New NIH Clinical Trial Requirements for Grants & Contracts 2017/2018
Changes in Human Subjects Research

• **IRB**
  – Single IRB
  – Common Rule Changes
  – Certificates of Confidentiality

• **Clinical Trial Requirements**
  – NIH Clinical Trial Definition
  – GCP Training
  – ClinicalTrials.gov registration

• **Grant Application Process**
  – Clinical Trial Applications
3 Steps: How to Submit a Clinical Trial to the NIH

1. Determine if proposed study meets NIH definition of a clinical trial—see NIH decision tree

2. Identify a Corresponding Funding Opportunity Announcement (FOA)—see NIH website

3. Prepare NIH Application—see new FORMS-E Application Packages
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.”

• Can be:
  – Safety and efficacy
  – Mechanistic exploratory studies
An "intervention" is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.
Decision Tree for NIH Clinical Trial Definition

Does the study involve human participants research?

- **Yes**
- **No**

Are participants prospectively assigned to an intervention?

- **Yes**
- **No**

Is the study designed to evaluate the effect of the intervention on the participants?

- **Yes**
- **No**

Is the effect being evaluated a health-related biomedical or behavioral outcome?

- **Yes**
- **No**

The study is NOT a clinical trial.

This study is a clinical trial.

Examples of Mechanistic Clinical Trials

• Studies that use a manipulation (physiological or behavioral) to answer basic science questions about normal functions.
• Studies that use an experimental manipulation in order to understand normal functioning or the pathophysiology of a disease or disorder, but do not aim to demonstrate clinical improvement.
• Studies that involve the prospective use of efficacious interventions where the intent is to obtain and analyze biospecimens to identify genetic risk associations, novel biomarkers, examine the disease process, or characterize mechanisms of therapeutic response.
• Studies in which an intervention with demonstrated efficacy for a population is being studied to understand mechanisms of response, non-response, or risk of adverse effects of the efficacious intervention.
Research Not Considered CTs

- **Not** considered a clinical trial if the following:
  - Surveys
  - Questionnaires
  - User preferences, focus groups
  - Secondary research with biospecimens or health information
  - Educational studies with outcomes focusing on memorization or retention & recall of information to assess teaching methods
Why does it matter how NIH defines a Clinical Trial?

Expanded NIH definition of a clinical trial broadens requirements:

• **Limits** on applying for grants to *clinical trial-specific FOAs*
  - Training awards not allowed for clinical trials
  - New human subjects & clinical trial forms *(proposals could be rejected if wrong form/information submitted)*

• **GCP training** for all investigators & clinical trial staff

• Use of **single IRB** for multi-site studies

• **ClinicalTrials.gov** registration, updates & results reporting
NIH Case Studies

• The simplified case studies illustrate the *differences between clinical trials and clinical studies* using the criteria from the NIH decision tree.

• Revised versions lack clarity & caused confusion

• Some inconsistent with original definition & greatly expand scope

• May lead to different conclusions for NIH definition of clinical trial

*NIH determinations are FINAL*
Comprehension and Retention...

- **Case #24**: The study involves evaluating different types of printed announcements to identify the best designs for ensuring comprehension and retention of information in adults. Visitors to public libraries will be selected at random and asked to read one of the two announcements and then to take a short survey to elicit their perspectives about readability.

  - **Clinical Trial? NO**

- **Case #26**: The study involves randomizing individuals to different processes for informed consent. It is designed to assess the effectiveness of interactive and multimedia components in enhancing participants’ understanding of the study’s purpose and procedures.

  - **Clinical Trial? YES**
Case #31a: A study involves the recruitment of school children to evaluate two different tools for monitoring food intake. Food consumption behavior will be measured by asking children to activate a pocket camera during meals and to use a diary to record consumed food. The accuracy of the two food monitoring methods in measuring energy intake will be assessed.

- Clinical Trial? NO

Case #31b: A study involves the recruitment of school children to evaluate two different tools for monitoring food intake. Food consumption behavior will be measured by asking children to activate a pocket camera during meals and to use a diary to record consumed food. Changes to eating behavior will be assessed.

- Clinical Trial? YES
What can you do?

