RESPONSE TO RFP - Title Page

Request for Proposal (RFP) Number: 002
Issue Date: July 16, 2008
Proposal Due Date: August 18, 2008

Title of RFP: Central Laboratory for a Randomized Trial of Genotype-Guided Dosing of Warfarin Therapy (GGDWT)

Issued by:
University of Pennsylvania School of Medicine
Center for Clinical Epidemiology and Biostatistics (CCEB)
Clinical Trial Coordinating Center for the Randomized Trial of Genotype-Guided Dosing of Warfarin Therapy (GGDWT)
Philadelphia, PA 19104

Principal Investigator’s Name, Title, Address, Phone, Email:

Provide additional contact information if different from above:

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PACKAGING AND DELIVERY OF THE PROPOSAL

DUE DATE: 4:00 PM local time on August 18, 2008.

Proposals not received at the place and time specified will be considered late and may not be reviewed in time for consideration.

EXTERNAL PACKAGE MARKING:
In addition to the address cited below, mark each package as follows:
Warfarin Central Laboratory. “TO BE OPENED BY AUTHORIZED PERSONNEL ONLY”

FORMATTING INFORMATION:
Send the complete Proposal including all attachments and checklists.
The font size must be no smaller than 11 point with single spacing.
Provide 1 original paper document and 1 photocopy.
Also include electronic versions of all submitted documents on CD. Label the CD with the last name of the investigator. The document must be one complete .pdf entitled as follows:
“PI-LASTNAME-Laboratory-RFP-2008MMDD.pdf” (example: kimmel-laboratory-RFP-20080610.pdf)

Arrange the documents in the following order:
1. Title page
2. Technical proposal
3. Checklist
4. Signature page
5. Biosketches
6. Letters and certifications

DELIVER TO:

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Genotype Guided Dosing of Warfarin Clinical Trial – Central Laboratory

Request for Proposal Instructions

Distributed by the University of Pennsylvania School of Medicine

Statement of Work

1. Background

This Request For Proposals (RFP) for the Genotype Guided Dosing of Warfarin Clinical Trial, sponsored by the National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health (NIH), solicits applications from suitable clinical laboratories to serve as the Central Laboratory (CL) for the trial. The University of Pennsylvania serves as the Clinical Trial Coordinating Center (CTCC) for this study. A Steering Committee will provide leadership to the study. Dr. Robert Califf will serve as the Steering Committee Chair. The Central Laboratory Principal Investigator will participate on the Steering Committee.

The objective of this study is to advance the field of clinical treatment and dose management of warfarin sodium by determining the optimal dosing of warfarin. Warfarin is highly efficacious at preventing thromboembolism (TE), a condition associated with substantial morbidity and mortality. However, warfarin must be dosed properly to avoid life-threatening complications (from overdosing) and lost efficacy (from underdosing). Current practice relies primarily on empirical dosing, leading to improper levels of anticoagulation (AC), particularly during the dose titration period. Because of improper dosing and warfarin’s tremendous use, warfarin contributes to substantial complications in the population. Improper dosing can lead to increased medical costs, reduced quality of life, patient dissatisfaction, and discontinuation of highly- efficacious therapy.

Although clinical research has identified clinical and genetic factors that can alter warfarin dose requirements, limited prospective, clinical research has examined the utility of using clinical and genetic information to improve outcomes among a large, diverse group of patients using warfarin. In August 2007, the U.S. Food and Drug Administration (FDA) announced the approval of updated labeling for warfarin, to explain that patients’ genetic makeup may influence how they respond to the drug. In addition, genetic tests are now widely available that provide rapid results to potentially inform clinical decisions about warfarin dosing.

