate labels with different directions to reflect what the subject's assigned dose is. Refer to the Outpatient (Weekly) Dosing Chart to see what sorts of instructions will be used most often.

- NOTE: In situations where the subject is returning in 2-3 days, or when one strength is only needed on one day, pharmacists may dispense individual doses rather than a full bottle of 10. Document that on the top section of the patient worksheet. If all spaces on the worksheet are filled, continue onto a second worksheet page and just mark them clearly as Page 1 of 2 / Page 2 of 2.

Medication Storage

Each site is responsible for establishing a secure, controlled medication storage area. A site pharmacy or an unblinded medication dispenser, is required at each site in order to maintain the blind. A mechanism for secure storage of medications should be determined prior to shipment.

Study sites that maintain and monitor their own medication inventory (within a clinic) should ensure the following:

- Adequate space is available in which to receive and hold medication shipments;

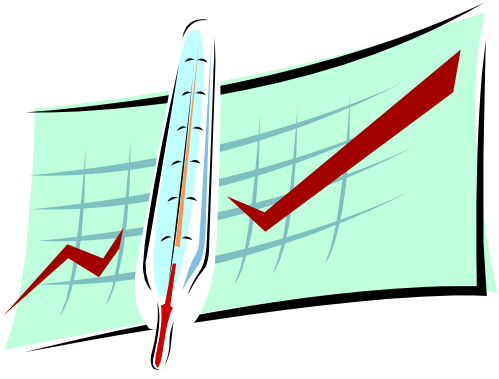
- Provisions are made so that study medication bottles can be dispensed to participants at discharge and at return visits during the month of blinded treatment;

- Provisions are made so that returned, expired, damaged, or other unusable medication bottles can be destroyed on-site and documentation faxed back to the central pharmacy (see medication returns section later in this document); and

- Packing invoices can be maintained, and that the center ensures that access to the area where this activity takes place is limited.

For space planning, site pharmacies should plan on individual bottles that are 3" tall x 1.5" diameter and quantities between 2 and 10 bottles of each strength in the initial shipment (depending on strength – only 2-3 bottles will be provided for strengths that are not commonly used) or about 50-75 total bottles to start. A mechanism for separating out the 13 different strengths (without marking on the bottles themselves as this would unblind) should be determined in advance; options might include separate Ziploc bags for each strength, or separate shelf bins or dividers; whatever works best for the individual site.

Medication is to be stored at room temperature (15 to 30 Celsius / 59 to 86 Fahrenheit). This study is not mandating continuous or daily temperature logs, however the site should have some mechanism in place to know whether medication has been exposed to damaging conditions (such as prolonged high heat and humidity, which could damage the capsules). Sites should contact the central pharmacy at (215) 349-8817 or PennIDS@med.upenn.edu when medication appears to be damaged or may have been exposed to prolonged temperatures



outside of the requested range, in order to evaluate the suitability of the medication for continued use and/or the need for replacement.

Reordering

When the site pharmacy requires additional medication or supplies, these can be requested from the the central pharmacy. This is done by filling out a Resupply Request Form and faxing that to the central study pharmacy at (215) 349-5132. The original should be kept at the site. Small orders often can be shipped within 2-3 business days, while larger orders may take 5 business days (particularly if additional bottles need to be packaged first). These will be shipped by traceable courier to the address provided. In addition to medication (bottles of 10), the site may also request empty bottles for inpatient dispensing, or instruction labels for outpatient dispensing.

Medication Returns

Medication returns may be destroyed by the local site pharmacy, once the site has first submitted one of the following:

- A copy of the site's current drug destruction policy, which identifies how capsules or tablets would normally be destroyed
- In the absence of a formal policy, a memo documenting how the site plans to destroy medications left over in this trial.

The policy or memo, should be faxed to the central pharmacy at (215) 349-5132. The central pharmacy will store this along with all medication-related records (in order to ensure blinding is maintained).

Medications Returned by Patients

The quantity of unused capsules should be documented on the Patient Specific Worksheet. For inpatient doses, this would be one dose if the patient did not take the dose (there is no need to document '0' if the dose was used, unless the site's local policy is to do this). For outpatient doses, this would be the # of capsules remaining in the bottle.

Once all patient returns are documented, they can be destroyed. Make sure that if you are discarding empty bottles, the patient's name (if present) is blocked out. If there are any bottles unaccounted for, check with the coordinator to see if he/she expects these bottles to still be returned, before destroying everything. The records are much cleaner if everything for one patient is destroyed at once.

Documentation of destruction is done at the bottom of the form. The completed form is then faxed back to the central pharmacy at (215) 349-5132 and the original is kept secure in the local pharmacy's records.

Expired or Damaged Bottles (Undispened)

These should be signed out of the perpetual inventory log, then documented on a Drug Destruction Form. Paste the bottle labels (tear-off portion) onto this form. Once completed, fax it to the central pharmacy at (215) 349-5132 and keep the original in your site's pharmacy records.

Expired or Damaged Capsules (from an opened bottle, Undispensed)

If you were using the inventory log provided for tracking partial bottles (inpatient dispensing), sign out the remaining capsules on this log. If you were using your own substitute form, document on that log. Then record the quantity and lot number on a Drug Destruction Form.

Outpatient (Weekly) Dosing Chart

Calculated Weekly Dose	Administered Weekly Dose	Bottles to Dispense	M	T	W	Th	F	Sa	Su
3 mg	3 mg	0.5mg	0.5	0.5	0.5	0.5	0.5	0.5	0
3.5 mg	3.5 mg	0.5mg	0.5	0.5	0.5	0.5	0.5	0.5	0.5
4 mg	4 mg	0.5mg and 1mg	1	0.5	0.5	0.5	0.5	0.5	0.5
4.5 mg	4.5 mg	0.5mg and 1mg	1	0.5	0.5	1	0.5	0.5	0.5
5 mg	5 mg	0.5mg and 1mg	0.5	1	0.5	1	0.5	1	0.5
5.5 mg	5.5 mg	0.5mg and 1mg	1	0.5	1	0.5	1	0.5	1
6 mg	6 mg	0.5mg and 1mg	1	1	0.5	1	1	0.5	1
6.5 mg	6.5 mg	0.5mg and 1mg	1	1	1	1	1	1	0.5
7 mg	7 mg	1mg	1	1	1	1	1	1	1
7.5 mg	7.5 mg	1mg and 1.25mg	1	1.25	1	1.25	1	1	1
8 mg	8 mg	1mg and 1.25mg	1.25	1	1.25	1	1.25	1	1.25
8.5 mg	8.5 mg	1mg and 1.5mg	1	1.5	1	1.5	1	1.5	1
9 mg	9 mg	1mg and 1.5mg	1.5	1	1.5	1	1.5	1	1.5
9.5 mg	9.5 mg	1.25mg and 1.5mg	1.25	1.5	1.25	1.5	1.25	1.5	1.25
10 mg	10 mg	1mg and 1.5mg	1.5	1.5	1.5	1.5	1.5	1.5	1
10.5 mg	10.5 mg	1.5mg	1.5	1.5	1.5	1.5	1.5	1.5	1.5
11 mg	11 mg	1.5mg and 2mg	1.5	1.5	1.5	1.5	1.5	1.5	2
12 mg	12 mg	0.5mg and 1.5mg	1.5	1.5+0.5	1.5	1.5+0.5	1.5	1.5+0.5	1.5
13 mg	13 mg	1mg and 2mg	2	2	2	2	2	2	1
14 mg	14 mg	1mg (2 bottles)	1+1	1+1	1+1	1+1	1+1	1+1	1+1
15 mg	15 mg	2mg and 3mg	2	2	2	2	2	2	3
16 mg	16 mg	2mg and 2.5mg	2.5	2	2.5	2	2.5	2	2.5
17 mg	17 mg	2mg and 3mg	2	3	2	3	2	3	2
17.5 mg	17.5 mg	2.5mg	2.5	2.5	2.5	2.5	2.5	2.5	2.5
18 mg	18 mg	2mg and 3mg	3	2	3	2	3	2	3
19 mg	19 mg	2.5mg and 3mg	2.5	3	2.5	3	2.5	3	2.5
20 mg	20 mg	2mg and 3mg	3	3	3	3	3	3	2
21 mg	21 mg	3mg	3	3	3	3	3	3	3
22 mg	22 mg	3mg and 4mg	3	3	3	3	3	3	4
23 mg	23 mg	3mg and 5mg	3	3	3	3	3	3	5
24 mg	24 mg	3mg and 4mg	3	4	3	4	3	4	3
25 mg	25 mg	3mg and 4mg	4	3	4	3	4	3	4
26.25 mg	26.25 mg	3.75mg	3.75	3.75	3.75	3.75	3.75	3.75	3.75
27 mg	27 mg	3mg and 5mg	3	5	3	5	3	5	3
28 mg	28 mg	2mg (2 bottles)	2+2	2+2	2+2	2+2	2+2	2+2	2+2
29 mg	29 mg	3mg and 5mg	5	3	5	3	5	3	5
30 mg	30 mg	4mg and 6mg	4	4	4	4	4	4	6

Calculated Weekly Dose	Administered Weekly Dose	Bottles to Dispense	M	T	W	Th	F	Sa	Su
31 mg	31 mg	4mg and 5mg	4	5	4	5	4	5	4
32 mg	32 mg	4mg and 5mg	5	4	5	4	5	4	5
33 mg	33 mg	3.75mg and 6mg	3.75	6	3.75	6	3.75	6	3.75
34 mg	34 mg	4mg and 6mg	4	6	4	6	4	6	4
35 mg	35 mg	5mg	5	5	5	5	5	5	5
36 mg	36 mg	2mg and 4mg	4+2	4	4+2	4	4+2	4	4+2
37 mg	37 mg	5mg and 6mg	5	6	5	6	5	5	5
38 mg	38 mg	5mg and 6mg	5	6	5	6	5	6	5
39 mg	39 mg	5mg and 6mg	6	5	6	5	6	5	6
40 mg	40 mg	5mg and 6mg	6	5	6	5	6	6	6
41 mg	41 mg	5mg and 6mg	6	6	6	6	6	6	5
42 mg	42 mg	6mg	6	6	6	6	6	6	6
43 mg	42.5 mg	5mg and 7.5mg	5	7.5	5	7.5	5	7.5	5
44 mg	43.5 mg	6mg and 7.5mg	6	6	6	6	6	6	7.5
45 mg	45 mg	5mg and 7.5mg	7.5	5	7.5	5	7.5	5	7.5
46 mg	46 mg	6mg and 10mg	6	6	6	6	6	6	10
47 mg	48 mg	6mg and 7.5mg	7.5	6	7.5	6	7.5	6	7.5
48 mg	48 mg	6mg and 7.5mg	7.5	6	7.5	6	7.5	6	7.5
49 mg	49 mg	1mg and 6mg	6+1	6+1	6+1	6+1	6+1	6+1	6+1
50 mg	50 mg	5mg and 7.5mg	7.5	7.5	7.5	7.5	7.5	7.5	5
51 mg	51 mg	6mg and 7.5mg	7.5	7.5	7.5	7.5	7.5	7.5	6
52 mg	52.5 mg	7.5mg	7.5	7.5	7.5	7.5	7.5	7.5	7.5
53 mg	52.5 mg	7.5mg	7.5	7.5	7.5	7.5	7.5	7.5	7.5
54 mg	54 mg	6mg and 10mg	6	10	6	10	6	10	6
55 mg	56 mg	2mg and 6mg	6+2	6+2	6+2	6+2	6+2	6+2	6+2
56 mg	56 mg	2mg and 6mg	6+2	6+2	6+2	6+2	6+2	6+2	6+2
57 mg	56 mg	2mg and 6mg	6+2	6+2	6+2	6+2	6+2	6+2	6+2
58 mg	58 mg	6mg and 10mg	10	6	10	6	10	6	10
59 mg	58 mg	6mg and 10mg	10	6	10	6	10	6	10
60 mg	60 mg	7.5mg and 10mg	7.5	10	7.5	10	7.5	10	7.5
61 mg	60 mg	7.5mg and 10mg	7.5	10	7.5	10	7.5	10	7.5
62 mg	63 mg	3mg and 6mg	6+3	6+3	6+3	6+3	6+3	6+3	6+3
63 mg	63 mg	3mg and 6mg	6+3	6+3	6+3	6+3	6+3	6+3	6+3
64 mg	63 mg	3mg and 6mg	6+3	6+3	6+3	6+3	6+3	6+3	6+3
65 mg	65 mg	5mg and 10mg	10	10	10	10	10	10	5
66 mg	65 mg	5mg and 10mg	10	10	10	10	10	10	5
67 mg	67.5 mg	7.5mg and 10mg	10	10	10	10	10	10	7.5
68 mg	67.5 mg	7.5mg and 10mg	10	10	10	10	10	10	7.5
69 mg	70 mg	10mg	10	10	10	10	10	10	10
70 mg	70 mg	10mg	10	10	10	10	10	10	10

