## RESPONSE TO RFP - Title Page

<table>
<thead>
<tr>
<th>Request for Proposal (RFP) Number: 001</th>
<th>Issue Date: June 16, 2008</th>
<th>Proposal Due Date: July 14, 2008</th>
</tr>
</thead>
</table>

**Title of RFP:** Clinical Site 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:**

**Institution Name:**

**For Information Contact:**
- Denise Cifelli, MS
  - Project Director, Clinical Trial Coordinating Center, University of Pennsylvania
  - PHONE: 215-573-4534, email: cifelli@mail.med.upenn.edu
- Rosemary Madigan, MPH
  - Project Manager, Clinical Trial Coordinating Center, University of Pennsylvania
  - PHONE: 215-573-6314, email: rmadigan@mail.med.upenn.edu
PACKAGING AND DELIVERY OF THE PROPOSAL

DUE DATE: 4:00PM local time on July 14, 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 Clinical Site. “TO BE OPENED BY AUTHORIZED PERSONNEL ONLY”

NUMBER OF COPIES:
Send the complete Proposal including all attachments and checklists.
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-Clinical-RFP-2008MMDD.pdf” (example: kimmel-clinical-RFP-20080610.pdf)

Arrange the documents in the following order:
1. Title page
2. Technical proposal
3. Checklist
4. Information Table
5. Targeted Enrollment Form
6. Signature page
7. Biosketches
8. Letters and certifications

DELIVER TO:

Sandra A. Barile
Executive Assistant to Stephen E. Kimmel, MD, MSCE
Center for Clinical Epidemiology and Biostatistics (CCEB)
University of Pennsylvania School of Medicine
715 Blockley Hall, 423 Guardian Drive
Philadelphia, PA 19104-6021

Phone: 215-898-1740; Fax: 215-573-3106
Email: sabarile@mail.med.upenn.edu
Genotype Guided Dosing of Warfarin Clinical Trial

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 research centers. The University of Pennsylvania serves as the Clinical Trial Coordinating Center (CTCC) for this study. Clinical sites will participate as a subcontract to the CTCC. A Steering Committee will provide leadership to the study. Dr. Robert Califf will serve as the Steering Committee Chair. Clinical site Principal Investigators will participate on the Steering Committee on a rotating basis.

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

This is a randomized, multicenter, double-blind trial comparing three approaches to guiding warfarin therapy initiation. 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 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. Warfarin dosing will be via supplied, masked warfarin tablets 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 and manage masked dose adjustment therapy. Sites must also be capable of entering study data into an electronic data management system, made available at a secure location on the Internet.

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</th>
<th>II B</th>
<th>II C</th>
</tr>
</thead>
</table>

4. Clinical Trial Site Requirement List

A. All clinical sites must meet the following requirements:

1. **Initial dose requirement.** Clinicians must be willing to start patients on 5 mg of warfarin for the first 3 days of treatment.
2. **Numbers of recruitable patients.** Sites must demonstrate a large patient population eligible to participate. Sites must be able to recruit at least 164 patients who are new starters of warfarin into the trial, or approximately 9 patients per month.
3. **Previous Experience.** Clinical sites must demonstrate prior or ongoing experience in patient-oriented research, preferably in warfarin treated patients, including prospective studies requiring patient recruitment, and clinical trials.
4. **AC Clinic or similar practice model.** Sites must manage their warfarin patients in specialized AC clinics or similar practice models.
5. **Point-of-care anticoagulation management.** Patients must be managed in a setting where INR results are available at the time of in-person study visit (e.g., fingerstick assays for immediate INR results with a formal visit to the clinic) for the first 30 days of follow-up for each patient.

6. **Ability to do on-site, rapid-turnaround DNA extraction and genotyping.** Sites must have the capability of performing rapid-turnaround genotyping using currently available technology (either currently on-site or to be provided to the site). This is defined as a “DNA extraction to results” time of no longer than 4 hours. The genotype platform will be selected by the Steering Committee; genotype platform and reagents will be provided, if necessary.

7. **Ability to recruit both hospitalized patients and outpatients.** Participating sites must have access to both inpatient and outpatient facilities and the ability to recruit patients within those facilities.

8. **Ability to manage blinded warfarin.** Sites must be able to manage the distribution and tracking of blinded study medication.

9. **Clinical Equipoise.** The clinicians within the AC clinics or practice sites that will be managing patients during the trial must be in clinical equipoise with respect to clinical-algorithm and genetic-based dosing.

10. **Absence of Competing Studies.** Sites that are enrolling a large proportion of their anticoagulation patients into clinical trials that prohibit enrollment in this trial (e.g., comparing warfarin with alternative forms of therapy) will be ineligible.

11. **Institutional Support.** Each clinical site must have the full support of their overseeing institution.

