



# Preparing the Human Subjects Section of Your NIH Grant Application

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**NIH** National Institutes of Health  
Office of Extramural Research

# True Story



# ***Learning Objectives***

After this presentation, you will be able to:

- **Correctly designate the involvement of human subjects in your application**
- **Recognize the requirements for human subjects and inclusion in NIH grant applications**
- **Identify the post award requirements for research involving 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**

# HS Questions in NIH Application

- SF424 Other Project Info
  - Are Human Subjects Involved      Y      N
  - If yes
    - Is the project Exempt      Y      N
    - If yes, select the number 1   2   3   4   5   6

**YES to HS: must upload HS section**

- PHS 398 R&R Other Project Info
  - 2. Human Subjects
    - Clinical Trial?      Y      N
    - Phase II Clinical Trial?      Y      N

# ***“No” Human Subjects Involved***

- If using human materials (data or biospecimens) from LIVING individuals, you 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
    - State source (repository, purchased commercially)
  - None of investigators access to ID (or code key)
    - Investigator = anyone involved in conduct of the research apart from 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

# *Options for using coded data/samples*

- If possible, break the link for the purposes of proposed study
  - **Honest broker to assemble data/samples w/o linkable code**
- Can provider not have a role beyond providing?

# ***Completing 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**

# ***Scenario A: No Human Subjects***

**Are Human Subjects Involved? \_\_\_ Yes     X  No**

**Human subjects section NOT required BUT must provide justification if using human specimens/ data**



# Scenario B: Non-Exempt Research

Are Human Subjects Involved?  Yes  No  
Research Exempt?  Yes  No  
Clinical Trial?  Yes  No  
NIH-Defined Phase III CT?  Yes  No

- **Human Subjects Section- NO page limitations**
  - Address 4 required points (risk, protections, benefits, knowledge)
- **Inclusion**



# ***Human Subjects Section In NIH Application (Non-exempt HSR)***

- **Risks**
  - **Human subjects involvement and characteristics; vulnerable populations**
  - **Sources of materials – what, how, access to identifiers**
  - **Potential Risks – physical, psychological, social**
- **Adequacy of Protection Against Risks**
  - **Recruitment; consent**
  - **Procedures to minimize risks**
  - **Additional protections for vulnerable subjects**

# ***Human Subjects Section In NIH Application (Non-exempt HSR) -2***

- **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**
- **Importance of Knowledge to be Gained**
  - **Discuss in relation to risks**

# ***For Research with Identifiable Human Samples/Data***

HS Section Should:

- Describe Source and who has access to ID
- 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?

# ***Inclusion in NIH Funded Research***

- NIH policies on the inclusion of women, minorities, and children
- Require that these groups be included in NIH-defined clinical research unless there is a compelling rationale for their exclusion
  - Inappropriate with respect to health
  - Risks
- What is NIH-defined clinical research
  - **Definition:** [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 research considered human subjects research meets this definition (NOT Exemption 4)
- Additional requirements 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](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
- 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



# *Revised NIH Definition of Child*

- Starting in January 2016, NIH is defining a child as anyone under 18 years  
[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](http://grants.nih.gov/grants/funding/children/pol_case_science.htm)



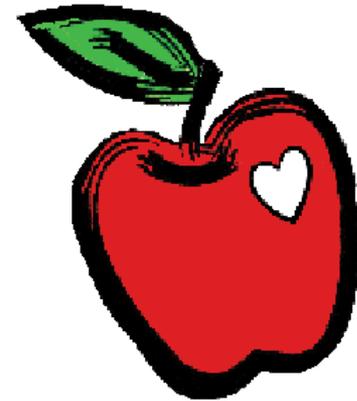
# ***Inclusion Enrollment Report Forms***

- **Inclusion Enrollment Report Forms**
  - **Structured data form in Forms C**
  - **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)

# Scenario C: Exempt Research

Are Human Subjects Involved?     X  Yes        \_\_\_ No  
Research Exempt                       X  Yes        \_\_\_ No  
Exemption Number                   X  1    \_\_\_ 2    \_\_\_ 3    \_\_\_ 4    \_\_\_ 5    \_\_\_ 6

- Human Subjects Section
  - Justify selection of exemption(s)
    - NOT verbatim of regulatory definition!
  - Sources of research materials
- Inclusion of Women, Minorities, and Children \*



\*Not required for Exemption 4

# Scenario D: Delayed Onset HS Research

Are Human Subjects Involved?  Yes  No

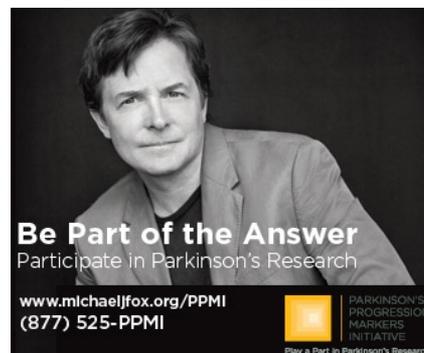
Research Exempt?  Yes  No

- **Delayed Onset:** Human subjects research anticipated but specific plans can't be described in the application
- **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**