Calculated Weekly Dose	Administered Weekly Dose	Bottles to Dispense	M	T	W	Th	F	Sa	Su
71 mg	70 mg	10mg	10	10	10	10	10	10	10
72 mg	72 mg	0.5mg and 10mg	10+0.5	10	10+0.5	10	10+0.5	10	10+0.5
73 mg	73 mg	1mg and 10mg	10	10+1	10	10+1	10	10+1	10
74 mg	74 mg	1mg and 10mg	10+1	10	10+1	10	10+1	10	10+1
75 mg	75 mg	1.25mg and 10mg	10+1.25	10	10+1.25	10	10+1.25	10	10+1.25
76 mg	77 mg	1mg and 10mg	10+1	10+1	10+1	10+1	10+1	10+1	10+1
77 mg	77 mg	1mg and 10mg	10+1	10+1	10+1	10+1	10+1	10+1	10+1
78 mg	77 mg	1mg and 10mg	10+1	10+1	10+1	10+1	10+1	10+1	10+1
79 mg	78 mg	2mg and 10mg	10+2	10	10+2	10	10+2	10	10+2
80 mg	80 mg	2.5mg and 10mg	10+2.5	10	10+2.5	10	10+2.5	10	10+2.5
81 mg	80 mg	2.5mg and 10mg	10+2.5	10	10+2.5	10	10+2.5	10	10+2.5
82 mg	82 mg	4mg and 10mg	10+4	10	10+4	10	10+4	10	10
83 mg	84 mg	2mg and 10mg	10+2	10+2	10+2	10+2	10+2	10+2	10+2
84 mg	84 mg	2mg and 10mg	10+2	10+2	10+2	10+2	10+2	10+2	10+2
85 mg	84 mg	2mg and 10mg	10+2	10+2	10+2	10+2	10+2	10+2	10+2
86 mg	86 mg	4mg and 10mg	10	10+4	10	10+4	10	10+4	10+4
87 mg	87.5 mg	2.5mg and 10mg	10+2.5	10+2.5	10+2.5	10+2.5	10+2.5	10+2.5	10+2.5
88 mg	87.5 mg	2.5mg and 10mg	10+2.5	10+2.5	10+2.5	10+2.5	10+2.5	10+2.5	10+2.5
89 mg	87.5 mg	2.5mg and 10mg	10+2.5	10+2.5	10+2.5	10+2.5	10+2.5	10+2.5	10+2.5
90 mg	91 mg	3mg and 10mg	10+3	10+3	10+3	10+3	10+3	10+3	10+3
91 mg	91 mg	3mg and 10mg	10+3	10+3	10+3	10+3	10+3	10+3	10+3
92 mg	91 mg	3mg and 10mg	10+3	10+3	10+3	10+3	10+3	10+3	10+3
93 mg	94 mg	6mg and 10mg	10+6	10	10+6	10	10+6	10	10+6
94 mg	94 mg	6mg and 10mg	10+6	10	10+6	10	10+6	10	10+6
95 mg	94 mg	6mg and 10mg	10+6	10	10+6	10	10+6	10	10+6
96 mg	98 mg	4mg and 10mg	10+4	10+4	10+4	10+4	10+4	10+4	10+4
97 mg	98 mg	4mg and 10mg	10+4	10+4	10+4	10+4	10+4	10+4	10+4
98 mg	98 mg	4mg and 10mg	10+4	10+4	10+4	10+4	10+4	10+4	10+4
99 mg	98 mg	4mg and 10mg	10+4	10+4	10+4	10+4	10+4	10+4	10+4
100 mg	100 mg	7.5mg and 10mg	10+7.5	10	10+7.5	10	10+7.5	10	10+7.5
101 mg	100 mg	7.5mg and 10mg	10+7.5	10	10+7.5	10	10+7.5	10	10+7.5
102 mg	100 mg	7.5mg and 10mg	10+7.5	10	10+7.5	10	10+7.5	10	10+7.5
103 mg	105 mg	5mg and 10mg	10+5	10+5	10+5	10+5	10+5	10+5	10+5
104 mg	105 mg	5mg and 10mg	10+5	10+5	10+5	10+5	10+5	10+5	10+5
105 mg	105 mg	5mg and 10mg	10+5	10+5	10+5	10+5	10+5	10+5	10+5
106 Mg	105 mg	5mg and 10mg	10+5	10+5	10+5	10+5	10+5	10+5	10+5
107 Mg	105 mg	5mg and 10mg	10+5	10+5	10+5	10+5	10+5	10+5	10+5
108 Mg	105 mg	5mg and 10mg	10+5	10+5	10+5	10+5	10+5	10+5	10+5
109 Mg	112 mg	6mg and 10mg	10+6	10+6	10+6	10+6	10+6	10+6	10+6
110 Mg	112 mg	6mg and 10mg	10+6	10+6	10+6	10+6	10+6	10+6	10+6

Calculated Weekly Dose	Administered Weekly Dose	Bottles to Dispense	M	T	W	Th	F	Sa	Su
111 Mg	112 mg	6mg and 10mg	10+6	10+6	10+6	10+6	10+6	10+6	10+6
112 Mg	112 mg	6mg and 10mg	10+6	10+6	10+6	10+6	10+6	10+6	10+6
113 Mg	112 mg	6mg and 10mg	10+6	10+6	10+6	10+6	10+6	10+6	10+6
114 Mg	115 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10
115 Mg	115 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10
116 Mg	115 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10
117 Mg	115 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10
118 Mg	115 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10
119 Mg	122.5 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5
120 Mg	122.5 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5
121 Mg	122.5 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5
122 Mg	122.5 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5
123 Mg	122.5 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5
124 mg	122.5 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5
125 mg	122.5 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5
126 mg	122.5 mg	7.5mg and 10mg	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5	10+7.5
127 mg	130 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10
128 mg	130 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10
129 mg	130 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10
130 mg	130 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10
131 mg	130 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10
132 mg	130 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10
133 mg	130 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10
134 mg	130 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10
135 mg	140 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10+10
136 mg	140 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10+10
137 mg	140 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10+10
138 mg	140 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10+10
139 mg	140 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10+10
140 mg	140 mg	10mg (1-2 btls)	10+10	10+10	10+10	10+10	10+10	10+10	10+10
>140 mg	If assigned dose is > 140mg/week call medical monitor before proceeding								

Clarification of Optimal Anticoagulation Through Genetics (COAG)

Resupply Request Fax

SITE: _____ DATE NEEDED ON-SITE: _____

SHIPPING ADDRESS: _____

_____

CONTACT NAME & PHONE: _____

(1) WARFARIN (BLINDED): BOTTLES OF 10 CAPSULES:

0.5mg	**1mg**	**1.25mg**	**1.5mg**	**2mg**	**2.5mg**	**3mg**	**3.75mg**	**4mg**	**5mg**	**6mg**	**7.5mg**	**10mg**
#	#	#	#	#	#	#	#	#	#	#	#	#

(2) EMPTY BOTTLES FOR INPATIENT DISPENSING:

Quantity Needed:	#

(3) PRE-PRINTED PRESCRIPTION LABELS (FOR OUTPATIENT DISPENSING):

Directions:	# (Sheets of 10):
"Take one capsule once daily"	#
"Take one capsule on Mon-Wed-Fri"	#
"Take one capsule on Tue-Thur-Sat-Sun"	#
"Take two capsules once daily"	#
"Take one capsule on this day only: _____"	#

FAX this form to:

University of Pennsylvania School of Medicine – Investigational Drug Service
(215) 349-5132

Thank you!

Patient-Specific Worksheet

Subject: _____ ID Number: _____

INPATIENT DOSING:

Date	Dose (mg)	Lot / Exp	Dispensed By	Dose Used? Notes?
				[ ] Used [ ] Returned Unused
				[ ] Used [ ] Returned Unused
				[ ] Used [ ] Returned Unused
				[ ] Used [ ] Returned Unused
				[ ] Used [ ] Returned Unused

DISCHARGE AND OUTPATIENT DOSING:

Date	Assigned Weekly Dose	Bottle Dispensed	Second Bottle Dispensed (if Applicable)	Returns
		Bottle Label Here	Bottle Label Here	Btl #1: ____ Btl #2: ____ [ ] N/A Notes:
		Bottle Label Here	Bottle Label Here	Btl #1: ____ Btl #2: ____ [ ] N/A Notes:
		Bottle Label Here	Bottle Label Here	Btl #1: ____ Btl #2: ____ [ ] N/A Notes:
		Bottle Label Here	Bottle Label Here	Btl #1: ____ Btl #2: ____ [ ] N/A Notes:

DESTRUCTION ON SITE (ONCE ALL BOTTLES ACCOUNTED) *Fax to U of Penn 215/349-5132 once complete.*

Destroyed by: _____ Date: _____ Witness: _____

Inventory Record for Partial Bottles

Instructions:

- When using a single bottle for multiple dispenses, document the dispensing of the bottle contents here.
- If you keep the original bottle to dispense from, DO NOT REMOVE the tear-off label until all doses are dispensed; then paste the label here when bottle is empty. If you are unit-dosing, remove tear-off label once the bottle is empty.
- If remaining capsules are expired/unusable, zero out balance and document the destruction on a Drug Destruction Form.
- REMEMBER, all drug dispensed to a subject, is also recorded on the patient-specific worksheet.

