# NIH INSTRUCTIONS TO REVIEWERS FOR EVALUATING RESEARCH INVOLVING HUMAN SUBJECTS IN GRANT AND COOPERATIVE AGREEMENT APPLICATIONS

## April 5, 2002

Please read the instructions contained in this document, whether this is your first time as a reviewer or you have reviewed previously. **NIH has revised the reviewer responsibilities and applicant requirements with respect to the human subjects elements identified below.** Each assigned application and project within an application involving human subjects must be evaluated with respect to elements listed below.

**Note:** The first page of this document summarizes a reviewer's responsibilities, and the subsequent pages of the document provide additional details, explanations and guidance.

## REVIEWER CRITIQUE HEADINGS AND EVALUATION CODING OPTIONS

1. **PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: (page 3)**

   **Absent** (no information provided in the application – Call the Scientific Review Administrator.) or
   **Acceptable** or
   **Unacceptable** or
   **Exempt** (see definitions)

   **If the proposed research includes a clinical trial then a DATA AND SAFETY MONITORING PLAN** is required and must be evaluated (page 4).
   **Absent** (no information provided in the application – Call the Scientific Review Administrator) or
   **Acceptable** or
   **Unacceptable**

2. **INCLUSION OF WOMEN PLAN: (required for clinical research - page 5)**

   **Clinical Research Not an NIH-defined Phase III Clinical Trial:**
   **Absent** (no information provided in the application – Call the Scientific Review Administrator) or
   **Acceptable** (coded 1-4 see instructions) or
   **Unacceptable** (coded 1-4 see instructions) or

   **NIH-defined Phase III Clinical Trial:** (see special analyses requirements)
   **Absent** (no information provided in the application – Call the Scientific Review Administrator) or
   **Acceptable** (representation coded 1-4, see instructions) or
   **Unacceptable** (representation coded 1-4)

3. **INCLUSION OF MINORITIES PLAN: (page 6)**

   **Clinical Research Not an NIH-defined Phase III Clinical Trial:**
   **Absent** (no information provided in the application – Call the Scientific Review Administrator) or
   **Acceptable** (coded 1-5, see instructions) or
   **Unacceptable** (coded 1-5, see instructions) or

   **NIH-defined Phase III Clinical Trial:** (see special **analyses requirements**):
   **Absent** (no information provided in the application – Call the Scientific Review Administrator) or
   **Acceptable** (coded 1-5, see instructions) or
   **Unacceptable** (coded 1-5, see instructions)

4. **INCLUSION OF CHILDREN PLAN: (page 9)**

   **Absent** (no information provided in the application – Call the Scientific Review Administrator) or
   **Acceptable** or
   **Unacceptable**

**APPLICANT REQUIREMENTS (Page 2)**

**GLOSSARY OF TERMS (page 10)**

**ADDITIONAL GUIDANCE –** Please refer to the Decision Trees:

**Protection of Humans**

**Data and Safety Monitoring Plans in Clinical Trials**

**Women in Clinical Research**

**Women in NIH-Defined Phase III Clinical Trials**

**Minorities in Clinical Research**

**Minorities in NIH-Defined Phase III Clinical Trials**

**Children in Human Subjects Research**

## APPLICANT REQUIREMENTS:

The following requirements are described in detail in the PHS 398 application instructions.

### 1. PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK (page 3)

In the Human Subjects Research section, applicants must (1) address the involvement of human subjects and protections from research risk relating to their participation in the proposed research plan, or (2) provide sufficient information on the research subjects to allow a determination by peer reviewers and NIH staff that a designated exemption is appropriate.

Note: NIH policy no longer requires documentation of Institutional Review Board (IRB) approval at the time of the initial peer review.

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html.

If the application includes a clinical trial then the applicant must also include a **DATA AND SAFETY MONITORING PLAN (page 5).** This issue is evaluated as part of the protection of human subjects from research risk.

As of the October 2000 receipt date applicants must supply a general description of the Data and Safety Monitoring Plan for all clinical trials (see glossary definition) as part of the research application (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). The principles of data and safety monitoring require that all biomedical and behavioral clinical trials be monitored to ensure the safe and effective conduct of human subjects research, and to recommend conclusion of the trial when significant benefits or risks are identified or if it is unlikely that the trial can be concluded successfully. Risks associated with participation in research must be minimized to the extent practical and the method and degree of monitoring should be commensurate with risk.

