New Policies for NIH Clinical Grants and Research

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Changes to NIH Clinical Trial Policies

- Broadened Clinical Trial Definition
- ClinicalTrials.gov registration/reporting
- GCP training expectations

2014

2017

Clinical trial specific FOAs required
New Human Subject and Clinical Trial Information Form
FORMS-E
Updated peer review criteria
Single IRB for multi-site research
New appendix policy
Clinical Trials Protocol Template (optional, Phase 2/3)

2018

Why the changes?

Problems with clinical trials enterprise:

- Concerns about transparency
- Unreported data
- Failure to report negative results
- Untimely dissemination of results

“The failure to share results is so pervasive that it... is a systemic problem.”

Harlan Krumholz, NPR
Delayed or non-publication of clinical trial results

Results: Only 46% (n=635) of clinical trials published in peer reviewed journal within 30 months
NIH plan to address these problems:

Goal of changes:
- more oversight of trials
- improved transparency
- enhanced efficiency
- maximize public’s trust and investment in research

Toward a New Era of Trust and Transparency in Clinical Trials

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.

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 ele-
New NIH policies encompass entire clinical trial lifespan

https://grants.nih.gov/policy/clinical-trials.htm
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NIH definition of a clinical trial:

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.
Is your human subjects research a clinical trial?

1. Does the study involve **human participants**?
2. Are the participants prospectively assigned to an **intervention**?
3. Does the study **evaluate the effect of the intervention** on the participants?
4. Does it have a **health-related biomedical or behavioral outcome**?

**If** YES to all 4, then NIH considers your study a clinical trial

NOT-OD-15-015, October 23, 2014 (Revised NIH definition of “Clinical Trial”)

Broad definition of clinical trial

More study types now considered clinical trials!

NOT considered clinical trial

- Surveys
- Questionnaires
- User preferences
- Focus groups
- Secondary research with biospecimens or health information

Per NIH slideset: https://grants.nih.gov/policy/clinical-trials/training-resources.htm
For help determining if your study is a clinical trial:

Changes to NIH Clinical Trial Policies

- **2014**: Broadened Clinical Trial Definition
- **2014-2017**: ClinicalTrials.gov registration/reporting
- **2017**: GCP training expectations
- **2017**: Clinical trial specific FOAs required
- **2017**: New Human Subject and Clinical Trial Information Form
- **2017**: FORMS-E
- **2017**: Updated peer review criteria
- **2017**: Single IRB for multi-site research
- **2017**: New appendix policy
- **2017-2018**: Clinical Trials Protocol Template (optional, Phase 2/3)

NIH aims to beef up clinical trial design as part of new data sharing rules

By Jocelyn Kaiser  |  Sep. 16, 2016, 12:00 PM

Drug companies and academic researchers will have to step up their public reporting of clinical trial results under new federal policies released today. The National Institutes of Health (NIH) in Bethesda, Maryland, also laid out a new plan for submitting clinical trial proposals that aims to beef up the rigor of the studies.
NIH Dissemination Policy: ClinicalTrials.gov registration and reporting

*For clinical trials funded all or in part by NIH:*

**Step 1:** Must register NIH funded trials at ClinicalTrials.gov
(within 21 calendar days after first human subject enrolled)

*Data required: descriptive information, recruitment, location, contact info, administrative data*

**Step 2:** Must submit results of trials upon completion*
(by 1 year after final data collection for primary outcome measure)

*Data required: participant flow, demographic and baseline characteristics, primary and secondary outcomes, statistical test results, adverse event information, full protocol, statistical analysis plan*

*May be delayed up to 2 years if product studied is not FDA approved*
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**Submit protocol and original statistical analysis plan will “dissuade P-value hacking, where people sort of shop around for a statistical test to give them the P-value that they love.”** – Francis Collins, quoted in Science, 2016
How to Register Your Study

Contents
- Steps for Registering a Clinical Study
- Considerations for Observational Studies and Expanded Access Records
- ClinicalTrials.gov Protocol Information Review Process
- Required Registration Updates

Do you or someone you know want to participate in a clinical study? See information for patients and families.
Good clinical practice training required
(effective January 1, 2017)

- All investigators and staff involved in clinical trials must have GCP training
- Must update training every 3 years
- Must retain documentation of training, provide to NIH upon request
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- 2017
- 2018

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*Also applies to all research involving human participants

Must apply to specific FOA for clinical trial (effective Jan 25, 2018)

What this policy means:
Do not submit a clinical trial grant proposal through a parent announcement (i.e. Parent R01)
You must find a FOA specifically designed for clinical trials
**Many clinical trial specific FOAs have not yet been released; look for them this fall**

Why:
NIH will include specific review criteria for clinical trials, such as adequate sample sizes
Trials can be routed to peer review panels with appropriate expertise
Prevent interesting proposal but weak design from being funded
Clinical trial-specific FOAs: what we know so far

- May be shifting away from R01 mechanism for clinical trials
- FOAs accepting clinical trials will vary by institute
- New clinical trial FOAs will likely include multiple mechanisms: R33, R61/R33, U01, U24, UG3/UH3...
Example of new FOAs: R61/33 mechanism

- Biphasic design, for phase 2 and up
- R61: start-up phase, finalize protocol and documents, begin enrollment
- Milestone driven: Administrative review of peer-reviewed milestones for R33 Go/No Go
- R33: full enrollment phase and clinical trial execution

Will be used by:
- NHLBI
- NIAID
- NIMH
- NCCIH
- NIDDK?
- Others?