Fill in blanks and/or paste bottle label here:	Subject Initials/ID#	Quantity (start = 10)	Balance	Dispenser Initials
STRENGTH: ____mg				
LOT #: ____________				
USE BY: __________				

Fill in blanks and/or paste bottle label here:	Subject Initials/ID#	Quantity (start = 10)	Balance	Dispenser Initials
STRENGTH: ____mg				
LOT #: ____________				
USE BY: __________				

Fill in blanks and/or paste bottle label here:	Subject Initials/ID#	Quantity (start = 10)	Balance	Dispenser Initials
STRENGTH: ____mg				
LOT #: ____________				
USE BY: __________				

Perpetual Inventory Record

**** MUST REMAIN IN PHARMACY ****

Site: _____ Investigator: _____

Date	Subject Initials / ID#	WARFARIN CAPS ___ MG			WARFARIN CAPS ___ MG			WARFARIN CAPS ___ MG			Recorded by
		#	Lot/Exp	Balance	#	Lot/Exp	Balance	#	Lot/Exp	Balance	

NOTES:

Page # ___

Drug Destruction Record

Use this form to document destruction of capsules that were NOT DISPENSED TO PATIENTS. For capsules dispensed to patients, destruction is documented on the Patient Specific Worksheet instead, there is no need to document here as well.

PARTIAL BOTTLES:

Bottle Strength (MG)	Lot Number	Use-by Date	# of Capsules

FULL BOTTLES: Paste tear-off portion of bottle labels here. Make sure that the STRENGTH, LOT # and USE-BY DATE are visible.

Method of Destruction: _____

Date Destroyed: _____ By: _____ Witness: _____

Fax completed worksheet to University of Pennsylvania at 215-349-5132. Keep original in your pharmacy records. Thank you!

Clarification of Optimal Anticoagulation Through Genetics (COAG):
A Randomized, Multicenter, Double-Blind Clinical Trial to Evaluate Efficacy in theUse of Clinical Plus Genetic Information to Guide Warfarin Therapy Initiation and Improve Anticoagulation Control for Patients.

http://www.coagstudy.org

COAG Laboratory Manual of Procedures and Data Management Users Guide

Version 1.2 – May 2011 - Please see page 5 and page 10 for Updates

Prepared by:
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Table of Contents

1. SUMMARY OF RESPONSIBILITIES 1

1.A. Central Laboratory 1

1.B. Clinical Site Research Coordinator 1

1.C. Clinical Site Molecular Diagnostic (Genotype) Laboratory 2

2. Outline of Patient Flow for Laboratory Procedures 2

3. Research Coordinator Instructions for Blood Specimen Collection, Handling, and Shipping 3

3.A. General Information 3

3.A.1. Blood Specimen Collection Instructions 3
3.A.2. Labeling and Handling Blood Specimens 4
3.A.3. Delivery of 2 ml tube to Clinical Site Molecular Diagnostic Laboratory 5
3.A.4. Packaging and Shipping of 6ml tube to COAG Central Laboratory 5

4. Sample Processing in the Clinical Site Molecular Diagnostic Laboratory 8

4.A. RECORDING GENOTYPE RESULTS 8

4.B. Completing the Genotyping Information Case Report Form 8

4.C. Entering the information on the Genotyping Information Form into the Data Management System (DMS) 9

4.D. Communication with the Research Coordinator (RC) 9

4.E. Communications with the Clinical Trial Coordinating Center (CTCC) 9

5. Retaining Extracted DNA and Residual Whole Blood and Extracted DNA 10

6. DNA EXTRACTION FAILURE 10

6.A. Genotype Failure 11

7. Data Management System Users Guide 13

7.A. Introduction 13

7.B. Oracle JInitiator 13

7.C. SSL Certificate: 15

7.D. Data Management System Web Site 17

7.D.1. COAG Main Menu 18
7.D.2. Data Management System Log In 18

7.E. COAG – Laboratory Menu 20

7.E.1. Entering Genotyping Information Case Report Form 20
7.E.2. First Entry of Genotyping Information 21
7.E.3. Second Entry of Genotyping Information 23

8. Sponsored Project Help Desk 25

8.A. Technical Support 25

8.B. Assignment of Data Management System Account 25

SUMMARY OF RESPONSIBILITIES

1.A. Central Laboratory

The Central Laboratory will coordinate the laboratory and genotyping activities for the COAG study. Washington University School of Medicine-Department of Pathology and Immunology in St. Louis, MO serves as the Central Laboratory (CL) for the COAG study The Central Lab will be responsible for implementing a quality assurance (QA) plan, ensuring accurate genotyping results from the clinical sites by replicating genotyping on samples sent from the Clinical Sites. The CL will provide a process for QA periodic random sampling and testing over the course of the study. During the study the CL will coordinate with the CTCC to provide genotyping data as needed. The CL will provide a process for data transfer of the comprehensive lab data set to the CTCC. At the end of the contract period, the CL will transfer all biospecimens and laboratory data to an NIH-designated repository. The following is contact information for key CL personnel:

Charles Eby MD

Laboratory Director
Washington University School of Medicine
Department of Pathology & Immunology
660 S. Euclid Avenue
St. Louis, MO 63110
Phone: 314-362-1302
Fax: 314 362-1461
E-mail: eby@wustl.edu
Pager: 314-672-9738

Rhonda Porche-Sorbet

Laboratory Supervisor
Washington University School of Medicine
Department of Pathology & Immunology
660 S. Euclid Avenue
St. Louis, MO 63110
Phone: 314 362-8852
Fax: 314 362-1461
E-mail: rhonda@wustl.edu
Pager: 314-871-7603

1.B. Clinical Site Research Coordinator

Clinical and genotype data will be collected on all patients who have given consent for study participation. The goal of recruitment will be to enroll as many patients as possible who have genotyping available prior to receiving the first dose of warfarin. The clinical site Research Coordinator will ensure the timely collection and delivery of the genotype blood specimen to the site molecular laboratory and will ensure the timely shipment of the genotype blood specimen to the central laboratory. If the genotype specimen cannot be obtained before the patient receives the first dose of warfarin, every effort will be made to obtain the specimen as soon as possible thereafter.

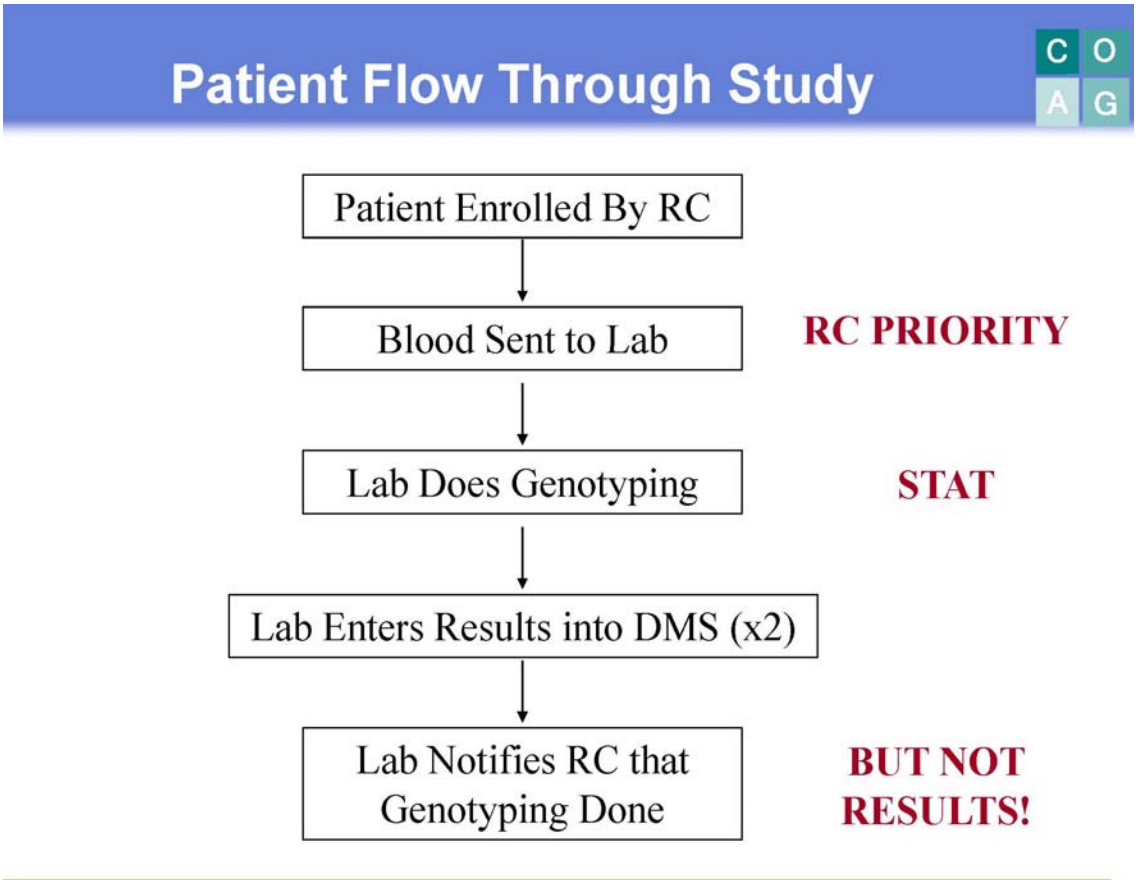
1.C. Clinical Site Molecular Diagnostic (Genotype) Laboratory

The site genotype laboratory is responsible for:

- Extracting DNA from participant specimen received from the site research coordinator, and conducting genotyping
- Complete Genotype case report form information
- Enter Genotype case report form information into the COAG data management system and notify the Research Coordinator when data entry has been completed
- Maintaining the blinding of genotype information and will not reveal participant genotype to site PI, other investigators, or Research Coordinator.
- Contacting the Central Laboratory if genotyping fails after second attempt.
- Conducting ongoing quality assurance proficiency testing on samples specified by the Central Laboratory

2. OUTLINE OF PATIENT FLOW FOR LABORATORY PROCEDURES

The following diagram outlines the Patient Flow through the study as it pertains to genotyping specimen collection and genotype testing:



3. RESEARCH COORDINATOR INSTRUCTIONS FOR BLOOD SPECIMEN COLLECTION, HANDLING, AND SHIPPING

3.A. General Information

Clinical Sites are responsible for the costs of FedEx shipping and for the supplies to collect blood and send samples to the Central Lab. The Central Lab will provide labels, collection tubes, and biohazard bags with absorbent material. Central Laboratory will ship a supply of materials to enroll 50 participants, and will replenish supplies as enrollments accrue.

Before enrolling your first subject, contact your local Federal Express office to confirm pickup location and times to ensure overnight priority delivery to St. Louis. Remember, shipments can only be delivered to the COAG Central Laboratory on week days and not on weekends or holidays. Shipments should be made Monday-Thursday and not the day before a holiday. If a package must be shipped on Friday, please contact the Central Laboratory immediately

3.A.1. Blood Specimen Collection Instructions

Precautions for Handling Blood Specimens:

- All specimens are handled as potentially infectious for laboratory workers. Hepatitis and HIV can be transmitted via “needle stick” skin punctures.ear disposable plastic gloves when collecting and processing specimens.
- Use 0.1% sodium hypochlorite (household bleach) to clean up any spills of blood, plasma, or serum. Use this solution to clean up all laboratory work surfaces at the completion of work activities.
- Dispose of all needles and tubing in puncture-resistant sharps containers for safe disposal.
- Place all used Vacutainer tubes and non-sharp blood contaminated materialsin spill proof liquid biohazard sharps containers for disposal.