### 2. WOMEN AND MINORITY INCLUSION (page 5)

The NIH Revitalization Act of 1993 (Public Law 103-43) requires that women and minorities must be included in all NIH-supported biomedical and behavioral clinical research projects involving human subjects, unless a clear and compelling rationale and justification establishes that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

The most recent "NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research" (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html) were published in the NIH Guide on August 2, 2000. All human clinical research (see glossary definition) is covered by this NIH policy. Each project of a multi-project application must be individually evaluated for compliance with the policy.

Since a primary aim of clinical research is to provide scientific evidence leading to a change in health policy or a standard of care, it is imperative to determine whether the intervention or therapy being studied affects women or men or members of minority groups and their subpopulations differently.

Applicants must include a description of plans to conduct valid analyses (see glossary definition) to detect significant differences (see glossary definition) in intervention effect for an NIH-defined Phase III Clinical Trial (see glossary definition).

### 3. INCLUSION OF CHILDREN (page 9)

NIH requires that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

This policy (http://grants.nih.gov/grants/guide/notice-files/not98-024.html) applies to all NIH conducted or supported research involving human subjects, including research that is otherwise "exempt" in accord with Sections 101(b) and 401(b) of 45 CFR 46 - Federal Policy for the Protection of Human Subjects. The inclusion of children as subjects in research must be in compliance with all applicable subparts of 45 CFR 46 as well as with other pertinent federal laws and regulations. Therefore, applications for research involving human subjects must include a description of plan for including children. If children will be excluded from the research, the application must present an acceptable justification for the exclusion. This policy applies to all initial applications (Type 1) proposals and intramural projects submitted for receipt dates after October 1, 1998.

## PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK

**REVIEWER RESPONSIBILITIES:** Create a "**Protection Of Human Subjects From Research Risk**" heading in your written critique (using upper and lower case letters as shown).

Federal regulations (45 CFR 46.120) require that the information provided in the application (Human Subjects section e or other sections of the application) must be evaluated with reference to the following four criteria:

**(1)** Risk To Subjects; **(2)** Adequacy Of Protection Against Risks; **(3)** Potential Benefits Of The Proposed Research To The Subjects And Others; **(4)** Importance Of The Knowledge To Be Gained.

Evaluate the information provided in the application, and indicate whether the information is **"Absent"** or Protection Of Human Subjects From Research Risk is **Acceptable** or **Unacceptable** or that the proposed research is **"Exempt".**

**Scoring Considerations:**

If the Protection Of Human Subjects From Research Risk is **Unacceptable** it should be reflected in the priority score for scientific and technical merit assigned to the application. The negative impact on the score should reflect the seriousness of the human subjects concerns that are identified. Reviewers may also recommend limitations on the scope of the work proposed, imposition of restrictions, or elimination of objectionable (risky) procedures involving human subjects.

If the research risks are sufficiently serious and protections against the risks are so inadequate as to consider the proposed research unacceptable on ethical grounds, reviewers may recommend that no further consideration be given to the application and score the application as **NRFC** (**Not Recommended for Further Consideration**).

Your evaluation is independent of any other group who will review the research. (NIH policy no longer requires documentation of Institutional Review Board (IRB) approval at the time of the initial peer review http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html ).

**Absent** If the applicant does not address any of the Human Subjects elements that are specifically required in the PHS 398 instructions, begin your comments in the Human Subjects section with the words **"Human Subjects Information Absent"** and call the Scientific Review Administrator. The application cannot be reviewed without this information.

**Acceptable** If the applicant has adequately and appropriately addressed the four Human subjects criteria and there are no concerns as defined in the glossary of terms, then, enter the words **Acceptable risks and/or adequate protections**.

Other issues related to the inclusion of human subjects, which are not concerns, may be communicated to the applicant or NIH staff in this section of your critique.

**Unacceptable** If the applicant has not adequately and appropriately addressed the four criteria in the application and/or you identify human subjects concerns, then, begin your comments with the words "**Unacceptable Risks and/or Inadequate Protections.**" Document and specify the actual or potential issues that constitute the unacceptable risks or inadequate protections against risks.

Human subjects concerns **(see Glossary)** should be described in your reviews, whether or not you recommend that the application be scored.

**Exempt:** If the application indicates that the Human Subjects research is exempt from coverage by the regulations, then determine whether the information provided conforms to one of the categories of exempt research and whether the information justifies the exemption claimed. If it is exempt, state "**Exempt**" and specify which exemption or exemptions apply (see Glossary for list of Exemption categories).

If an exemption is claimed and you determine that the information provided does not justify the exemption, then, indicate **Unacceptable** and indicate why you have determined that the information provided does not justify the exemption.

Where is the human subjects information located in an application?

