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

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TRUE STORY
LEARNING OBJECTIVES

After this presentation, you will be able to:

• Designate the involvement of human subjects

• Recognize the HS requirements in the NIH grant applications

• Identify the post award requirements for HS
Have you conducted HS research?

A. Yes, I am conducting or have conducted HS research. 0%

B. No, but I plan to.

C. I'm not sure.
Have you conducted multi-site human subjects research?

A. Yes
B. No
C. I will
D. Maybe
Write and Submit NIH Application

Peer Review

Award is made

HS monitoring

Submit:
• FWA
• IRB certification
• HS education

Annual IRB review/ approval

HS Unacceptable (bar to funding)

Resolution through OEP

Written response to resolve concerns

Just-in-Time (all HS research)

SRG Concern (few applications)

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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

**RESEARCH & RELATED Other Project Information**

1. Are Human Subjects Involved?*  
   - Yes  
   - No

1a. If YES to Human Subjects
   - Is the Project Exempt from Federal regulations?  
     - Yes  
     - No
   - If YES, check appropriate exemption number:  
     - 1  
     - 2  
     - 3  
     - 4  
     - 5  
     - 6
   - If NO, is the IRB review Pending?  
     - Yes  
     - No

2. Are Vertebrate Animals Involved?  
   - Yes  
   - No

2a. If YES to Vertebrate Animals
   - Is the IACUC review pending for animal use?  
     - Yes  
     - No  
     - Approved
   - IACUC Approval Date

You must provide a Protection of Human Subjects section.
HUMAN SUBJECTS SECTION IN NIH APPLICATION (NON-EXEMPT HSR)

1. Risks

• Human subjects involvement and characteristics; vulnerable populations
• Sources of materials – what, how, access to identifiers
• Potential Risks – physical, psychological, social, legal

2. Adequacy of Protection Against Risks

• Recruitment; consent
• Procedures to minimize risks
• Additional protections for vulnerable subjects
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
ADDITIONAL NIH REQUIREMENTS

• For Clinical Trials:
  • Data and Safety Monitoring Plan or Board
  • Registration in ClinicalTrials.gov

• For NIH-Defined Clinical Research
  • Inclusion of Women, Minorities, and Children
HS Section Should:

• Describe source; who has access to identifiers
• Address consent
• Main risk is disclosure
• Describe steps to protect the identity of subjects
• Will any results be provided to subjects; if so, what are considerations for doing this?
**WOMEN, MINORITIES & CHILDREN**

- **Must be** included in NIH-defined clinical research unless there is a compelling rationale for their exclusion
  - Inappropriate with respect to health
  - Risks

- **Definition:** patient-oriented research; epidemiologic & behavioral studies; and outcomes research
  
  [http://grants.nih.gov/grants/funding/women_min/women_min_qa.htm#3877](http://grants.nih.gov/grants/funding/women_min/women_min_qa.htm#3877)
  
  - Take-home message: Almost all human subjects research meets this definition (except Exemption 4)

- Add’l requirements for NIH-defined **Phase III clinical trials**
  - Plans for a valid analysis

- Decision tree for determining inclusion requirements:
Inclusion in NIH-funded Research

• Children are under 18 years - January 2016 NIH revised definition NOT-OD-16-010

• 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
  • 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
Your study is determined to be an Exemption 1 (research on educational practices). You must still target and monitor inclusion of women, minorities, and children.

A. True

B. False

C. Not sure
All applications involving the use of human materials must mark "yes" to human subjects.

A. True
B. False
C. Not sure
“NO” HUMAN SUBJECTS INVOLVED

• Data or specimen *not collected specifically* for this study and *no access* to identifiers
  • Check “No” on application

• Must *justify* your designation of “No” human subjects
  • Explain in Research Strategy OR
  • Can add separate HS section

**Key Points**

• Not collected for your proposed research
  • Discuss source (repository, purchased commercially)

• None of investigators have access to ID (or code key)
  • Investigator = anyone involved in conduct of the research beyond providing samples/data
TRICKY SITUATIONS

• Investigator was involved in original data collection or has association w/ source

• Excess samples

• Vague Terminology: de-identified, anonymized

• Collecting samples w/o identifiers

• Cell lines

Never assume. Make sure it’s in the application
I will use human tissue from 5 different repositories however that's a lot to explain in the Research Strategy of my application. What should I do?