Preparation for Blood Collection:

After obtaining consent from an eligible subject, prepare to collect a blood sample using the following materials:

- 6 ml plastic EDTA Vacutainer collection tube (provided by Central Lab)
- 2 ml plastic EDTA Vacutainer collection tube (provided by Central Lab)
- 21 gauge butterfly needle with adaptor and collection tube holder
- Alcohol swabs
- Band aid
- Bubble wrap (provided by Central Lab)
- 2 sealable plastic bags (provided by Central Lab)
- Cardboard shipping box, with a Styrofoam liner
- Two frozen cold packs (shipped inside shipping boxes, keep supply frozen at all times)
- Tourniquet

- Extra butterfly in case first attempt is unsuccessful
- Sheet of 10 barcode labels for each participant (provided by Central Lab)
- Preprinted, postage-paid Federal Express label (see 2.A.3 for instructions)

Blood should be collected from an upper extremity peripheral vein using aseptic technique and in accordance with your institution's phlebotomy policy and procedure to minimize risk of pain or injury to the subject and phlebotomist risk of needle injury or exposure to blood. The following is a brief overview of blood collection:

- Explain to the subject the purpose of collecting the blood sample.
- Open the butterfly collection set with Vacutainer adapter and collection tube holder; have the two EDTA collection tubes within reach.
- Glove, position subject so that subject and phlebotomist are in comfortable positions. Minimize risk of blood staining subject's clothing. Clean venipuncture site with alcohol swabs.
- Apply tourniquet.
- Perform venipuncture with 21 gauge butterfly, fill 6 ml EDTA tube first, then 2 ml EDTA tube. Invert each tube after filling is complete.
- Remove tourniquet, withdraw needle, apply light pressure with a gauze pad, have subject raise arm and apply light pressure to the site.
- Dispose of butterfly and collection system in approved biohazard/sharps container.
- Inspect venipuncture site. If not oozing, apply band aid. If still oozing, continue to apply light pressure, check again approximately every minute until not bleeding, and then apply band aid.
- If peripheral venous access is not adequate, or two attempts at peripheral venipuncture are unsuccessful, blood can be collected from an indwelling peripheral or central catheter in accordance with the local policy and procedures.

3.A.2. Labeling and Handling Blood Specimens

- To facilitate accurate tracking of specimens, after blood collection is completed, label each tube with a printed barcode label containing the Clinical Site ID number and a unique 3 digit identification number for the participant. Write the participant's first, middle, and last initials (if no middle initial, leave center space empty), date and military time of collection, and initials of person collecting blood on 5 labels. Retain remaining labels in participant file in case DNA extraction fails in the Clinical Site molecular diagnostic laboratory and the RC collects a second 2 ml. blood sample.
- Affix 1 label onto each of the tubes containing blood, affix 1 label on each of the two Genotyping Information case report forms (in box 7 – see page 7) below CYP2C9), and put the last label on the participant's clinical file case report form.
- The Research Coordinator (RC) completes the information requested in the header section of the Genotyping Information case report form and in boxes 1 and 2 of that form.

- One form is submitted with the 2 ml tube of blood to the Clinical Site molecular diagnostic laboratory and one form is submitted with the 6 ml tube of blood to the COAG Central Laboratory.

3.A.3. Delivery of 2 ml tube to Clinical Site Molecular Diagnostic Laboratory

- Notify the molecular diagnostic laboratory at your site and inform the technician who will be performing genotyping that a sample is on its way.
- Immediately transport in the most efficient manner, inside a sealed biohazard bag at ambient temperature, the 2 ml EDTA tube to the laboratory. Confirm the sample has been received, when processing and genotyping will begin, when the RC should expect to learn genotype is available, and means of communicating the information.

3.A.4. Packaging and Shipping of 6ml tube to COAG Central Laboratory

Once collected, the 6 ml EDTA tube must be shipped via overnight mail service to the Central Lab. Remember, shipments can only be delivered to the COAG Central Laboratory on week days and not on weekends or holidays. Shipments should be made Monday-Thursday and not the day before a holiday. If a participant is recruited on a Friday or the day before a holiday, store the labeled 6 ml tube at 4^0C until the next business day and then send by FedEx.

If a 6 ml tube of blood must be shipped on a Friday or before a holiday because genotype results will not be available from the local molecular laboratory that day, the RC will contact the Central Laboratory immediately.

Modification to frequency of shipping as of 5/10/11

Sites recruiting less than one subject per week should continue current procedure of shipping sample promptly (next day except if it will be a Friday) with ice pack, standard next day delivery.

Sites recruiting more than 1 subject per week can review local logistics (specimen collection, processing, shipping of blood samples to Central Laboratory) to determine if local storage and once a week shipping of samples can be done without adversely affecting Research Coordinator routines.

Packaging the 6 ml EDTA tube

- Wrap the 6 ml EDTA tube in bubble wrap, place the tube in the larger bag with the absorbent strip and seal it. Place the second Genotyping Information Form in the pouch of the large bag.
- Place the packaged blood and Genotyping Information Form into a cardboard box with a Styrofoam liner containing two frozen cold packs. Replace the Styrofoam lid in the cardboard box and seal the cardboard box with shipping tape.

FedEx Shipping Instructions

- We recommend you create a FedEx account for routine shipments. To create an account, please follow this link: http://www.fedex.com

- Prepare shipment and fill in the appropriate information to create your User ID for shipping with an account.
- Please follow this link: http://www.fedex.com/us/helpguide/shipping/
- Print the instructions for shipping within the U.S. (This will be useful as you fill in each box described below)
    - Box 1 From (fill in your address)
    - Box 2 To (see address below for the Central Lab)

      Dr. Charles Eby
      Washington University School of Medicine
      Pathology Department
      425 South Euclid Ave.
      St. Louis, MO 63110

      Phone: 314 362-8852

      Click save new recipient in the address book. This information, along with the email notification addresses) will be available for subsequent shipments in the My Shipment Profile box.

    - Box 3 Package and Shipment Details

      Service type is **Priority Overnight**
      Please include:
      Package weight (4 lbs)
      Value (100.00)
      Date (current date)
    - Box 4 Billing Details (your billing account number)
    - E-mail notification

      Please click edit and add the following email address for notification of shipment and notification of delivery

      YOUR email address

      eby@wustl.edu

      Rhonda@wustl.edu

      cking@path.wustl.edu
    - Box 5 Ship (print 2 copies of the shipping label)

      Affix one of the shipping labels onto the box using FedEx Air bill pouch (please contact FedEx to obtain pouches)

      Retain the other label for your records.

IF YOU HAVE ANY QUESTIONS, CALL THE CENTRAL LABORATORY AT 314-362-8852

Participant ID: _____ Participant Initials: _____ Clinical Center: ____

Visit Date: _____ Visit Number: ____ CRC Initials: _____

Laboratory ID: Local / Central Genotype attempt: __ __

GENOTYPING INFORMATION

Completed by the Research Coordinator:

1. Date and time specimen collected:	__ __/__ __/__ __ __ __ (*mm/dd/yyyy*) __ __ : __ __ (*military time*)
2. Date and time specimen transferred/shipped to the genotyping laboratory:	__ __/__ __/__ __ __ __ (*mm/dd/yyyy*) __ __ : __ __ (*military time*)

Completed by the genotyping laboratory personnel:

3. Date and time specimen received at the genotyping laboratory:	__ __/__ __/__ __ __ __ (*mm/dd/yyyy*) __ __ : __ __ (*military time*)
4. Date and time specimen was analyzed:	__ __/__ __/__ __ __ __ (*mm/dd/yyyy*) __ __ : __ __ (*military time*)
5. Check box if the specimen is not analyzable or the results are not available:	☐88 Results missing in item # 6 and 7
6. VKORC1 *(-1639 / 3673)*:	☐0 GG ☐2 AA ☐1 AG ☐88 Missing
7. CYP2C9 (*check one*):	

	CYP2C9*2	CYP2C9*3
☐1 *1*1	CC	AA
☐2 *1*2	CT	AA
☐3 *1*3	CC	AC
☐4 *2*2	TT	AA
☐5 *2*3	CT	AC
☐6 *3*3	CC	CC
☐88 Missing	Missing	Missing

Place label here

8. DNA concentration:	__ __ __ ng/µL
9. Total DNA:	__ __ __ . __ __ µg

Test results recorded by (signature): _____

Test results confirmed by (signature): _____

Enter genotyping results in the data management system (DMS) immediately.

Fax completed case report form to the CTCC at (215) 573-4790.

V2.0.20100219 Page 1 of 1 GENOTYPE

4. SAMPLE PROCESSING IN THE CLINICAL SITE MOLECULAR DIAGNOSTIC LABORATORY

Upon receipt of the genotype specimen, verify that the 2 ml EDTA tube specimen label is identical to the label attached on the Genotype Case Report Form (CRF). The header information and boxes 1 and 2 on the Genotype CRF should be completed by the Research Coordinator (RC). Contact the RC immediately to resolve any discrepancies or omissions that you find on this form.

DNA extraction: Method and volume of blood are determined by each laboratory. Quantifying amount of DNA extracted for future DNA archive database is optional and there is space for recording this information in boxes 8 and 9 on the Genotype CRF. (See Section 5 retention of residual whole blood and extracted DNA instructions.

DNA genotyping: Follow laboratory procedure for Osmetech or Infiniti specific PCR and genotype methods. (See Section 6 for procedure should genotyping fail.)

4.A. RECORDING GENOTYPE RESULTS

Once the genotyping analysis has been conducted, a report of the results of the analysis is printed out from the genotyping platform (Osmetech eSensor®Warfarin Sensitivity Test Report or Infiniti Assay:Warfarin Report). The results of the genotyping analysis is transcribed onto the Genotype case report form and then entered into the Data Management System (DMS).

To ensure accuracy of the data collected, the following procedural steps will be conducted in reporting genotype results:

1. Genotyping analysis results will be transcribed onto the appropriate sections of the genotype case report form.
2. The genotyping analysis results transcribed to the case report form will then be double checked in real time by a second person at the site molecular lab to confirm that the transcribed information accurately represents the analytic results from the laboratory's genotyping platform.
3. Both the technologist who records the analysis results on the case report form and the person who checks the accuracy of the recorded analysis results will sign the genotype case report form.
4. The data from the genotype case report form will then be entered into the DMS two separate times (double data entry) by the site genotyping laboratory technologist.

4.B. Completing the Genotyping Information Case Report Form

Boxes 3 through 9 of the genotype case report form are completed by the molecular diagnostic laboratory technologist and data **are not shared** with the study staff at the clinical site (RCs and PIs) or the Investigational Drug Service (research pharmacy) at the clinical site.

