PREPARING THE “Protection of Human Subjects” SECTION OF YOUR NIH GRANT APPLICATION

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LEARNING OBJECTIVES

After this presentation, you will be able to:

• Complete the human subjects and inclusion portions of the NIH grant application

• Understand how NIH evaluates human subjects and inclusion in grant applications

• Identify the requirements for research involving human subjects for NIH awards
Just-in-Time (all HS research)

Write and Submit NIH Application

Submit:
- FWA
- IRB certification
- HS education

Peer Review

Award is made

HS monitoring

* New PHS HS and CT Info Forms-E

Annual IRB review/ approval
REGULATORY REQUIREMENTS FOR SPONSORING AGENCY (NIH)

- Funding Agencies evaluate applications/proposals involving human subjects for:
  - risks
  - adequacy of protections,
  - benefits
  - importance of knowledge to be gained

- NIH delegates to Peer Review

- No award unless reg. requirements are met
  - Administrative procedures to ensure compliance
HS QUESTIONS IN THE APPLICATION

Possible HS scenarios:
Not HS
Exempt
Non-exempt, not Clinical Trail
Clinical Trial
Clinical Trial Research Experience (Ks & Fs)

You must provide a Protection of Human Subjects section.

OVERVIEW OF HS REQUIREMENTS IN NIH GRANT APPLICATION

• Justify claim of “No” if using human materials

• Justify claim of Exempt, complete HS/CT info forms and plans for inclusion

• If “Yes” to HS, must complete HS/CT info forms and plans for inclusion

• If Clinical Trial, MUST include data and safety monitoring plan (DSMP) and protocol synopsis as part of HS/CT info forms
PEER REVIEW

• Evaluate scientific & technical merit ➔ SCORE

• Evaluate HS section (including DSMP)
  • Acceptable or Unacceptable rating for HS

• Evaluate Inclusion
  • Acceptable or Unacceptable rating for Gender, Minority and Children plans

• Can impact overall score

• Overall score impacts funding decisions

• Administrative codes in Summary Statement
AWARD CONSIDERATIONS

• HS requirements at time of award:
  • FWA, IRB approval and HS education certification

• After award
  • CT.gov requirements for trials
  • Annual IRB approval
  • Enrollment reports
WHAT TO INCLUDE IN NIH GRANT APPLICATION

Write and Submit NIH Application

Peer Review

Award is made

HS monitoring
“NO” HUMAN SUBJECTS INVOLVED

• If research involves use of human materials, a justification for the claim of “No HS” is needed

Key Points of Justification

• Material is NOT collected for your proposed research
  • Discuss source (repository, purchased commercially)
• NO investigator has access to ID, including access to code key)
  • Investigator = anyone involved in conduct of the research beyond providing samples/data

Forms-E – PHS HS/CT Info Form; specific attachment to explain
SITUATIONS THAT CAUSE CONCERN

- Investigator was involved in original data collection or has direct association w/ source
- Excess samples
- Vague Terminology: de-identified, anonymized
- Collecting samples w/o identifiers
- Vague description of provider’s role
- PI won’t attempt to link

Never assume. Make sure it’s in the application.
5 sections

All human subjects research
  • Some Clinical Trials specific

Individual study records; one/protocol; up to 150

Structured data
  • Some information shuffled a bit

Aligns with ClinicalTrials.gov information
### SECTION 4 – PROTOCOL SYNOPSIS

#### 4.1. Brief Summary

**4.2. Study Design**

**4.2.a. Narrative Study Description**

**4.2.b. Primary Purpose**

**4.2.c. Interventions**

<table>
<thead>
<tr>
<th>Intervention Type</th>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
</table>

**Add New Intervention**

**4.2.d. Study Phase**

Is this an NIH-defined Phase III clinical trial? [ ] Yes [ ] No

**4.2.e. Intervention Model**

**4.2.f. Masking**

[ ] Yes [ ] No

[ ] Participant, Care Provider, Investigator, Outcomes Assessor

**4.2.g. Allocation**

**4.3. Outcome Measures**

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Time Frame</th>
<th>Brief Description</th>
</tr>
</thead>
</table>