A. Nothing. The peer reviewers should figure it out.

B. Use the valuable Research Strategy section and leave something out if I run out of space.

C. Upload a Protection of Human Subjects section and explain all of the sources of my human materials.
OPTIONS FOR USING CODED DATA/SAMPLES

• If possible, break the link for the purposes of proposed study
  • Honest broker to assemble data/samples without linkable code

• Can provider not have a role beyond providing?
PREPARING THE HUMAN SUBJECTS SECTION

• Use Instructions for Preparing HS section

• Select one of 6 scenarios:
  
  A. No Human Subjects
  B. Non-Exempt Human Subjects Research
  C. Exempt Human Subjects Research
  D. Delayed-Onset of Human Subjects Research
  E. Clinical Trial
  F. NIH-defined Phase III Clinical Trial
PREPARING THE HUMAN SUBJECTS SECTION

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If using human materials describe source; can upload a Protection of Human Subjects section. May need to discuss whether specimens or data were collected specifically for study and whether anyone can access subject identifiers.

Reviewers can’t assume. Not being clear can delay your award.
You will need to include:

- Protection of Human Subjects section *commensurate with risk*
- Inclusion information and Enrollment forms

If a **Clinical Trial**:
- A Data and Safety Monitoring Plan

If an **NIH-defined Phase III Clinical Trial**:
- A Data and Safety Monitoring Board

B. Non-Exempt Human Subjects Research
C. Exempt Human Subjects Research
D. Delayed-Onset of Human Subjects Research
E. Clinical Trial
F. NIH-defined Phase III Clinical Trial
**Delayed Onset:** Human subjects research anticipated but specific plans can’t be described in the application (pilot studies to be selected; HS dependent on findings in animal model)

Human Subjects Section – explain why delayed onset

If funded, awardee must provide FWA, IRB approval, human subjects and inclusion sections to NIH **before** involving human subjects

*Reviewers can’t assume. Not being clear can delay your award.*
PREPARING THE HUMAN SUBJECTS SECTION

• Justify selection of exemption(s)
• NOT verbatim of regulatory definition!
• Sources of research materials
• Inclusion monitoring is required, unless the entire study is considered Exemption 4

C. Exempt Human Subjects Research
D. Delayed-Onset of Human Subjects Research
E. Clinical Trial
F. NIH-defined Phase III Clinical Trial

Reviewers can’t assume. Not being clear can delay your award.
NIH CLINICAL TRIALS (CT) POLICIES

• NIH CT requirements:
  • Data and safety monitoring (DSM) plan
  • DSM Board for Phase III and some others

• IC specific policies

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

• CT.gov reporting

• 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
Current requirements for trials regulated by FDA:
  • Trial registration
  • Results

NIH is proposing registration and reporting summary of results through CT.gov for all NIH funded trials
  • All phases
  • All interventions (FDA regulated, behavioral, other)
  • All mechanisms (grant, coop. agreement, contract)
A Phase I clinical trial will need a Data and Safety Monitoring Plan (DSMP).