Box 3. Due to differences in genotyping processes at the clinical sites, there may be a discernable lag when the genotyping laboratory receives and processes the genotype specimen. Box 3 item requires the laboratory to acknowledge the receipt of the specimen and the date and time are noted by the laboratory personnel. Date is entered in the mm/dd/yyyy format and time is recorded in 24-hour clock (military time) format.

Box 4. This item notes the date and time the specimen is genotyped. Date is entered in the mm/dd/yyyy format and time is recorded in 24-hour clock (military time) format.

Box 5. Genotyping for CYP2C9 *2,*3 and VKORC1 -1369 SNPs is reported as all or none. A check in the box for question 5 indicates that the laboratory could not generate reportable results for all three SNPs and the assay should be repeated. If question 5 is checked, no results should be checked in boxes 7 and 8.

Box 6. VKORC1 genetic information is recorded here by checking the appropriate checkbox.

Box 7. CYP2C9 genetic information is recorded here by checking the appropriate checkbox.

Box 8 + 9. DNA yield and concentration (Optional).

Signature of the person recording the analytic results and the signature of the person confirming the accuracy of the recorded results is recorded on the signature lines at the bottom of the form.

4.C. Entering the information on the Genotyping Information Form into the Data Management System (DMS)

Please refer to the Data Management System (DMS) Users Guide **(Section 7.E.1)** for this procedure.

4.D. Communication with the Research Coordinator (RC)

Once you have entered the genotype information into the data management system, it is important that the Research Coordinator (RC) be contacted, as this contact from you is necessary in order for the RC to move on to the next steps of the enrollment and drug order process. Contact the RC and inform her/him that the **"genotype is available"**. If for some reason the genotype information is delayed or not completed, inform the RC that the **"genotype is not available"**.

4.E. Communications with the Clinical Trial Coordinating Center (CTCC)

Completed Genotyping Information case report forms will be faxed by the molecular lab to the CTCC at the following fax number: 215-573-4790. This information can be batched and faxed on a monthly basis. Please file all completed Genotyping Information case report forms in a secure area of the molecular diagnostic laboratory until the end of the trail. At that time you will be instructed when to send the filed Genotyping Information case report forms to the site Research Coordinator.

5. RETAINING EXTRACTED DNA AND RESIDUAL WHOLE BLOOD AND EXTRACTED DNA

Residual whole blood will be retained at 4C until the central laboratory has completed confirmatory genotyping. The central laboratory will contact the local site molecular laboratory to dispose of the residual blood per laboratory procedures. It is possible that the genotyping platform sub-committee may modify handling of residual blood, and if so, updates will be sent to all participants.

Modification approved by genotype subcommittee as of May 10, 2011

Delaying DNA extraction for up to a maximum of 8 days is allowed, if specimen is kept refrigerated (40C). Specimen can be shipped once a week via standard next day delivery with ice packs to Central Laboratory.

At the end of the trial, Clinical Sites will send all extracted DNA samples from participants to the Central Laboratory. All DNA will be sent to the NIH central repository, and stored for future studies approved by the COAG Trial Ancillary Studies subcommittee. On their consent form, participants may choose not to permit use of their DNA for future research. In such cases, the CTCC will inform the Central Laboratory and the extracted DNA collected from the Clinical Site and the Central Laboratory will be destroyed.

- Retain extracted DNA from all participants regardless of whether genotyping was successful or not.
- Store DNA in a cyrotube with an O ring cap that will fit in a cardboard storage box designed for a freezer rack.
- Label the tube with site number, participant number and initials, date extracted, and if known, DNA concentration and total DNA amount.
- Store DNA at -20 to -80^{0}C.
- When enrollment in COAG Trial is closed, contact the Central Laboratory to confirm arrangements to transport all DNA samples on dry ice in one shipment.
- When enrollment in COAG Trial is closed, deliver all hard copies of Genotyping Information Forms to the RC at your Clinical Site.DNA EXTRACTION FAILURE

It is unlikely that DNA extraction will fail due to inadequate viable leukocyte DNA since neutropenic patients will not be enrolled and there will be minimal delay between collection and processing.

- If the laboratory staff suspects inadequate DNA extraction (quantifying DNA extraction yield before genotyping, or COAG participant genotype fails despite successful positive control genotype) take one of the following options:
- If only a portion of the 2 mls of blood was used for extraction, repeat extraction from that sample, and consider doubling the blood volume.
- If all of the 2 mls of blood was used, immediately contact the site research coordinator (RC). The COAG protocol includes a provision for collection of a second 2 ml tube of blood from participants if the first DNA extraction fails. The first DNA extraction failure will be recorded on the Genotyping Information Form (check “results missing in item #6 and #7” in question 5 and indicate genotype attempt 01 in the header section).

- A second 2ml tube of blood must be correctly labeled, and accompanied by a new correctly labeled Genotyping Information case report form.
- If the second DNA extraction is successful, proceed with genotyping.
- If DNA extraction fails twice complete the Genotyping Information form, indicating the DNA extraction failed (check "results missing in item #6 and #7" and indicate genotype attempt 02 in the header section), enter the information in the DMS, and immediately inform the RC that genotype will not be available.
- Call the Central Laboratory and inform them that DNA extraction failed twice.

6. Genotype Failure

The combination of commercial instruments and reagents known to be accurate and reliable, and experienced technologists performing molecular tests in a CLIA certified laboratory will ensure that genotyping failures will be rare events. However, there must be contingencies in case genotyping partially or completely fails in order to obtain a complete genotype as soon as possible.

1. If the first genotype test partially or completely fails, based on each laboratory's procedure, the best option is to review the process, identify the likely source of error, correct it, and immediately repeat genotype testing. Record unsuccessful genotype results on the Genotyping Information Form. Check "missing" box for question 6 and/or 7 if either or both VKORC1 or CYP2C9 fail, indicate genotype attempt 01 in the header section, enter results into the DMS.

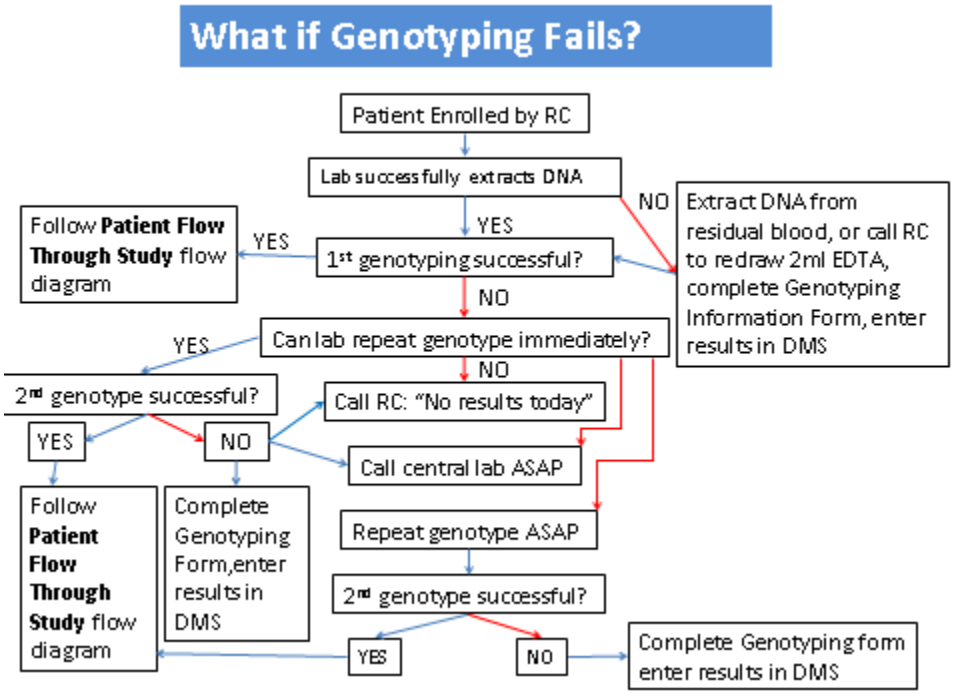
2. If the second genotype test is successful, contact the RC to inform him/her that genotype is available, download, print, and record results on a second Genotyping Information Form (indicate genotype attempt 02 in the header section), and enter them into the DMS.

3. If the second genotype test is unsuccessful, contact the RC to inform him/her genotype will not be available. Immediately contact the Central Laboratory to alert the staff to prepare to do STAT genotyping on the second tube of blood when it arrives. Download, print, and record results on a second Genotyping Information Form indicating it is the second time the genotype test failed. Check "missing" box for question 6 and/or 7 if either or both VKORC1 or CYP2C9 fail, indicate genotype attempt 02 in the header section, and enter the results in the DMS.

4. If the laboratory cannot immediately perform a second genotype, contact the RC to inform him/her genotype will not be available. Immediately contact the Central Laboratory to alert the staff to prepare to do STAT genotyping on the second tube of blood when it arrives. Perform second genotype the next day, or as soon as possible after weekends or holiday interruptions, complete a second Genotyping Information Form as described in steps 2 or 3 above, and enter results into the DMS.

5. If the second genotype test fails, **STOP**. The central laboratory will contact the laboratory director to document events and identify probable explanations for repeated failures.

The following is a flow diagram summarizing the steps to follow in the event of a DNA extraction or genotype failure:



7. DATA MANAGEMENT SYSTEM USERS GUIDE

7.A. Introduction

The data management system (***DMS***) is developed in accordance with the requirements of the **COAG** Project. The DMS is an Oracle-based application that utilizes java script. In order for users to connect to and run the DMS, it will be necessary to install the Oracle Jinitiator plug-in and security certificate. Updates are available at the following website: rt4.cceb.med.upenn.edu/crcu_html/jinit/jinit_download.htm.

This manual is developed as a reference guide for the data entry person on the project. To access the DMS, the user will need a computer with access to the internet through an internet browser. The DMS is used for entry of the data that is collected on the COAG CRFs. The data tables within the DMS are collectively labeled as the production database.

7.B. Oracle JInitiator

Before the data management system (DMS) is installed on a personal computer, two components need to be downloaded onto the computer first - Oracle JInitiator ver.1.3.1.22 and the SSL Certificate. The following instructions will guide the user through installation of these add-ons.

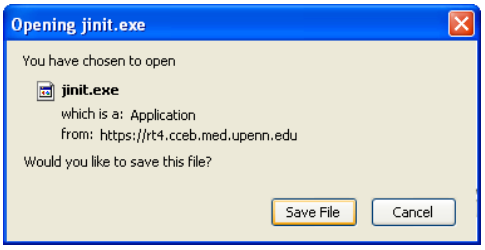
- Open a web browser: Internet Explorer (IE) 6.0 or FireFox 2.0 or higher or Netscape.
- Type in the following url:

https://rt4.cceb.med.upenn.edu/crcu_html/jinit/jinit_download

The Oracle JInitiator version 1.3.1.22 must be loaded first.

- Click the highlighted link, “Download Oracle JInitiator 1.3.1.22”

A prompt will next confirm the file name and the location of the executable.



