

Human Subjects Protection and Inclusion of Women, Minorities, and Children

Guidelines for Review of NIH Grant Applications

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HUMAN SUBJECTS PROTECTION

Requirements for Review

- Federal regulations for the protection of human research subjects (45 CFR 46), require that the evaluation of research applications that involve human subjects take into consideration the risk to subjects, the adequacy of protections against risk, potential benefits of the research to subjects and others, and the importance of the knowledge to be gained
- The NIH Peer Review regulations (42 C.F.R. 52h) specify that reviewers will take into account, in determining overall impact that the project in the application could have on the research field involved, the adequacy of the proposed protection for humans
- Therefore, reviewers must evaluate the proposed plans to protect human subjects from research risks, as appropriate for the research proposed, as one of the review criteria that factor into the evaluation of scientific and technical merit
- In addition to federal regulations about the protection of human research subjects, NIH policies require that applications involving Clinical Trials include a data and safety monitoring plan and that NIH-defined Phase III clinical trials also describe a data and safety monitoring board
- Data safety and monitoring plans must also be evaluated by peer reviewers.

Reviewer Responsibilities

- For applications involving human subjects:
 - Determine if a claim for exemption is adequately justified in applications that indicate the proposed research is exempt **OR**
 - Determine whether the involvement of human subjects in the proposed research is justified scientifically; evaluate the proposed plan for the involvement of human subjects in non-exempt human subjects research; and determine if subjects appear to

- be adequately protected from research risks.
- For applications that involve a clinical trial, determine if the plans for data and safety monitoring, including the description of a data and safety monitoring board if necessary, are adequate.
- For applications that claim no involvement of human subjects but propose the use of existing human data or biological specimens, evaluate if the justification provided for not involving human subjects is acceptable.
 - Rate the application as Acceptable, Unacceptable, or Not Applicable in terms of human subjects involvement and prepare written comments, including specific comments describing concerns for applications rated as Unacceptable.
- For applications that do not involve human subjects or the use of human data or specimens, rate the application as Not Applicable for this criterion. In this case, the Inclusion criterion, as described below, will also be Not Applicable.

Reviewer Comments

Reviewer Comments are required for Protections for Human Subjects (unless Not Applicable). An example follows:

- The applicant states that the proposed research involves minimal physical risk; however, genetics research is considered of moderate risk due to the possibility of breaches in confidentiality. Insufficient detail is provided regarding measures to protect against such risk.

INCLUSION OF WOMEN, MINORITIES, AND CHILDREN

Requirements for Review

- Public Law 103-43 requires that women and minorities be included in all clinical research studies, as appropriate for the scientific goals of the work proposed.
- Additionally, NIH policy requires that women and members of minority groups and their subpopulations be included in Phase III clinical trials in numbers adequate to allow for valid analyses of sex/gender, racial, and/or ethnic differences in intervention effects
- NIH policy also states that children (defined as persons under the age of 21) be included in human subjects research supported by NIH unless an acceptable justification for their exclusion is provided
- The NIH Peer Review regulations (42 C.F.R. 52h) specify that reviewers will take into account, in determining overall impact that the project in the application could have on the research field involved, the adequacy of plans to include both genders, minorities, children and special populations as appropriate for the scientific goals of the research
- Therefore, reviewers must evaluate the proposed plans for inclusion of women, minorities, and children as one of the review criteria that factor into the evaluation of scientific and technical merit.

Reviewer Responsibilities

- Evaluate whether the sex/gender, racial, and ethnic characteristics of the proposed sample and the plan for the inclusion of children are scientifically acceptable given the aims of the research.

- Rate the application as Acceptable or Unacceptable with respect to the proposed inclusion of Women, Minorities, and Children, assign codes, and include specific comments describing why the plans are acceptable or any concerns for applications rated as Unacceptable.

Reviewer Coding

Three digit alphanumeric codes are used to summarize reviewers' evaluation of inclusion of women, minorities, and children. The three digit code is comprised as follows.

- First digit: G, M, or C to indicate gender, minority, or children, respectively
- Second digit: A numerical code from 1-5 to identify what groups are included
- Third digit: A or U to indicate scientific acceptability, given the stated research aims and the proposed inclusion plans

Each application involving human subjects receives three separate alphanumeric codes, for sex/gender, minorities, and children, respectively. A code should be assigned to each individual project or subproject in an application containing multiple projects or subprojects and involving distinct populations or specimen collections. A single overall code ALSO should be assigned to the entire application. If any project/subproject is found "Unacceptable" (U), the overall code should be U. The overall coding should reflect the acceptability of inclusion for all projects/subprojects even if the proposed inclusion plans vary for different studies.