2. Overview

The Central Laboratory will coordinate the laboratory and genotyping activities for this randomized, multicenter, double-blind trial comparing three approaches to guiding warfarin therapy initiation. Study participants will be recruited from approximately 12 North American clinical sites prior to initiating warfarin. Based on the need for approximately 1,965 patients in the trial, each site will recruit approximately 164 patients into the trial over an 18 month period, or approximately 9 patients per month. Patients must be identified and enrolled prior to the first dose of warfarin, and they should be patients who are warfarin naïve or for whom any previous therapeutic warfarin dose is unknown.
Clinical and genotype data (using rapid, same-day genotyping methods at each clinical site), will be collected on all participants who will then be randomized to one of the three study arms: 1) initiation of warfarin therapy based on an algorithm using clinical information and an individual’s genotype using genes known to influence warfarin response (“genotype-guided dosing”); 2) initiation of warfarin therapy based on an algorithm using only clinical information (“clinical-guided dosing”); and 3) a standard, guideline-based initiation strategy (“empiric dosing”). The initial dosing of warfarin will be determined according to the study arm. Masked warfarin tablets will be supplied to clinical sites. Masked warfarin dosing will be distributed such that study investigators, clinicians, and participants will be masked to warfarin dose and thus to the treatment assignment, for the first 30 days of treatment. Dose adjustments following the initial dose, which will be determined by study arm, will be based on the INR response to the initial dose, using a standardized protocol to minimize possible biases in the subsequent management of the participants. Clinical information, including potential environmental modifiers of dose requirements, will be collected whenever an INR measurement is performed. All visits will be performed per current clinical practice (e.g., all protocol-required data will be collected during usual, clinically required visits). Data collection instruments will be completed during each clinical visit. Sites must be able to maintain masking procedures, manage masked dose adjustment therapy, and perform data entry and quality control procedures.

A. Laboratory Responsibilities

Each Clinical Site will do their own, on-site, rapid turnaround genotyping. The CL will be responsible for performing the initial quality assurance replication to ensure that sites’ genotyping methods are accurate prior to enrolling patients and for performing genotyping on samples sent from study patients throughout the trial to ensure that genotyping remains accurate. The CL thus will receive and store blood, plasma and related biospecimens (e.g., urine, buccal swabs, etc.) for both immediate and future studies of genetics/biomarkers contributing to the bleeding and thromboembolic risk in trial participants.

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. Initially, this will be performed on samples provided by the CL to each site to confirm accurate genotyping at each site. During the trial, genotyping will be performed in “real-time” (e.g., 24 hour turnaround) as samples are received by the lab on the first 15 subjects (approximately) recruited at each site. After this, QA genotyping will be done in monthly batches on all participants’ samples. It is anticipated that approximately 3 genetic variants will be genotyped for these QA efforts (CYP2C9*2, CYP2C9*3, and a single VKORC1 variant). The CL should describe a process of 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 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 biospecimens and data to an NIH-designated repository.

Use of study specimens for additional research and/or ancillary studies must be approved by a sponsor-appointed oversight committee.
**B. Genotyping and Biomarkers at the Central Laboratory**

The Central Laboratory will be responsible for:

1. extracting DNA from all participants’ blood samples for initial genotyping and long-term storage;
2. genotyping the variants that are used in the dosing algorithm to confirm the results of the individual centers (currently planned to be CYP2C9*2 [rs1799853], CYP2C9*3 [rs1057910], and a single VKORC1 variant, likely either VKORC1 1173C/T [rs9934438] or 1639G/A [rs9923231]); compiling and reporting allele frequencies, Hardy-Weinberg equilibrium; assessing potential platform/site/batch issues as CTCC/NIH requests;
3. assisting in the choice of genotyping platform selection at the clinical sites and training on genotyping platforms;
4. storing DNA on all participants for future genotyping of other variants of other genes that may be important in warfarin dose response; and
5. storing blood and related biospecimens for future biomarker (e.g., plasma vitamin K) studies, and tracking and transferring these samples as needed for additional analyses.