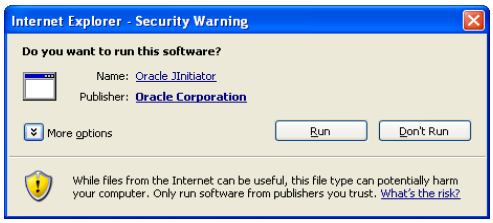
- Click the “Save File” button

The user will be prompted to run or save the self-extracting jinit.exe file.

- Click the “Save” button to save the file to the PC

Once this is done, JInitiator will begin the download.

The next window is a security warning about the download that is about to be



loaded.

- Click the “Run” button

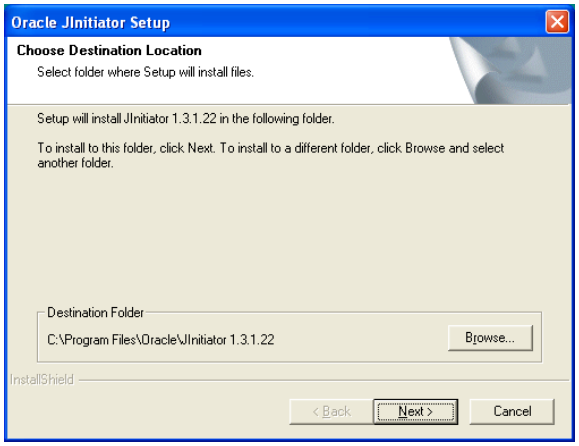
The installer will prompt the user for a destination location to save the file.

The default location the executable points to is C:\Program files\Oracle\JInitiator, on the hard drive of the PC.

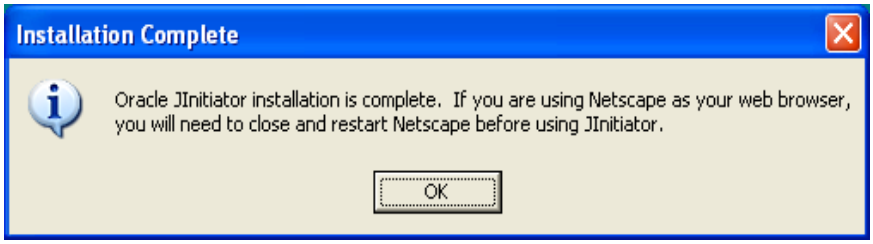
If this is the incorrect desired location for this file:

- Click the “Browse” button to choose a desired location to save this file on the PC.

If correct, click the “Next” button to continue the installation.



Once the installation is complete, the following window will appear:

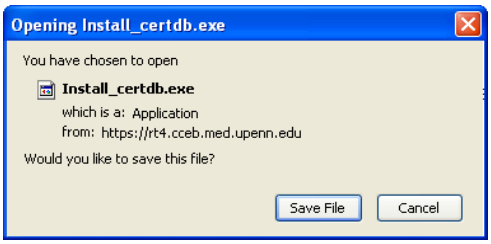


Note: If using the Internet Explorer browser or FireFox browser, it is not necessary to close and restart the browser, but if using the Netscape web browser, the user will need to close and restart the browser before using JInitiator.

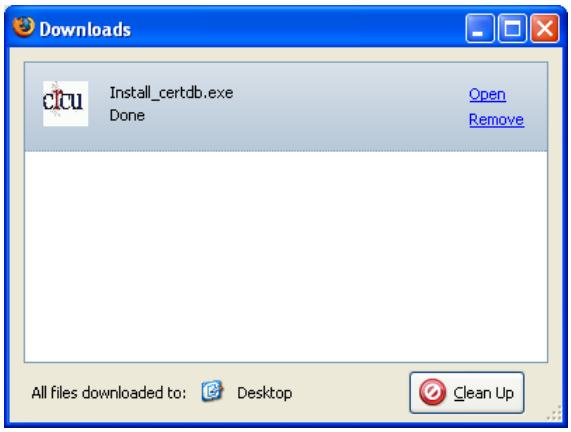
7.C. SSL Certificate:

Once the Oracle JInitiator executable is loaded onto the PC:

- Click the second plug-in, the SSL Certificate called, ”Certificate Installer”
- Once the link is chosen, the following window will appear:

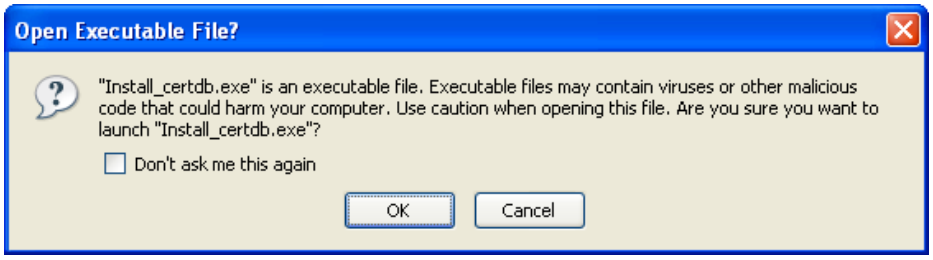


- When downloading this or any file, a separate window will open exclusive to download content.



- Select “Open” to begin the downloading process.

The next screen illustrates a security function that provides caution to downloading executable files that may contain viruses or other malicious code(s) that could harm the

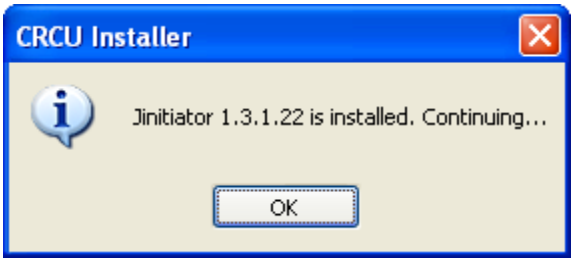


computer.

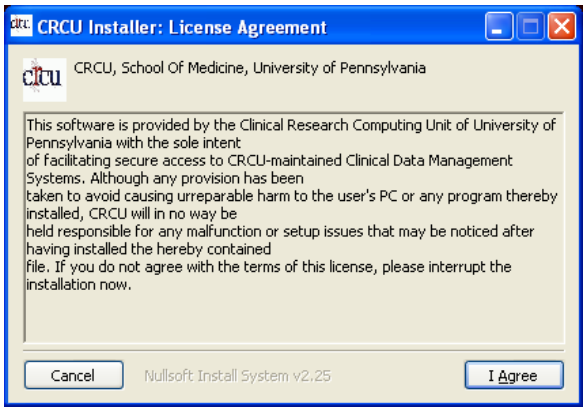
- Click “OK” to proceed with the installation

This window advises the user that the installation of the CERTDB.TXT file will begin.

- Click “Yes” to continue



- Click “OK” to continue with the installation



Once the License agreement is reviewed:

- Click “I Agree” to continue installation

Setup will provide a prompt that indicates the location for the installation to be downloaded. There is an option to choose a different location to save the certificate.

7.D. Data Management System Web Site

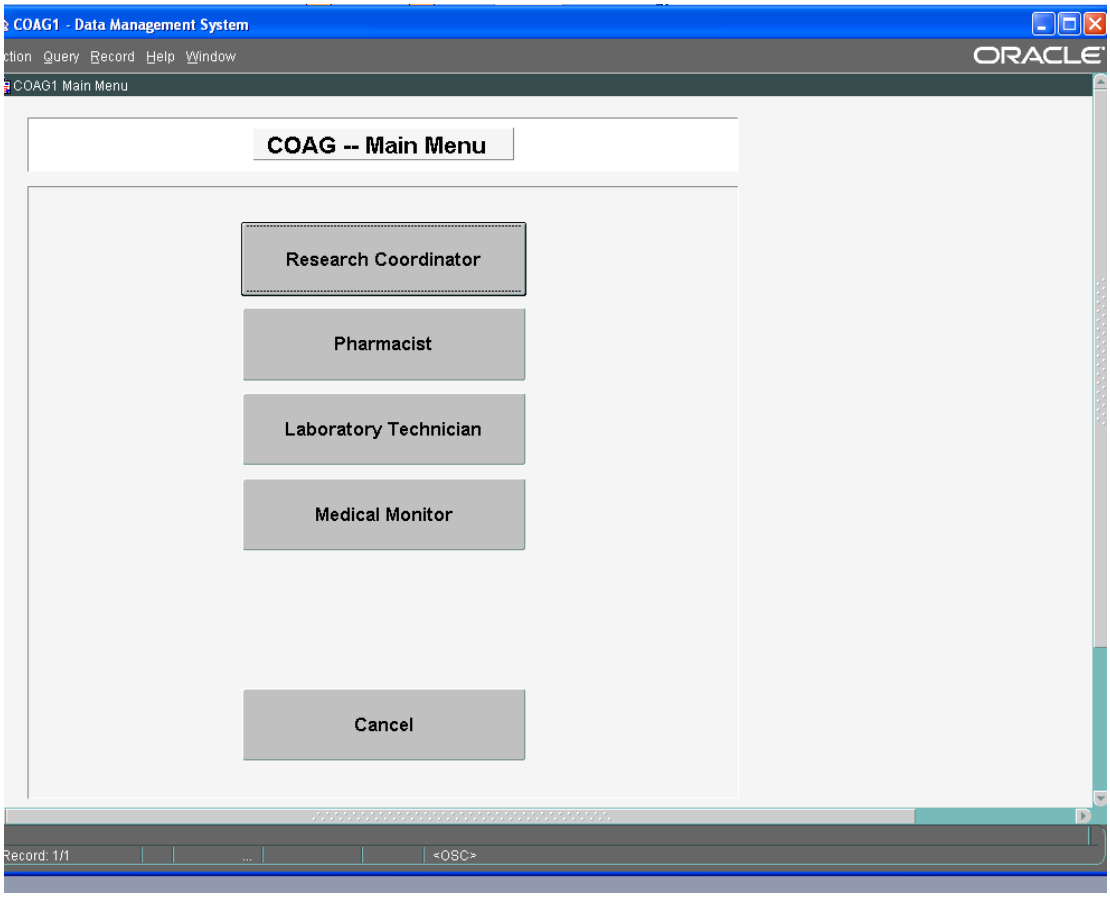
- Run a web browser while connected to the Internet
- Type the following web address in the space provided on the browser

https://rt4.cceb.med.upenn.edu/crcu_html/COAG1.htm.

- Save the address by selecting the "Favorites" option available within the browser and clicking on "Add to Favorites"

7.D.1. COAG Main Menu

Once you have successfully navigated to the Data Management System (DMS) web site, you will first be presented with the Main Menu screen. The Main Menu is used to navigate to the appropriate module of the DMS. The COAG Main Menu contains a set of buttons that will provide the user access to data entry modules. The privileges



provided to the user will determine the functions available in the DMS. The Laboratory Technician view is the Genotyping Information. Locate the Laboratory Technician button that represents your position on the study.

