HUMAN SUBJECTS PROTECTION AND INCLUSION

GUIDELINES FOR THE REVIEW OF HUMAN SUBJECTS RESEARCH

1. Determine if human subjects are involved (non-exempt) and in the research.
   a. Definition of Human Subject: a living individual about whom an investigator
      (whether professional or student) conducting research obtains
      i. Data through intervention or interaction with the individual, or
      ii. Identifiable private information—must be individually identifiable
   b. Research involving only coded private information or specimens does not
      involve human subjects if the following conditions are both met:
      i. The private information or specimens were not collected specifically for
         the currently proposed research project through an interaction or
         intervention with living individuals; and
      ii. The investigator(s) cannot readily ascertain the identity of the
         individual(s) to whom the coded private information or specimens
         pertain.
   c. Decision Tree to Determine If Human Subjects Are Involved/Not Involved

2. Determine if human subjects involved but Exempt—Although 45 CFR
   46.101(b) includes six Categories, only three Categories of Exempt Human
   Subjects Research are used by the NIH:
   a. Exemption 1: Human Subjects research conducted in an educational setting
      involving normal educational practice.
   b. Exemption 2: Human Subjects research using tests, interviews, or observations
      that do not pose risks or include personal identifiable information.
   c. Exemption 4: Human Subjects research that involves the collection or study of
      existing or future data or specimens that are publicly available or de-identified.

3. Determine if human subjects are not involved

4. If human subjects are involved and non-exempt, determine if they are
   adequately protected from research risks.
   a. Risks to Human Subjects
      i. Does the application adequately describe Human Subjects
         Involvement, Characteristics, and Design, Sources of Materials, and
         Potential Risk, including:
         1. Description and justification for the proposed involvement of
            human subjects
         2. Characteristics of subject population (number, age range, and
            health status)
         3. Inclusion/exclusion criteria
         4. Rationale for involvement of vulnerable populations (e.g.
fetuses, pregnant women, children, prisoners, institutionalized individuals, or others)
5. Role of collaborating sites where research will be performed
6. Description and justification of research procedures (including dosage, frequency, etc. of intervention)
7. Description of what research material, data, and information will be collected
8. Access to personally identifiable information collected and retained
9. Management and protection of materials and information
10. All potential risks to subjects (physical, psychological, financial, legal, or other), including likelihood and seriousness
11. Any alternative treatments or procedures

b. Adequacy of Protection Against Risks
   i. Does the application adequately describe Recruitment and Informed Consent and Protections Against Risk, including:
      1. How subjects will be recruited
      2. Description of informed consent, parental permission and assent
      3. Waiver for any elements of consent
      4. How risks described previously, including privacy and confidentiality, will be minimized
      5. Additional protections for vulnerable populations
      6. Ensuring necessary medical/professional intervention for adverse events

c. Potential Benefits of the Proposed Research to Human Subjects and Others
   i. Does the application adequately describe how potential risks to subjects appear reasonable in relation to anticipated benefits?

   d. Importance of the Knowledge to Be Gained
      i. Does the application adequately describe how potential risks to subjects appear reasonable in relation to the importance of the knowledge that may result from the study?

5. Evaluate whether the gender and minority representation in the sample and the inclusion of children are scientifically acceptable, given the aims of the research and why the inclusion plans for gender, minorities, and children are scientifically acceptable or not.

   a. Inclusion of Women
      i. Gender Representation Flow Chart

   b. Inclusion of Minorities
      i. Minorities Representation Flow Chart

   c. Inclusion of Children
      i. Children Representation Flow Chart

6. Assigning codes summarizing the inclusion and acceptability status.
a. **Human Subject Protection Codes:**
   
i. 10: No human subjects involved
   
ii. 30: Human subjects are involved, and protections are adequate
   
iii. 35: For institutional training mechanisms only: trainees may be assigned to projects in which human subjects are involved.
   
iv. 48: Human subjects are involved and there is a concern about human subjects that must be resolved before the application can be funded.
   
