Guidelines for the Review of Inclusion on the Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research

Requirements and Responsibilities. As required by federal law (<u>42 USC 289a-2</u>) and NIH policy, applications that propose to involve human subjects must address:

- 1. the inclusion of women, minorities, and children in the proposed research
- 2. for an NIH-defined Phase III clinical trial, plans for the valid analysis of group differences on the basis of sex/gender, race, and/or ethnicity as appropriate for the scientific goals of the study.

Background Information

- Federal law requires that women and minorities be included in all clinical research studies, as appropriate for the scientific goals of the work proposed.
- Additionally, women and members of minority groups and their subpopulations need to 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 (currently 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
- Therefore, when the research involves human subjects (excluding research that qualifies for IRB exemption 4), 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.
- It is not expected that every study will include both sexes/genders, all racial and ethnic
 groups and subgroups, and children. Inclusion on the basis of sex/gender, race, and
 ethnicity, as well as the inclusion of children should be guided by the scientific aims of the
 study. Applicants should describe and justify fully the distribution of individuals that will
 be included in the research.
- Policy links:
 - o http://grants.nih.gov/grants/funding/women_min/women_min.htm
 - o http://grants.nih.gov/grants/funding/children/children.htm

Applicant Responsibilities. Applicants must designate if human subjects are involved, and if so, whether the proposed activities meet the criteria for an IRB exemption. Applications that involve human subjects with the exception of those meeting the requirements for IRB Exemption 4 must address 1) inclusion of individuals on the basis of their sex/gender, race, and ethnicity and 2) inclusion of children (defined as persons under the age of 21). Applicants must also provide a planned enrollment table(s) with the proposed sample distributed on the basis of sex/gender, race, and ethnicity. When conducting an NIH-defined Phase III clinical trial, applicants must also provide a description of the plans for valid analysis of group differences on the basis of sex/gender, race, and ethnicity.

Scientific Review Group (SRG) Responsibilities. 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 sexes/genders, minorities, children, and special populations as appropriate for the scientific goals of the research. Therefore, the SRGs must factor their evaluation of the proposed plans for the inclusion of individuals on the basis of their sex/gender, race, ethnicity, and age into their overall evaluation of an application's scientific and technical merit.

Reviewer Responsibilities

- 1. Evaluate the applicant's plans for inclusion on the basis of sex/gender, race, and ethnicity
- i. Does the applicant provide a description of their plans for including individuals on the basis of their sex/gender, race, and ethnicity considering the points in Section I of the Inclusion worksheet?
 - If NO Rate the application as UNACCEPTABLE
 - If YES is there an adequate justification for the proposed sample considering the required four points (see the worksheet for additional details)?
 - If YES Rate the application as ACCEPTABLE
 - If NO (the justification is inadequate) Rate the application as UNACCEPTABLE for the inclusion of women and minorities and EXPLAIN WHY
- ii. <u>In addition to (i), for NIH-defined Phase III clinical trials</u>, does the applicant address plans for a valid analysis of group differences on the basis of sex/gender, race, and/or ethnicity considering the points in Section II of the Inclusion worksheet?
 - If NO Rate the application as UNACCEPTABLE [even if acceptable for (i)]
 - If YES Does the description of expected sex/gender, racial, and ethnic differences in intervention effect include selection and discussion of one of the required analysis plans? (see Section II of the Inclusion worksheet for details)
 - If the discussion is inadequate—Rate the application as UNACCEPTABLE for the inclusion of women and minorities and EXPLAIN WHY
- 2. Evaluate the applicant's plans for the inclusion of children (currently defined as individuals under the age of 21)

Does the applicant provide a description of their plans for including children (currently defined as individuals under the age of 21)?

- If NO, Rate the application as UNACCEPTABLE
- If YES- is there an adequate justification for the inclusion or exclusion of children considering the points in Section III of the Inclusion worksheet?
 - If Yes Rate the application as ACCEPTABLE
 - If NO (the justification is inadequate)— Rate the application as UNACCEPTABLE for the inclusion of children and EXPLAIN WHY

Prepare written comments, including specific comments describing all inclusion concerns, for applications rated as Unacceptable.

Worksheet to Assist in Reviewing the Required Points of Section on the Inclusion of Women, Minorities, and Children in Clinical Research and Clinical Trials

I. Evaluating inclusion on the basis of sex/gender, race, and ethnicity:

Point 4.2.1 Planned Distribution of Subjects

Does the applicant describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study considering the following?
Is there a description of the planned distribution using the Planned Enrollment Report format? If there is no report, does the applicant provide sufficient information to understand the planned distribution of subjects by sex/gender, race, and ethnicity?
 For studies planning to use an existing dataset(s): Is there a description of the planned distribution using the Planned Enrollment Report format?, or
 Is there an explanation if sex/gender, racial, and/or ethnic composition of existing dataset is unknown?, if so Is there a description of the sex/gender, racial, and ethnic composition for the population base of the existing dataset(s), if known
Point 4.2.2 Description and Rationale of Subject Selection
Does the applicant adequately describe the subject selection criteria and rationale for selection considering the population at risk for the disease/condition under study and the scientific objectives and proposed study design?
Point 4.2.3 Rationale for Exclusion
If the proposed sample is not representative of those at risk for the disease/condition under study, does the applicant provide an adequate justification of this considering the following: the literature on the existence of (or lack of) differences on the basis of sex/gender, race and ethnicity the proposed sample size the need to fill a particular research gap the feasibility of establishing collaborative arrangements (cost is not an acceptable justification) the purpose of the research constrains applicant selection (e.g., unique stored speciments)
rare surgical specimens etc.)

Point 4.2.4 Description of Outreach Programs for Recruitment

Does the applicant adequately describe recruitment and outreach plans or other methods for enrolling the individuals proposed as part of the sample?

II. Additional requirements when evaluating NIH-defined Phase III Clinical Trials:

Does the applicant adequately consider whether clinically important sex/gender, racial, and/or ethnic differences are expected?

	Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender, racial, and/or ethnic subgroups when prior studies strongly support these significant differences among subgroups, or
	Plans to include and analyze sex/gender, racial, and/or ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender, racial, and ethnic groups is not required as subject selection criteria, but inclusion is encouraged), or
	Plans to conduct valid analyses of intervention effect in sex/gender, racial and/or ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect among subgroups.
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i. Lva	luation inclusion of children (individuals under the age of 21):
Does	illuation inclusion of children (individuals under the age of 21): the applicant adequately describe plans for the inclusion/exclusion of children (individuals under ge of 21) including:
Does	the applicant adequately describe plans for the inclusion/exclusion of children (individuals under

Does the applicant describe one of the following?

III.

References and Resources

I. 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

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II. NIH 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.

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.

III. Policy links:

- a. http://grants.nih.gov/grants/funding/women_min/women_min.htm
- b. http://grants.nih.gov/grants/funding/children/children.htm