

VIEWPOINT

Toward a New Era of Trust and Transparency in Clinical Trials

Kathy L. Hudson, PhD
National Institutes of Health, Bethesda, Maryland.

Michael S. Lauer, MD
National Institutes of Health, Bethesda, Maryland.

Francis S. Collins, MD, PhD
National Institutes of Health, Bethesda, Maryland.



Supplemental content

Clinical trials are the most publicly visible component of the biomedical research enterprise, from the potential human application of novel laboratory findings to the generation of robust evidence about treatments or preventive interventions in routine clinical care. These trials are also the point at which biomedical research most directly engages human participants—dedicated volunteers who trust investigators to uphold the highest standards of scientific rigor and ethical oversight. While clinical trials have evolved and improved over time—producing impressive advances in diagnosis, treatment, and prevention—there are still major challenges. Therefore, fundamental changes are needed to reflect science and society's movement to increase efficiency, accountability, and transparency in clinical research.

As the largest public funder of clinical trials in the United States, currently investing more than \$3 billion each year, the National Institutes of Health (NIH) takes its stewardship of the nation's clinical trial enterprise very seriously. Therefore, NIH must ensure that supported trials investigate a mission-relevant question that is of high priority, do not needlessly duplicate previously conducted trials (in contrast to providing needed replication), and have the highest likelihood to advance knowledge and improve health. To achieve this goal, a number of challenges in the design, efficiency, and reporting of clinical trials need to be addressed.^{1,2} For example, too often clinical trials are overly complex, have small sample sizes, rely on surrogate end points that lack clinical relevance, have unrealistic accrual rates, and have inadequate budgets. Of particular concern is the existence of trials from which the results are never published or data submitted to a public database.^{3,4}

Therefore, the NIH has launched a multifaceted effort to improve the quality and efficiency of clinical trials, an effort that is focused on a variety of key points along the "lifespan" of a clinical trial (eFigure in the Supplement). These initiatives will reengineer the process by which clinical investigators develop ideas for new trials, how NIH reviews and selects clinical trials for support and oversees the progress of the research, and how results and aggregate data are shared broadly and rapidly. Specifically, these changes are aimed at enhancing the application and award processes, increasing NIH's ability to assess the merits and feasibility of clinical trial applications; improving oversight and transparency; and increasing the sharing of clinical trial results. In combination, these initiatives are intended to ensure rigor and efficiency in the US clinical trial enterprise.

As a crucial first step, NIH will require Good Clinical Practice (GCP) training for investigators and NIH staff responsible for conducting or overseeing clinical trials.

The aim is to help ensure that all involved in the clinical trial enterprise have the appropriate knowledge about the design, conduct, monitoring, recording, analysis, and reporting of clinical trials. While GCP training on its own may not be sufficient, it provides a consistent and high-quality standard.

Another important change at the beginning of the clinical trial lifecycle is a new NIH policy that will require all applications for clinical trials to be submitted in response to clinical trial-specific Funding Opportunity Announcements (FOAs). This will mean that applications including one or more clinical trials will no longer be accepted in response to parent funding announcements, which are broad FOAs that allow researchers to submit investigator-initiated applications without specific elements appropriate to describe and evaluate a trial. Under this policy, NIH trial applications will need to contain specific information about protocols and other information necessary for effective peer and programmatic review. In addition, clinical trial-specific FOAs will include review criteria that focus on the rationale, design, and operational and analysis plans, all of which will inform assessments of proposed studies.

Peer review of NIH clinical trial applications must be conducted by study sections with appropriate expertise, such as clinical trialists, biostatisticians, and pharmacologists, as well as the basic science experts needed to evaluate the scientific rigor of relevant preclinical data provided. The advisory councils of NIH's institutes and centers (ICs) also will be responsible for ensuring that clinical trials supported by their respective ICs address these important priorities. After funding decisions have been made, terms specific to clinical trial research will be incorporated into Notices of Award to remind awardees of their responsibilities, including timely sharing of research results.

Inconsistent information submitted to the NIH for clinical trial applications and to the US Food and Drug Administration (FDA) under the investigational new drug (IND) application process has long been recognized as a source of delays and inefficiencies. To assist NIH-funded investigators to plan their studies in a way that is also consistent with the FDA IND process, the NIH is encouraging the use of a clinical trial protocol template that was developed through a collaboration between NIH and FDA⁵ and that meets International Council for Harmonisation (ICH) E6 Good Clinical Practice Guidance.⁵ Use of the protocol template will help ensure that investigators prepare protocols that contain all the information necessary to enable efficient and timely review by institutional review boards (IRBs) and to be in compliance with FDA IND application regulations.

Corresponding Author: Kathy L. Hudson, PhD, National Institutes of Health, Bldg 1, 1 Center Dr, Room 103, Bethesda, MD 20814 (Kathy.Hudson@nih.gov).

