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

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Revision Notes – March 2019

- Added guidance for considering plans for inclusion of individuals across the lifespan, including:
    - Consideration of age-appropriate inclusion and justification for age-based exclusions (including children and older adults)
    - Addition of definition of older adult
- Clarified language on requirements for valid analysis by sex/gender and race/ethnicity for NIH-defined Phase IIII clinical trials

Requirements and Responsibilities

As required by federal law (42 USC 289a-2) and NIH policy (NOT-OD-18-014 and NOT-OD-18-116), applications that propose to involve human subjects must address:

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

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, for NIH-defined Phase III clinical trials, applicants must also consider whether the study can be expected to identify potential differences by sex/gender, race, and/or ethnicity. Unless there is clear evidence that such differences are unlikely to be seen, they must include plans for valid analysis, describing how potential group differences will be evaluated. As described in a January 8, 2018 Open Mike blog, valid analyses refers to stratified analyses that explore how well the intervention works among sex/gender and racial/ethnic groups. Further

information about valid analysis is available at https://grants.nih.gov/grants/funding/women_min/guidelines.htm.

- NIH policy also states that individuals of all ages (including children and older adults) must 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 individuals of all ages 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 all age groups. Inclusion on the basis of sex/gender, race, ethnicity, and age should be guided by the scientific aims of the study. Applicants should describe and fully justify the distribution of individuals that will be included in the research.**
- Cost is not an acceptable justification for exclusion according to NIH policy.
- Policy resources:
    - http://grants.nih.gov/grants/funding/women_min/women_min.htm
    - https://grants.nih.gov/grants/funding/lifespan/lifespan.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 individuals of all ages, including children (defined as persons under the age of 18), and older adults (individuals 65 years of age or older). Applicants must also provide a planned enrollment table(s) with the proposed sample distributed on the basis of sex/gender, race, and ethnicity (or a cumulative inclusion enrollment report if working with an existing dataset), and provide the expected age range of participants. When conducting an NIH-defined Phase III clinical trial, applicants must also provide a description of the plans for valid analysis and evaluation of potential group differences on the basis of sex/gender, race, and ethnicity.

Scientific Review Group (SRG) Responsibilities

The NIH Peer Review regulations (42 CFR 52h.8) 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. The NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects further specifies that SRGs will assess and evaluate each application/proposal with regard to the age-appropriate inclusion or

exclusion of individuals in the research project and identify plans as acceptable or unacceptable.

Reviewer Responsibilities

I. 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 (provided below)?

If NO, rate the inclusion plans 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 inclusion plans as ACCEPTABLE.

If NO (the justification is inadequate), rate the plans as UNACCEPTABLE for the inclusion of women and minorities and EXPLAIN WHY.

ii. In addition to (i), for NIH-defined Phase III clinical trials, 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 plans for valid analysis 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 plans for valid analysis as UNACCEPTABLE and EXPLAIN WHY.

II. Evaluate the applicant's plans for the inclusion of individuals across the lifespan (including children and older adults)

Does the applicant provide a description of their plans for including individuals across the lifespan?

If NO, rate the inclusion plans as UNACCEPTABLE.

If YES, is the justification for the inclusion or exclusion of individuals based on age scientifically and ethically appropriate, considering the points in Section III of the Inclusion worksheet?

If YES, rate the inclusion plans as ACCEPTABLE.

If NO (the justification is inadequate), rate the plans as UNACCEPTABLE for age and EXPLAIN WHY.

III. Prepare written comments, including specific comments describing all inclusion concerns when plans are rated as Unacceptable.

Worksheet to Assist in Reviewing the Required Points of the Section on the Inclusion of Women, Minorities, and Individuals Across the Lifespan 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 or Cumulative Enrollment Report format? Or,
- ___ Is there an explanation if the 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 specifically excludes a group(s) at risk for the disease/condition under study, does the applicant provide an adequate justification?
Considerations may include the following:

- ___ The literature on the existence of (or lack of) differences on the basis of

sex/gender, race, and ethnicity

___ The need to fill a particular research gap

___ The use of existing data or samples when more representative data/samples are not available (e.g., unique stored specimens, 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:

- Considerations for valid analysis are required for NIH-defined Phase III Clinical Trials. Valid analyses may be described as stratified analyses that explore how well the intervention works among sex/gender and racial/ethnic groups. Depending on current knowledge of the disease/condition under study, the analyses may need to be adequately powered to detect differences in individual subgroups.
- Applicants should address whether they plan to test or not test for differences in effect among sex/gender, racial, and/or ethnic groups and why that is or is not appropriate. This may include supporting evidence and/or data derived from animal studies, clinical observations, metabolic studies, genetic studies, and pharmacology studies as well as observational, natural history, epidemiology and/or other relevant studies. Additional factors may include planned primary and secondary outcomes and whether there are previous studies that support or negate the likelihood of differences between groups.
- The plans must include selection and discussion of one of the following analysis plans.