**EXPECT  
DELAYS**

# Scenarios E & F: Clinical Trial

- **Recently revised Definition of Clinical Trial:** A research study in which 1 or more subjects are prospectively assigned to 1 or more interventions (including placebo) to evaluate effects on health-related biomedical or behavioral outcomes.
- **NIH Defined Phase III Trial:** A broad-based, prospective trial, often to provide scientific basis for change in health policy or standard of care (Scenario F)
- **All other Phases (Scenario E)**



# NIH Clinical Trials (CT) Policies

- NIH CT requirements:  
[http://grants.nih.gov/grants/policy/hs/data\\_safety.htm](http://grants.nih.gov/grants/policy/hs/data_safety.htm)
  - Data and safety monitoring (DSM) plan
  - Commensurate w/ risk
  - 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:**
  - **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 > minimum risk and generally for Phase III trials**
- **Funding IC approval before enrollment begins**

# *ClinicalTrials.gov*

- 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. agreem., contract)

# Scenario E: Clinical Trial (not Phase III)

Are Human Subjects Involved?      X   Yes    \_\_\_ No  
Research Exempt?                    \_\_\_ Yes      X   No  
Clinical Trial?                           X   Yes    \_\_\_ No  
NIH-Defined Phase III CT?         \_\_\_ Yes      X   No

- Provide information required for Scenario B (Non-Exempt Human Subjects Research)
- Must have a Data and Safety Monitoring Plan
- ClinicalTrials.gov registration

# ***Scenario F: NIH-Defined Phase III Clinical Trial***

**Are Human Subjects Involved?**      X   Yes                 No  
**Research Exempt?**                         Yes              X   No  
**Clinical Trial?**                              X   Yes                 No  
**NIH-Defined Phase III CT?**          X   Yes                 No

- **Provide information required for Scenario E**
- **Generally requires DSMB**
- **Additional inclusion policy requirements to be addressed related to study design**

# *FDA Human Subjects Regulations*

- **Regulations:**
  - **IRB- 21 CFR 56**
  - **Informed Consent- 21 CFR 50**
  - **Additional protections for Children – 21 CFR 50**
- **Apply to NIH grants that are:**
  - **Clinical investigations regulated by FDA or that support applications for research or marketing permits for regulated products**
  - **In addition to 45 CFR 46**



# ***NOT Required in NIH Application***

- Federalwide assurance from OHRP (FWA)
- IRB Approval

Will be requested prior to award

# ***Regulatory Requirements for Sponsoring Agency (NIH)***

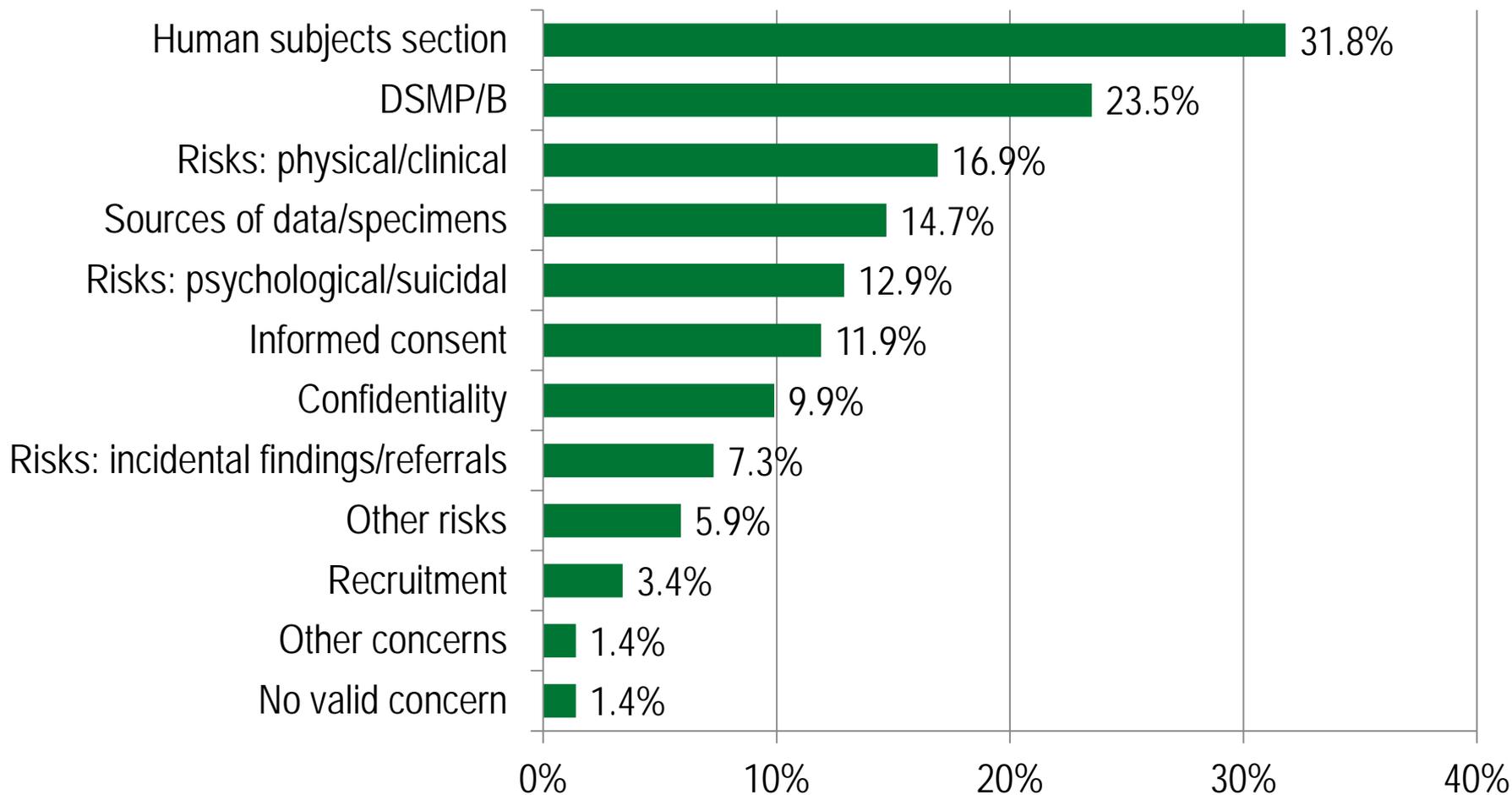
- **Agencies evaluate applications/proposals involving human subjects for**
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  - **adequacy of protections,**
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# Peer Review of Human Subjects Section