The PHS form 398 grant application requires that applicants provide information about human subjects involvement and protections from research risk in the RESEARCH PLAN and the Appendices (if applicable).

See decision tree for **Protection of Humans**

http://grants.nih.gov/grants/peer/tree_protection_hs.pdf

## DATA AND SAFETY MONITORING PLAN

**REVIEWER RESPONSIBILITIES:** The evaluation of the Data and Safety Monitoring Plan is part of the evaluation of the Protection of Human Subjects Section described previously.

If the application contains clinical trials research **(see Glossary),** evaluate the acceptability of the proposed Data and Safety Monitoring Plan provided in the application's research plan. Data and Safety Monitoring Plan are required of all applications that involve a clinical trial

On the basis of the information provided in the application, document the extent to which you judge the plan is **Absent, Acceptable**, or **Unacceptable.**

**Scoring Considerations:** If the Data And Safety Monitoring Plan is **unacceptable**, then, the unacceptability must be reflected in the priority score that you assign to the application.

The Data and Safety Monitoring Plan must be appropriate with respect to the potential risks to human participants, and complexity of study design.

**Absent**: If the applicant does not provide any information about a Data and Safety Monitoring Plan, indicate "**Absent**" in the Data and Safety Monitoring section of the critique and call the Scientific Review Administrator.

**Acceptable:** If the general description of the Data and Safety Monitoring Plan is adequate, (e.g. defines the general structure of the monitoring entity and mechanisms for reporting Adverse Events to the NIH, the IRB, etc.), your comments should include a statement to the effect that the plan is **Acceptable.**

**Unacceptable:** If the information provided about Data and Safety Monitoring is inadequate, your comments should include a statement that the plan is **Unacceptable** and subsequently specify what is unacceptable about the plan and/or what information is missing.

### Components of a Monitoring Plan

NIH requires the establishment of Data and Safety Monitoring Boards (DSMBs) for multi-site clinical trials involving interventions that entail potential risk to the participants.

(http://grants.nih.gov/grants/guide/notice-files/not98-084.html ).

Generally, NIH-defined Phase III Clinical Trials require DSMBs. Smaller and earlier phase clinical trials may not require this level of oversight, and alternate monitoring plans may be more appropriate.

Applicants must submit a general description of the Data and Safety Monitoring Plan for all clinical trials. Monitoring plans are also required as part of the PHS 398 section "e. Human Subjects".

The general description of the Data and Safety Monitoring Plan should describe the entity that will be responsible for monitoring, and the policies and procedures for adverse event reporting. All monitoring plans must include a description of how Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the NIH, the Office of Biotechnology Activities (OBA) (if required), and the Food and Drug Administration (FDA) in accordance with IND or IDE regulations.

Monitoring entities may include, but are not limited to:

Principal Investigator
Independent individual/Safety Officer
Designated medical monitor
Internal Committee or Board with explicit guidelines
DSMB (required for multi-site NIH-defined Phase III Clinical Trials)
IRB (required)

A detailed Data and Safety Monitoring plan will be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to award. The detailed monitoring plan must be approved by the funding IC prior to the accrual of human participants.

(http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html )

In addition applications involving human gene transfer research must comply with NIH Guidelines for Research Involving Recombinant DNA Molecules be and must submit protocols to the NIH Office of Biotechnology Activities (OBA), for review by the Recombinant DNA Advisory Committee (RAC) prior to final approval by the Institutional Biosafety Committee. OBA recommends that RAC review also occur prior to IRB review and submission to FDA for regulatory permission to proceed with the study.

See decision tree for **Data and Safety Monitoring Plans in Clinical Trials**

http://grants.nih.gov/grants/peer/tree_dsm_plans.pdf

See also:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html.

## WOMEN AND MINORITY INCLUSION

**REVIEWER RESPONSIBILITIES:** Create two headings: "**Inclusion of Women**" and "**Inclusion of Minorities**" in your written critique (using upper and lower case letters as shown). Evaluate the assigned applications and each individual project within multicomponent applications to assess the plan for the inclusion of Women and then the plan for inclusion of Minorities or the acceptability of the justifications for exclusion of women or minorities provided in the application's research plan.

On the basis of the information provided in the application, designate that the information is **"Absent," "Acceptable"** or **"Unacceptable."**

**Absent**: If no information is provided about the Inclusion of Women, the Inclusion of Minorities, or both, indicate "**Absent**" in the appropriate heading section. In the absence of information or proposed plans for inclusion, reviewers should call the Scientific Review Administrator. The absence of plans are grounds for returning the application to the applicant without peer review.

