

Request for Proposal

Studies of the Right Ventricular Response to Therapy in Patients with Pulmonary Arterial Hypertension

Introduction

The *Cardiovascular Medical Research and Education Fund* is seeking proposals from qualified academic medical centers with the ability to coordinate and conduct a clinical study evaluating right ventricular function in patients with pulmonary hypertension, its adaptive and maladaptive responses, and the effects of therapy.

Background

The purpose of this clinical feasibility study is to better characterize the status of the right ventricle in patients with advanced pulmonary hypertension (PH) who are candidates for a new or additional treatment. Research in this field has identified changes in the right ventricle as predictive of survival in chronic PH. Understanding how the right ventricle adapts to pulmonary hypertension, and how that response may be altered with medical therapies appears to be critical. Scientific studies that may be relevant to this project cover a broad spectrum of disciplines that include genomics, imaging, and assessments of RV contractility, hypertrophy and metabolism.

It is hoped that knowledge gained from this study will impact clinical trials of future therapies developed to treat advanced pulmonary hypertension.

Project Guidelines

- Study hypotheses: Maladaptation to the pulmonary hypertensive state is largely responsible for right ventricular failure in chronic pulmonary hypertension. Changes that occur in the right ventricle predict clinical improvements in patients undergoing treatments for pulmonary hypertension. The applicant is requested to propose one or more related hypotheses that will be tested in this study.
- The patient inclusion criteria for the study should include Category 1 pulmonary arterial hypertension, preferably from one specific etiology, and advanced disease in which a new or additional medical therapy is clinically indicated.
- This can be an open label study where the patients will serve as their own controls, or randomized, placebo controlled.
- It is suggested that the number of patients enrolled be adequate to test the hypotheses, rather than powered to show statistically significant drug efficacy.
- The follow-up assessments should be over 6 months, and patient enrollment should be completed within a 2 year period.
- The state of the right ventricle should be characterized with multiple parameters that will provide insight into the adaptive and maladaptive state, and reflect changes that occur from therapy that will further the understanding of how therapies may work. These parameters may include measures of:

- Genetics and genomics
- Metabolism
- Cellular signaling
- Imaging (ultrasound, PET and MRI)
- Contractility and hypertrophy
- Hemodynamics
- RV function
- Myocardial ischemia and/or perfusion

The applicant is expected to develop a clinical research study plan that will identify several assessments that will be studied in the enrolled patients. While it is desirable for a single center to enroll all patients in this study and perform all of the assessments, this may not be practical or feasible. Because PAH is an uncommon disease, it is understood that multiple clinical centers may need to participate in patient enrollment (a clinical center is one that will enroll patients into the study). In addition, given the uniqueness of some of the promising assessments, it is also understood that multiple centers may need to participate as core laboratories to evaluate specific measures (a core laboratory is one that will perform analyses of specific measured assessments collected at the clinical centers). Thus, the research plan should include an organizational plan that identifies the Principle Center, collaborating clinical centers, and core laboratories. The Principle Center will be responsible for all of the data management, and for providing oversight of the entire conduct of the study. The Principle Center should also serve as a clinical center and a core laboratory. Having other clinical centers also serving as core laboratories to expand the different types of assessments will be considered a strength of the proposal. This award can be made to the Principle Center, with subcontracts to clinical and core centers, or to each participating center directly.

The applicant should submit a research plan using the NIH R01 format that will include the collaborating investigators for all phases of the study. Required activities by the applicant include, but are not limited to:

- finalizing the clinical protocol and protocol-related documents (e.g. informed consent form, case report forms, etc.);
- implementation and conduct of the clinical study in accordance with Federal requirements;
- management and oversight of the conduct of the clinical study;
- providing clinical research support services;
- providing monitoring and safety oversight;
- organizing investigator meetings and teleconferences;
- recruiting patients;
- organizing, conducting, and reimbursing for patient protocol evaluations and tests (including follow-up);
- analyzing the data and authoring and submitting papers on the study for publication.

Application Guidelines

- The deadline for grant submission is July 1, 2012. Funding will begin October 1, 2012. All applicants are requested to submit a letter of intent with a brief description of their proposal, and the collaborating institutions.
- The direct award for this study will be limited to \$2 million, inclusive of all subcontracts. Overhead of 20% will be added to the amount awarded. The award may not be used to cover healthcare related costs that are otherwise clinically indicated, including but not limited to the costs of the medical therapy to be studied if it is clinically indicated.
- Because of the high expense of healthcare costs, the applicant is advised to recruit patients where the preponderance of tests and treatments are otherwise clinically indicated and thus will not need to be covered by the grant.
- The project should be constructed to meet the following timelines:
 - 6 months start-up
 - Case report form completion
 - Study protocols completed
 - Research assessments specified
 - Consent and IRB approvals
 - 24 months patient enrollment
 - Enrollment monitors
 - 6 months close-out
 - Data analyses
 - Publications
- The NIH R01 research application form should be used, including Specific Aims, Background and Importance and Approach (Research Plan), Human Subjects Section, and Biosketches and description of facilities and resources. The following should be included in the response to the RFP:
 - The research strategy should include a clear description of the study design, study population, subject eligibility and inclusion/exclusion criteria, recruitment and enrollment plans, and outcome measures.
 - State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved. The major research question and hypothesis being studied should be clearly stated.
 - The significance of the proposed clinical trial must be clearly stated. The application should make clear how the results will advance our knowledge of theory and practice in this area and the potential impact of the results of the trial.
 - Explain how the application challenges and seeks to shift current research or clinical practice paradigms.
 - A list of subject eligibility and inclusion and exclusion criteria should be provided. A recruitment and enrollment plan, including a discussion of the availability of subjects for

the proposed study, the ability of enrollment sites to recruit the required number of subjects, and the timeline for completion of recruitment, should be described.

- There should be a detailed description of the assessments to be tested. Potential biases and approaches for minimizing bias should be described. The primary and secondary endpoints, and methods/measures to be used to assess these, should be clearly described. The link between endpoints, outcome measures, and hypotheses should be stated clearly.
- Data collection plans and statistical methods appropriate for the particular design proposed should be presented. Methods to be used for data collection, preparation, management, quality control should be thoroughly described.
- Data from preliminary or pilot studies which show the need for and the feasibility of the trial should also be presented. Additional supporting data from other research should be included so that the approach chosen is clearly justified. This information will also help to establish the experience and competence of the investigators to pursue the proposed project.
- A timetable for completion of the various stages of the trial must be included.

Data Safety and Monitoring

All applications must include a general description of the monitoring plan, policies, procedures, responsible entities, and approaches to identifying, managing and reporting reportable events (adverse events and unanticipated problems), to the applicable regulatory agencies (*e.g.*, Institutional Review Board (IRB), the NHLBI/NIH, the Office of Biotechnology Activities, Office of Human Research Protections (OHRP), the (FDA), and the Data and Safety Monitoring Board (if one is used).

Contact information

Inquires, letters of intent, applications or questions should be addressed to:

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