- Each reviewer will assess human subjects protections
  - Is 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



# Concerns Identified by SRGs as a Percentage of All Concerns



# ***What Makes a Good HS Section***

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

# ***Characteristics of Good HS Section***

- Subjects:
  - Recruitment
    - Voluntary
    - Research vs clinical care
  - Inclusions and Exclusions
- All Risks are described
  - Intervention &/or experimental procedures
    - Existing data on safety in specific study population
  - Monitoring procedures
- How risks for all are minimized
  - If is a less risky approach not taken – EXPLAIN WHY

# Characteristics of Good HS Section

- Plan for incidental findings
  - Screening
  - Testing that may produce info not focus of study (genetics, imaging)
- Vulnerable subjects
  - Risk level clearly explained (minimal, minor increase or greater than minimal)
    - If > minimal, describe prospect of direct benefit
  - Consent
    - Assent for children
    - Unable to consent

# ***Characteristics of Good HS Section***

- Careful monitoring to ensure safety of subjects
  - May be needed even if study is NOT clinical trial
  - Frequency, who will monitor
  - Need for stopping rules
- Confidentiality
  - How maintained
  - Limit access
- Don't oversell Benefits
  - Compensation is not a benefit
  - Prospect of benefit NOT certain benefit

# *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**

# ***Regulatory Requirements for Sponsoring Agency (NIH)***

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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
- All engaged sites
  - **FWA**
    - Can cover under awardee's FWA
      - 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>

# *Use of Single IRB for Multi-site Studies*

- **Coming Soon:** 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 that increase risk**
    - **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?



- Provide cumulative inclusion enrollment (e.g., actual enrollment) information at least annually or as frequently as specified by the funding Institute/Center
  - Provided in Inclusion Management System through RPPR or through Commons Status
- For NIH-defined Phase III Clinical Trial– report any analysis or findings related to outcomes by sex/gender, race, and ethnicity if available
- Note progress (or challenges) in recruitment as needed in RPPR
- 2012 Policy – Prior NIH Approval for changes in human subjects research that increase risk
  - Changes the project from no to yes for human subjects involvement 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 Institute/Center 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

U.S. Department of Health & Human Services | National Institutes of Health

HOME | APPLY GRANTS | FUNDING | FORMS & DEADLINES | GRANTS POLICY | FAQ | NEWS & EVENTS | ABOUT OHR

**NIH** National Institutes of Health  
Research Involving Human Subjects

BULK DOWNLOADS | ARE YOU CONDUCTING HUMAN SUBJECTS RESEARCH? | ADDITIONAL INFORMATION

## Research Involving Human Subjects

Please Select

- Investigator
- Institution
- Peer Review
- Special Award

PROTECTING | CERTIFICATE OF

# Resources for NIH HS Policies

- **Instructions for HS section**  
<http://grants.nih.gov/grants/funding/424/SupplementalInstructions.pdf>
- **NIH OER Human Subjects Website:**  
<http://grants.nih.gov/grants/policy/hs/>
- **NIH Revised Definition of Clinical Trial:**  
<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>
- **NIH Data and Safety Monitoring**  
[http://grants.nih.gov/grants/policy/hs/data\\_safety.htm](http://grants.nih.gov/grants/policy/hs/data_safety.htm)
- **Protecting Human Research Participants on line training:**
  - <http://grants.nih.gov/grants/funding/424/SupplementalInstructions.pdf>

# ***Resources for NIH Inclusion Policies***

- **For Women and Minorities**

- [http://grants.nih.gov/grants/funding/women\\_min/women\\_min.htm](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:**

- <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-005.html>