DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington, DC 20420

Date: DRAFT

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In Reply Refer to: 121

Office of Research and Development Information Letter

Clinical Science Research and Development Service
Request for Applications

CLINICAL TRIAL DEVELOPMENT AWARDS FOR EVALUATING EFFECTIVENESS OF TREATMENT-DIAGNOSTIC COMBINATIONS

Introduction. Clinical Science Research and Development Service requests Merit Review applications to investigate novel clinical trial design and biostatistical strategies assessing the effectiveness a diagnostic device (test) in combination with a clinical treatment (drug) on a disease of particular relevance to veterans. Proposals will include a methodology development stage and a small clinical trial stage to evaluate the effectiveness of a drug-diagnostic device combination in therapeutic decision making. Successful proposals are expected to result in novel clinical trial designs which can be adapted to a variety of specific combination products and which may be widely adopted throughout the biomedical community.

Background. The development of "personalized medicine" is based upon the proposition that through the use of appropriate clinical laboratory testing one may identify the most appropriate treatment for an individual patient. This concept is becoming well-established in cancer treatment, in which the decision to use a therapeutic drug (such as Herceptin® for breast cancer) is based upon identification of proteomic or genomic evidence of a genetic abnormality (such as amplification of the ERBB2 gene). It has been suggested that similar use of pharmacogenomic data may be useful in therapeutic decision making for a variety of drugs used to treat chronic conditions, including mental disorders, hypertension, and diabetes.

Evaluation of these drug-diagnostic device combinations has proven difficult for both clinicians and regulatory agencies. In many cases, clinical trials are being performed under the supposition that the diagnostic laboratory device (test) is both specific and sensitive for determining therapeutic response, in the absence of supporting evidence. Evaluation of the laboratory device may be limited to analytical characteristics, without a full understanding of the test performance until adopted by the medical community. To some extent, this state appears to reflect absence of widely accepted clinical trial methodologies designed to

effectively test both the laboratory diagnostic, and the therapeutic intervention, of these “drug-device combinations.”

Scope. There are two cases of particular interest:

1. The use of a single laboratory test to select patients for therapy. Both the effectiveness of the laboratory test for selecting therapy, and the effectiveness of the therapy itself, must be evaluated. An example of such a combination is the use of an immunohistochemical or gene amplification test to select patients for cancer therapy (for example, Gleevec or Herceptin).

2. The use of a group of related laboratory tests to determine the appropriate dosage of a therapeutic drug. An example would be the use of a pharmacogenomic profile consisting of several independent genomic markers to select a dose of an antipsychotic drug, with the objective of achieving effective therapy while minimizing potential adverse drug reactions.

Applications prepared in response to this RFA should propose two stages:

Stage 1. Methodology development stage to develop the methodology to advance the clinical trial design capable of assessing the sensitivity and specificity of the laboratory test(s) for selecting therapy and assessing the effectiveness of the therapy.

Stage 2. Test stage to apply the methodology developed in a small clinical trial study designed to evaluate the effectiveness of the proposed laboratory test(s) and therapeutic intervention in a veteran population. Successful results should be further developed into a full clinical trial in a separate Merit Review proposal.

Information generated may be integrated into the electronic medical record for both treatment and research purposes.

An interim review will assess whether the first methodology development stage has met administrative and scientific milestones to progress to the second stage to conduct a clinical trial pilot. Funding for the second test stage is contingent upon a satisfactory progress with methodology development.

Eligibility. It is anticipated that a team of investigators (non-clinician methodologists and clinicians) would be involved in the proposed work, including, but not limited to:

1. Biostatistician/epidemiologist – an expert with knowledge of advanced scientific principles in clinical trial design and statistical analyses.

2. Clinical investigator/trialist – a clinician or investigator with clinical research experience who has a thorough understanding of key clinical trial methodological principles.

While not required, it is recommended that the team collaborate with a Cooperative Studies Program Coordinating Center (see www.vacsp.gov).

The Principal Investigator may be a biostatistician, epidemiologist, and/or clinical investigator meeting current eligibility requirements (described in VHA Handbook 1200.15, Eligibility for VA Research Support, http://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=440. Individual exceptions to the rule limiting a principal investigator to a single project funded by CSRD will be considered on a case-by-case basis, dependent on the alignment of proposed research to VA research priorities.