Another frequently cited source of delay in moving a trial forward is duplicative IRB review in studies conducted at multiple sites. Multiple, often conflicting, reviews from different IRBs slows initiation of trials and in the vast majority of instances does nothing to enhance the protection of human research participants.⁶ To address this problem, NIH has adopted a policy for using a single IRB of record for the review of NIH multisite studies.⁷ To facilitate adoption of this new approach, NIH has developed standardized agreements that will allow institutions to rely on a single IRB of record for multisite studies.⁸

An additional enhancement at the beginning of the lifespan of the clinical trial is the new regulation and complementary NIH policy that clinical trials be registered in the ClinicalTrials.gov database within 21 days of enrollment of the first participant.⁹ Easy to search, publicly accessible information about clinical trials will enable physicians, patients, and family members to more readily find trials that may be of interest. NIH is also working to enhance the usability of ClinicalTrials.gov in terms of features and formatting, so that it can better serve health care professionals and patients in identifying relevant clinical trials. It is possible that increased registration of clinical trials could also aid recruitment, reducing the number of trials that fail because they do not meet their enrollment targets and thus do not have the statistical power to give meaningful results.

To realize the benefits of a clinical trial, the data must be broadly shared quickly after the trial has concluded. However, timely dissemination of clinical trial results continues to be a serious problem.^{3,4} To uphold promises to research participants, inform the public about clinical trials, and enable the biomedical community to make the most of the results of completed trials, the Department of Health and Human Services has released a regulation outlining requirements for clinical trial registration and summary results information reporting.⁹⁻¹¹ This regulation applies to certain clinical trials (except phase I and early device trials) of FDA-regulated drug, biologic, and device products, irrespective of who funds or conducts the study. In addition, NIH has issued a complementary policy⁹ to cover all NIH-funded trials, including those not subject to the regulations,

such as phase 1 studies or clinical trials of behavioral interventions or non-FDA-regulated products.

The NIH expects the clarity of the new regulation and NIH policy, together with their comprehensive compliance and enforcement provisions, will result in rapid increases in the percentage of trials that are registered and share aggregate data through ClinicalTrials.gov. Investigators and sponsors who fail to comply with the regulation may be subject to civil monetary penalties assessed by FDA. In addition, NIH will withhold clinical trial funding to grantee institutions if the agency is unable to verify adequate registration and results reporting from all trials funded at that institution. The availability of results will promote innovations in clinical trial design and avoid duplication of unsuccessful strategies, thereby avoiding unnecessary risks to research participants.

The final effort in this suite of activities is the development of a standardized electronic system for NIH to use for management and oversight of NIH-funded clinical trials and ensure accountability to stakeholders. The system will permit the collection of clinical trial information across the NIH-supported biomedical research enterprise, which will be used for strategic planning and identifying the best, safest, and least burdensome ways to gather important data to improve human health.

This set of interconnected, complementary initiatives will help enhance NIH stewardship of clinical research. However, far more remains to be done. The actions outlined in this article constitute the first wave in what will be an ongoing intense effort aimed at improving NIH-funded clinical trials, with each wave being informed by a thoughtful evaluation of its predecessor.

Although the process of enhancing the clinical trial pipeline may be a work in progress, the goal of all of these varied activities remains constant: to maintain public trust and to encourage advances in the design, conduct, and oversight of clinical trials. These innovations are intended to help NIH better fulfill its mission of supporting scientific discovery to improve human health while elevating the entire biomedical research enterprise to a new level of transparency and accountability.

ARTICLE INFORMATION

Published Online: September 16, 2016.
doi:[10.1001/jama.2016.14668](https://doi.org/10.1001/jama.2016.14668)

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Additional Contributions: We would like to acknowledge the NIH Clinical Trials Working Group for their expertise and contributions to clinical trial stewardship reforms.

REFERENCES

- Institute of Medicine Forum on Drug Discovery, Development, and Translation. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary.* Washington, DC: National Academies Press; 2010.
- Kramer JM, Smith PB, Califf RM. Impediments to clinical research in the United States. *Clin Pharmacol Ther.* 2012;91(3):535-541.
- Hudson KL, Collins FS. Sharing and reporting the results of clinical trials. *JAMA.* 2015;313(4):355-356.
- Chen R, Desai NR, Ross JS, et al. Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers. *BMJ.* 2016;352:i637.
- National Institutes of Health. NIH and FDA Request for Public Comment on Draft Clinical Trial Protocol Template for Phase 2 and 3 IND/IDE Studies. <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-043.html>. Accessed September 7, 2016.
- Wagner TH, Murray C, Goldberg J, Adler JM, Abrams J. Costs and benefits of the national cancer institute central institutional review board. *J Clin Oncol.* 2010;28(4):662-666.
- National Institutes of Health. Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html>. Accessed September 7, 2016.
- National Center for Advancing Translational Sciences, National Institutes of Health. NCATS SMART IRB Reliance Authorization Agreement. <https://ncats.nih.gov/files/smart-authorization-agreement-6-2016.pdf>. Accessed September 7, 2016.
- National Institutes of Health. NIH Policy on dissemination of NIH-funded clinical trial information. *Fed Regist.* 2016;81(183). <https://www.federalregister.gov/>.
- Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov—the final rule. *N Engl J Med.* doi:10.1056/NEJMr1611785
- Department of Health and Human Services. Final Rule—Clinical Trials Registration and Results Information Submission. Washington, DC. *Fed Regist.* 2016;81(183). <https://s3.amazonaws.com/public-inspection.federalregister.gov/2016-22129.pdf>.