**Scoring Considerations:** If the plans for Inclusion of Women and/or Inclusion of Minorities are unacceptable, then, the unacceptability must be reflected in the priority score that you assign to the application.

Provide a brief narrative text to answer the following **Questions** and evaluate the **Criteria for Acceptable/ Unacceptable plans** separately for women and for minorities

**Questions about Inclusion-** Does the applicant propose a plan for the inclusion of minorities and both genders for appropriate representation? How does the applicant address the inclusion of women and members of minority groups and their subpopulations in the development of a research design that is appropriate to the scientific objectives of the study? Does the research plan describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and does it provide a rationale for selection of such subjects.

**Questions about Exclusion -** Does the applicant propose justification when representation is limited or absent? Does the applicant propose exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the health of the subjects and/or with respect to the purpose of the research? Evaluate the justifications for exclusion in terms of the criteria for **Acceptable/Unacceptable** (see pages 6-8).

**Questions about Analysis Plans -** Does the applicant propose an NIH-defined Phase III Clinical Trial (see Glossary for definition)? If yes, does the research plan include either (a) an adequate description of plans to conduct analyses to detect significant differences of clinical or public health importance in intervention effect by sex/gender and/or racial/ethnic subgroups when the intervention effect(s) when prior research indicates such differences in intervention effect or (b) an adequate description of plans to conduct valid analyses (see Glossary) of the intervention effect between subgroups when there is no clear-cut scientific evidence to rule out such differences in intervention effect.

**GENDER INCLUSION IN CLINICAL RESEARCH (NOT A NIH-DEFINED PHASE III CLINICAL TRIAL): Criteria for Determining Acceptable/ Unacceptable Plans**

**Acceptable:** One or more of the following may apply:

1. Both genders are included in the study in scientifically appropriate numbers.

2. One gender is excluded from the study because:

- inclusion of these individuals would be inappropriate with respect to their health;
- the research question addressed is relevant to only one gender;
- evidence from prior research strongly demonstrates no difference between genders;
- sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.

3. One gender is excluded or severely limited 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).

4. Gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete gender documentation are used), and this does not compromise the scientific objectives of the research.

**Unacceptable:** One or more of the following may apply:

1. Representation fails to conform to NIH policy guidelines summarized in this document and the

NIH Guidelines pertinent to the scientific purpose and type of study;
2. The application provides insufficient information;
3. The application does not adequately justify limited representation of one gender.

**GENDER REQUIREMENTS FOR NIH-DEFINED PHASE III CLINICAL TRIALS: ADDITIONAL CRITERIA**

**Acceptable:** One or more of the following may apply based on review of prior evidence:

1. Available evidence strongly indicates significant sex/gender differences of clinical or public health importance in intervention effect, and the study design is appropriate to answer two separate primary questions -- one for males and one for females -- with adequate sample size for each gender. **The research plan must include a description of plans to conduct analyses to detect significant differences in intervention effect.**

2. Available evidence strongly indicates there is no significant difference of clinical or public health importance between males and females in relation to the study variables. (Representation of both genders is not required; however, inclusion of both genders is encouraged.)

3. There is no clear-cut scientific evidence to rule out significant differences of clinical or public health importance between males and females in relation to study variables, and study design includes sufficient and appropriate representation of both genders to permit valid analyses of a differential intervention effect. **The research plan must include a description of plans to conduct the valid analyses (see glossary definition) of the intervention effect.**

4. One gender is excluded from the study because:

   - Inclusion of these individuals would be inappropriate with respect to their health;
   - 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).

**Unacceptable:** One or more of the following may apply:

1. Representation fails to conform to NIH policy guidelines summarized in this document and the NIH Guidelines pertinent to the scientific purpose and type of study;
2. The application provides insufficient information;
3. The application does not adequately justify limited representation of one gender;
4. The application fails to provide an appropriate analysis plan.

**Evaluation And Coding:** For single project applications, assign an overall code as described below. For multi-project applications, a code should be assigned to each individual project or subproject in an application containing multiple projects or involving distinct populations or specimen collections. If only one project in a multiproject application involves clinical research, the codes assigned to that project will apply to the overall document; if there is more than one project covered by the policy, ALSO assign an overall code to the entire application as follows:

**Representation Proposed in Project.** Coding should reflect the total representation proposed for all projects or subprojects, even if some are single-gender.

