A Step Toward Optimizing the NHLBI Clinical Trial Enterprise:
Development of a New Funding Opportunity Announcement for Multi-site Clinical Trials

NHLBI Webinar
June 29, 2016
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Instructions for Q&A Session

- We anticipate participants will have many questions. We will address them approximately in order of receipt, but we will be give priority to new topics not raised by previous questions.

- Selected questions will be read aloud. Panelists will answer them orally.

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**2:00 pm - 2:10 pm**

**Welcome and Introduction to NHLBI Efforts to Optimize its Clinical Trials Enterprise**

Amy P. Patterson, M.D.
NHLBI Chief Science Advisor, and Director of Scientific Research Program, Policy, and Strategic Initiatives

**2:10 pm - 2:35 pm**

**An Overview of NHLBI’s News Funding Opportunity Announcement for Multi-site Clinical Trials (Phase II and Above)**

Keary Cope, Ph.D., Scientific Review Officer, NHLBI Division of Extramural Research Activities
Simone Glynn, M.D., M.Sc., M.P.H., Chief of the Blood, Epidemiology, and Clinical Therapeutics Branch, NHLBI Division of Blood Diseases and Resources
Yves Rosenberg, M.D., M.P.H., Chief of the Atherothrombosis and Coronary Artery Disease Branch, NHLBI Division of Cardiovascular Sciences

**2:35 pm - 2:55 pm**

**Questions from Participants**

**2:55 pm - 3:00 pm**

**Conclusion**

Amy P. Patterson, M.D.
NHLBI Chief Science Advisor, and Director of Scientific Research Program, Policy, and Strategic Initiatives
Optimizing the NHLBI Clinical Trials Enterprise

Amy P. Patterson, M.D.
Chief Science Advisor, and Director of Scientific Research Programs, Policy, and Strategic Initiatives, and Chief Scientific Advisor

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NHLBI Clinical Trials: A Partnership

- Investigators, research participants, and NHLBI have a shared goal: to produce interpretable, timely, and useful results (positive or negative) that inform prevention, diagnosis, and/or treatment of HLBS disorders.

- We have successfully partnered on hundreds of clinical trials that have shaped medical practice and improved the health of millions of patients.
Overview of Challenges

- Legacy of successful trials notwithstanding, there are many opportunities for improvement

- Challenges can occur at the individual trial level and/or at the enterprise level and include:
  - Delayed start up
    - Regulatory hurdles
    - Difficulties in contracting
  - Failure to accrue/retain participants
  - High financial costs/cost overruns
  - Inexperienced investigators/diminishing CT workforce
  - Change in clinical landscape affecting equipoise
  - Disconnect between clinical trials and health care
Challenges widely recognized and effective solutions will include collaboration between investigators, funders, and regulators.

- Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020 – Workshop Summary (NAS)

- A National Cancer Clinical Trials System for the 21st Century (NAS)

- Randomized Clinical Trials – Removing Unnecessary Obstacles (NEJM)

- Clinical Trials: Can Technology Solve the Problem of Low Recruitment? (BMJ)
The increasingly complex environment at the local, national, and international level raises the cost of trials and jeopardizes the ability to effectively conduct trials.

Various deliberative groups are endeavoring to address some of these challenges (e.g., CTTI, Critical Path Initiative).

NHLBI has an important opportunity to enhance and facilitate trials within its portfolio.
Optimal State: A Vision for the NHLBI Clinical Trials Enterprise

To optimize the NHLBI clinical trials enterprise across entire clinical trial life cycle such that NHLBI clinical trials:

- Address major compelling scientific questions in HLBS disorders
- Yield interpretable, timely, and useful results (positive or negative) that can inform the diagnosis, treatment, and/or prevention of HLBS disorders
- Identify, assess, and manage risks – including safety, financial, resources and other risks
- Make trial results broadly accessible in a timely fashion

To enable collection, analysis, and communication of data regarding processes, performance, and outcomes such that NHLBI becomes an efficient learning organization.
Broad Consultation and Analysis

Seminal Reports

Literature

Think Tanks

NHLBI Staff

Paul Ridker, MD  Co-chair

Pam Douglas, MD  Co-chair

Council Working Group

Formal Consultation with Scientific Community and Public

Public Private Consortiums
Starting Point: FOA for Investigator-initiated Multi-site Clinical Trials (>Phase II)

- Funding Opportunity Announcements define NIH expectations for applications and projects (once funded)

- In particular, FOAs are an important tool for developing a shared understanding of performance milestones and metrics
The imminent expiration of the previous FOA for multisite clinical trials (PAR-13-128) presented an opportunity to:

- Examine NHLBI’s current approach to solicitation and review
- Explore new approaches to enhancing likelihood of success

The experience with the new FOAs for multi-site clinical trials will inform development of subsequent FOAs
Goals for New FOAs

- Establish expectations up front including asking that PIs develop and follow a project management business plan (including contingency plan); helps with risk management later
- Facilitate peer review evaluation of operational feasibility
- Allow for earlier identification of problems in trials and facilitate work with investigators to address problems
- Enable, if necessary, earlier termination of trials

The new FOAs are part of a multi-pronged approach

**Shared, long-term goal of NHLBI and the clinical trials community:**
Optimize the clinical trials enterprise in order to answer important scientific questions and improve public health.
The New Funding Opportunity Announcements

- Targeted to phase II and above investigator-initiated multi-site clinical trials (CTs)
  - Clinical Coordinating Center for Multi-Site Investigator-Initiated Clinical Trials
    PAR-16-300, collaborative UG3/UH3 awards
  - Data Coordinating Center for Multi-Site Investigator-Initiated Clinical Trials
    PAR-16-301, collaborative U24 award
These Funding Opportunity Announcements do not pertain to clinical trials that are:

- Single site
- Phase I
- Part of SBIR applications
- Part of P01s (Program Project Grants) applications
- Solicited through specific RFAs (networks) / RFPs
Applying Under the New Funding Opportunity Announcements

Applications should

- Address heart, lung, blood, or sleep scientific priorities with the potential to change clinical practice and impact health
- Demonstrate operational feasibility
- Include performance milestones - to be met, how, and when
  - Provide the information that will allow for both science AND operational feasibility to be evaluated by peer review
Key Elements

- Linked Clinical Coordinating Center (CCC) and Data Coordinating Center (DCC) applications
- Up to 7-year phased awards
  - CCC: UG3 (up to 1 year), then UH3 (up to 6 years)
  - DCC: U24 (first year), then U24 (up to 6 years)
- Milestone-driven and performance-based awards
Coordinated submission of CCC and DCC project management plans that...

- Describe how major aspects of the project will be managed to ensure success on schedule and within budget

- Identify project activities crucial to project completion

- Explain the process to manage and coordinate key project activities to achieve successful completion of the study on-time and on-budget – who does what, when, and effort

- Outline strategies to monitor operational risks

- Proactively identify potential issues and propose contingency plans
Key Elements

- **Detailed information required up front** including supporting data and processes for reaching key milestones within indicated timelines, e.g.,
  - Supporting information for accrual targets/site

- **Peer-review criteria** that ensure rigorous evaluation of not only scientific impact but also operational feasibility
Key Elements

- For trials using an FDA regulated product and requiring an IND or IDE application:
  - The grant application must include evidence regarding the outcome of a pre-IND or pre-IDE meeting, or other evidence of communication with FDA.
  - The IND application or IDE application must be submitted to the FDA at least a month prior to a potential award so that documentation of the FDA determination regarding the application is available to NHLBI prior to a possible award.
    - Will facilitate early identification of regulatory issues

IND=Investigational New Drug; IDE=Investigational Device Exemption
Required Attachments for the CCC

- Protocol Synopsis
- Study Organization Plan
- Clinical Trial Experience in last 5 years
- FDA or Other Applicable Regulatory Agency Strategy and Communication Plan
  - Application includes pre-IND /IDE communications
  - Requires IND/IDE submission by time of award
- Project Management Plan
Research Strategy for the CCC

- Significance
- Innovation
- Approach
- Supporting Data (e.g., pilot data)
- Experimental Approach
  - Timeline
  - Study population
  - Description of study design
  - Recruitment and retention plan (site and PD/PI table; enrollment goals/site table)
- Milestone Plan for UG3 and UH3 phases
Other Specific Elements for the CCC

- **Data and Safety Monitoring Plan that includes**
  - The entities that will monitor the study
  - The procedures to monitor study safety, minimize risks, maintain confidentiality of participant data, and identify/review/report adverse events and unanticipated problems

- **Central IRB, per NIH policy (NOT-OD-16-094)**
  - Effective for applications received ≥ May 25, 2017

- **Resource Sharing Plan**
  - What data will be made available
  - Plan for publishing and disseminating results in a timely manner
DCC Attachments and Research Plan

- Project Management Plan (≤ 3 pages attachment)
- Clinical Trial Experience (≤ 3 pages attachment)
- Research Plan
  - Significance
  - Innovation
  - Approach
  - Coordination
  - Study Design
  - Data Management and Quality Control
  - Statistical Analysis Plan
  - DCC Milestone Plan corresponding to activities in the preparation and full enrollment phase, respectively
Other Specific Elements for the DCC

- Regular transfer of data to the NHLBI clinical trials database through tools provided by the Institute at the time of award

- Resource Sharing Plan
  - What datasets will be made available
  - How timely publication(s) and dissemination of results will be supported

- Registration on ClinicalTrials.gov
  - Study description
  - Results for primary outcome paper
Frequently Asked Questions
A “clinical trial” is defined by the NIH as:

“A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.” (NIH Guide for Grants and Contracts, 10/23/2014)

A “multi-site” clinical trial is one that enrolls participants at two or more recruitment sites.
How is “Phase II” defined for the purpose of these FOAs?

- Phase II clinical trials are those being conducted to obtain preliminary data on the efficacy of a drug, device, biologic, or other clinical intervention, as well as determine the common short-term side effects and risks associated with the intervention.

- In contrast, a trial introducing an agent into a human for the first time, or for a new indication, that is aimed primarily at understanding the safety profile of an agent would be considered a Phase I (rather than a Phase II) and would not be responsive to these new multi-site clinical trial FOAs.
Yes. The new FOAs articulate peer-review criteria that will promote rigorous evaluation of not only the study’s scientific impact but also its operational feasibility.
No. If the combined direct costs of the DCC and CCC applications equal or exceed $500,000 in any one year, the investigator still must contact program staff to obtain documented approval in the form of a letter from the Institute stating that it will accept the application for initial peer review.
Will the preapproval process change for appl’ns with a combined budget of ≥$500K? (cont’d)

- Program staff will continue to have consultations (staff visits) with the investigators.

- Investigators should submit a letter of request to the relevant Division Director, and if the application is accepted, append the corresponding letter of approval to the cover letter of the CCC and DCC applications.

- The letter of approval needs to be submitted with the applications.
Even if the combined direct cost budget being proposed does not meet the $500,000 direct cost threshold, NHLBI nonetheless strongly encourages investigators to discuss their applications with NHLBI program staff.
I am already running a funded trial. Are there new requirements that I must follow?

- If you submit for renewal, then the new FOAs’ requirements apply; otherwise, an ongoing trial is subject to the original terms of the Notice of Grant Award.
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Contacting NHLBI

Send questions, comments, and suggestions about the new FOAs to:

OCTET@nhlbi.nih.gov