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b. **Inclusion and Acceptability Codes:** A three-digit alphanumeric coding system is used (e.g. G1A):
   
i. Gender Inclusion Codes:
      
1. G1 = Both genders
2. G2 = Females only
3. G3 = Males only
4. G4 = Unknown (cannot be known)
   
ii. Minority Inclusion Codes:
      
1. M1 = Both minorities and non-minorities
2. M2 = Minorities only
3. M3 = Non-minorities only
4. M4 = Unknown (cannot be known)
5. M5 = Only foreign (non-US) subjects
   
iii. Children Inclusion Code:
      
1. C1 = Both children and adults
2. C2 = Children only
3. C3 = Adults only
4. C4 = Unknown (cannot be known)

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7. **Representation Coding for Multi-project Grant Applications**

   a. A code should be assigned to each individual project, core, or subproject in a grant application containing multiple projects, cores, or subprojects and involving distinct populations or specimen collections. A single overall code also should be assigned to the entire multi-project application as follows:

   i. **Representation:** Coding should reflect the representation in all projects/cores/subprojects combined, even if some are single-gender or involve no minorities.

   ii. **Acceptability/ Unacceptability:** Each project/core/subproject must satisfy at least one of the acceptability conditions for an "Acceptable" (A) code to be assigned to the application as a whole. If any
project/subproject is found to be "Unacceptable" (U), the overall code should be U.

8. NIH Single (sIRB) Policy and Review Considerations for Multi-Site Research

   a. NIH-funded multi-site domestic studies involving non-exempt human subjects research are expected to use a single IRB (sIRB).
      i. Conducting the same protocol.
      ii. All Human Subjects; not just Clinical Trials.
      iii. All new and re-competing applications.

   b. Policy excludes:
      i. Foreign sites.
      ii. K, T, and F Award Mechanisms.

   c. Policy allows for exceptions.

   d. The applicant is expected to submit a plan describing the use of a sIRB that will be selected to serve as the IRB of record for all study sites.

   e. Information provided relating to single sIRB is NOT considered.
      i. In overall scoring, or
      ii. in Overall rating of Protection of Human Subjects section.

   f. Reviewers may note if policy appears to be applicable to the proposed research but the application did not include a sIRB.
      i. Reviewers SHOULD NOT propose changes to the sIRB budget.

9. Special Considerations

   a. Inclusion of Human Embryonic Stem Cells (hESCs).
      i. Most hESC research does not involve human subjects and is not considered human subjects research, i.e. the identity of the embryo donor(s) cannot readily be ascertained by the investigator. However, research using cell lines that are identifiable with the embryo donor(s), including cell lines that retain links to coded information that would allow identification of the donor(s), may be considered human subjects research. The NIH Stem Cell Registry includes over 300 approved hESC lines. Therefore, applications proposing the use of hESCs must:
         1. Specify a cell line(s) from the NIH Stem Cell Registry that will be used in the proposed research and provide certification, or
         2. Provide a strong justification for why an appropriate cell line cannot be chosen from the Registry at this time. The justification should be included in the Research Strategy section of the application.
         3. Reviewers will evaluate the scientific appropriateness of the proposed cell line(s). This evaluation will be allowed to affect individual criterion scores, assessments of overall
merit, and overall impact scores during initial peer review. Comments about the appropriateness of the proposed cell line(s) may be included under the Approach criterion.

ii. These uses of Human Pluripotent Stem Cell Research are prohibited with NIH funding, even if derived from embryos donated in accordance with the NIH Guidelines and listed on the NIH Registry or human-induced pluripotent stem cells.

b. Inclusion of Fetal Tissue Research

i. Human fetal tissue is defined as tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion or stillbirth. This definition does not include established human fetal cell lines. Research involving the transplantation of human fetal tissue must be conducted in accordance with applicable Federal, State, and local laws as well as the following NIH guidance.

ii. NIH expects informed consent to have been obtained from the donor for any NIH-funded research using human fetal tissue (NOT-OD-16-033).

iii. Research involving human fetal tissue must be conducted in accordance with applicable Federal, State, and local laws, regulations, and policies (NOT-OD-15-143), including the NIH Grants Policy Statement.

c. Inclusion of Dried Blood Spots Obtained Through Newborn Screening

i. A new provision of the Newborn Screening Saves Lives Reauthorization Act of 2014 (P.L. 113-240) requires federally funded research using newborn dried blood spots collected on or after March 18, 2015 to be considered non-exempt human subjects research.

ii. NIH funded research using newborn dried blood spots collected on or after March 18, 2015 will be considered non-exempt human subjects research, and therefore, it must follow the HHS protection of human subjects regulations at 45 CFR part 46.

iii. Grant applications and R&D contract proposals submitted to NIH that will use such materials in research should be designated as non-exempt human subjects research and include a complete human subjects section per relevant NIH instructions including plans for inclusion on the basis of sex/gender, race, ethnicity, and age per the NIH Policies on the Inclusion of Women, Minorities, and Children.