**Gender Coding**

**Format.** Each code is a three digit alphanumeric string:

1st character **G** (indicates gender code)
2nd character **1, 2, 3, or 4** (representation proposed in project – see below)
3rd character **A or U** (acceptable or unacceptable – see guidance below)

**Representation Proposed in Project**

(2nd character)

**1** = both genders
**2** = only women
**3** = only men
**4** = gender unknown

**GENDER CODES**

| Gender Representation | Scientifically… Acceptable | Unacceptable |
|---|---|---|
| both included | G1A | G1U |
| women only | G2A | G2U |
| men only | G3A | G3U |
| Unknown | G4A | G4U |

## MINORITY INCLUSION

A minority group is defined as "...a readily identifiable subset of the US population which is distinguished by either racial, ethnic and/or cultural heritage." In accordance with OMB Directive No.15, the basic racial and ethnic categories are: American Indian or Alaska Native; Asian; Black or African American, Hispanic or Latino; Native Hawaiian or Other Pacific Islander and White. It is not anticipated that every study will include all minority groups and subgroups. The inclusion of minority groups should be determined by the scientific questions under examination and their relevance to racial or ethnic groups. Applications should describe the subgroups that will be included in the research.

In foreign research projects involving human subjects, the definition of minority groups may be different than in the US; if there are scientific reasons for examining minority group or subgroup differences in such settings, studies should be designed to accommodate such differences.

Reviewers should provide a brief narrative text to answer the **Questions about Inclusion, Exclusion, and Analysis Plans** (see page 5) and use the following **Criteria for Determining Acceptable /Unacceptable Minority plans**.

### MINORITY INCLUSION IN CLINICAL RESEARCH; (NOT A NIH DEFINED NIH-DEFINED PHASE III CLINICAL TRIAL): Criteria for Determining Acceptable/Unacceptable Plans

**Acceptable:** One or more of the following may apply:

1. Minority individuals are included in scientifically appropriate numbers and recruitment/retention has been realistically addressed.

2. Some or all minority groups or subgroups are excluded from the study because:

- Inclusion of these individuals would be inappropriate with respect to their health;
- The research question addressed is relevant to only one racial or ethnic group;
- Evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
- A single minority group study is proposed to fill a research gap;
- Sufficient data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.

4. Some minority groups or subgroups are excluded or poorly represented 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;
- The feasibility of making a collaboration or consortium or other arrangements to include representation.

Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, 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).

5. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) and this does not compromise the scientific objectives of the research.

**Unacceptable:** One or more of the following may apply:

1. Minority representation fails to conform to NIH policy guidelines summarized in this document and in the NIH Guidelines pertinent to the scientific purpose and type of study;
2. Insufficient information is provided;
3. The application does not adequately justify limited representation of minority groups or subgroups.
4. The application does not adequately address recruitment/retention of some or all minority groups or subgroups.

### MINORITY REQUIREMENTS FOR NIH-DEFINED PHASE III CLINICAL TRIALS : ADDITIONAL CRITERIA

**Acceptable:** One or more may apply:

1. Available evidence strongly indicates significant racial or ethnic differences in intervention effects, and the study design is appropriate to answer separate primary questions for each of the relevant

racial or ethnic subgroups, with adequate sample size for each. **The research plan must include a description of plans to conduct analyses to detect** significant differences **in intervention effect.**

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

3. There is no clear-cut scientific evidence to rule out significant differences of clinical or public health importance among racial or ethnic groups or subgroups in relation to the effects of study variables, and the study design includes sufficient and appropriate representation of minority groups to permit valid analyses (see note below) of a differential intervention effect. **The Research Plan in the application or proposal must include a description of plans to conduct the** valid analyses **(see Glossary definition) of the intervention effect in subgroups.**

4. 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 not relevant to all subgroups).

**Unacceptable:** One or more of the following may apply:

1. Minority representation fails to conform to NIH policy guidelines summarized in this document and in the NIH Guidelines pertinent to the scientific purpose and type of study;
2. Insufficient information is provided;
3. The application does not adequately justify limited representation of minority groups or subgroups;
4. The application fails to provide an appropriate analysis plan.

**Minority Codes**

**Format.** Each code is a three digit alphanumeric string:

1st character **M** ( indicated minority code)
2nd character **1, 2, 3, 4, or 5** (representation proposed in project – see below)
3rd character **A or U** (scientifically acceptable or unacceptable – see below)

**Representation Proposed in Project** (2nd character)

**1** = minority and nonminority
**2** = only minority
**3** = only nonminority
**4** = minority representation unknown
**5** = only foreign subjects in study population (no U.S. subjects). If the study population includes both foreign and U.S. study subjects then use codes 1 thru 4 to describe the U.S. component (do not use code 5).

