HUMAN SUBJECTS
PROTECTION AND INCLUSION

WHAT THE REVIEWER NEEDS TO EVALUATE

Reviewers of extramural research grant applications are asked to:

1. Determine if human subjects are involved in the research.
2. If human subjects are involved, determine if they are adequately protected from research risks.
3. Determine if the research is a Phase III clinical trial, and if so, determine the adequacy of the Data and Safety Monitoring Board.
4. Evaluate whether or not 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. Also, for a Phase III clinical trial, determine if this inclusion plan is adequate to conduct a valid analysis for detecting significant differences among minorities and gender. Determine if a planned enrollment table(s) with the proposed sample distributed on the basis of sex/gender, race, and ethnicity (or a cumulative inclusion enrollment report if working with an existing dataset) is provided.
5. Assign codes summarizing the protection, inclusion and acceptability status.

Note: Substantive human subject issues should affect the overall impact/priority score. Minor human subject issues may be addressed administratively. The applicant must ensure that all subcontractors and collaborators (both US and non-US) provide the required information for this special issue, and that this information is provided for each performance site listed.

GUIDANCE FOR MAKING THESE EVALUATIONS

1. Are Human Subjects involved in the research?

A Yes/No code will be used to decide if there are human subjects and if the research proposed is a Phase III clinical trial.

Human subjects research is comprised of all research involving the use of human organs, tissues, and body fluids from living individuals or graphic, written, or recorded information derived from living individuals.

Human subjects are not considered to be involved if:

1. The research uses only coded private information or specimens, AND
2. This information meets the conditions that:
   a. The private information or specimens are not collected specifically for the proposed research, AND
b. Any of the involved investigator(s) cannot identify the individual(s) providing the coded private information or specimens, because the key to decipher the code has either been destroyed or a formal agreement exists that prohibits the release of that key to the investigators during the lifetime of the subjects.


Please see below for preliminary guidance related to Use of Human Fetal Tissue, Use of Newborn Dried Blood Spots and Use of Humanized Animals.

NIH defines clinical research as comprising three areas:

1. **Patient-oriented research.** Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects (excluded from this definition are *in vitro* studies utilizing human tissues that cannot be linked to a living individual, as described above).
   
   This research includes:
   
   - Mechanisms of human disease
   - Therapeutic interventions
   - Clinical trials
   - Development of new technologies

2. **Epidemiologic and behavioral studies.** By NIH policy, all human behavioral research is clinical research, whether it is large or small scale, observational, survey, focus group, or other types of behavioral research.

3. **Outcomes research and health services research.**

2. **Are Human Subjects adequately protected from research risks?**

To assess the adequate protection of human subjects, four requirements must be considered:

**Requirement 1:** Risks to subjects, including:

- Characteristics of the study population such as anticipated number, age range, and health status; inclusion and exclusion criteria; and the rationale for involvement of any vulnerable populations
- The source and type of research data or specimens, how this will be collected, who will have access to identifiable private information, and whether materials will be collected specifically for the proposed project
- Potential risks (physical, psychological, financial, legal, or other)

**Requirement 2:** Adequacy of protection against risks, including:
- Plans for the recruitment and informed consent process
- Protections against risk, including procedures for protecting against risks to privacy and confidentiality of data, and plans for medical intervention and reporting of adverse events

**Requirement 3:** Potential benefit of the proposed research to the subjects and others as well as why risks are reasonable in relation to the anticipated benefits.

**Requirement 4:** Importance of the knowledge to be gained in relation to the risks to subjects. If a clinical trial is proposed, a data and safety monitoring plan must be included.

### 3. Is the research a Phase III Clinical Trial?

NIH definition: Phase III clinical trials are broadly based, prospective clinical investigations for the purpose of investigating the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand). These trials compare the intervention to other standard or experimental interventions, monitor adverse effects, and collect information that will allow the intervention to be used safely. Phase III clinical research trials may include pharmacologic, non-pharmacologic, and behavioral interventions that are given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

In the case of an NIH-defined Phase III clinical trial, a data and safety monitoring board must be in place.

### 4. Are the gender and minority characteristics of the study subjects and the inclusion of children scientifically acceptable given the aims of the research?

The judgment of scientific acceptability requires that reviewers first evaluate the human subjects protection plans in terms of the scientific questions posed.

Note: the judgment of scientific acceptability for Phase III clinical trials research requires the consideration of additional criteria. These criteria include the assessment of sample retention plans, sample recruitment plans, and plans (or the reason that plans are not needed) to conduct a valid analysis to detect significant differences among minorities and genders in the intervention effect (see section below entitled “Gender and Minority Representation Requirements for Phase III Clinical Trials.”

It is not anticipated that every study will include both genders, all minority groups and subgroups, and children. Inclusion should be determined by the scientific questions under examination. Grant applications should describe and justify fully the human subject composition that will be included in the research.

In some cases, sample representation is unknown because sample composition cannot be accurately determined (e.g. pooled blood samples or stored specimens without gender designation). This may or may not be scientifically acceptable, depending on the research questions.
In foreign research projects involving human subjects, the definition of minority groups may be different from those in the US. If there are scientific reasons for examining minority groups/subgroup differences in such settings, the studies should be designed accordingly.

For foreign applications as well as foreign components of applications, the policy on the inclusion of both genders applies fully.

The inclusion plan is scientifically unacceptable if it fails to conform to NIH policy guidelines in relation to the scientific purpose and type of study, it fails to provide sufficient information, it does not adequately justify the limited or lack of representation of one gender or minority persons or children, or for Phase III clinical trials, it does not realistically address recruitment/retention.