iv. Parental permission must have been obtained in order to use newborn dried blood spots in NIH-funded research collected on or after March 18, 2015. Waiver of parental permission for such research is not permitted under this legislation.

v. Non-identifiable newborn dried blood spots collected prior to March 18, 2015 may continue to be used in NIH-funded research without parental permission, and this activity would continue to be considered research that does not involve human subjects under the current human subjects regulations.
vi. NIH recognizes that there is no universal agreement on the optimal timing for collection of parental permission for research purposes.

vii. For more information, please read NOT-OD-15-127.

d. Use of Humanized Animals

i. Applications that include the development and/or use of humanized animals must address any applicable aspects of human subjects protection.

Clinical Trial-Specific Review Criteria and Resources

1. Revised NIH Definition of "Clinical Trial"

a. A research study in which one or more human subjects are prospectively assigned. The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial to one or more interventions. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g. surgical techniques); delivery systems (e.g. telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g. diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies. (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

a. Clinical Trial Research must meet ALL the following criteria

   i. Involves human participants

   ii. Prospectively assigns people to interventions

   iii. Evaluated the effect of the intervention on the participants

   iv. Has a health-related biomedical or behavioral outcome

   v. Still unsure? Click Here

2. Types of Clinical Trials

a. Diagnostic trials determine better tests or procedures for diagnosing a particular disease or condition.

b. Natural history studies provide valuable information about how disease and health progress.

c. Prevention trials look for better ways to prevent a disease in people who have never had the disease or to prevent the disease from returning.

d. Quality of life trials (or supportive care trials) explore and measure ways to improve the comfort and quality of life of people with a chronic illness.
3. Phases of Clinical Trials

a. **Phase I trials** — An experimental drug or treatment in a small group of people (20–80) for the first time. The purpose is to evaluate its safety and identify side effects.

b. **Phase II trials** — The experimental drug or treatment is administered to a larger group of people (100–300) to determine its effectiveness and to further evaluate its safety.

c. **Phase III trials** — The experimental drug or treatment is administered to large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, and compare it with standard or equivalent treatments.

d. **Phase IV trials** — After a drug is licensed and approved by the FDA researchers track its safety, seeking more information about its risks, benefits, and optimal use.

4. All applications involving one or more independent clinical trials must be submitted through Funding Opportunity Announcements (FOAs) specifically designated as “**Clinical Trial Required or Clinical Trial Optional**”. These FOAs may contain important unique review criteria (in Section V: “Application Review Information”) in addition to **Clinical Trial-Specific Review Criteria** that focus on the rationale, study design, and other specific considerations for mechanistic studies to inform assessments of the proposed studies that are unique to different types of awards:

a. **Research Project Applications (R Awards)**

   i. **Scored Clinical Trial-specific Review Criteria:**

      1. Significance
      2. Investigator(s)
      3. Innovation
      4. Approach
      5. Environment

   ii. **Additional Clinical Trial-specific Review Criteria:**

      1. Study Timeline

5. FOAs that do not accept clinical trials but permit clinical trial research experience include additional review criteria unique to the following types of awards:

a. **Individual Career Development Applications (K Awards)**

   i. **Scored Review Criteria**

      1. Career Development Plan/Career Goals and Objectives
      2. Research Plan
3. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s)
   
   b. **Individual Fellowship Applications (F Awards)**
      
      i. **Scored Review Criteria**
         1. Sponsor(s), Collaborator(s), and Consultant(s)
         2. Research Training Plan
   
   c. **Institutional Training Applications (T Awards)**
      
      i. **Scored Review Criteria**
         1. Preceptors/Mentors

6. **Data and Safety Monitoring:** Reviewers must certify that an adequate [Data Safety Monitoring Plan](#) is included in applications proposing Phase I and Phase II Clinical Trials, and that an Adequate [Data Safety Monitoring Board](#) is included in application proposing Phase III Clinical Trials.
   
   a. [Data and Safety Monitoring Plan Decision Tree](#)

7. **Human subjects, inclusion enrollment, and clinical trial information** are consolidated in the [NIH 'FORMS-E' Grant Application Package](#) that is included in all NIH Clinical Trial Grant Applications. The expansion and use of discrete form fields for human subject and clinical trial information in a single package within the application is provided to assist reviewers in their evaluation of all the required key human subjects and clinical trial information.