• Increase knowledge about the new NIH requirements

• We **highly encourage** investigators to contact their NIH program officer to **confirm** whether their study meets the NIH definition of a clinical trial. *FDA-regulated studies (investigational drugs & devices) automatically meet the NIH definition.*

  ✓ Document & save the discussion for future reference—will upload in ERMS

• Encourage scientific societies and professional associations to contact NIH
3 Steps: How to Submit a Clinical Trial to the NIH

1. Determine if proposed study meets NIH definition of a clinical trial—see NIH decision tree

2. Identify a Corresponding Funding Opportunity Announcement (FOA)—see NIH website

3. Prepare NIH Application—see new FORMS-E Application Packages
Allowability of Clinical Trials

• All NIH Funding Opportunity Announcements (FOAs) will be updated in Fall 2017
• Implementation date – application due dates on/after January 25, 2018 – is concurrent with implementation of NIH Forms E application kit version
• All FOAs will explicitly specify the allowability of clinical trials (in FOA Title and in Section II – Award Information)
• Any clinical trial application MUST be submitted to an FOA that accepts or requires clinical trials
Allowability of Clinical Trials

• NIH will issue “parent” FOA’s for clinical trials.
• Some NIH Institutes/Centers (ICs) will participate in the parent FOA’s.
• Some IC’s will issue their own IC-specific clinical trial FOAs.
• When using a parent CT FOA, it will be important to insure that the intended IC participates in the parent.
Allowability of Clinical Trials

• Mechanism-specific considerations
  
  – Training (T) awards
    • All Training award FOAs will designated “Clinical Trials Not Allowed”, but
    • Appointed trainees ARE permitted to obtain research experience in a clinical trial led by a mentor/co-mentor
    • Some D43 and K12 FOAs will be designated as “Clinical Trial Optional”
  
  – Fellowship (F) awards
    • All Fellowship award FOAs will be designated “No Independent Clinical Trial”, but
    • Fellows are permitted to propose research experience in a CT led by a sponsor/co-sponsor
    • In those cases, applicants will provide details on their contributions to the study in the Research Strategy rather than in the CT specific fields on the new PHS Human Subjects and Clinical Trials Information form
Allowability of Clinical Trials

• Mechanism-specific considerations (continued)
  – Career Development (K) awards
    • CDA FOAs will indicate either “Clinical Trials Allowed” or “No Independent Clinical Trials” in the Title and Section II
    • An FOA indicating “Clinical Trials Allowed” will support independent clinical trials conducted by the CDA applicant
    • An FOA indicating “No Independent Clinical Trials” will permit the applicant to propose research experience in a clinical trial led by a sponsor/co-sponsor
      – In these cases, the applicant should provide details of their contribution to the study in the Research Strategy rather than via the new clinical trial specific fields on the PHS Human Subjects & Clinical Trials Information form
      – Additionally, it is the mentor or individual receiving support for the larger trial who retains overall responsibility for the trial
Understanding NIH FOAs

• All FOAs will now clearly indicate whether clinical trials may be submitted to the program
• The FOA will be clearly marked in both the Title and in Section II – Award Information
Understanding NIH FOAs

<table>
<thead>
<tr>
<th>Department of Health and Human Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1. Overview Information</td>
</tr>
<tr>
<td>Participating Organization(s)</td>
</tr>
<tr>
<td>National Institutes of Health (NIH)</td>
</tr>
<tr>
<td>Components of Participating Organizations</td>
</tr>
<tr>
<td>National Cancer Institute (NCI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Funding Opportunity Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multilevel Interventions in Cancer Care Delivery: Follow-up to Abnormal Screening Tests (R01 Clinical Trial Optional)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>R01 Research Project Grant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Announcement Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Related Notices</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Funding Opportunity Announcement (FOA) Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA-17-495</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section II. Award Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding Instrument</td>
</tr>
<tr>
<td>Grant: A support mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Application Types Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
</tr>
<tr>
<td>Renewal</td>
</tr>
<tr>
<td>Resubmission</td>
</tr>
<tr>
<td>Revision</td>
</tr>
</tbody>
</table>

The NIH Grants and the SF424 (R&R) Application Guide provide details on these application types.