There will be two types of genetic and biomarker data: (1) primary genotype data required for the dosing algorithms, and (2) other genetic and biomarker data that will be used for additional, ancillary analyses. The latter will be derived from the stored blood at the Central Laboratory and will not be genotyped at the Clinical Sites. The former, genotype data required for the dosing algorithm, will be assayed at the clinical sites, in order to ensure same-day genotyping results required for this trial. However, the Central Laboratory will also perform genotyping of the same genetic variants for quality assurance purposes, as discussed below.

As of this writing, only variants in the CYP2C9 and VKORC1 genes have been clearly demonstrated to be of importance in dosing algorithms for warfarin. However, if other variants are identified that add useful predictive ability and therefore are incorporated into the final dosing algorithm, such variants will be included.

Samples will be labeled with the subject’s study identification (ID) number and a bar code only so that laboratory personnel are masked to the patient’s identity. All samples will be tracked using the bar code and tracking system.

The CL is responsible for:

1. establishing a method for implementation of lab procedures at clinical sites, as well as providing a Manual of Procedures for all procedures;
2. providing shipping materials to each clinical site;
3. providing a bar-coded or other laboratory information management or sample tracking system;
4. training sites in the proper use of the system;
5. storing and protecting laboratory data and ensuring appropriate data back-up procedures;
6. reporting quantity and quality of specimens received and processed at the CL,
7. participating in the Steering Committee proceedings;
8. transferring specimens and related data to an NIH-designated repository at the close of the contract; and
9. communicating with the clinical site laboratories, solving problems as necessary, as well as interacting with the Clinical Trial Coordinating Center (CTCC) regarding laboratory data quality assurance, oversight and transfer procedures.
C. Sample Collection for Storage and Analyses in Central Laboratory

The CL will also serve as the repository for the initial sample from all study participants. During the first study visit, six (6) ml of whole blood will be drawn from each subject into plastic purple-top (EDTA) Vacutainer tubes. A 0.5 ml aliquot will be retained by the clinical site, and the remainder shipped via overnight service to the Central Laboratory in a chilled insulated container. Samples will be labeled with the subject’s study identification (ID) number and a bar code only so that laboratory personnel are masked to the patient’s identity. All samples will be tracked using the bar code and tracking system.

3. Period of Performance

The period of performance for the project is estimated to be August, 2008 through July 2011. The study will be conducted according to the schedule below:

<table>
<thead>
<tr>
<th>Contract Phase</th>
<th>I</th>
<th>II A-C</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Activity</td>
<td>Preparation and genotyping QA [3 months]</td>
<td>Enrollment &amp; follow-up phase: Banking, genotyping QA [30 months]</td>
<td>Close-out phase [3-4 months]</td>
</tr>
</tbody>
</table>

4. Central Laboratory Requirement List

The CL will serve as a DNA and plasma repository for immediate and future analyses and will perform quality control of the local genotype laboratories.

The CL must be able to perform DNA extraction, perform the highest quality genotyping, and store samples for future genetic and other biomarker analyses. These future studies (not including in the current protocol or budget) may include, but are not limited to, DNA analysis for investigation of relevant pathway genes, genome-wide association studies, DNA sequencing, and other evolving technologies assessing the structure and function of genes and their products. Such studies are intended to define the full spectrum of variants functionally responsible for differences in dose requirements and for bleeding and thromboembolic risk. The CL will be responsible for the development and distribution of specific procedures for genotyping methods at the clinical sites. The CL will also be responsible for all ongoing quality assurance of the genotyping being performed at the clinical sites.

