

A Step Toward Optimizing the NHLBI Clinical Trial Enterprise:

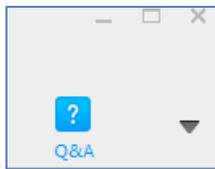
Development of a New Funding Opportunity Announcement for Multi-site Clinical Trials

NHLBI Webinar
June 29, 2016

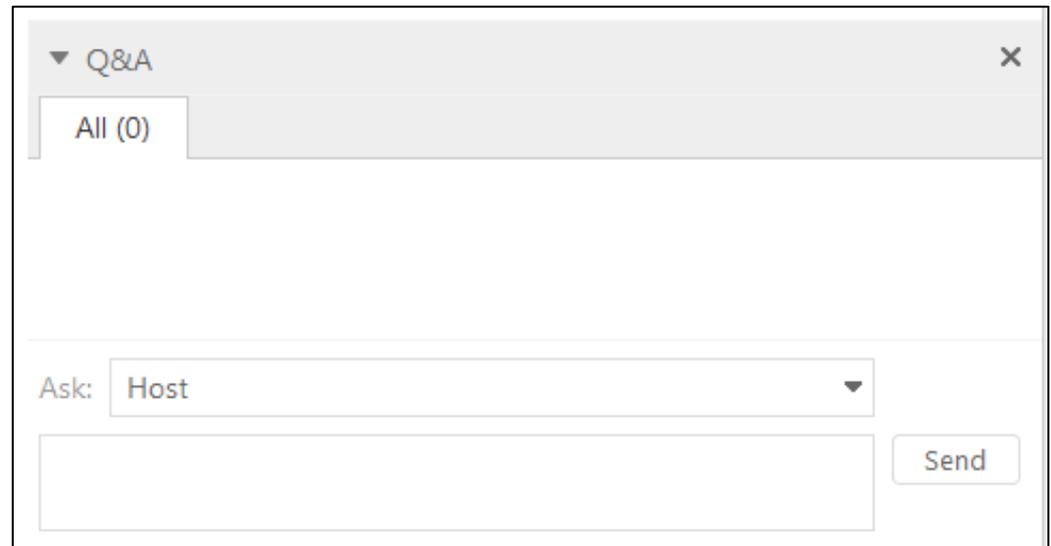


Logistics

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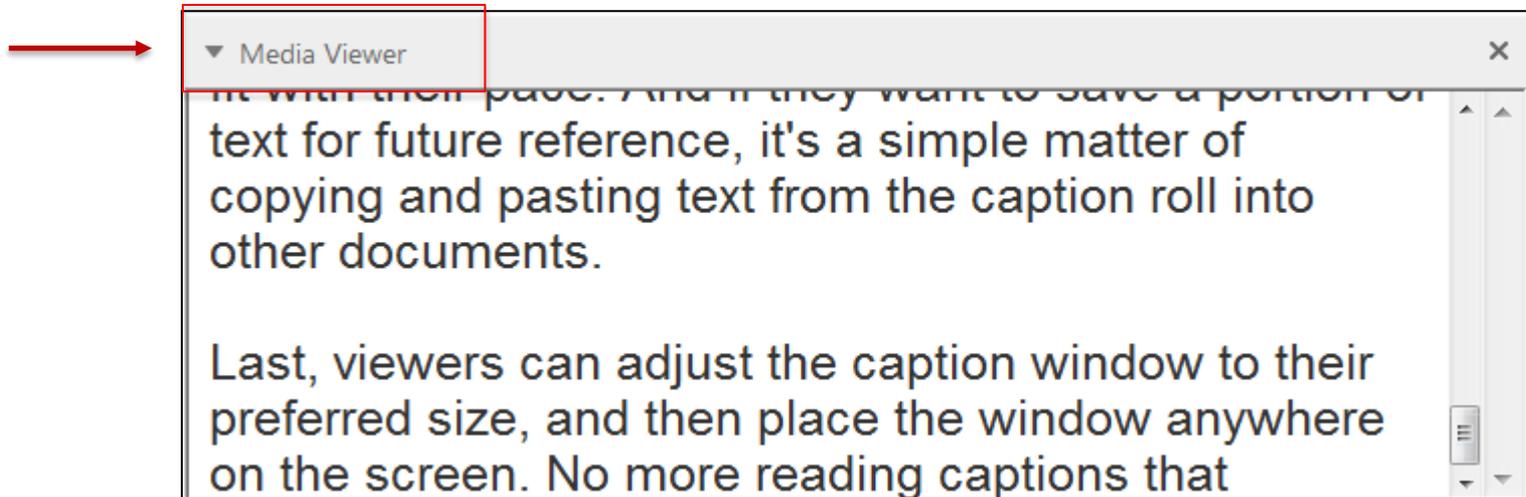


Select Q&A tab on top, right-hand corner of your screen



Logistics

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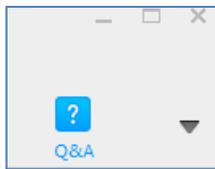


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Select Q&A tab on top,
right-hand corner of
your screen

A screenshot of a Q&A interface. At the top, there is a dropdown menu labeled "Q&A" with a downward arrow and a close button (X) on the right. Below this, there is a section labeled "All (0)". At the bottom, there is a form with a dropdown menu labeled "Ask: All Panelists" and a text input field with the placeholder text "Enter question here...". A "Send" button is located to the right of the input field.

Agenda

2:00 pm - Welcome and Introduction to NHLBI Efforts to Optimize its Clinical Trials Enterprise

2:10 pm

Amy P. Patterson, M.D.