Sex/Gender Inclusion Codes

- **G1A** = Both genders, acceptable
- **G1U** = Both genders, unacceptable
- **G2A** = Only women, acceptable
- **G2U** = Only women, unacceptable
- **G3A** = Only men, acceptable
- **G3U** = Only men, unacceptable
- **G4A** = gender composition unknown, acceptable
- **G4U** = gender composition unknown, unacceptable

Minority Inclusion Codes

- **M1A** = Minority and nonminority, acceptable
- **M1U** = Minority and nonminority, unacceptable
- **M2A** = Only minority, acceptable
- **M2U** = Only minority, unacceptable
- **M3A** = Only nonminority, acceptable
- **M3U** = Only nonminority, unacceptable
- **M4A** = minority composition unknown, acceptable
- **M4U** = minority composition unknown, unacceptable
- **M5A** = only foreign subjects, acceptable
- **M5U** = only foreign subjects, unacceptable

Children Inclusion Codes

- **C1A** = Children and adults, acceptable
- **C1U** = Children and adults, unacceptable
- **C2A** = Only children, acceptable
- **C2U** = Only children, unacceptable
- **C3A** = No children included, acceptable

- **C3U** = No children included, unacceptable
- **C4A** = Representation of children unknown, acceptable
- **C4U** = Representation of children unknown, unacceptable

It is not expected that every study will include both sexes/genders, all minority groups and subgroups, and children. Inclusion on the basis of sex/gender, race, and ethnicity, as well as the inclusion of children should be determined by the scientific aims of the study. Applicants should describe and justify fully the distribution of individuals that will be included in the research.

Reviewer Comments

Reviewer comments are required for Inclusion of Women, Minorities, and Children regardless of acceptability rating, unless inclusion is Not Applicable. Examples of comments follow.

- (G1U) Gender representation is unacceptable. Although both genders are represented, too few members of one gender are included to answer the questions posed.
- (G2A) Gender composition is scientifically acceptable, although only females are represented, because the disease under study is not found in male subjects.
- (G1A) Although there are relatively few females in the sample, the representation reflects the sex/gender ratio in the prevalence of the disorder; the plan is scientifically acceptable.
- (C3A) No children included. This is acceptable as knee replacement is rare in children as compared to adults.
- (M4U) Minority representation is unknown. The applicant does not provide sufficient information about the racial and ethnic composition of the study population. The application does not comply with requirements and is unacceptable.

BACKGROUND AND REFERENCES

Human Subjects Protection

Federal Regulations for Protection of Human Research Subjects (45 CFR 46):

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

More Information

[Peer Review Decision Trees for Human Subjects Protections and Inclusion Issues](#)

Definition of Human Subject

A living individual about whom an investigator (whether professional or student) conducting research obtains

- 1) Data through intervention or interaction with the individual, or
- 2) Identifiable private information.
 - *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject.
 - *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual

and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Research Involving Coded Private Information or Biological Specimens

Research that involves only the use of human specimens or data is not considered human subjects research if:

- All subjects are deceased **OR**
- The data/specimens were not obtained specifically for the proposed research AND none of the investigators involved in the research can ascertain the identity of the subjects, either directly or indirectly.

See <http://www.hhs.gov/ohrp/policy/cdebiol.html> for more detailed information

Human Subjects Research Exemptions (45 CFR 46.101)

- 1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as
 - i. research on regular and special education instructional strategies, or
 - ii. research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- 2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
 - i. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
 - ii. any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- 3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph [\(b\)\(2\)](#) of this section, if:
 - i. the human subjects are elected or appointed public officials or candidates for public office; or
 - ii. (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- 4) Research involving the collection or study 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.
- 5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
 - i. public benefit or service programs;
 - ii. procedures for obtaining benefits or services under those programs;
 - iii. possible changes in or alternatives to those programs or procedures; or
 - iv. possible changes in methods or levels of payment for benefits or services under those programs.

- 6) Taste and food quality evaluation and consumer acceptance studies,
 - i. if wholesome foods without additives are consumed or
 - ii. if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Data and Safety Monitoring Plan

For information, visit [Data and Safety Monitoring Plan](#).

Inclusion of Women, Minorities, and Children

[NIH Policies Regarding Inclusion of Women and Minorities](#)

[NIH Policies Regarding Inclusion of Children](#)

Definitions

Clinical research:

- 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 that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.
- 2) Epidemiologic and behavioral studies.
- 3) Outcomes research and health services research.

<p>Note: Research that meets the criteria for Exemption 4 is not considered “clinical research” as defined by NIH. Therefore the NIH policies for inclusion of women, minorities, and children in clinical research, and planned enrollment reports do not apply to research projects covered by Exemption 4.</p>
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Phase III clinical trials research:

Phase III clinical trials research is defined as 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) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

Sex/Gender: For the purposes of reporting inclusion data, individuals are classified as either female or male. Sex/gender classification is based on self-report by participants enrolled in the research study. NIH policy does not require that inclusion data be based on sex assigned at birth. Reviewers should be aware that the proposed research may include individuals whose gender identity differs from their sex assigned at birth

Minority group: A readily identifiable subset of the U.S. population distinguished by either

racial, ethnic, and/or cultural heritage. In accordance with OMB Directive No. 15, the currently defined racial groups are American Indian/Alaskan Native; Asian; Native Hawaiian or Other Pacific Islander; Black or African American; White. Currently defined ethnic groups are Hispanic or Latino; Not Hispanic or Latino. It is expected that study participants will be asked to identify their ethnicity and their race(s).

Children: Individuals under the age of 21 years.