Up to **29 additional pages** of info may be required in application (depending on RFA)

- Aims + research strategy (13 pages)
- Clinical protocol synopsis (12 pages)
- Study organization plan (6 pages)
- Clinical trial experience (3 pages)
- FDA strategy and communications plan (2 pages)
- Project management plan (3 pages)
- Data management plan (3 pages)
- Statistical analysis plan (3 pages)
- Single site justification plan (2 pages)
Updated Peer Review Criteria for Clinical Trials will be released in coming months with new FOAs
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**New review criteria will likely focus on:**
- Rationale and trial design
- Operational and analysis plans
- Study timeline and milestones

**Examples of new clinical-trial specific language: from R61/R33 FOAs:**

- **Significance:** Will results contribute critical clinical knowledge? Will results contribute to improvement of clinical care?
- **Investigator:** PI’s experience and capability to conduct trial and meet milestones? Expertise in study coordination, data management, statistics?
- **Approach:** Strengths and weaknesses in study design? Clearly defined endpoints?
- **Environment:** Does institution have available resources to conduct clinical trial?

Additional review criteria: Milestones, protection for human subjects, etc.

**READ YOUR FOA CAREFULLY, ADDRESS NEW REVIEW CRITERIA IN PROPOSAL**
New Human Subjects and Clinical Trials Information form, FORMS-E

New Human Subjects and Clinical Trial Information Form

A new Human Subjects and Clinical Trial Information form will be required for all human subjects and/or clinical trial research beginning for January 25, 2018 due dates. Learn more about this new form and what it means for your grant application or contract proposal.

https://grants.nih.gov/policy/clinical-trials.htm
New Human Subjects and Clinical Trials Information form, FORMS-E

- Consolidates human subjects, inclusion enrollment, clinical trial information
- Collects study level information
- Uses form fields to collect extensive detail needed for peer review
- Presents key info to reviewers in standardized format
- Aligned with ClinicalTrials.gov format

https://grants.nih.gov/policy/clinical-trials.htm
New Human Subjects and Clinical Trials Information form, FORMS-E

- New form requires very detailed study information
- Information in this form should not be duplicated in Research Strategy
- Advice: allow extra time for proposal development
Annotated form available

New FORMS-E for January 2018

Resources

1. Take a video tour of the new form.

2. Annotated Form Set for NIH Grant Applications - FORMS-E Series

3. High Level Summary of Form Changes: FORMS-E to learn about other form changes.

New forms: dates to remember

- **September 25, 2017**: FORMS-E instructions available
- **October 25, 2017**: FORMS-E application packages for FOAs due on/after Jan 25, 2018
- **January 25, 2018**: First due dates for new forms
New appendix policy

Only allowable appendix items are:
• Blank data collection forms, survey forms, questionnaire forms
• Simple lists of interview questions
• Blank informed consent/assent forms
• Other items ONLY if specified in FOA

DO NOT INCLUDE PROTOCOL UNLESS SPECIFIED IN FOA
(new form collects key protocol elements)
Streamlining IRB process: single IRB for multi-site clinical trials


Notice Number: NOT-OD-16-094

Key Dates
Release Date: June 21, 2016
Effective Date: New Date - January 25, 2018 as per issuance of NOT-OD-17-076

Proposal must include plan for:
• Using single IRB (sIRB) for all study sites
• Describing communications plan between sIRB and study sites

Why single sIRB?
• Decrease administrative burden and time to study launch
• Encourage consistent adherence to protocols, use of standardized protocols
• Decrease duplicative review with multiple IRBs

https://www.sbm.org/UserFiles/file/Panel5_Culp.pdf
Optional Protocol Template

NIH and FDA Release Protocol Template for Phase 2 and 3 IND/IDE Clinical Trials

Notice Number: NOT-OD-17-064

Key Dates
Release Date: May 2, 2017

Related Announcements
NOT-OD-16-043

Issued by
National Institutes of Health (NIH)

Purpose
The National Institutes of Health (NIH) and Food and Drug Administration (FDA) developed a clinical trial protocol template with instructional and example text for NIH-funded investigators to use when writing protocols for phase 2 and 3 clinical trials that require Investigational New Drug application (IND) or Investigational Device Exemption (IDE) applications. In March 2016 a draft template was released for public comment generating nearly 200 comments from 60 respondents. All comments were carefully considered and many were incorporated into the final template. The agencies’ goal is to encourage and make it easier for investigators to prepare clinical trial protocols that are organized consistently and that contain all of the information necessary for the review of the protocol. The template follows the International Conference on Harmonisation (ICH) E6 (R2) Good Clinical Practice and is available as a Word document.
Summary: how does this affect my clinical trial grant proposal?

- Use appropriate FOA
- Read FOA carefully, ensure your proposal addresses review criteria
- Complete new Human Subjects and Clinical Trials Information form
- Research strategy: do not duplicate info provided in new form
- Describe sIRB and plan for communication, if applicable
- Retain documentation of GCP training
- Ensure appendix materials comply with new policy: no protocol
Clinical Trial Requirements for Grants and Contracts

NIH is launching a series of initiatives that are rolling out in 2017-2018 to enhance the accountability and transparency of clinical research. These initiatives target key points along the whole clinical trial lifecycle from concept to results reporting. Learn more about these changes and how they will affect your research.

NIH Definition of a Clinical Trial

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https://grants.nih.gov/policy/clinical-trials.htm
Open Mike

Helping connect you with the NIH perspective, and helping connect us with yours

Posted on September 16, 2016 by Mike Lauer and Carrie Wolinetz

Building Better Clinical Trials through Stewardship and Transparency

Posted on September 16, 2016 by Mike Lauer and Carrie Wolinetz

Improving Visibility of NIH-supported Clinical Trial Activities and Results

Posted on September 8, 2017 by Mike Lauer

Continuing to Clarify the NIH Definition of a Clinical Trial
Thank you!

Please provide feedback and share your experiences during upcoming peer review

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