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**B. All clinical sites must adhere to the following timelines in conducting the clinical trial:**

1. Enrollment of the required number of study participants must be completed within 18 months of initiating enrollment; and

2. Completion of follow-up (up to 12 months) will be completed no later than 30 months after initiating enrollment.

3. The majority of personnel effort will be required during the 1st month of patient follow-up, during the period of blinded medication and more frequent dose titration. The study visit schedule is as follows:

<table>
<thead>
<tr>
<th>Proposed Visit Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Screening:</strong></td>
</tr>
<tr>
<td>Eligibility Confirmation &amp; Randomization (Baseline)</td>
</tr>
<tr>
<td>May be combined or separate</td>
</tr>
</tbody>
</table>
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 page]

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 Research Coordinator(s) and other support staff in clinical research and expertise in screening and recruiting patients. [Maximum of 1 page]

5. Describe your recruitment plan for this study, the research barriers to be addressed, and the user community to be engaged. Specifically describe how and where patients (both inpatient and outpatient) will be identified, how they will be approached to explain the study and obtain informed consent, and where (all locations) patients will be seen for follow-up visits. Describe a plan to retain patients and collect data during point of care visits. [Maximum of 2 pages]

6. List the location and features of clinical and laboratory facilities, specifically the location of the genotyping facility relative to clinical care facilities. [Maximum of 1 page]

7. Provide documentation from Laboratory Director ensuring facilities and resources to conduct genotyping activities that meet the requirements of the contract. Specifically, describe the ability to perform DNA extraction and genotyping of CYP2C9 and VKORC1 SNP’s within 4 hours of blood collection. Describe quality control procedures used for human genotyping including procedures for receiving and storing samples, materials, and reagents in accordance with applicable safety and other regulatory guidelines. [Maximum of 1 page]

8. Describe the process for management of research study drug and capacity to administer blinded study drug. [Maximum of 1 page]
9. 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]

B. Proposal Requirements

Each proposal must include the following documents:
1. Title page
2. Comprehensive technical proposal address all sections of Section 5.A. 1-9 listed above.
3. Completed Checklist, including Targeted Enrollment Table and signed Signature Page.

C. Budget Information

Clinical sites will function as subcontracts to the Clinical Trial Coordinating Center (CTCC) at the University of Pennsylvania. Each subcontract will be managed by the CTCC.

Payment Schedule
Each selected site will receive six (6) months of fixed funding to cover start-up and close-out of the trial in the amount of $40,000 total costs (including indirect costs). During enrollment, sites will be paid $1,300 per participant on a per capita basis for each patient successfully enrolled:

The CTCC will provide without charge the following to each clinical site:
- Supply of warfarin for each participant for the first 30 days of participant’s therapy.
- Cost of laboratory genotyping assays (not including technician time).
- Cost of travel (to study related meetings or training) including transportation in domestic coach class, lodging and meals at the per diem rate.
- All Case Report Forms and other study documentation

D. Clinical Site Selection Criteria

A review panel will be responsible for selecting clinical sites, under the guidance of NHLBI. Review criteria will include responsiveness to the requirements specified and ability to perform all study duties within the budget approved by NHLBI.

All sites, regardless of previously expressed interest must apply and undergo review. Additional information may be required from potential sites prior to making a final decision on site selection.

Due Date

All materials must be received at the University of Pennsylvania by Monday, July 14, 2008.
Genotype Guided Dosing of Warfarin Clinical Trial
Request for Clinical Site Proposal
Distributed by the University of Pennsylvania School of Medicine

Instructions: Complete this checklist providing complete information in the Information Table on following pages, the Targeted Enrollment Table, 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. ☐ Information Table

D. ☐ Targeted Enrollment Table.

E. ☐ Signature Page.

F. ☐ Biosketches or equivalent from the Principal Investigator and all other key personnel.

G. ☐ Letter from Laboratory Director. [See RFP Instructions - Technical Proposal Section 5.A.7.].

H. ☐ Laboratory CLIA certification documentation, if applicable.
<table>
<thead>
<tr>
<th>Information Table – Must be Included with Response (can use additional blank pages for responses if needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI Name:</td>
</tr>
<tr>
<td>Name and location of clinical facilities: (Provide all)</td>
</tr>
<tr>
<td>Number of new patients started on warfarin at your institution last year:</td>
</tr>
<tr>
<td>______ patients/year</td>
</tr>
<tr>
<td>Indicate the percentage of these patients that are inpatients versus outpatients.</td>
</tr>
<tr>
<td>____  % Inpatient</td>
</tr>
<tr>
<td>____  % Outpatient</td>
</tr>
<tr>
<td>Indicate the estimated percentage of new starters who will require 3 or more months of warfarin therapy</td>
</tr>
<tr>
<td>____  %</td>
</tr>
<tr>
<td>Anticoagulation Clinic (AC) or similar practice model? (Yes or No)</td>
</tr>
<tr>
<td>If yes, Name of Director and Location.</td>
</tr>
<tr>
<td>Investigational Drug Service (IDS)/Research Pharmacy Available? (Yes or No)</td>
</tr>
<tr>
<td>If yes, Name of Director and Location.</td>
</tr>
<tr>
<td>Location of laboratory facilities for genotyping: (Provide all and approximate proximity to site of patient enrollment)</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Point-of-care AC management? (Yes or No)</th>
</tr>
</thead>
</table>

**INR results.** Provide method and result turnaround time (check all that apply):

- ☐ Phlebotomy (provide documentation of Laboratory CLIA certification and typical time to receive results)

  Turnaround time to INR ______ minutes

- ☐ POC (provide equipment make and model).

  Turnaround time to INR ______ minutes

**Absence of competing studies.** Describe other studies that may include the same patients and how this will impact recruitment. Sites must agree that patients in this study will not participate in competing, prohibited studies during the first 6 months of patient’s participation.
Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

**Study Title:** Genotype Guided Dosing of Warfarin Trial

**Total Planned Enrollment:**

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of All Subjects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Racial Categories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Racial Categories: Total of All Subjects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”
Signature Page

I have read the Clinical Trial Site Requirement List in Section 4.A. and B. of the RFP Instructions and Information document. My signature indicates that the personnel and facility described are able to meet these requirements.

________________________________________   ____________
Signature           Date