Does the applicant address their plans in the context of one of the following?

___ **When prior studies strongly support significant differences**: Plans to conduct adequately powered valid analyses to detect significant differences in intervention effect among sex/gender, racial, and/or ethnic subgroups for each primary outcome.

___ **When prior studies strongly support no significant differences**: Plans to include and analyze intervention effect in sex/gender, racial, and/or ethnic subgroups. (Representation of sex/gender, racial, and ethnic groups is not required as subject selection criteria, but inclusion is encouraged).

___ **When prior studies neither support nor negate significant differences**: Plans to conduct valid analyses of intervention effect in sex/gender, racial and/or ethnic subgroups (without requiring high statistical power for each subgroup) for each primary outcome.

- Applicants should address the following issues for ensuring valid analyses:
    - inclusive eligibility criteria – in general, the cost of recruiting certain groups

and/or geographic location alone are not acceptable reasons for exclusion of particular groups;
- allocation of study participants of both sexes/genders (males and females) and from different racial and/or 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 by sex/gender, race, and/or ethnicity, particularly if prior evidence strongly suggests that differences exist. Stratification or other methods may be utilized.

III. Evaluation of inclusion across the lifespan:

Does the applicant adequately describe plans for the inclusion of individuals across the lifespan (particularly children, defined as individuals under the age of 18, and older adults, defined as individuals 65 and older) including:

___ Description and rationale of the age range(s) of individuals expected to be recruited
___ Description and justification of the exclusion of individuals based on age (refer here for a description of justifications for age-based exclusion).
___ Expertise of the investigative team for working with individuals of the included age groups
___ Facilities available to accommodate children and older adults
___ Inclusion of an appropriate distribution of children and older adults to contribute to a meaningful analysis relative to the purpose of the study

References and Resources

I. Inclusion Coding

The reviewer coding of inclusion on the critique template has been simplified to focus on whether the distribution of individuals is scientifically justified for the proposed study(ies). Reviewers should assess inclusion according to these guidelines and select the following options for the given categories:

- Sex/gender:
  - Distribution justified scientifically = Acceptable
  - Distribution not justified scientifically = Unacceptable
- Race/ethnicity:
  - Distribution justified scientifically = Acceptable
  - Distribution not justified scientifically = Unacceptable
- For Phase III Clinical Trials, plans for valid design and analysis:
  - Plans justified scientifically = Acceptable
  - Plans not justified scientifically = Unacceptable
- Age:
  - Distribution justified scientifically = Acceptable
  - Distribution not justified scientifically = Unacceptable

II. NIH Definitions

Child

For the purposes of the NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects, a child is defined as an individual under the age of 18 years. The intent of the NIH policy is to provide the opportunity for individuals, including children and older adults, to participate in research studies when there is a sound scientific rationale for including them and participation is appropriate under existing Federal guidelines. Thus, children must be included in NIH-conducted or supported human subjects research unless there are scientific or ethical reasons not to include them.

For the purpose of providing consent for research participation, the definition of a child stated within the DHHS Regulations (45 CFR part 46, Subpart D, Sec. 402) should be applied. Please see the NIH Human Subjects website or 45 CFR 46, Subpart D for more information.

Clinical research

Research with human subjects that is:

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.
Studies falling under 45 CFR 46.104(d) (4) (Exemption 4) are not considered clinical research by this definition.

NIH-Defined Phase III Clinical Trial

An NIH-defined Phase III clinical trial is a broadly based prospective 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 controlled 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.

Older Adult

For the purposes of the NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects, an older adult is defined as an individual 65 years of age or older. The intent of the NIH policy is to provide the opportunity for individuals, including children and older adults, to participate in research studies when there is a sound scientific rationale for including them, and their participation is appropriate. Thus, older adults must be included in NIH-conducted or supported human subjects research unless there are scientific or ethical reasons not to include them**.**

Valid Analysis

This term 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 and/or 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 by sex/gender, race, and/or ethnicity.

III. Policy resources

- http://grants.nih.gov/grants/funding/women_min/women_min.htm
- https://grants.nih.gov/grants/funding/lifespan/lifespan.htm