Human Subjects Protection and Inclusion

As reviewers of extramural research grant applications you are asked:

1. to determine if human subjects are involved in the research and, if so,
2. to determine if the human subjects are protected from research risks,
3. to determine if the research meets the criteria for an exemption,
4. to determine if the research is a Phase III Clinical trials project,
5. to evaluate whether the gender and minority characteristics of the sample and the inclusion of children are scientifically acceptable, given the aims of the research,
6. to indicate why the sample inclusion plans are scientifically acceptable or not, and
7. to assign codes summarizing the inclusion and acceptability status.

1. HHS REGULATIONS (45CFR46) DEFINE:

Human subjects research as all research involving the use of human organs, tissues, and body fluids from living individuals, as well as graphic, written, or recorded information derived from living individuals. The exception to this definition of human subject research is that 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) the 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 prohibiting release of that key to the investigators during the lifetime of the subjects.

2. HHS REGULATIONS (45CFR46) DEFINE:

Protection of human subjects according to four criteria:

- Risks to subjects, including the likelihood and seriousness of potential risk
- Adequacy of protection against risks
- Potential benefit of the proposed research to the subjects and others
- Importance of the knowledge to be gained

If a clinical trial is proposed, then another level of protection must be considered. A Data and Safety Monitoring Plan must be included and, in the case of an NIH defined Phase III clinical trial, a Data and Safety Monitoring Board must be in place.

3. HHS REGULATIONS (45CFR46) DEFINE:

Human subjects research as exempt if all of the proposed research meets the criteria for one or more of the following:

Exemption 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.

Exemption 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.

Exemption 2 for research involving survey or interview procedures or observation of public behavior, does not apply to research with children (see 45 CFR Part 46, Subpart D), except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Exemption 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) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Exemption 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. (Note that if the data or specimens were not/are not/will not be collected specifically for the proposed research and if no member of the research team can potentially ascertain the identity of the individuals to whom the coded private information or specimens pertain, then the project should be coded no for human subjects research.)

Exemption 5: Research and demonstration projects that are conducted by or subject to the approval of Department or Agency heads and that 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.

Exemption 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.

4. HHS REGULATIONS (45CFR46) DEFINE:

Clinical research as:

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.

Phase III clinical trials research 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.

5. HHS REGULATIONS (45CFR46) DEFINE:

Gender as the classification of humans as either female or male.

Minority group as 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 groups are American Indian or Alaskan Native; Asian or Pacific Islander; Black, not of Hispanic origin; and Hispanic.

Children as individuals under the age of 21 years.

6. HHS REGULATIONS (45CFR46) DEFINE:

Scientifically Acceptable/Unacceptable as a determination by reviewers as to whether or not the gender, minority and children representation proposed in the research protocol conforms with NIH policy guidelines pertinent to the scientific purpose and type of study.

- The judgment of scientific acceptability requires that reviewers evaluate the sample inclusion plans in terms of the scientific questions posed.
- The judgment of scientific acceptability for Phase III clinical trials research requires the consideration of additional criteria (see page 4).
- Consideration of the scientific acceptability of gender, minority and inclusion plans is required.
- The scientific acceptability evaluation includes the assessment of both sample retention plans and sample recruitment plans.

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

7. HHS REGULATIONS (45CFR46) DEFINE THE FOLLOWING CODES:

A yes/no code will be used to decide:
- whether there are human subjects
- whether the research proposed is a Phase III clinical trial

A three digit alphanumeric coding system will be used for other reviewer decisions:
- G, M, or C to indicate gender, minority or children respectively

— 1-5 to define the inclusion status
— A or U to indicate scientific acceptability

Gender Inclusion Code
G1 = Both genders
G2 = Only women
G3 = Only men
G4 = gender composition unknown

Minority Inclusion Code
M1 = Minority and nonminority
M2 = Only minority
M3 = Only nonminority
M4 = minority composition unknown
M5 = only foreign subjects

Children Inclusion Code
C1 = Children and adults
C2 = Only children
C3 = No children included
C4 = Representation of children unknown

Scientific Acceptability Code (Third character)
A = scientifically acceptable
U = scientifically unacceptable

Thus, for example, G1A means that
1) both genders are represented in the sample, and
2) the research is scientifically acceptable
and M3U means that
1) only nonminorities are represented in the sample, and
2) this is scientifically unacceptable, given the stated aims of the research.

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. Applications should describe and justify fully the samples that will be included in the research.