<table>
<thead>
<tr>
<th>Clinical Trial?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optional: Accepting applications that either propose or do not propose clinical trial(s)</td>
</tr>
<tr>
<td>Need help determining whether you are doing a clinical trial?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Funds Available and Anticipated Number of Awards</th>
</tr>
</thead>
<tbody>
<tr>
<td>The number of awards is contingent upon NIH appropriations and the submission of a sufficient number of meritorious applications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Award Budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application budgets are not limited but need to reflect the actual needs of the proposed project</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Award Project Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>The maximum project period is five years</td>
</tr>
</tbody>
</table>
Implementation of NIH Clinical Trials Requirements

- NIH is implementing a new version of the NIH application forms kit (FORMS-E) in concert with the implementation of their new policies related to clinical trials
- Care must be used during the transition period to prepare applications using the correct forms kit
- FORMS-E contains a new PHS Human Subjects & Clinical Trials Information form that will be used to gather required information on each clinical trial
## Implementation of NIH Clinical Trials Requirements

### Which form do I use?

<table>
<thead>
<tr>
<th>If your due date is…</th>
<th>You must use…</th>
</tr>
</thead>
<tbody>
<tr>
<td>On or before January 24, 2018, including:</td>
<td>FORMS-D application package</td>
</tr>
<tr>
<td>• Applications submitted for due dates on or before January 24, 2018</td>
<td></td>
</tr>
<tr>
<td>• Applications submitted under <strong>NIH Late Policy</strong> 2-week window of consideration for intended due dates on or before January 24, 2018</td>
<td></td>
</tr>
<tr>
<td>• Applications submitted by February 7, 2018 under NIH <strong>Continuous Submission Policy</strong> for January 7, 2018 AIDS intended due date</td>
<td></td>
</tr>
<tr>
<td>On or after January 25, 2018, including:</td>
<td>FORMS-E application package</td>
</tr>
<tr>
<td>• Applications submitted for due dates on or after January 25, 2018</td>
<td></td>
</tr>
<tr>
<td>• All application types (New, Resubmission, Renewal, Revision)</td>
<td></td>
</tr>
<tr>
<td>• Applications submitted early for intended due dates on or after January 25, 2018</td>
<td></td>
</tr>
</tbody>
</table>

Additional guide notices for individual FOAs with unique due date considerations will be issued as needed and referenced in the Related Notices section of each FOA.
Implementation of NIH Clinical Trials Requirements

• FORMS-E application packages will start to be published on October 25, 2017

• NIH has issued a “preview” for FORMS-E, including detailed information on the data required in the PHS Human Subjects and Clinical Trials Information form
3 Steps: How to Submit a Clinical Trial to the NIH

1. Determine if proposed study meets NIH definition of a clinical trial—see NIH decision tree

2. Identify a Corresponding Funding Opportunity Announcement (FOA)—see NIH website

3. Prepare NIH Application—see new FORMS-E Application Packages
NIH Protocol Template

• Applicants conducting phase 2 or 3 clinical trials that require Investigational New Drug applications (IND) or Investigational Device Exemption (IDE) applications can use a NIH-FDA template with instructional and sample text to help write protocols.
• Use of this template is optional.
• IRB will review the protocol as with any other protocol submitted to us

• You can find the tool here: https://osp.od.nih.gov/clinical-research/clinical-trials/

Questions can be referred to the IRB as you develop your protocol using the tool.
NIH Protocol Template

Clinical Trial E-Protocol Tool and Template Documents

The electronic protocol writing tool aims to facilitate the development of phase 2 and 3 clinical trial protocols that require a Food and Drug Administration (FDA) Investigational New Drug (IND) or Investigational Device Exemption (IDE) Application. The development of the Phase 2 and 3 clinical trial protocol template was an initiative supported by the NIH-FDA Joint Leadership Council and the NIH Clinical Trial Stewardship Reform Task Force, and meets the standards outlined in the International Conference on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance (ICH-E6). Questions about the tool can be sent to SciencePolicy@od.nih.gov.