**Add New Outcome**

**4.4. Statistical Design and Power**

**4.5. Subject Participation Duration**

**4.6. Will the study use an FDA-regulated intervention?** [ ] Yes [ ] No

**4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/Investigational Device Exemption (IDE) status**

**4.7. Dissemination Plan**

**Sections 4 & 5**

- Clinical Trial specific
- Should align with info from CT.gov
- Section 5 is FOA specific attachments

EXEMPT HUMAN SUBJECTS RESEARCH

• Human Subjects Section should include a clear justification for the exemption(s) selected

• DO NOT just repeat the description from the regulations

• 2018 Common Rule has more exempt categories – very important to be sure PIs understand these
NON-EXEMPT HS RESEARCH

90% of Human Subjects research funded by NIH*

Protection of Human Subjects Section (no page limits):

1. Risks
   - Human subjects involvement and characteristics; meets reg requirements for vulnerable populations
   - Sources of materials – what, how, access to identifiers
   - Potential Risks for ALL research interventions: physical, psychological, social, legal

2. Adequacy of Protection Against Risks
   - Recruitment; consent
   - Procedures to minimize identified risks
   - Additional protections for vulnerable subjects

*Could change w/ new Common Rule
3. Potential Benefits of Research to Human Subjects and Others

- May not be direct benefit to subjects
- Discuss risks in relation to anticipated benefits
- Should not include monetary compensation

4. Importance of Knowledge to be Gained

- Discuss in relation to risks
CLINICAL TRIALS

• All Clinical Trials:
  • Data and Safety Monitoring Plan

• In addition, for NIH Phase III Clinical Trials
  • Usually require Data and Safety Monitoring Board

• **IC specific policies**

• **AE/UP reporting**
  • IRB, OHRP, funding agency, institution, FDA

• **Register and report in** [ClinicalTrials.gov](http://ClinicalTrials.gov)

• **FDA requirements may apply**
DATA AND SAFETY MONITORING PLAN

• Data and Safety Monitoring Plan (DSMP) includes:
  • Commensurate with risks
  • Overall framework for data and safety monitoring
  • Responsible party for monitoring
  • Procedures for reporting Adverse Events/Unanticipated Problems

• Data and Safety Monitoring Board (DSMB) required for:
  • Multi-site trials with > than minimum risk and generally for Phase III trials

• Funding IC approval before enrollment begins
CLINICAL TRIAL RESEARCH EXPERIENCE

• The involvement of a Career Development (K) applicant or Fellowship (F) applicant in a clinical trial led by another investigator which provides experience relevant to their research project and/or career development goals.

• The K or F applicant is working on a part of a clinical trial led by a sponsor or mentor.

Fellowship awardees are not allowed to conduct independent clinical trials.

Career development awardees are allowed to conduct independent clinical trials or CT research experience. Check the FOA.
Delayed Onset: HS anticipated but specific plans cannot be described at time of application

- **Must provide justification** - explain why delayed onset
  - Lab and animal studies in Aims 1 & 2 will determine how Aim 3 with human volunteers will be designed
  - As part of our support of junior faculty, after award, we will select and fund 3 promising clinical pilot projects to generate data that faculty can use in future R01 applications

- If funded, you will have to submit appropriate information before involving human subjects [e.g., HS/CT info form, a human subjects section, FWA, IRB approval, inclusion plans, and inclusion enrollment report(s)]

Include a delayed onset study record
WHAT MAKES A GOOD HS SECTION

One that follows the applicable instructions and provides the required information 😊

Reviewers can’t assume. Not being clear can delay your award.
CHARACTERISTICS OF A GOOD HS SECTION

