

THE NIH CLINICAL TRIALS WORKING GROUP EXECUTIVE SUMMARY

Interventional clinical trials are among the most complex and challenging research activities supported by the National Institutes of Health (NIH). No area is closer to the NIH mission of improving the nation's health. Trials evaluating diagnostics, therapeutics, vaccines, preventive measures, and behavioral interventions must be conducted at the highest level of reproducibility to generate the quality of knowledge capable of changing clinical practice, improving patient care, and developing new products. Adherence to best practices generates a quality management structure necessary for the successful conduct of important clinical studies. Components essential to assure the excellence of study conduct include high quality science, up to date knowledge and training of investigators and study personnel, and the effectiveness of the systems supporting and overseeing the trial. To assure that the NIH supports only the highest quality, publicly-funded clinical trials, NIH Institutes and Centers (ICs) must ensure that each trial:

- investigates a mission-relevant question that is an IC priority and is not unnecessarily duplicative of previously-conducted trials;
- can be feasibly completed within a planned, reasonable timeframe;
- is appropriately designed to answer the questions(s) posed;
- is adequately powered to provide a definitive answer; this is particularly important for Phase 3 clinical trials;
- is clearly articulated, following peer-review, in a clinical protocol document, following Good Clinical Practice (GCP) and, if appropriate, a manual of procedures;
- is conducted efficiently by qualified, GCP-trained investigators and support staff;
- is carefully monitored by the IC commensurate with risk and complexity;
- has independent safety and data quality oversight that is commensurate with human subjects risk and trial complexity;
- is supported by an award mechanism and terms of award that optimize quality and successful outcome by promoting the appropriate level of study oversight by the IC;
- is monitored for enrollment targets or endpoint milestones and resource usage at a frequency that allows for timely problem-solving so that: (1) the trial either enrolls fully and meets its milestones in the projected timeframe or is terminated early to avoid waste of resources, and (2) is ultimately published so that the findings, whether positive or negative, are available to guide future research directions.

These guiding principles and best practices echo many thoughts expressed by the IC Directors at the NIH Leadership Forum, September 27 – 28, 2012. The NIH Clinical Trials Working Group (NIH-CTWG) is an outcome of that Leadership Forum and was charged with considering a range of issues and concerns related to the agency's role in the stewardship, leadership, and management of clinical trials and clinical trial networks; evaluating options for NIH actions; and making recommendations to the NIH Director to enhance the quality and transparency of NIH-

supported clinical trials. The NIH-CTWG focused on a small number of issues that are of the highest priority to the NIH Director and the IC Directors. It became clear at the inception of the NIH-CTWG that clinical trial networks in various ICs already receive significant attention, resources, and oversight, and that the focus of the NIH-CTWG should be on investigator-initiated clinical trials supported by non-network awards.

Issues of highest priority were solicited from the IC Directors through the members of the NIH-CTWG; five sub-groups were formed to address these issues in depth. Each was charged with making recommendations to the CTWG based on their focus:

Sub-group #	Co-Chairs	Charge Topic	Cross-walk to IC Director Questionnaire
1	Jack Killen, NCCAM Petra Kauffman, NINDS	Clinical trials acceptance policies, award mechanisms, and funding decisions	<ul style="list-style-type: none"> The clinical trial poses a mission-relevant question that is an IC priority and is not unnecessarily duplicative of previously conducted trials. This may require additional consideration following peer-review. The trial is appropriately designed to answer the question(s) posed, is adequately powered to provide a definitive answer, can be feasibly conducted within a timeframe that is not protracted, and is clearly articulated, following peer-review, in a structured written format including a clinical protocol document and a manual of procedures if appropriate. The trial is supported by an award mechanism and terms of award that optimize quality, rigor and IC oversight.
2	Betty Tai, NIDA, Rosemary Higgins, NICHD	Monitoring systems for accrual for clinical trials	<ul style="list-style-type: none"> The trial is monitored for enrollment targets at a frequency that allows for problem-solving and implementation of solutions so that the trial either meets its target enrollment in the projected timeframe or the trial is terminated early to avoid waste of resources, and undermines the premise under which subjects enrolled into the study.
3	Cliff Lane, NIAID Elaine Collier, NCATS	IRB issues in multi-site trials	<ul style="list-style-type: none"> The need for approval from multiple IRBs for multicenter trials inhibits efficiency of trial start-up and completion. This requires facilitating central IRBs for multicenter studies.
4	David Gordon, NHLBI Joan McGowan, NIAMS	Publication and dissemination of clinical trial results	<ul style="list-style-type: none"> The trial and its outcomes are published in a reasonable timeframe so that the findings, whether positive or negative, are available to guide future research directions.
5	Raye Litten, NIAAA	GCP training for all clinical trials investigators	<ul style="list-style-type: none"> The trial is conducted efficiently by qualified, knowledgeable and trained investigators and

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		and NIH staff managing clinical trials	support staff. This will require training in Good Clinical Practice (GCP).

A single remaining issue from the IC Director questionnaire was not assigned to any subgroup: “The trial has independent safety and data quality oversight, commensurate with human subjects risk and trial complexity; and if more than minimal risk or complex in nature, is also clinically monitored by the IC.” A separate NIH group will be addressing DSMB issues as a follow-up to the OIG report.