Intent to Submit Information. An E-mail attachment from the VA research office (ACOS for Research or Administrative Officer), with the Subject line "Intent to Submit Methodology Development Merit", should be sent to: vhacocenter@va.gov, with the following information:

(a) Principal Investigator's Name, Degree, and VA appointment (in eighths),
(b) VA Medical Center
(c) Title of proposal
(d) Keywords (up to six keywords covering major topic area and any special methodology)
(e) List of collaborating investigators. Include names, VA and/or university affiliation, laboratory locations of personnel to contribute more than 5% effort
(f) Abstract (limit one page, single-spaced) information about the hypotheses to be tested, specific objectives, relevance, subject population, procedures to be used, and the significance of potential new findings. It must include enough information so that the proposal can be referred to the appropriate Merit Review Subcommittee and reviewers.
(e) Requests for exception, if required, to the CSRD single-project rule.

Due Date: The email notification of intent to submit must be received by BLRD/CSRD sixty days prior to the submission cycle for the Merit Review round (January 15 for March 15 Merit Review deadline, July 15 for September 15 Merit Review deadline). Intent information received after the deadline will be referred to the next round.

A confirmation e-mail acknowledging receipt of intent to submit information will be sent to the local VA research office. This confirmation must be included as the last page of the full proposal when submitted. Intent to submit notification from anyone other than the local facility research office personnel (e.g. the Principal Investigator, etc.) will not be accepted or acknowledged.

Intent to submit information will be reviewed for responsiveness to the scope of this solicitation, for eligibility, and to plan for expertise needed in the review process.

Proposal Preparation and Submission. In general applications should follow the guidance provided for the Merit Review program, specifically for the Clinical Research Program (described in Appendix C of the Merit Review Handbook, http://www.research.va.gov/resources/policies/docs/1202_Merit_Review_Handbook_JIT.doc). The narrative however should include two sections to describe Stage 1 and Stage 2.

Stage1. As a specific addition to the Merit Review narrative, the proposal must contain a section describing the plan for the methodology development stage. Describe the proposed plan for developing the clinical trial design and analytic/methodological strategies to evaluate the specificity and sensitivity of the diagnostic-treatment combination.

Included in this section must be one to three proposed milestones for assessing acceptable completion of this stage of the program. Milestones are concrete, quantitative measures of success of the feasibility stage (the methodology development stage) of the proposal. They are not the steps to proceed through the specific aims but rather should be the set of criteria to assess the success of Stage1 and to make the decision as to whether or not Stage 2 funding is approved. Thus, these milestones should be sufficiently precise and comprehensive to guarantee that any clinical trial conducted during Stage 2 is scientifically sound. One method by which this objective can be achieved is to propose a milestone that includes submission of a scientifically sound and novel protocol for the Stage 2 clinical trial to ORD for internal and external evaluation.

If approved for funding, VA staff and the PI may work together to refine the assessment measures. A clear timeline must be included that shows the total duration for the entire program, including the steps and duration of time planned for Stage 1and Stage 2. If funded, VA staff will determine the interim assessment schedule for evaluating Stage 1 progress.

Stage 2. This section of the narrative should provide a broad outline for conducting a small clinical trial. Because the final clinical trial design will depend upon the outcome of Stage 1, we would expect this section of the proposal to be relatively abbreviated and based upon currently accepted methodology. We would further expect that the proposal will provide substantial rationale for the clinical problem selected for investigation, as well as detailed evaluation of patient selection criteria and clinical trials recruitment issues. This section should follow the guidelines for a Clinical Merit Review trial. Approval for this stage will be contingent upon satisfactory progress on Stage 1.

The overall goal will be to obtain sufficient information to submit a Merit Review proposal for full support of an interventional trial or a Letter of Intent to the Cooperative Studies Program for a multi-site trial.

Review. Proposals will be reviewed in a Merit Review subcommittee. Proposals that do not address the programmatic objectives outlined in this announcement or follow stated guidelines will not be accepted for review.

Funding. Proposals are limited to $750,000 over a maximum of five years. Stage 1 (methodological development) will be limited to $200,000 over two years. Satisfactory administrative and scientific review of Stage 1 milestones and progress is required prior initiation of Stage 2; Stage 2 is limited to three years, but may utilize funds not expended during Stage 1. The proposed research program should be appropriate and efficient, with all budget categories well justified. In planning budgets, applicants are reminded to adhere to ORD guidelines regarding allowable use of research funds for specific items. Appropriateness of the proposed budget will be evaluated by the Merit Review subcommittee; the budget may be adjusted if not adequately justified or supported by the proposed research.

Term. This Information Letter is valid until the last working day of March 2007 unless otherwise rescinded.

Inquiries. Please direct all questions regarding this RFP to Terri Gleason, Ph.D., at Theresa.gleason@va.gov.

Joel Kupersmith, MD
Chief Research and Development Officer

Attachment
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