Commensurate with the level of risk
NOT REQUIRED IN NIH APPLICATION

• Federalwide assurance from OHRP (FWA)
  • IRB Approval

Requested prior to award at Just-in-Time
INCLUSION OF WOMEN, MINORITIES & CHILDREN IN NIH FUNDED RESEARCH

• **Must be** included in “Clinical Research” unless there is a compelling rationale for their exclusion
  • Inappropriate with respect to health
  • Risks

• **Clinical Research**: patient-oriented research; epidemiologic & behavioral studies; and outcomes research
  • Take-home message: All human subjects research not E4

• For NIH-defined **Phase III clinical trials**: Plans for a valid analysis

• Decision tree for determining inclusion requirements:
  http://grants.nih.gov/grants/funding/women_min/Women_and_Minorities_Inclusion_Decision_Tree.pdf
INCLUSION IN NIH-FUNDED RESEARCH

• Children are under 18 years (as of January 2016)
• Age range of subjects must always be justified
  • Case Studies to help evaluate when to include children: [http://grants.nih.gov/grants/funding/children/pol_case_science.htm](http://grants.nih.gov/grants/funding/children/pol_case_science.htm)
• Cost or convenience is NOT an acceptable reason for exclusion
• Inclusion should be tied to scientific goals of project
• Describe plans for outreach and recruitment
INCLUSION ENROLLMENT REPORT FORMS

- Inclusion Enrollment Report Forms
  - Structured data form
  - Need to consider race and ethnicity separately

- Separate report forms for US and International participants (even if part of the same study)
  - [http://grants.nih.gov/grants/funding/women_min/women_min.htm](http://grants.nih.gov/grants/funding/women_min/women_min.htm)
Write and Submit NIH Application → Peer Review → Award is made → HS monitoring
Most scientists regarded the new streamlined peer-review process as ‘quite an improvement.’
HOW IS HS SECTION EVALUATED?

• Each reviewer will assess human subjects protections
  • Is HS designation correct?
  • Are 4 points addressed?
  • For CT: appropriate DSMP?
  • Written comments in summary statement

• Peer review group will discuss and determine overall rating of “acceptable” or “unacceptable”
COMMON HS CONCERNS IDENTIFIED IN PEER REVIEW

• HS section is inadequate or missing
• DSMP is inadequate or missing
• Risks and/or strategies to mitigate inadequate or not described
• Source of data/specimens or access to identifiers is not clear
• Informed consent
• Confidentiality
HOW ARE INCLUSION PLANS EVALUATED?

• Each reviewer will assess the inclusion plans
  • Plans for inclusion
  • Justification in the context of the science

• Peer review group will discuss and determine overall rating of “acceptable” or “unacceptable”
COMMON INCLUSION CONCERNS IDENTIFIED IN PEER REVIEW

• Inadequate information describing the sex/gender, race, ethnicity, and/or age(s) of the sample

• Inadequate justification for proposed sample
  • Sex/gender, race, ethnicity, and/or age(s) breakdown not appropriate for the scientific goals of the study or not adequately justified

• Unrealistic sampling
  • Appropriate from scientific perspective but not realistic
  • Collaborations and outreach plans may help
SUMMARY STATEMENT

PROGRAM CONTACT: (Privileged Communication)
08/11/2016
Ann Hardy
240 111-5555
hardyan@od.nih.gov

Application Number: 1 R01 IC12345-01

Principal Investigator
DOE, JOHN

Applicant Organization: ABC SCHOOL OF MEDICINE

Review Group: ZRG1 ABC-D(50)
Center for Scientific Review Special Emphasis Panel
US-Canada Program for Collaborative Biomedical Research

Meeting Date: 07/20/2016
Council: OCT 2016
Requested Start: 12/01/2016

Project Title: An Excellent Research Project

SRG Action: Impact Score: 24

Human Subjects: 30- Human subjects involved – no SRG concerns
Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted
   Gender: 1A-Both Genders, scientifically acceptable
   Minority: 5A-Only foreign subjects, scientifically acceptable
   Children: 1A-Both Children and adults, scientifically acceptable
   Clinical Research - not NIH-defined Phase III Trial