Given these requirements, the criteria for selection for the CL are below. The technical proposal should thoroughly describe laboratory operations and experience in the following areas:
a. Capability for rapid (within 24 hour of receipt) DNA extraction and genotyping of trial specific SNPs.

b. Capability for automated DNA extraction and highest quality high-throughput genotyping for non-trial SNPs using large sample batches and/or multiplex genotyping platforms.

c. Genotyping quality assurance and quality control procedures, and experience producing high quality genotypes in at least one other study of more than 500 subjects.

d. Blood and DNA archiving capabilities with computerized sample tracking and inventory management, web-based private access to an archive database, and secure low-temperature storage with monitors/alarms and emergency backup.

e. Methods of sample tracking and processing including information about volume used, volume remaining and sample/DNA quality. Identify the Lab Information Management System (LIMS), if any, in use.

f. Experience working with external collection sites to transfer samples and annotation data into the CL, and experience with data formatting and transfer from the laboratory to a data coordinating center. Describe methods of coordination and organization of lab data and how the CL will interface with the CTCC.

g. Methods and standard for laboratory data documentation, security and back-up (continuity) procedures.

h. A description of the documentation and Standard Operating Procedure associated with training external laboratory personnel in methods of sample handling, labeling and shipping.

i. Specific quality control procedures. The CL should provide evidence of formal QA and QC processes in order to ensure delivery of accurate data. The QA activities include Standard Operating Procedures (SOP) documentation, staff training program and equipment maintenance. QC activities include preparation and use of sample handling and genotyping controls, trending analysis and process optimization. Data analysis QC includes review of samples prior to the start of genotyping (pre-genotyping QC) and review of genotyping results before report delivery (post-genotyping QC). The CL must be able to produce accurate reports of sample status to the CTCC and Steering Committee.

j. Transfer of specimens and data to NIH-designated repository at the end of the contract.

Central Laboratory (CL) Selection Criteria

The CL will be selected based on the information provided in response to requirements a – j above.
5. **Proposal Content**

The information required in response to this RFP has been determined to be essential in the evaluation and contract award process. The following components must be submitted, using the forms provided. Components of the proposal are:

A. **Technical Proposal**

The technical proposal should demonstrate your organization’s capability and approach to carrying out the tasks described in the Statement of Work. The technical proposal should document availability and adequacy of facilities, equipment, and other resources necessary to conduct the trial.

Include the following in the Technical Proposal:

1. Title page with contact person, address, phone, fax and email address.

2. Name the Principal Investigator responsible for overall implementation of the subcontract and key contacts for project. Describe the qualifications, experience and accomplishments of the PI in the area of clinical trials, prospective studies, warfarin research, and genetic studies. [Maximum of 1.5 pages]

3. Other Investigators. Same as #2 above [Maximum of ½ page per investigator].

4. Describe the availability, experience and qualifications of personnel who will work directly on this study. Document experience of the staff in the performance of required procedures. [Maximum of 1 page]

5. List the location and features of laboratory facility. [Maximum of 1 page]

6. Provide standard NIH Biosketches or equivalent for the Principal Investigator and all key personnel assigned to work on this project. [Maximum of 4 pages each key personnel]

7. Address the ability and experience to meet all laboratory requirements described in Section 4. a – j, above. [Maximum of 6 pages]

B. **Budget Information**

Provide a draft estimate of the total cost of providing comprehensive central laboratory (personnel, supplies, shipping) services for the period of time noted above. Note that this figure will be considered a preliminary budget only. If selected, a detailed budget will be requested for review and approval by the CTCC and NHLBI.

**Due Date**: All materials must be received at the University of Pennsylvania by Monday, August 18, 2008.
Genotype Guided Dosing of Warfarin Clinical Trial
Request for Central Laboratory Proposal
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Instructions: Complete this checklist and the Signature Page.

CHECKLIST

Use this checklist to indicate the documents included in your proposal:

A. □ Title page. [See pages 1 – 2].
B. □ Proposal. See RFP Instructions.
C. □ Signature Page.
D. □ Biosketches or equivalent from the Principal Investigator and all other key personnel.
E. □ Laboratory CLIA certification documentation, if applicable.
Signature Page

I have read the Central Laboratory Requirements in the RFP Instructions and Information document. My signature indicates that the personnel and facility described are able to meet these requirements.

________________________________________   ____________
Principal Investigator Signature       Date

(Administrative signatures are not required at this time.)