A. True
B. False
C. Not sure
NOT REQUIRED IN NIH APPLICATION

- Federalwide assurance from OHRP (FWA)
- IRB Approval

Requested prior to award at Just-in-Time
REGULATORY REQUIREMENTS FOR SPONSORING AGENCY (NIH)

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  • benefits
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YOUR SUMMARY STATEMENT

PROGRAM CONTACT:
Mercy Prabhudas

Principal Investigator
MCCUNE, JOSEPH M MD, PHD

Applicant Organization: UNIVERSITY OF CALIFORNIA SAN FRANCISCO

Review Group: IHD
Immunity and Host Defense Study Section

Meeting Date: 10/14/2010
Council: JAN 2011
Requested Start: 04/01/2011

Project Title: Human immune system layering and the neonatal response to vaccines

SRG Action: Impact/Priority Score: 14
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 1A-Both Children and Adults, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

Project Year

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<th>Estimated Total Cost</th>
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<td>TOTAL</td>
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ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

(Special thanks to Dr. McCune, UCSF, and NIAID)
• Before the peer review meeting, each reviewer individually critiques the human subjects plan
• During the meeting, the group makes a determination as to acceptable or unacceptable
• The final decision is noted in the Summary Statement
PEER REVIEW OF HUMAN SUBJECTS SECTION

- 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 determine overall rating of “acceptable” or “unacceptable”
- Summary Statement:
  - PROTECTION OF HUMAN SUBJECTS: UNACCEPTABLE (Code 44)
  - Code 44 is a bar to award
YOUR SUMMARY STATEMENT

(Special thanks to Dr. McCune, UCSF, and NIAID)
CONCERNS IDENTIFIED BY SRGS AS A PERCENTAGE OF ALL CONCERNS

- Human subjects section: 31.8%
- DSMP/B: 23.5%
- Risks: physical/clinical: 16.9%
- Sources of data/specimens: 14.7%
- Risks: psychological/suicidal: 12.9%
- Informed consent: 11.9%
- Confidentiality: 9.9%
- Risks: incidental findings/referrals: 7.3%
- Other risks: 5.9%
- Recruitment: 3.4%
- Other concerns: 1.4%
- No valid concern: 1.4%
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
My IRB has approved my study. I don't need to respond to the SRG concerns in my summary statement.

A. True
B. False
C. Not sure
PEER REVIEW IS NOT THE IRB

• Peer Review is coordinated by the NIH
• Peer Reviewers are scientific peers
• The scientific review of the proposal.
• HS as part of the larger study
• Done for making funding decisions

• IRB is local review of the HS research at the site of the research
• IRB takes into consideration local context
• Detailed assessment of the HS plan; approval of the consent form, recruitment, etc
• Must be done annually
WHAT MAKES A GOOD HS SECTION

One that follows the applicable instructions and provides the required information 😊
CHARACTERISTICS OF A GOOD HS SECTION

Commensurate with the level of risk
PEER REVIEW OF INCLUSION

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

• Peer review group will determine overall rating of “acceptable” or “unacceptable”

• Summary Statement:
  • INCLUSION OF WOMEN, MINORITIES, AND/OR CHILDREN: UNACCEPTABLE (U CODE)
  • Unacceptable (U) code is a bar to award
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
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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
JUST-IN-TIME REQUIREMENTS

• Resolution of unacceptable Human Subjects Section
  • Written response to IC
  • NIH OER concurrence

• Work with Institute/Center staff to resolve unacceptable inclusion concerns
  • Written response to IC
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
  • Written agreement http://www.hhs.gov/ohrp/assurances/forms/irbauthagree.html
SINGLE IRB FOR MULTI-SITE STUDIES

- **May 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
- **Exceptions**
  - Single IRB can’t meet needs of a specific population
  - Local IRB required by law
- Provide resources for reliance agreements
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
    • Add HS activities to non-HS award or add Clinical trial
    • New enrollment of preg. women, children or prisoners
    • Addition that is greater than minimal risk or new info that study procedure/intervention is higher risk
    • Discuss plans with PO before starting!!
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
- 2012 Policy – 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)
RECENT POLICY CHANGES

• Informed Consent for research w/ human fetal tissue
• Use of newborn blood spots in research
• Rigor and transparency/reproducibility
• Age of child
REDESIGNED HUMAN SUBJECTS WEB

humansubjects.nih.gov
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
  • http://grants.nih.gov/grants/funding/children/children.htm

• New NIH Inclusion Management System:
Q & A