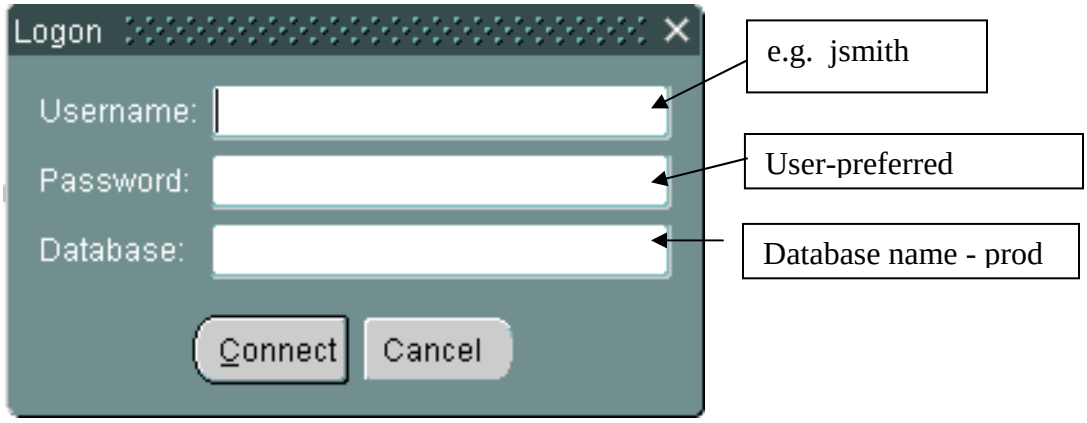
- Click on the Laboratory Technician button

7.D.2. Data Management System Log In

You will now be prompted to log into the database with your user name and password.

- Enter requested log-in information in the dialog box
  - Username - the first initial and last name, limited to 8 characters

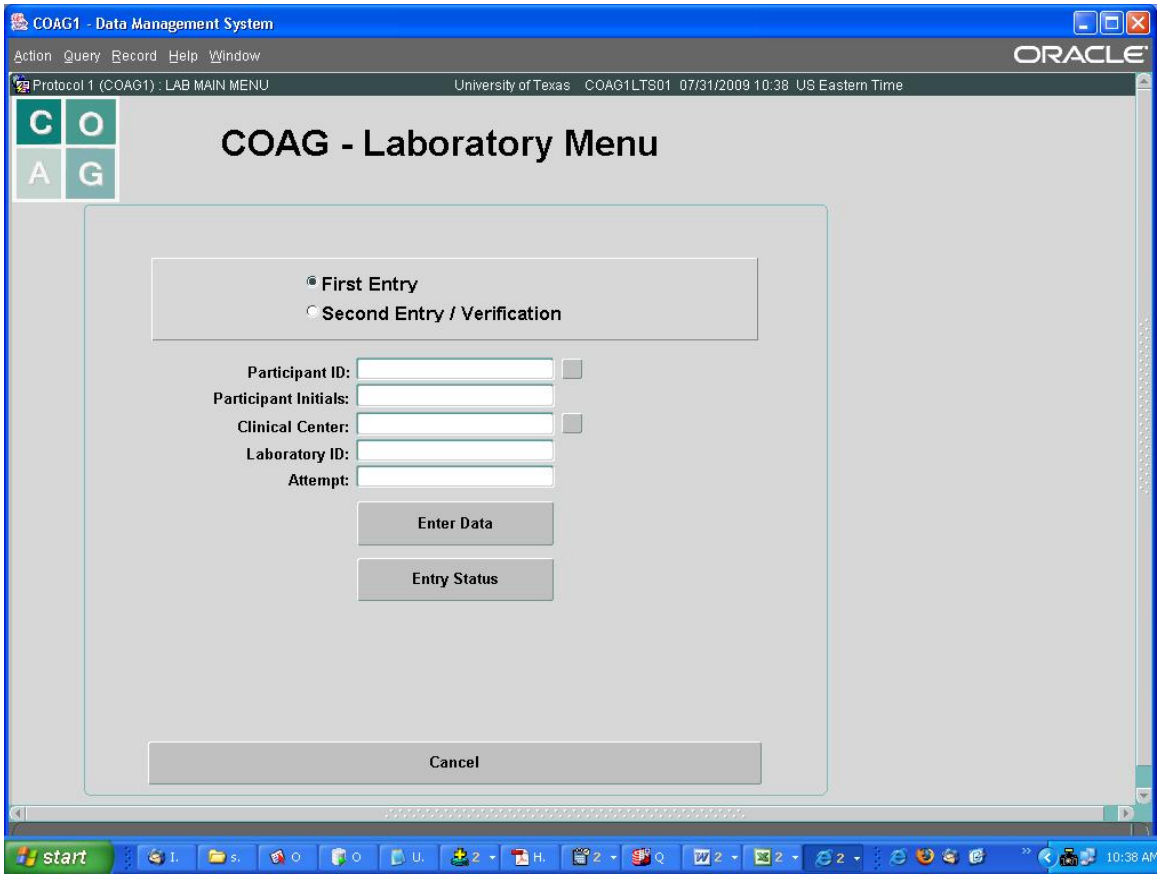
- Password - for the first time user a temporary password – “temp01” - is provided; a prompt will request the user to create a new password that is easily remembered for future log-ins
- Database - ‘PROD’; will give the user access to the COAG database



- Click on the “Connect” button to access the main menu of the Data Management System
  - You will then be taken to the COAG Laboratory Menu.

7.E. COAG – Laboratory Menu

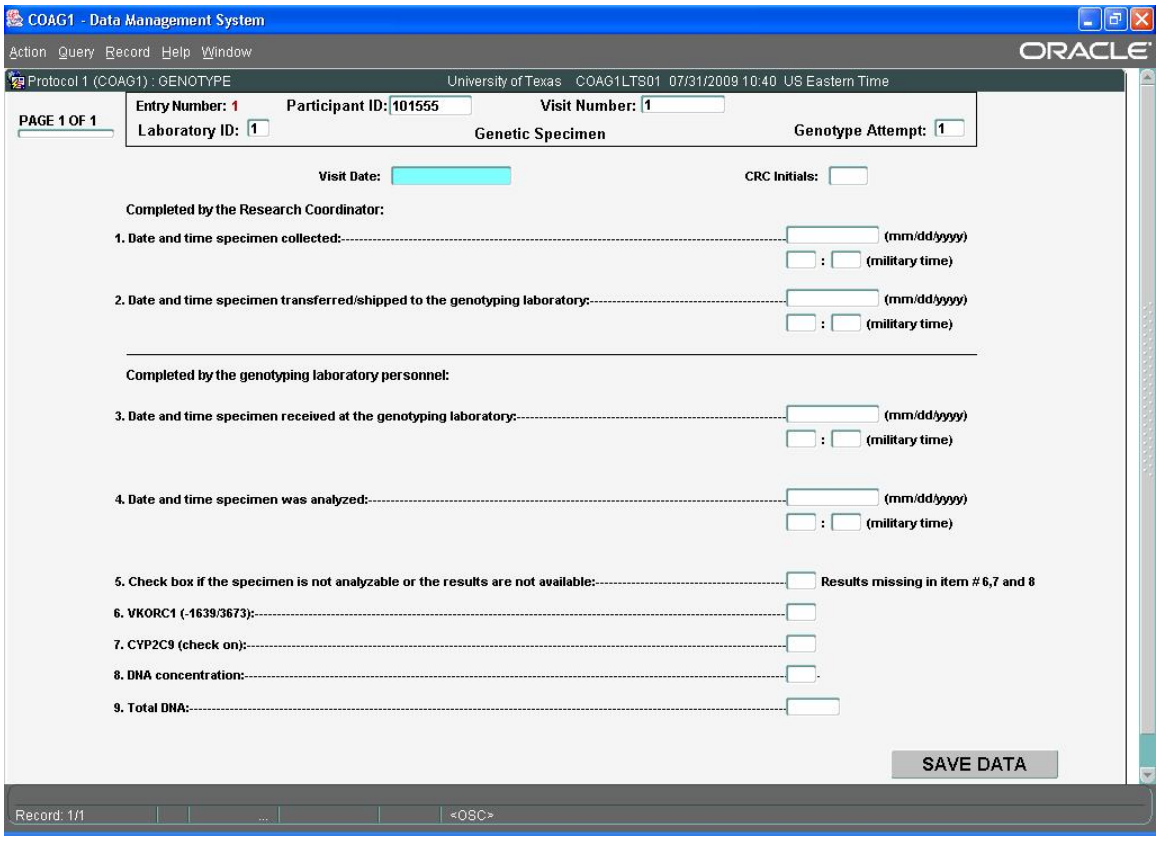
- Select “First Entry”
- Select the Participant ID (PID) from the drop box or type it in. The Participant Initials and Clinical Center will automatically populate if you select from the drop box.
- If you type in the Participant ID, you will have to type in the Participant initials and Clinical Center.
- In the Laboratory ID box, type in a 1 for “Local” if you are entering information from the Site Laboratory. If entering information from the Central Laboratory, type in a 2 for Central Laboratory.
- Type in the number 1 for the first genotype attempt. If this was a second genotype attempt, the number 2 would be typed in.
- Click “Enter Data” button



7.E.1. Entering Genotyping Information Case Report Form

Once the genotyping analysis has been conducted, the information is entered on the paper case report form and then entered into the Data Management System (DMS). To ensure accuracy of the data collected, the information from the case report form will be entered into the DMS two separate times (double data entry) by the site genotyping laboratory

technician. This process requires going to the Laboratory Menu, clicking on "first entry" button, entering the menu information, and completing the fields in the screen shown below. This same process would be completed a second time by clicking on the "second entry" button, entering the menu information, and again completing the fields in the screen shown below.



7.E.2. First Entry of Genotyping Information

When entering the Genotyping Information Case Report Form:

- The Participant ID number and Visit Number will automatically populate
- The Laboratory ID and the Genotype Attempt will also automatically populate.

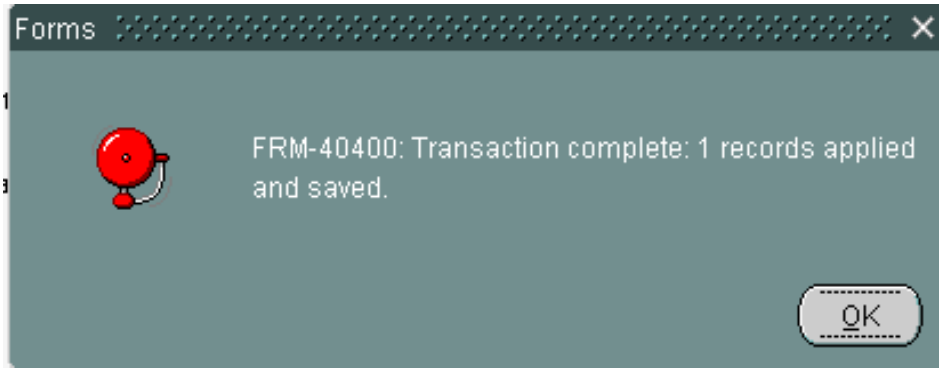
Along with the 2ml genotype specimen sent to the genetics laboratory, the clinical site Research Coordinator (RC) will have sent a Genotyping Information Case Report Form with the header information and Box 1 and 2 completed in hard copy. The genotype laboratory will enter this information from the case report form into the DMS as follows;

- Type in the visit date as recorded on the case report form (CRF) header
- Type in the CRC (Clinical Research Coordinator) Initials as written on CRF header
- Item #1 - Type in the date and time the specimen was collected by the RC
- Item #2 - Type in the date and time the specimen was transferred/shipped to the lab by the RC

The Genotype Laboratory will now enter the Genotyping Information from the paper CRF into the DMS fields indicated for items 3 through 9.