NHLBI Chief Science Advisor, and Director of Scientific Research Program, Policy, and Strategic Initiatives

2:10 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 - Questions from Participants

2:55 pm

2:55 pm - Conclusion

3:00 pm

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

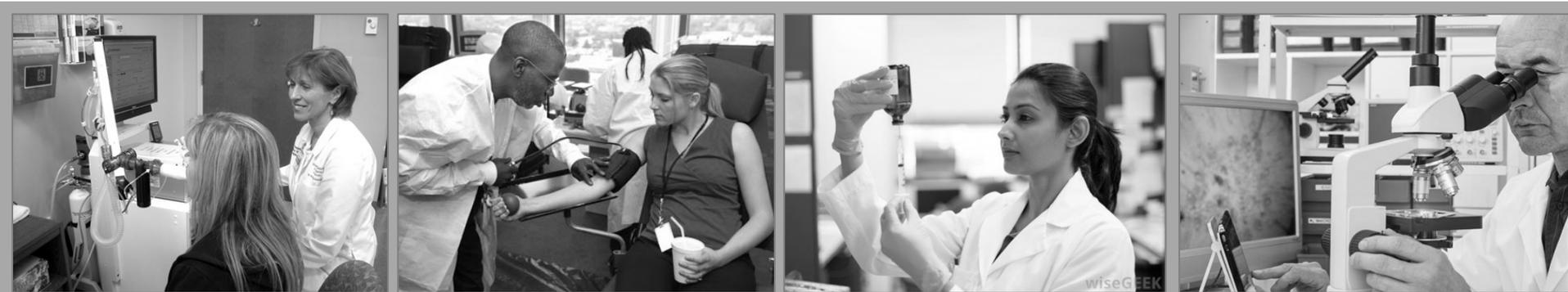
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NHLBI Clinical Trials: A Partnership

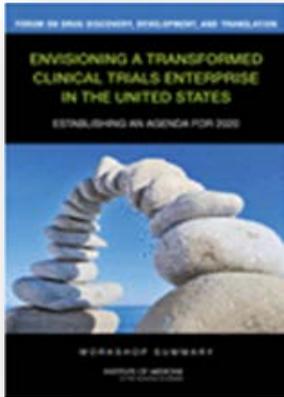
- **Investigators, research participants, and NHLBI have a shared goal: to produce interpretable, timely, and useful results (positive or negative) that inform prevention, diagnosis, and/or treatment of HLBS disorders**
- **We have successfully partnered on hundreds of clinical trials that have shaped medical practice and improved the health of millions of patients**



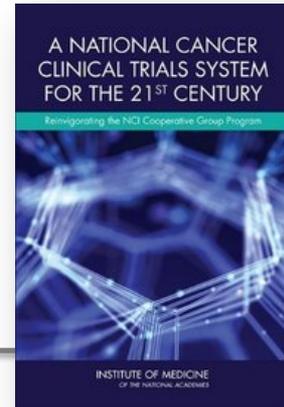
Overview of Challenges

- **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)



Broader Context: Operating within a Complex Framework

- 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**



APPLIED CLINICAL TRIALS

Barriers to Clinical Trial Recruitment and Possible Solutions: A Stakeholder Survey

Sep 03, 2015

By Elizabeth Mahon [1], Jamie Roberts [2], Pat Furlong [3], Gina Uhlenbrauck [4], Jonca Bull, MD [5]

Applied Clinical Trials

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



NHLBI Staff

Formal Consultation with Scientific Community and Public



Paul Ridker, MD
Co-chair

Pam Douglas, MD
Co-chair

Think Tanks



Council Working Group

Public Private Consortia



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**

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

- **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.**

Highlights of Major Changes in the Investigator-Initiated Multi-site Clinical Trial FOA

Keary Cope, Simone Glynn, and Yves Rosenberg

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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

The New Funding Opportunity Announcements

- **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 \geq 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

What is a “multi-site clinical trial” for the purpose of these FOAs?

- 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.**

Will the review criteria change from those used previously?

- **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**

Will the preapproval process change for appl'ns with a combined budget of \geq \$500K?

- **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 \geq \$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.**

What if my appl'n has a combined budget of less than \$500K?

- **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**

Question and Answer Session

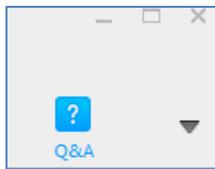


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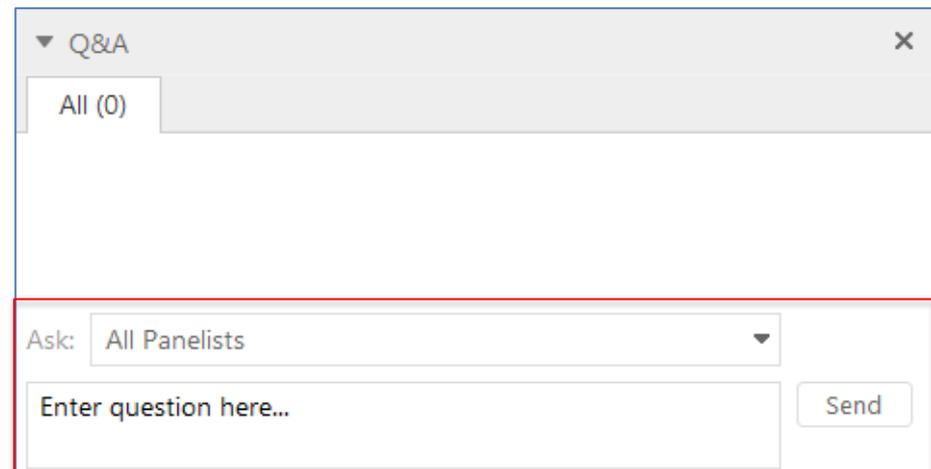
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Contacting NHLBI

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

OCTET@nhlbi.nih.gov

