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

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TRUE STORY
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

HS= Human Subjects
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
Write and Submit NIH Application
Peer Review
Award is made
Post Award
Possible HS scenarios:
Not HS
Exempt
Non-exempt, not clinical trial
Clinical trial

HS application Instructions:  https://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/supplemental-instructions-forms-d.pdf
OVERVIEW OF HS REQUIREMENTS IN NIH GRANT APPLICATION

• Justify claim of “No” if using human materials
• If “Yes” to HS, must include HS section and plans for inclusion
• If “yes to clinical trial, MUST include data and safety monitoring plan (DSMP)
PEER REVIEW OF NIH APPLICATIONS

- Evaluate scientific & technical merit → SCORE
- Evaluate HS section (including DSMP) and Inclusion
  - Acceptable or Unacceptable rating for HS, Gender, Minority and Children plans
  - Can impact overall score
- After peer review, each application gets codes for HS and Inclusion
- Overall score impacts funding decisions
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

1. Write and Submit NIH Application
2. Peer Review
3. Award is made
4. HS monitoring
**“NO” HUMAN SUBJECTS INVOLVED**

- If research involves use of human materials, a justification for the claim of “No HS” is needed
  - Explain in Research Strategy OR
  - Can add separate HS section

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**Key Points**

- 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
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.
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

• The new 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
REQUIREMENTS FOR APPLICATIONS PROPOSING CLINICAL TRIALS

• For Clinical Trials NOT NIH Phase III:
  • 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

• FDA requirements may apply
DATA AND SAFETY MONITORING PLAN

• Data and Safety Monitoring Plan 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
WHAT IF HS INVOLVEMENT CANNOT BE DESCRIBED IN THE APPLICATION?

Delayed Onset: Human subjects research anticipated **but** specific plans cannot be described at time of application

- Human Subjects Section – 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 a human subjects section, FWA, IRB approval, inclusion plans, and inclusion enrollment report(s) before involving human subjects

**EXPECT DELAYS**
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.
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
- 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
PEER REVIEW OF NIH GRANT APPLICATIONS

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

Release Date: 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

<table>
<thead>
<tr>
<th>HS Code</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>10</td>
<td>No HS</td>
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<tr>
<td>30</td>
<td>HS – no concerns</td>
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<tr>
<td>44</td>
<td>SRG concerns</td>
</tr>
<tr>
<td>E1-E7</td>
<td>Exemption</td>
</tr>
<tr>
<td>54</td>
<td>HS - Resolved concerns</td>
</tr>
</tbody>
</table>

RFA/PA: IC16-006
PCC: M51B B
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Project Title: An Excellent Research Project

SRG Action: Impact Score: 24
Human Subjects: 44-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
WHAT MAKES A GOOD HS SECTION

One that follows the applicable instructions and provides the required information 😊
Write and Submit NIH Application

Just-in-Time
Submit:
- FWA
- IRB certification
- HS education

SRG Concern (few applications)

Peer Review

Awards made

HS Monitoring

Resolution through OEP

Written response to resolve concerns

HS Unacceptable (bar to funding)
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
    • https://phrp.nihtraining.com/users/login.php
  • GCP training for clinical trials
    • https://gcplearningcenter.niaid.nih.gov/Pages/default.aspx
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

  • IRB Approval

• Awardee must track these for sites; provide to NIH upon request

• Sites can agree to rely on one IRB (required after Sept 2017)
  
  • Written agreement http://www.hhs.gov/ohrp/assurances/forms/irbauthagree.html
RESOLVING HS CONCERNS

• Written response to address concerns
• Clearly and completely address the concerns in the Resume of SS
• Respond to individual critiques
• Work with your Program Officer if you need assistance or clarification
WHAT HAPPENS TO THE 44s?

- PI submits written response to IC
- IC requests OER to resolve
- OER reviews original application and PI’s response
- 2 outcomes:
  1. OER agrees that resolution is adequate and changes HS code, or
  2. OER requests additional information from PI in order to resolve request
- IC can issue an award
Write and Submit NIH Application

Peer Review

Award is made

HS monitoring

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

SRG Concern (few applications)

HS Unacceptable (bar to funding)

Resolution through OEP

Written response to resolve concerns
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 from no to yes for clinical trial
  • 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
• 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
RESOURCES FOR NIH HS POLICIES

• Instructions for HS section:

• NIH OER Human Subjects Website:
  https://humansubjects.nih.gov

• NIH Revised Definition of Clinical Trial:

• NIH Data and Safety Monitoring:

• Protecting Human Research Participants on line training:
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

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NIH OFFICE OF EXTRAMURAL PROGRAMS (OEP), OER
MAY 2017
WHY THESE CHANGES

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

• Clinical Trials Policies
  • 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
SINGLE IRB FOR MULTI-SITE STUDIES

For Application submitted as of Sept 2017:

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 Exceptions
  • Fs, Ks, Ts
  • Laws/regs/policies requiring local IRB review (Tribal populations)
• Ad Hoc exemptions to be consider upon request (RARE)
• Provide resources for reliance agreements
**ADDITIONAL 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/](https://gcp.nihtraining.com/)
    - NIAID's GCP Training [https://gcplearningcenter.niaid.nih.gov/Pages/default.aspx](https://gcplearningcenter.niaid.nih.gov/Pages/default.aspx)
  - Register all NIH funded trials and report results in [ClinicalTrials.gov](https://clinicaltrials.gov)

- January 2018: New Application Requirements
  - FOA must allow submission of proposed clinical trial
NEW HS AND CT FORMS IN NIH APPLICATION

• More information on planned trial
• Separate section for Single IRB
• Application Submission System & Interface for Submission Tracking (ASSIST)
  • On line system to help w/ preparation, submission and tracking of grant application

https://era.nih.gov/services_for_applicants/apply/assist.cfm
REDESIGNED HUMAN SUBJECTS WEB

humansubjects.nih.gov
RESOURCES FOR NEW POLICIES

• Single IRB


  • FAQ’s:
    http://osp.od.nih.gov/sites/default/files/sIRB_Extramural_FAQs_0.pdf (policy)

    • http://osp.od.nih.gov/sites/default/files/FAQs_on_sIRB_Costs.pdf (costs)