EXAMPLES

G1A - Although there are relatively few females in the sample, previous work indicates that there are no relevant gender differences in the issues of interest; the plan is scientifically acceptable.

M4A - Minority representation is unknown. The racial/ethnic composition of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens), and this does not compromise the scientific objectives of the research.

C3A - No children included. This is acceptable as knee replacement is rare in children as compared to adults.

G2A - Gender composition is scientifically acceptable, although only females are represented, because similar research already has been done or is underway using male subjects.

G1U - Gender representation is unacceptable. Although both genders are represented, there are too few members of one gender to answer the questions posed.

M3A - Minority groups or subgroups are excluded because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of the size of the study, the relevant characteristics of the disease, disorder, or condition, or the

feasibility of making a collaboration or consortium or other arrangements to include representation.

G3A - Females are not included because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens.)

C3A - The study will include subjects 21 years of age and older.

M4U - Minority representation is unknown. The application does not provide sufficient information about the racial/ethnic composition of the study population. The application does not comply with requirements and is unacceptable.

G3A - Gender representation is scientifically acceptable. Although only males are represented, a suitable justification is presented, i.e., the condition under study is only seen in males.

M2A - Although no non-minority subjects are represented, the project is scientifically acceptable since information is already available on non-minority subjects and the proposed research fills a gap in knowledge.

GENDER AND MINORITY REPRESENTATION REQUIREMENTS FOR PHASE III CLINICAL TRIALS

One or more of the following 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 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 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, 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 sufficient and appropriate representation of both genders and/or minority groups to permit 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 inclusion of these individuals would be inappropriate with respect to their health or inclusion of these individuals would be inappropriate with respect to the purposes of the research, e.g., the research question addressed is only relevant to one gender or ethnic/racial group or subgroup.

NOTE: A Code should be assigned to each individual project or subproject in an application or proposal containing multiple projects or subprojects and involving distinct populations or specimen collections. A single overall code ALSO should be assigned to the entire applications as follows:

Acceptability/Unacceptability - Each project/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.

Representation Proposed in Project - Coding should reflect the representation in all projects/subprojects, even if some are single gender or involve no minorities.

ADDITIONAL NOTES:

- Information on the new definition of Human Subjects, "NIH Implementation of Office for Human Research Protections (OHRP) Guidance on Research Involving Coded Private Information or Biological Specimens", may be found at the web site http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-05-020.html.

- Information on NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research" was published 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.

- Information on NIH Policy and Guidelines on the Inclusion of Children in Clinical Research may be found at the web site http://grants.nih.gov/grants/funding/children/children.htm.

- With the exception of exemption 4, research exempted from human subjects protection regulations as defined by 45 CFR46.101(b) is not exempted from NIH policies on inclusion of both genders, minorities and children in study populations and must be evaluated and coded. A study falling under Exemption 4 is not considered clinical research and, therefore, does not need to be coded.

- All human behavioral research is, by NIH policy, clinical research, whether it is large or small scale, observational, survey, focus group or other types of behavioral 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.

- Not all clinical trials research is Phase III clinical trials research.

- Phase III clinical research trials may include pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

- It is only necessary to assign inclusion codes to applications that are scored by the review panel. Applications designated either "NRFC" or unscored are not coded. In contrast to inclusion codes, Human Subjects Protection codes are required on unscored applications.

- A determination of "unacceptable" by the review panel bars funding until the issue has been resolved by NIH staff.

- When the research under review is essentially a service (e.g., statistical center or analysis laboratory) in support of another activity already found to be in compliance with this policy, a second review is not necessary.

- Training grants (T32, T34, T35) are exempt from coding requirements, but a term or condition of award will specify that all projects to which trainees are assigned must already be in compliance with NIH policy.

- The codes are intended to apply to grant and cooperative agreement applications and awards, contract proposals and awards, as well as intramurally-supported research which involves human subjects.

- In foreign research projects involving human subjects, the definition of minority groups may be different from those in the United States. If there are scientific reasons for examining minority groups/subgroup differences in such settings, studies should be designed accordingly.

- For foreign applications, proposals, and awards, as well as foreign components of domestic awards, the policy on inclusion of both genders applies fully.

- For multi-project applications/proposals, if only one project in a multi-project application/proposal involves clinical research, the codes assigned to that project will apply to the overall application. Further, each project of a multi-project application must be individually evaluated for appropriate gender/minority inclusion.