RFA/PA: IC16-006
PCC: M51B B

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<td>30</td>
<td>Non-exempt HS</td>
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<tr>
<td>48</td>
<td>SRG concerns</td>
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<tr>
<td>E1-E7</td>
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Project Title: An Excellent Research Project

SRG Action: Impact Score: 24
Human Subjects: 48-Human subjects involved - SRG concerns
Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted
   Gender: 4U-Gender representation unknown, scientifically unacceptable
   Minority: 5A-Only foreign subjects, scientifically acceptable
   Children: 4U-Child representation unknown scientifically unacceptable
Clinical Research - not NIH-defined Phase III Trial
Write and Submit NIH Application

Peer Review

Award is made

HS monitoring

JUST-IN-TIME
Submit:
• FWA
• IRB certification
• HS education
JUST-IN-TIME REQUIREMENTS

After peer review, for grants likely to be funded:

• OHRP Assurance Number (FWA)

• Certification of IRB approval

• Certification that Key Personnel have completed appropriate human subjects research education
  • [link]

• GCP training for clinical trials
  • [link]
MULTI-SITE STUDY CONSIDERATIONS

• Generally awardee is considered to be engaged in HS research

• For all engaged sites
  • FWA
    • Can cover under awardee’s FWA, if
      • Site does not routinely do HS research
      • Written agreement
        • [http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.html](http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.html)
  • IRB Approval
    • Awardee must track these for sites; provide to NIH upon request
    • Sites to rely on one IRB (required after Jan 2018)
      • Written agreement [http://www.hhs.gov/ohrp/assurances/forms/irbauthagree.html](http://www.hhs.gov/ohrp/assurances/forms/irbauthagree.html)
PEER REVIEW OF NIH GRANT APPLICATIONS

1. Write and Submit NIH Application
2. Peer Review
3. Award is made
4. HS monitoring
AFTER THE AWARD... NOW WHAT?

- Human Research Protections:
  - Annual IRB approval
  - UP/AE Reports – within specified time frame
  - Prior NIH approval for changes in human subjects research
AFTER THE AWARD... NOW WHAT?

- 2012 Guide Notice (2015 update) – Prior NIH Approval for changes in human subjects research that increase risk
  - Changes from no to yes for HS or increase risks
  - Discuss plans with NIH PO before starting
  - Ensure that inclusion plans and/or inclusion enrollment are provided (prior to start or at RPPR—check with funding IC for specific procedures)

- Discuss any planned changes w/ funding IC prior to start

NOT-OD-15-128
AFTER THE AWARD... NOW WHAT?

- Cumulative inclusion enrollment (e.g., actual enrollment) at least annually or as frequently as specified by the funding IC
  - Inclusion Management System through RPPR or through Commons Status

- NIH-defined Phase III Clinical Trials – report any analysis/findings related to outcomes by sex/gender, race, and ethnicity, if available

- Note progress or challenges in recruitment in RPPR
  - For new awards, RPPR will include milestone fields
RESOURCES FOR NIH HS POLICIES


RESOURCES FOR NIH INCLUSION POLICIES

• For Women and Minorities:
  http://grants.nih.gov/grants/funding/women_min/women_min.htm

• For Children:

• New NIH Inclusion Management System:
NEW NIH POLICIES FOR HUMAN SUBJECTS RESEARCH AT NIH
# NEW REFORMS & INITIATIVES

## All Research Involving Human Participants

- ✔ New forms to collect human subjects information
- ✔ Use of a single Institutional Review Board (IRB) for domestic multi-site studies

## Research that Meets the NIH Definition of a Clinical Trial

- ✔ Training in Good Clinical Practice (GCP)
- ✔ Clinical trial-specific Funding Opportunity Announcements (FOAs)
- ✔ New review criteria
- ✔ Expanded registration and results reporting in ClinicalTrials.gov
WHY THESE CHANGES