**MINORITY CODES**

| Minority Representation | Scientifically… Acceptable | Unacceptable |
|---|---|---|
| minorities and non-minorities included | M1A | M1U |
| minorities only | M2A | M2U |
| non-minorities only | M3A | M3U |
| Unknown | M4A | M4U |
| Foreign | M5A | M5U |

**Additional Information on the Inclusion of Women and Minorities**

**See decision trees for:**

**Women in Clinical Research**

**http://grants.nih.gov/grants/peer/tree_women_clinical_research.pdf**

**Women in NIH-Defined Phase III Clinical Trials**

**http://grants.nih.gov/grants/peer/tree_women_clinical_trials.pdf**

**Minorities in Clinical Research**

**http://grants.nih.gov/grants/peer/tree_minorities_clinical_research.pdf**

**Minorities in NIH-Defined Phase III Clinical Trials**

**http://grants.nih.gov/grants/peer/tree_minorities_clinical_trials.pdf**

**Answers to Frequently asked questions:**

http://grants1.nih.gov/grants/funding/women_min/women_min.htm

## INCLUSION OF CHILDREN IN HUMAN SUBJECTS RESEARCH

**REVIEWER RESPONSIBILITIES:** Create an "**Inclusion of Children Plan**" heading in your written critique (using upper and lower case letters as shown)

Evaluate the acceptability of the proposed plan for the inclusion of children or the acceptability of the justifications for exclusion provided in the application's research plan.

On the basis of the information provided in the application document the extent to which you judge the plan is "**Absent",** "**Acceptable**," or "**Unacceptable.**"

**Scoring Considerations:** If the Inclusion Plan is unacceptable, then, the unacceptability must be reflected in the priority score that you assign to the application.

Reviewers are asked to evaluate the appropriateness of the population studied in terms of the aims of the research and ethical standards, the expertise of the investigative team in dealing with children at the ages included, and the appropriateness of the facilities. Evaluate and code (see instructions below) each project and subproject separately for inclusion of children.

The PI must describe in the application, under a section "Participation of Children," the plans to include children and a rationale for selecting or excluding a specific age range of child, or an explanation of the reason(s) for excluding children. Additional information is provided in the Human Subjects section.

**Absent**: If no information is provided about the Inclusion of Children, indicate "**Absent**" in the heading section.

In the absence of information on the proposed plans for inclusion, reviewers should call the Scientific Review Administrator.

An **Acceptable** plan is one in which the representation of children is scientifically appropriate and recruitment/retention has been realistically addressed, or an appropriate justification for exclusion has been provided.

For those plans, which are "**Acceptable**" provide one of the following codes:

**C1A** Both children and adults are included (e.g. inclusion is scientifically acceptable).

**C2A** Only children are represented in the study (e.g. inclusion is scientifically acceptable).

**C3A** No children included (e.g. acceptable justification for exclusion is provided).

**C4A** Representation of children is not known (e.g. The information on age of individuals providing specimens or in existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens), and this does not compromise the scientific objectives of the research).

An **Unacceptable** plan is one, which fails to conform to NIH policy guidelines in relation to the scientific purpose of the study; or fails to provide sufficient information; or does not adequately justify that children are not included; or does not realistically address recruitment/retention

For those plans that are **Unacceptable** provide one of the following codes**:**

**C1U** Both children and adults are included; (e.g. no rationale is provided for selecting or excluding a specific age range of children).

**C2U** Only children are represented in the study (e.g. but age range is too restricted to be scientifically acceptable, such as including only children of ages 18-21).

**C3U** No children included (e.g. acceptable justification for exclusion is not provided).

**C4U** Representation of children is not known (e.g. the application does not provide sufficient information about the age distribution of the study population. the application does not comply with requirements and is unacceptable).

In all cases explain the basis for your judgment.

**ADDITIONAL GUIDANCE –** Please refer to the Decision Tree:

**Children in Human Subjects Research**

and NIH Policy:

http://grants.nih.gov/grants/guide/notice-files/not98-024.html

**Answers to Frequently asked questions:**

http://grants2.nih.gov/grants/funding/children/pol_children_qa.htm

## GLOSSARY OF TERMS

### AMERICAN INDIAN OR ALASKA NATIVE:

A person having origins in any of the original peoples of North, Central, or South America and maintains tribal affiliation or community

### ASIAN:

A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam

### BLACK OR AFRICAN AMERICAN:

A person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

### CHILD:

For purposes of this policy, a child is an individual under the age of 21 years. This policy and definition do not affect the human subject protection regulations for research on children 45 CFR 46) and their provisions for assent which remain unchanged.