**Gender and Minority Representation Requirements for Phase III Clinical Trials**

A Phase III clinical trial must include plans (or the reason that plans are not needed) to conduct a valid analysis to detect significant differences among minorities and genders in the intervention effect. Applicants should provide one or more of the following rationales that may apply for a scientifically acceptable project:

- Available evidence strongly indicates significant gender differences of clinical or public health importance in intervention effect, and the study design is appropriate to answer separate primary questions, one for males and one for females, with an adequate sample size for each gender.

- Available evidence strongly indicates significant racial/ethnic differences of clinical or public health importance, and the study design is appropriate to answer separate primary questions for each of the relevant racial/ethnic subgroups with an adequate sample size for each group.

- Available evidence strongly indicates that there are no significant differences of clinical or public health importance among racial/ethnic groups or subgroups and/or between genders in relation to the effects of study variables (minority representation and representation of both genders are not required as subject selection criteria; however, the inclusion of both genders and minority group/subgroup members is encouraged).

- There is no clear-cut scientific evidence to rule out significant differences of clinical or public health importance between males and females and/or among racial/ethnic groups or subgroups in relation to study variables, and the study design includes a sufficient and appropriate representation of both genders and/or minority groups to permit the valid analysis of a differential intervention effect (high statistical power is not required to determine differential effects).

- One gender and/or some minority groups or subgroups are excluded from the study because the inclusion of these individuals would be inappropriate with respect to their health or because the inclusion of these individuals would be inappropriate with respect to the purposes of the research, e.g. the research question that is addressed is relevant only to one gender or ethnic/racial group or subgroup.
"Information on NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research" was published the *NIH Guide* in October, 2001. Among these provisions for all clinical research are special requirements for Phase III clinical trials. The amended policy "Inclusion of Women and Minorities Policy Implementation" may be found at the web site [http://grants.nih.gov/grants/funding/women_min/women_min.htm](http://grants.nih.gov/grants/funding/women_min/women_min.htm).

“Inclusion of Children Policy Implementation” may be found at the web site: [http://grants.nih.gov/grants/funding/children/children.htm](http://grants.nih.gov/grants/funding/children/children.htm)


5. Assigning codes summarizing the inclusion and acceptability status.

**Human Subject Protection Codes:**
- 10: No human subjects involved
- 30: Human subjects are involved and protections are adequate
- 35: For institutional training mechanisms only: trainees may be assigned to projects in which human subjects are involved.
- 44: Human subjects are involved and there is a concern about human subjects that must be resolved before the application can be funded.
- E4: Research involving the use of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Rarely used (for NIAID) additional exemption codes you may see can be found here: [https://www.niaid.nih.gov/researchfunding/sci/human/pages/hsinvcodes.aspx](https://www.niaid.nih.gov/researchfunding/sci/human/pages/hsinvcodes.aspx)

**Inclusion and Acceptability Codes:**
A three-digit alphanumeric coding system is used (e.g. G1A):
- G, M, or C indicates *Gender*, *Minority* or *Children*.
- A number 1-5 indicates inclusion status.
- An A or U indicates scientific *Acceptability* or *Unacceptability*.

**Gender: The classification of humans as either female or male.**

**Gender Inclusion Codes:**
- G1 = Both genders
- G2 = Females only
- G3 = Males only
- G4 = Unknown (cannot be known)
Minority group: A readily identifiable subset of the US population that is distinguished by racial, ethnic, and/or cultural heritage. In accordance with OMB Directive No. 15, the currently defined groups are American Indian or Alaskan Native; Asian or Pacific Islander; Black, not of Hispanic origin; and Hispanic.

Minority Inclusion Codes:
- M1 = Both minorities and non-minorities
- M2 = Minorities only
- M3 = Non-minorities only
- M4 = Unknown (cannot be known)
- M5 = Only foreign (non-US) subjects

Children: Individuals under the age of 18 years. Starting with applications/proposals submitted for due dates on or after January 25, 2016, for the purposes of inclusion policy, the age of a child will be defined as individuals under 18 years old as specified in NOT-OD-16-010: Inclusion of Children in Clinical Research: Change in NIH Definition.

Children Inclusion Code:
- C1 = Both children and adults
- C2 = Children only
- C3 = Adults only
- C4 = Unknown (cannot be known)


Scientific Acceptability Code (third character):
- A = Scientifically Acceptable
- U = Scientifically Unacceptable

Thus, for example:

G1A indicates that both genders are represented in the research; the research is scientifically acceptable.

M3U indicates that only non-minorities are represented in the research; the research is scientifically unacceptable, given the stated aims of the research.

For more information, please read:
http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html
Representation Coding for Multiproject Grant Applications
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 multiproject application as follows:

- **Representation**: Coding should reflect the representation in all projects/cores/subprojects combined, even if some are single-gender or involve no minorities.
- **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 "Unacceptable" (U), the overall code should be U.

Use of Human Fetal Tissue
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 human fetal tissue is also subject to the HHS Regulations for the Protection of Human Subjects (45 CFR 46 Subparts A and B) Human Subjects Research (45 CFR 46) | HHS.gov. 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.

Guidance for recipients conducting research on human fetal tissue and other information on the governing Federal statute is found in sections 498A and 498B of the PHS Act, 42 U.S.C. 298g-2 Office for Human Research Protections (OHRP) | HHS.gov.


For legal requirements regarding the acquisition and use of human fetal tissue for research purposes see Guide Notice NOT-OD-15-143.

Use of Newborn Dried Blood Spots
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.

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

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

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.

NIH recognizes that there is no universal agreement on the optimal timing for collection of parental permission for research purposes.

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

**Use of Humanized Animals**

Applications that include the development and/or use of humanized animals must address any applicable aspects of human subjects protection. If the proposed activities are claimed to be exempt, the application/proposal should include a justification for claiming exemption from human subjects regulations.

**Human Embryonic Stem Cells**