- Date and Time the laboratory received the genotype specimen
- Date and Time the specimen was analyzed
- In Item #5 – record the number 88 only if specimen is not analyzable or if the results are not available.
- Item #6 - record only one appropriate number to indicate VKORC1 results
- Item #7 - record only one appropriate number to indicate CYP2C9 results
- Item 8 - Record DNA concentration
- Item 9 - Record Total DNA

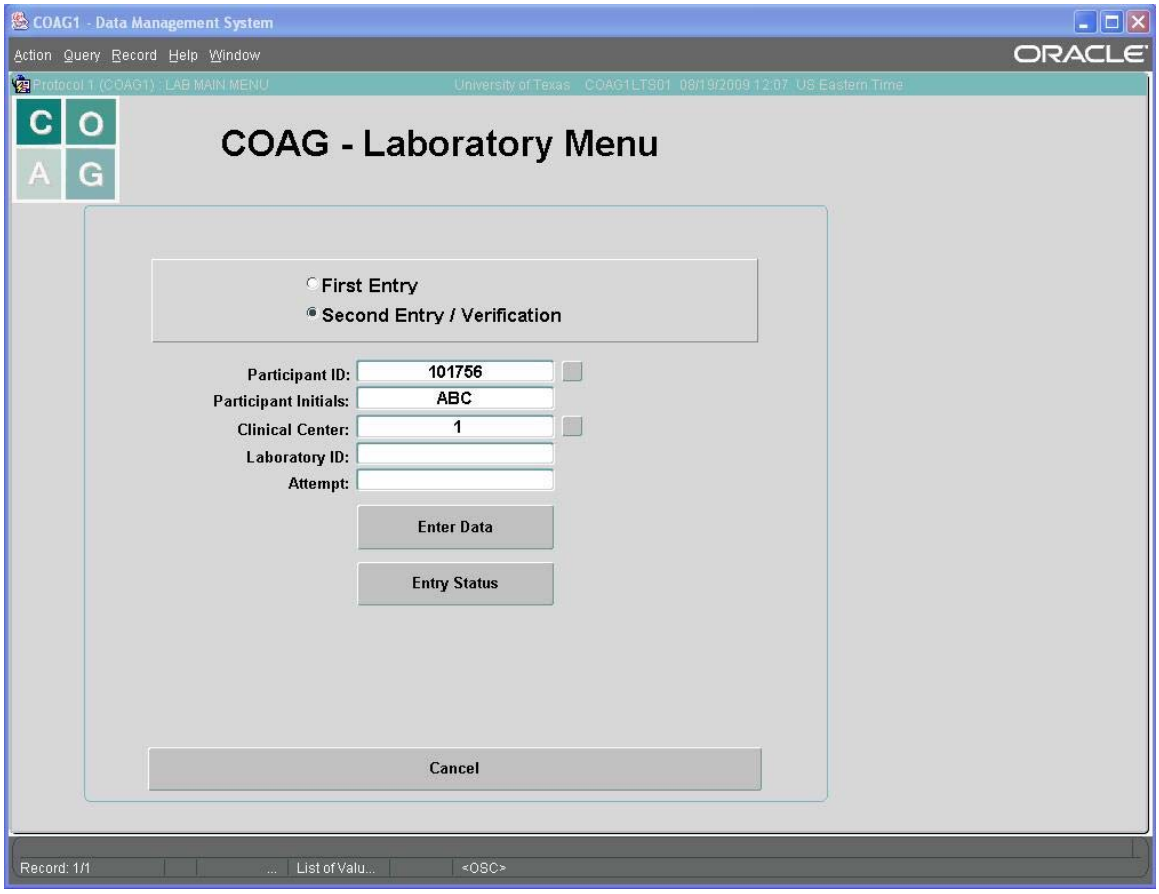
When data entry is complete, click on “Save Data”. The following dialog box will appear to inform the user that the data is successfully saved:



- Click the “Ok” button to return to the COAG Laboratory menu
- A Second entry of the Genotyping Information CRF must be completed immediately in order to verify this data in the DMS

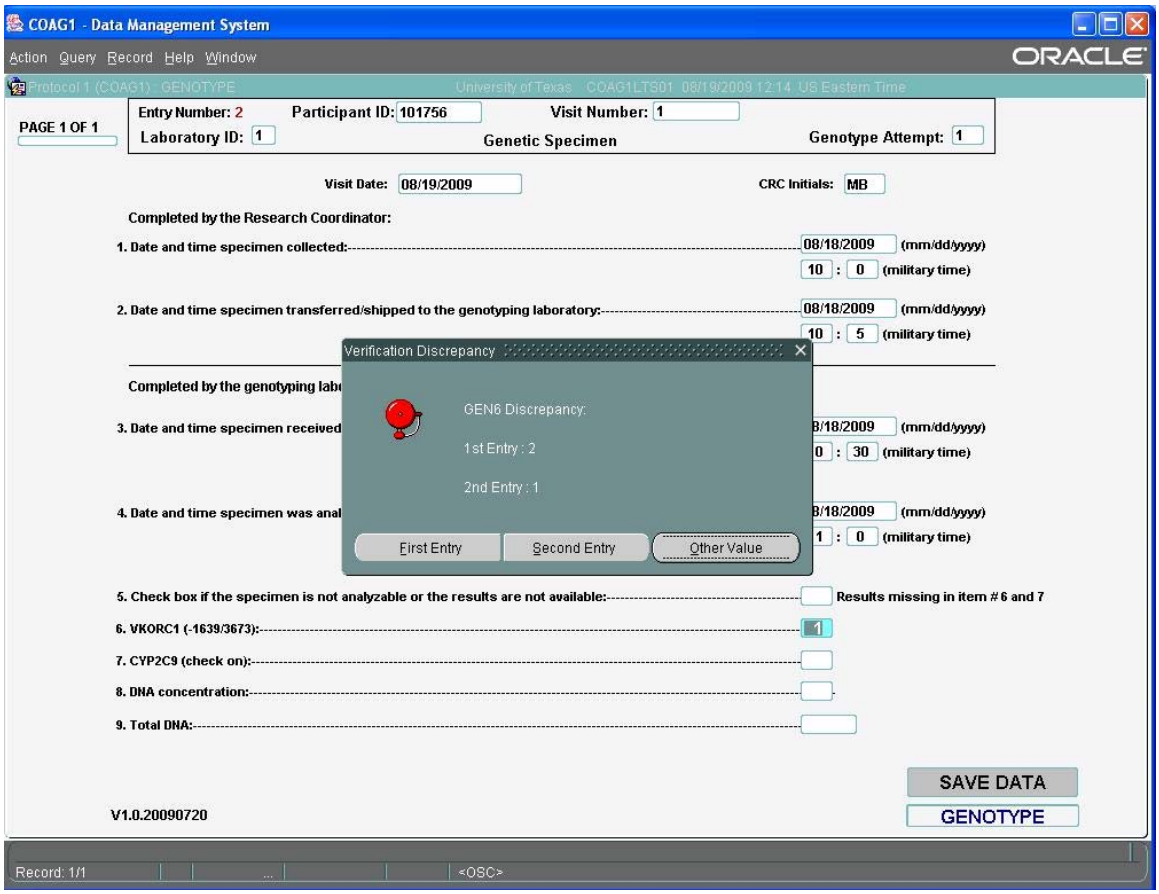
7.E.3. Second Entry of Genotyping Information

- From the COAG Laboratory Menu, select "Second Entry/Verification
- Select the PID from the drop box, type in the Laboratory ID, type in genotype attempt
- Click "Enter Data" button



- Enter the data according to the first entry instructions
- During the "Second Entry/Verification" process, a "Verification Discrepancy" box may appear as you try to go through the fields.
- The box appears if you enter a value under second entry that differs from first entry as illustrated on the following screen.

- The box contains the following: the question number where the discrepancy occurred; the value that was entered under first and second entry; and three options to rectify the discrepancy. They are:
  - First Entry: value entered under first entry
  - Second Entry: value entered under second entry
  - Other Value: allows you to change the value if both first and second entry are incorrect



- Select First Entry or Second Entry, or, if both are incorrect, enter the correct value and proceed with data entry

8. SPONSORED PROJECT HELP DESK

The sponsored project help desk will answer questions concerning the operation of the Data Management System (DMS) and will assist in resolving any issues that hinder the effective use of the software.

8.A. Technical Support

The Help Desk will provide technical support related to problems and issues that may arise when working with the application provided by the CTCC.

The Help Desk will not be responsible for providing technical support for hardware and/or software that are not provided by the CTCC (e.g. word processors, spreadsheets, modems, printers, and hardware) and has direct local institutional support.

Helpdesk Phone Number: 215.573.4623

Helpdesk E-mail: crcuhelp@mail.med.upenn.edu

The COAG helpdesk will be available at the CTCC from 9am – 5pm EST Monday through Friday. The helpdesk can be reached via telephone or e-mail using the contact information above. If contacting helpdesk via telephone, you will be prompted to leave a message indicating the nature of your support requested. Your message will be saved electronically and forwarded to helpdesk support personnel, who will review your message and contact you as soon as possible (typically within an hour). E-mails will be handled in a similar fashion. Each helpdesk support staff member will receive a copy of e-mails sent to the helpdesk e-mail address, and will respond as soon as possible. Support requests that are submitted after 5pm EST will be addressed the following business day.

Requests to the helpdesk should be limited to technical support of the COAG Data Management System (DMS) as it pertains to the COAG study. This would include any issues involving connectivity / access to the COAG DMS, installation on your computer, Error Messages, etc. Questions related to general study operations or the protocol, or other technical issues that are not directly related to the COAG DMS should be directed to Project Management (PJM) or Clinical Data Management (CDM) at the CTCC.

8.B. Assignment of Data Management System Account

A DMS account consists of a username and password that uniquely identifies a user. DMS accounts are required for a user to gain access to the data entry area, and are the primary means for ensuring data security and confidentiality. **Therefore, it is critically important that each individual's DMS user accounts is kept secure and confidential and is not shared with anyone.**

NOTE: The username and password used to individually access your project Web site (http://www.coagstudy.org/) is **not** your DMS username and password. Access to the project Web site infers no access to the project DMS. You may reach the project DMS through a link from within the project Web site but will then be prompted for a specific DMS account username and password.

In addition to providing data security and confidentiality, DMS accounts provide a means to trace all database activities to individual user accounts.

To obtain DMS accounts, a Clinical Center or Site representative will notify the CTCC project manager of the requested user's name and provide a description of what functions

the user will be performing in the DMS. The CTCC Project Manager will in turn notify the Sponsored Project Help Desk of the new user request.

*****Important*****

When a DMS account has been created, the Sponsored Project Help Desk will contact the user with his/her account information.

When personnel leave the project, a representative from the Clinical Center or Site should promptly contact the CTCC Project Manager. The Sponsored Project Help Desk will then take the necessary actions to deactivate that user's database account.