Take me to the e-Protocol Writing Tool

Final Template Documents

- Word Version of Final Template
- NIH Guide Notice
- NIH Director’s Statement
- Under the Poliscope blog
- FDA Voice blog
NIH Single IRB Policy
Effective January 25, 2018

• Requires reliance on single IRB (sIRB) for
  – Domestic sites in...
  – NIH-funded...
  – Multisite studies (not just CTs) where all sites performing same non-exempt protocol

• Only applies to new proposals submitted on or after the effective date.
NIH Single IRB Policy

*Effective January 25, 2018*

• What will change for you?
  – May require revision to **subaward language** if we are relying on central IRB
  – May require different type of **IRB documentation** to release Emory funds (Emory site approval from central IRB, vs. overall protocol approval)
  – May need **letters of support** from participating sites if Emory is lead site, stating agreement with single IRB plan
  – May need lead time to get **quote** for commercial IRB review if Emory is lead site
NIH Single IRB Policy

*Effective January 25, 2018*

- What will change for you?
  - If Emory is prime, NIH grant application must include single IRB plan
  - Emory IRB will post template language/guidelines for this section of grant application; NIH also provides guidance
NIH Single IRB Policy

• NIH will **not** select the sIRB but will approve or not
• Allowance for “exceptions” based on local/state/tribal law OR “other compelling” (including local policies)
• Does **not** have to be selected prior to award; award would be restricted until selected
• NIH says you can put cost in budget; caveats
sIRB: Roles and Responsibilities for Applicants per NIH

- **Applicant/Offeror**: In the application/proposal for research funding, the applicant/offeror is expected to submit a plan describing the use of an sIRB that will be selected to serve as the IRB of record for all study sites.
- The plan should include a statement confirming that participating sites will adhere to the sIRB Policy and describe how communications between sites and sIRB will be handled.
- If, in delayed-onset research, an sIRB has not yet been identified, applications/proposals should include a statement that awardees will follow this Policy and communicate plans to use a registered IRB of record to the funding NIH Institute/Center prior to initiating a multi-site study.
- The applicant/offeror may request direct cost funding for the additional costs associated with the establishment and review of the multi-site study by the sIRB, with appropriate justification; all such costs must be reasonable and consistent with cost principles, as described in the NIH Grants Policy Statement and the Federal Acquisition Regulation (FAR) 31.302 (Direct Costs) and FAR 31.203 (Indirect Costs).
Emory’s sIRB Plan

Rely on sIRBs when required

If selected as sIRB, rely on commercial IRB as direct cost
Additional sIRB Q&A

• Does the NIH single IRB policy apply to larger cooperative groups or networks that are funded before the policy effective date but with studies that will be determined/started after the effective date?

➢ Only at renewal – so you may be asked to start relying on a single IRB for cooperative group studies at some point.

Additional sIRB Q&A

• Must the participating sites proposed in the NIH application agree ahead of time to rely on the single IRB identified in the application?
  ➢ It is strongly suggested that the sites agree to a single IRB arrangement prior to the submission of an application or proposal. Participating sites can indicate their willingness to rely on the selected single IRB in letters of support.

• Can an NIH Funding Opportunity Announcement (FOA) specify the IRB that will serve as the single IRB?
  ➢ Yes. Some FOAs will specify the use of a particular single IRB.

Requests to Rely on External IRBs – for Researchers

- The Emory IRB will ask for information about the study and whether reliance is mandatory (Reliance Agreement Worksheet)
- Will require an eIRB submission for administrative (not ethics) review
  - Local context items like ancillary reviews, study team training, departmental review
- Emory IRB must help you with local context input requested by central IRB
- Emory IRB will be posting information about the main sIRBs that Emory relies on, with links to SOPs, reporting requirements, etc (but will be growing quickly)
- See our website for guidance and updates: http://irb.emory.edu/forms/external-irbs/index.html

Resources for Researchers

http://irb.emory.edu/forms/external-irbs/index.html

Information available:

- How do I request an IAA or IIA?
- What happens after I submit the IRB Reliance Agreement Worksheet?
- How long does it take to get an IRB Authorization Agreement in place? (Note: it’s taking a while, but we have posted a Reliance Specialist position)
- Are there collaborations for which IRB Authorization Agreements are not appropriate?
- ...and more
Certificates of Confidentiality for NIH-Funded Studies