It should be noted that the definition of child described above will pertain notwithstanding the FDA definition of a child as an individual from infancy to 16 years of age, and varying definitions employed by some states. Generally, state laws define what constitutes a “child,” and such definitions dictate whether or not a person can legally consent to participate in a research study. However, state laws vary, and many do not address when a child can consent to participate in research. Federal Regulations (45 CFR 46, subpart D, Sec.401-409) address DHHS protections for children who participate in research, and rely on state definitions of “child” for consent purposes. Consequently, the children included in this policy (persons under the age of 21) may differ in the age at which their own consent is required and sufficient to participate in research under state law. For example, some states consider a person age 18 to be an adult and, therefore, one who can provide consent without parental permission (see also http://grants.nih.gov/grants/guide/notice-files/not98-024.html).

### CLINICAL RESEARCH:

The NIH definition of clinical research is based on the 1997 Report of the NIH Director's Panel on Clinical Research that defines clinical research in the following three parts:

(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.

Note: Autopsy material is not covered by the policy. 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 the NIH policy on inclusion of women and minorities in clinical research.

### CLINICAL TRIAL:

For purposes of reviewing applications submitted to the NIH, a clinical trial is operationally defined as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective. Clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

Phase I clinical trials are done to test a new biomedical or behavioral intervention in a small group of people (e.g. < 80) for the first time to evaluate safety (e.g. determine a safe dosage range, and identify side effects).

Phase II clinical trials are done to study the biomedical or behavioral intervention in a larger

group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III studies are done to study 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.

Phase IV studies are done after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

**NIH-DEFINED PHASE III CLINICAL TRIAL:**

For the purpose of the Guidelines on the Inclusion of Women and Minorities, an NIH-defined Phase III clinical trial is a broadly based prospective NIH-defined Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes 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.

**EXEMPTION CATEGORIES:**

The six categories of research that qualify for exemption from coverage by the regulations include activities in which the only involvement of human subjects will be in one or more of the following six categories:

The six categories of research that qualify for exemption from coverage by the regulations include one or more of the following six categories:

**Exemption 1:** Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (a) research on regular and special education instructional strategies, or (b) 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: (a) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (b) 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 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 (2)(b) of this section, if: (a) the human subjects are elected or appointed public officials or candidates for public office; or (b) 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.

**Exemption 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: (a) public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; (c) possible changes in or alternatives to those programs or procedures; or (d) 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, (a) if wholesome foods without additives are consumed or (b) if a food is consumed that contains a food ingredient at or below the level and 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.

**GENDER:**

Refers to the classification of research subjects into either or both of two categories: women and men. In some cases, representation is unknown, because gender composition cannot be accurately determined (e.g., pooled blood samples or stored specimens without gender designation).

**HISPANIC OR LATINO:**

A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino".

**HUMAN SUBJECTS:**

The CODE OF FEDERAL REGULATIONS, TITLE 45, PART 46, PROTECTION OF HUMAN SUBJECTS (45-CFR-46) defines human subjects as follows:

Human subject means 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 (see also the decision charts provided by the Office of Human Research Protection)

Legal requirements to protect human subjects apply to a much broader range of research than many investigators realize, and researchers using human tissue specimens are often unsure about how regulations apply to their research. Legal obligations to protect human subjects apply, for example, to research that uses–

Bodily materials, such as cells, blood or urine, tissues, organs, hair or nail clippings, even if you did not collect these materials

Residual diagnostic specimens, including specimens obtained for routine patient care that would have been discarded if not used for research

Private information, such as medical information, that can be readily identified with individuals, even if the information was not specifically collected for the study in question.

Research on cell lines or DNA samples that can be associated with individuals falls into this category.

**HUMAN SUBJECTS CONCERN:**

A human subject concern is defined as any actual or potential unacceptable risk, or inadequate protection against risk, to human subjects as described in any portion of the application.

**HUMAN SUBJECTS RISK AND PROTECTION CRITERIA:**

The PHS 398 application instructions require that applicants address the following four criteria in the Research Plan – Section e of their applications:

1. **RISKS TO THE SUBJECTS**

   Human Subjects Involvement and Characteristics: The applicant must describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section. Describe the characteristics of the subject population, including their anticipated number, age range, and health status. Identify the criteria for inclusion or exclusion of any subpopulation. Explain the rationale for the involvement of special classes of subjects, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations.

   Sources of Materials: The applicant must identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.

   Potential Risks: The applicant must describe the potential risks to subjects (physical, psychological, social, legal, or other) and assess their likelihood and seriousness to the subjects. Where

appropriate, describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures to participants in the proposed research.