• New Forms
  • **Consolidates** HS, inclusion enrollment, and CT information into one form
  • Collects information at the **study-level**
  • Uses **discrete form fields** to capture CT information and detail needed for peer review
  • Presents key information to reviewers and staff in a **consistent format**
  • **Aligns** with ClinicalTrials.gov (where possible) for future data exchange

• Single IRB Policy
  • To reduce time to enrollment of subjects without compromising protections

• Clinical Trials Stewardship Reform
  • To ensure that NIH funds trials that have high likelihood of successful completion
  • To increase transparency about what NIH has funded
  • To make data on funded trials broadly available
NIH CLINICAL TRIALS REQUIREMENTS

Effective NOW

• Training in Good Clinical Practice for investigators and staff
  • Free training:
    • NIDA's GCP Training https://gcp.nihtraining.com/
    • NIAID's GCP Training https://gcplearningcenter.niaid.nih.gov/Pages/default.aspx
    • For Social/behavioral trialists: http://www.sbm.org/training/good-clinical-practice-for-social-and-behavioral-research-elearning-course

• Register all NIH funded trials and report results in ClinicalTrials.gov

• January 2018: New Application Requirements
  • FOA must allow submission of proposed clinical trial
  • PHS Human Subjects and Clinical Trial Information Form
SINGLE IRB FOR MULTI-SITE STUDIES

New NIH policy requiring single IRB of record

• Domestic multi-site studies w/ same protocol
• Can use a site’s IRB or a fee-based IRB
• Mechanisms to be established to consider local context
• Policy Excludes
  • Fs, Ks, Ts & Foreign sites
• Exceptions
  • Policy-based - laws/regs/policies requiring local IRB review (Tribal populations)
  • Ancillary studies to on-going parents (time limited)
  • Ad Hoc exemptions to be consider upon request (RARE)
CERTIFICATES OF CONFIDENTIALITY (CoC)

- **Purpose:** enables investigators to refuse to disclose identifiable research information (subpoena)
  - Encourages participation

- **DHHS Agencies, including NIH:** issued COCs upon request for funded and unfunded studies

- **21st Century Cures Bill – new approach**
  - For NIH-funded research – automatic
  - Upon request for unfunded research
  - Stricter about disclosures

- **Policy published September 7, 2017**
## KEY CHANGES TO CoCS

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<thead>
<tr>
<th>Issue</th>
<th>Previous CoC</th>
<th>Current CoC</th>
</tr>
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<tbody>
<tr>
<td>How to get one</td>
<td>Issued upon approval of application</td>
<td>• NIH-funded – <strong>automatic</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Non-NIH funded – upon application</td>
</tr>
<tr>
<td>Disclosure</td>
<td>PI/ Institution could voluntarily disclose</td>
<td>Disclosure is prohibited unless within a statutory exception or with consent</td>
</tr>
<tr>
<td>Admissibility as evidence</td>
<td>Information protected by a CoC could be used in a legal proceeding if disclosed</td>
<td>Protected information cannot be used in a legal proceeding even if it is disclosed elsewhere</td>
</tr>
<tr>
<td>Copies of information</td>
<td>Unclear; typically advised to amend or extend</td>
<td>All information, including copies, is protected</td>
</tr>
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REDESIGNED HUMAN SUBJECTS WEB

humansubjects.nih.gov
RESOURCES FOR NEW POLICIES

• Single IRB
  • Web:  https://osp.od.nih.gov/clinical-research/irb-review/
  • FAQs:
    • Implementation  https://osp.od.nih.gov/clinical-research/implementation-of-the-sirb-policy/
    • Costs  https://osp.od.nih.gov/clinical-research/nih-policy-on-the-use-of-a-single-irb-for-multi-site-research-faqs-on-costs/

• Clinical Trials:  https://grants.nih.gov/policy/clinical-trials.htm