• Applies to all Human Subjects Research funded (whole or in part) by NIH commenced on or after December 13, 2016. Effective October 1st, 2017.
• In addition, this covers studies involving de-identified specimens that generate genomic data and any other research where there is “at least a very small risk” that one could deduce the identity of an individual.
• “For studies in which informed consent is sought, NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.”
• IRB sent out (and posted) a CoC addendum just prior to the effective date, to be used when consenting prospective subjects
• Not yet required to reconsent subjects enrolled prior to effective date
• Applies to studies under no-cost extensions
Certificates of Confidentiality for NIH-Funded Studies

Note: Emory is responsible for informing subawardees/other collaborators about the presence of CoC
3 Steps: How to Submit a Clinical Trial to the NIH

1. Determine if proposed study meets NIH definition of a clinical trial—see NIH decision tree

2. Identify a Corresponding Funding Opportunity Announcement (FOA)—see NIH website

3. Prepare NIH Application—see new FORMS-E Application Packages
NIH Requirements for GCP Training

• Effective January 1, 2017

• Requires all NIH-funded investigators and staff who conduct, oversee, or manage clinical trials to be trained in **Good Clinical Practice (GCP)**, consistent with International Conference on Harmonization (ICH-E6-R2)

• Available on CITI website

• Must retain documentation of training & **refresh every 3 years**
Dissemination of Information

• The National Institutes of Health (NIH) Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by the NIH, will ensure that their NIH-funded clinical trials are registered at, and that summary results information is submitted to, ClinicalTrials.gov for public posting.

• This policy applies to all NIH-funded clinical trials regardless of study phase, type of intervention, or whether they are subject to the regulation.

• As part of their applications or proposals, applicants, and offerors seeking NIH funding will be required to submit a plan for the dissemination of NIH-funded clinical trial information that will address how the expectations of this policy will be met.
ClinicalTrials.gov Requirements

For PI-initiated clinical trials, the PI is required to:

• Register project in ClinicalTrials.gov within 21 days of enrollment of first subject
  *(ICMJE requires registration prior to enrollment of first subject.)*

• Complete periodic updates as required

• Report summary results information within one year of primary completion date

• Include statement in consent form on posting of information at ClinicalTrials.gov
Required in Proposal/Application

• Add statement on posting of clinical trial information

• Add service center fee to budget section

Emory established a ClinicalTrials.gov Service Center to facilitate compliance:

• For all awards issued on or after September 1, 2017, the service center in OCR will manage all PI-initiated studies

• NIH allows direct charging for cost of complying with reporting requirements

• A one-time fee of $3,500 for study duration
NIH Communication/Education Plan

• All **RAS Units** including pre-award team & directors trained in October/November 2017
  ▪ Quick reference guide/checklist for RAS units

• **OSP/IRB/OCR** training completed

• **Investigators/Clinical Research Coordinators**
  o **Email communication** sent to OSP, IRB & OCR listservs with NIH summary
    ▪ Will send reminder mid-January
  o NIH clinical trial resource section added to **OSP website**
    ▪ [http://osp.emory.edu/nih_clinical_trial_requirements/index.html](http://osp.emory.edu/nih_clinical_trial_requirements/index.html)
  o ORA Newsletter, IRB Webinars, Research Matters
  o Present at **departmental research team** meetings: CHOA quarterly staff meeting, DOP/CHOA faculty meeting, Winship Mastering Clinical Research Series, SON faculty meeting, Psychology faculty meeting, & Cardiology ECCRI Research Group. Awaiting response from others.

• **Institutional committee** presentations: Clinical Trials Executive Committee, Clinical Trials Operations Committee, Clinical Investigators Advisory Committee, Clinical Research Coordinators Advisory Committee, SOM Research Deans, & RAC. Awaiting response from others.
For NIH clinical trial determinations, contact your NIH Program Officer

For questions on FOAs or NIH forms, contact your RAS unit & copy OSP@emory.edu

For questions on ClinicalTrials.gov, contact Jennifer Prozonic (jprozon@emory.edu)

For questions on single IRB or CoC, contact Rebecca Rousselle (rrouss2@emory.edu)

For more info, see http://osp.emory.edu/nih_clinical_trial_requirements/index.html