2. **ADEQUACY OF PROTECTION AGAINST RISKS**

   Recruitment and Informed Consent: The applicant must describe plans for the recruitment of subjects and the process for obtaining informed consent. Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. The informed consent document need not be submitted to the PHS unless requested.

   Protection Against Risk: The applicant must describe the planned procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. In studies that involve clinical trials (biomedical and behavioral intervention studies), describe the plan for data and safety monitoring of the research to ensure the safety of subjects.

3. **POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS**

   The applicant must discuss the potential benefits of the research to the subjects and others. Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

4. **IMPORTANCE OF THE KNOWLEDGE TO BE GAINED**

   The applicant must discuss the importance of the knowledge gained or to be gained as a result of the proposed research. Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

**MAJORITY GROUP:**

White, not of Hispanic Origin: A person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

NIH recognizes the diversity of the U.S. population and that changing demographics are reflected in the changing racial and ethnic composition of the population. The terms “minority groups” and “minority subpopulations” are meant to be inclusive, rather than exclusive, of differing racial and ethnic categories.

**MINORITY GROUPS:**

A minority group is a readily identifiable subset of the U.S. population, which is distinguished by racial, ethnic, and/or cultural heritage.

It is not anticipated that every study will include all minority groups and subgroups. The inclusion of minority groups should be determined by the scientific questions under examination and their relevance to racial or ethnic groups.

Applicants should describe the subgroups to be included in the research. In foreign research projects involving human subjects, the definition of minority groups may be different than in the US.

**NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER:**

A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

**NIH-DEFINED PHASE III CLINICAL TRIAL:**

For the purpose of the Guidelines on the Inclusion of Women and Minorities, an NIH-defined Phase III Clinical Trial is a broadly based prospective NIH-defined Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes 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.

**OUTREACH STRATEGIES:**

These are outreach efforts by investigators and their staff(s) to appropriately recruit and retain populations of interest into research studies. Such efforts should represent a thoughtful and culturally sensitive plan of outreach and generally include involvement of other individuals and organizations relevant to the populations and communities of interest, e.g., family, religious organizations, community leaders and informal gatekeepers, and public and private institutions and organizations. The objective is to establish appropriate lines of communication and

cooperation to build mutual trust and cooperation such that both the study and the participants benefit from such collaboration.

**RACIAL AND ETHNIC CATEGORIES:**

The Office of Management and Budget (OMB) Directive No. 15 defines the minimum standard of basic racial and ethnic categories, which are used by NIH. These definitions are used because they allow comparisons to many national databases, especially national health databases. Therefore, the racial and ethnic categories described in this document should be used as basic guidance, cognizant of the distinction based on cultural heritage.

**RESEARCH PORTFOLIO:**

Each Institute and Center at the NIH has its own research portfolio, i.e., its "holdings" in research grants, cooperative agreements, contracts and intramural studies. The Institute or Center evaluates the research awards in its portfolio to identify those areas where there are knowledge gaps or which need special attention to advance the science involved. NIH may consider funding projects to achieve a research portfolio reflecting diverse study populations. With the implementation of this new policy, there will be a need to ensure that sufficient resources are provided within a program to allow for data to be developed for a smooth transition from basic research to NIH-defined Phase III clinical trials that meet the policy requirements

**SCIENTIFICALLY ACCEPTABLE OR UNACCEPTABLE:**

A determination, based on whether or not the gender or minority representation proposed in the research protocol conforms with NIH policy guidelines pertinent to the scientific purpose and type of study. A determination of unacceptable is reflected in the priority score assigned to the application. In addition, the definition of what constitutes SCIENTIFICALLY ACCEPTABLE OR UNACCEPTABLE changes if the research being conducted is a clinical trial, as opposed to merely being clinical research.

**SIGNIFICANT DIFFERENCE:**

For purposes of the NIH policies, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

**SUBPOPULATIONS:**

Each minority group contains subpopulations, which are delimited by geographic origins, national origins and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific racial and ethnic origin. Attention to subpopulations also applies to individuals of mixed racial and/or ethnic parentage. Researchers should be cognizant of the possibility that these racial/ethnic combinations may have biomedical and/or cultural implications related to the scientific question under study.

**VALID ANALYSIS:**

The term "valid analysis" means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are:

Allocation of study participants of both sexes/genders (males and females) and from different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization,

Unbiased evaluation of the outcome(s) of study participants, and

Use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the gender and racial/ethnic groups.

**WHITE:**

A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.