The details of each sub-group’s work can be found in the attached sub-group reports. Most of the sub-groups conducted semi-structured surveys to gather data. It is important to note that the sampling of IC information on IC practices or opinions may be incomplete and that not all ICs responded in writing to each survey. Some ICs do not support investigator-initiated extramural clinical trials. The data should therefore be viewed as a snapshot of current IC practices rather than the output of a rigorous study. However, these data sets formed an important base for discussion by each NIH CTWG subgroup and by the CTWG as a whole.

Based on its deliberations, the NIH-CTWG makes the following recommendations to the NIH Director to enhance the quality and transparency of NIH-supported clinical trials:

1. Given the risks and costs associated with clinical trials, ICs should be encouraged to fully utilize their authorities to establish and apply research priorities in selecting specific clinical trial applications for review and award, and to determine that the investment in specific studies rests on a robust scientific, regulatory, and operational foundation. This could also include greater utilization of alternative award mechanisms for clinical trials that facilitate staged funding through a formal planning phase with criteria for “successful completion”, followed by use of “successful completion” criteria to determine responsiveness for a full clinical trial implementation phase. Requirements for the content of clinical trial applications, and the criteria for their review should be re-designed to focus on the specific elements of rationale, design, and quality of operational plans needed to adequately assess the scientific merits and potential of grant applications. This would include requiring submission of clinical trial applications under trial-specific Funding Opportunity Announcements (FOAs) rather than under the general parent FOAs. ; All of these approaches would facilitate better tracking across the NIH portfolio of clinical trial grant applications and awards. It is important to note that the current methods for identifying grants involving clinical trials are not robust. This hinders tracking and analysis of clinical trials across the NIH.

2. Peer review of clinical trial applications must be made more rigorous by ensuring that any study section reviewing clinical trials consists of appropriate clinical trial experts (e.g., clinical trialists, biostatisticians, pharmacologists), as well as the basic science experts needed to evaluate the scientific rigor of any pre-clinical data provided; and

secondary review by Advisory Councils should ensure that clinical trials address important IC clinical research priorities.

3. ICs should be strongly encouraged to incorporate trial-specific language into Notices of Grant Award (e.g. to establish timelines for start-up, to set feasibility milestones based on accrual, and to specify expectations for downstream data-sharing and publication).

4. ICs need appropriate clinical trials monitoring systems and tools so that oversight of funded trials is in place and optimized and permits the collection of essential data to assure accountability for the public funds spent on clinical trials. The needs of some ICs in this area have been addressed by their unique, existing systems, such as those developed by NCCAM, NINDS, NCI, NHLBI and NIAID. Other ICs do not have monitoring systems and face challenges to monitor enrollment and other clinical trial metrics in an ongoing, real-time fashion for the studies they support. NIH systems currently under development (e.g. the eRA Inclusion Management System) might, with additional resources, be modified to also serve as a clinical trials monitoring system; in any case, further attention to and support for developing such systems is warranted. However, whether one or several systems are utilized across ICs, the definitions of the core elements being collected should be standardized across the NIH to allow for interoperability across IC systems to facilitate data pooling and reuse. Regardless of the system used, clinical trial metrics should include key elements that contribute to a successful (or unsuccessful) trial, e.g. participants' safety, retention for primary and important secondary outcomes, treatment exposure, data quality, and protocol adherence. Frequency of data collection should be tailored to the clinical trial but should, at a minimum, be more frequent than annual and cannot rely solely on the annual grant progress report.

5. Program Officers (POs) responsible for clinical trials have a critical stewardship role and need appropriate initial and continuing training on the fundamentals of conducting and monitoring clinical trials to be able to evaluate their progress. ICs should also have an administrative infrastructure with authority/accountability to empower POs and to implement/enforce any actions that are warranted.

6. The CTWG strongly supports streamlining IRB review of multi-site studies. This includes: a) endorsing the Department of Health and Human Services Advanced Notice of Proposed Rulemaking for changes in 45 CFR Part 46. If an agreement cannot be reached to post of all elements of the proposed changes to 45 CFR Part 46, we recommend that NIH propose to OHRP/HHS that the element, "Streamlining IRB Review of Multi-Site Studies", be put forward separately while discussions continue on the other elements; b) developing standard language that can be used by all ICs as a term of award if mandating the use of a single IRB of record for all multi-site studies conducted under the award; and c) developing and posting a public, web-accessible toolbox

containing information on development and implementation of reliance agreements between institutions/IRBs such that a single IRB can function as the IRB of record for multi-site clinical studies.

7. The CTWG urges that NIH adopt the position that dissemination of results is a requirement for successful completion of clinical trial funding. Multiple approaches to enhancing the dissemination of clinical trial results must be developed. Approaches could include: a) expanding the range of clinicaltrials.gov to disseminate the results of clinical trials by including those not covered by FDAAA; b) requiring publication in the peer-reviewed literature or a summary of results (for example in clinicaltrials.gov) at some discrete period (24 months) after the end of funding as a term of award; or c) holding the grantee institution responsible for meeting the requirements in this recommendation. While we currently do not hold investigators accountable for publishing or otherwise disseminating their results, NIH should consider a new policy to place a hold on accepting any new clinical trial applications from the grantee institution until data sharing requirements of funded clinical trials at their institution are met.

8. NIH should require all personnel involved in clinical trials research supported by NIH grants or contracts as well as NIH staff overseeing or managing clinical trials to receive documented Good Clinical Practice (GCP) training. GCP is an international standard for design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials or studies. GCP compliance provides public assurance that the rights, safety, and well-being of human subjects involved in research are protected. In addition, GCP training refresher courses should be completed every three years to stay current on GCP, new regulations, and guidelines.

Respectfully,

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