Guidance for the Review of Participant Inclusion in Clinical Research and Clinical Trials

NOTE: this guidance covers Inclusion review criteria BOTH for funding opportunities using the Simplified Review Framework and for funding opportunities *not* using the Simplified Review Framework.

Requirements and Responsibilities

Federal law (42 USC 289a-2), and NIH policy (NOT-OD-18-014 and NOT-OD-18-116) require that the following be addressed in applications that propose to involve human subjects (excluding research that qualifies for human subjects Exemption 4):

- Women, members of racial and ethnic minority groups, and individuals across the lifespan (including children and older adults) must 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 differences in effect among women and members of racial and ethnic minority groups. 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.

Applicant Responsibilities

Applications proposing clinical research must complete **Section 2 – Study Population Characteristics** of the 'Study Record: PHS Human Subjects and Clinical Trials Information' form. **There is no expectation that every study include women, all racial and ethnic groups and subgroups, and all age groups.** Inclusion should be guided by the scientific aims of the study. However, applicants are expected to fully justify the distribution of individuals in the research.

Scientific Review Group (SRG) Responsibilities

SRGs are required to factor their evaluation of the proposed plans for the inclusion of women, members of racial and ethnic minority groups, and individuals across the lifespan into the overall assessment of an application's scientific and technical merit. The NIH Peer Review regulations (42 CFR 52h.8) specify that reviewers consider plans for inclusion of women, members of racial and ethnic minority groups, and children as appropriate for the scientific goals of the research. 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 with regard to the age-appropriate inclusion or exclusion of individuals in the research project. SRGs should refer to the Notice of Funding Opportunity (NOFO) to which the application was submitted for the review criteria specific to the application(s) under review.

For funding opportunities using the Simplified Review Framework

As part of the Simplified Review Framework, effective for most Research Project Grant (RPG) grant and cooperative agreement applications with receipt dates of January 25, 2025 and beyond, the review criteria for evaluating human subjects inclusion plans in applications are included in Factor 2 (Rigor and Feasibility) of the Scored Review Criteria:

- For applications involving human subjects, including clinical trials, assess the adequacy of inclusion plans as appropriate for the scientific goals of the research. Considerations of appropriateness may include disease/condition/behavior incidence, prevalence, or population burden, population representation, and/or current state of the science.
- For applications involving human subjects, including clinical trials, evaluate the adequacy and feasibility of the plan to recruit and retain a study population that appropriately models the target population. Additionally evaluate the likelihood of successfully achieving the proposed enrollment based on age, race, ethnicity, and sex.

Under Factor 2 the SRG will also evaluate the plans for valid design and analysis (for NIH-defined phase 3 trials).

For funding opportunities *not* using the Simplified Review Framework

For RPG applications, the review criteria for evaluating human subjects inclusion plans are located under the Approach criterion of the Scored Review Criteria:

- If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex, race, and ethnicity, as well as the inclusion or exclusion of individuals of all ages (including children and older adults), justified in terms of the scientific goals and research strategy proposed?

AND for both RPGs and non-RPGs, under the Additional Review Criteria section:

- When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex, race, and ethnicity (as required by statute), as well as the inclusion (or exclusion) of individuals of all ages (including children and older adults) to determine if it is justified in terms of the scientific goals and research strategy proposed.

Under the Additional Review Criteria section, the SRG will also evaluate the plans for valid design and analysis (for NIH-defined phase III trials).

Reviewer Responsibilities

Evaluate the application's plans for the inclusion of women and members of racial and ethnic minority groups, and individuals across the lifespan and prepare written comments, including comments describing specific concerns, unless Not Applicable.

I. Inclusion of Women and Racial and Ethnic Minorities

i. Does the applicant provide sufficient information to understand the planned distribution of women and racial and/or ethnic minorities?

If NO – rate the inclusion plans as UNACCEPTABLE.

If YES – is there an adequate justification for the proposed sample (considering the scientific objectives; the proposed study design; and factors including, but not limited to, the population characteristics of the disease or condition under study, the scientific literature on differences, research gaps, the availability of data or samples)?

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

If YES, does the application include an adequate description of outreach methods for enrollment?

If NO (i.e., the description is inadequate) - rate the plans as UNACCEPTABLE for the inclusion of women and/or racial and ethnic minorities and EXPLAIN WHY.

If YES – rate the inclusion plans as ACCEPTABLE.

ii. In addition to (i), for NIH-defined Phase III clinical trials, does the applicant adequately address plans for a valid analysis of group differences among women and racial and ethnic minorities?

If NO - rate the plans for valid analysis as UNACCEPTABLE [even if acceptable for (i)] and EXPLAIN WHY.

If YES - rate the plans for valid analysis as ACCEPTABLE.

II. Inclusion of Individuals Across the Lifespan

Does the applicant provide a description of their plans for including individuals across the lifespan (including children and older adults).

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?

If YES – rate the inclusion plans as ACCEPTABLE.

If NO (i.e., the justification is inadequate) - rate the plans as UNACCEPTABLE for the inclusion of age and EXPLAIN WHY.