

NIH Human Subjects Guidance

April 2016

Protection of Human Subjects

Risks to Human Subjects

a. *Human Subjects Involvement, Characteristics, and Design*

- Describe and justify the proposed involvement of human subjects in the work outlined in the Research Strategy section.
- Describe the characteristics of the subject population, including their anticipated number, age range, and health status if relevant.
- Describe and justify the sampling plan, as well as the recruitment and retention strategies and the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- If relevant to the proposed research, describe procedures for assignment to a study group. As related to human subjects protection, describe and justify the selection of an intervention's dose, frequency and administration.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.

b. *Sources of Materials*

- Describe the research material obtained from living individuals in the form of specimens, records, or data.
- Describe any data that will be collected from human subjects for the project(s) described in the application.
- Indicate who will have access to individually identifiable private information about human subjects.
- Provide information about how the specimens, records, and/or data are collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.

c. *Potential Risks*

- Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

Adequacy of Protection Against Risks

a. *Recruitment and Informed Consent*

- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.
- 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. If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. *Protections Against Risk*

- Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
- Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections. Refer to DHHS regulations, and OHRP guidance:
 - Additional Protections for Pregnant Women, Human Fetuses and Neonates: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb>
 - Additional Protections for Prisoners: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc>
 - OHRP Subpart C Guidance: <http://www.hhs.gov/ohrp/policy/index.html#prisoners>
 - Additional Protections for Children: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd>
 - OHRP Subpart D Guidance: <http://www.hhs.gov/ohrp/policy/index.html#children>
- Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a general description of the plan for data and safety monitoring of the clinical trials and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.

Potential Benefits of the Proposed Research to Human Subjects and Others

- Discuss the potential benefits of the research to research participants and others.
- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

Importance of the Knowledge to be Gained

- 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.

Data and Safety Monitoring Plan (separate document)

If the proposed research includes a clinical trial (See definition of “clinical trial” under Part III Section 3), create a document entitled “Data and Safety Monitoring Plan.” For all clinical trials, NIH requires a data and safety monitoring plan (DSMP) that is commensurate with the risks of the trial and its size and complexity. In this attachment, you must provide a description of the DSMP that you are proposing to establish for each clinical trial proposed, including:

- The overall framework for safety monitoring and what information will be monitored.
- The frequency of monitoring, including any plans for interim analysis and stopping rules (if applicable).
- The process by which Adverse Events (AEs), including Serious Adverse Events (SAEs) such as deaths, hospitalizations, and life threatening events and Unanticipated Problems (UPs), will be managed and reported as required to the Institutional Review Board (IRB), the person or group responsible for monitoring, the funding IC, the NIH Office of Biotechnology Activities (OBA; <http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines>), and the Food and Drug Administration (FDA; <http://www.fda.gov/>).
- The individual(s) or group that will be responsible for trial monitoring and advising the appointing entity. Because the monitoring plan will depend on potential risks, complexity, and the nature of the trial, a number of options for monitoring are possible. These include, but are not limited to, monitoring by a:
 - PD/PI: While the PD/PI must ensure that the trial is conducted according to the protocol, in some cases (e.g., low risk trials, not blinded), it may be acceptable for the PD/PI to also be responsible for carrying out the DSMP.
 - Independent safety monitor/Designated medical monitor: a physician or other expert who is independent of the study.
 - Independent Monitoring Committee or Safety Monitoring Committee: A small group of independent investigators and biostatisticians.
 - Data and Safety Monitoring Board (DSMB): a formal independent board of experts including investigators and biostatisticians. As noted in Part II Section 5.3, NIH requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials.

Although Phase I and Phase II clinical trials may also need DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate. If a DSMB is used, please describe the general composition of the Board without naming specific individuals.

Inclusion of Women and Minorities (separate document)

Although no specific page limitation applies to this section of the application, be succinct. The NIH Policy on the Inclusion of Women and Minorities in Clinical Research is described and referenced in SF424 Section 5.6.

Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the scientifically justified inclusion of women and minorities in NIH-defined clinical research.

In this section of the Research Plan, address, at a minimum, the following four points:

- The planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study using the format in the Planned Enrollment Report. (Instructions for completing this table are provided below in 4.3.) If using existing specimens or other types of existing data and information about sex/gender, race, and ethnicity is available, this information should be provided as with any other type of study. If using existing specimens or other types of existing data without access to information on the distribution by sex/gender, race, and/or ethnicity, so state and explain the impact on the goals of the research as part of the rationale that inclusion cannot be described (item 3 below). Alternatively, describe the sex/gender, racial, and ethnic composition of the population base from whom the specimens and/or data will be obtained. If you have information about sex/gender, race, and/or ethnicity, include the Planned Enrollment Report(s).
- A description of the subject selection criteria and rationale for selection of sex/gender, racial, and ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
- A compelling rationale for proposed sample specifically addressing exclusion of any sex/gender, racial, or ethnic group that comprises the population under study (see examples below).
- A description of proposed outreach programs for recruiting sex/gender, racial, and ethnic group members as subjects.
- Below are examples of acceptable justifications for the exclusion of. One sex/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 sex/gender;
 - evidence from prior research strongly demonstrates no difference between sexes/genders; or
 - sufficient data already exist with regard to the outcome of comparable studies in the excluded sex/gender, and duplication is not needed in this study.
- One sex/gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by sex/gender (e.g., uniquely valuable stored specimens or existing datasets are single sex/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).
- Sex/gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete sex/gender documentation are used), and this does not compromise the scientific objectives of the research.
- Some or all racial and/or ethnic 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 specific racial or ethnic groups;
 - evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
 - a specific racial or ethnic group(s) study is proposed to fill a research gap; or
 - 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.

- Some racial or ethnic groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:
 - the size of the study;
 - the relevant characteristics of the disease, disorder or condition; or
 - the feasibility of making a collaboration or consortium or other arrangements to include representation. In general, cost is not an acceptable justification for exclusion.
 - Some racial or ethnic 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 racial and/or ethnic 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).
 - 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 and/or ethnic documentation are used) and this does not compromise the scientific objectives of the research.
-

Instructions for Completing the Inclusion Enrollment Report(s) for Race and Ethnicity Data for Subjects in Clinical Research (separate document, form page must be used)

The PHS Inclusion Enrollment Report form is used for all applications involving [NIH-defined clinical research](#). This form is used to report both planned and cumulative (or actual) enrollment, and describes the sex/gender, race, and ethnicity of the study participants. In addition to providing inclusion plans (per Part II Section 4.2), applicants are instructed to provide the distribution of participants by sex/gender, racial, and ethnic categories using the PHS Inclusion Enrollment Report(s). See below for additional guidance on how to complete the PHS 398 Inclusion Enrollment Report form.

When completing each Enrollment Report:

- Provide a unique study title that will facilitate identification of each Planned Enrollment Report.
 - Check if the study is a delayed onset or not.
 - If the study is not delayed onset, then the following will need to be checked: enrollment type, using an existing dataset or resource, enrollment location, and clinical trial.
 - Provide the information as numbers of subjects, not percentages.
 - The Total Field on the Inclusion Enrollment Report (bottom right) means the number of subjects that are expected to be enrolled in the study, consistent with the definition in ClinicalTrials.gov. The total fields will be automatically calculated when submitting electronically.
 - Provide the numeric distribution of individuals on the basis of their sex/gender, ethnicity, and race. Note that Hispanic/Latino is an ethnic category, not a racial category. Subjects are permitted to select more than one race when self-identifying. If the sample is likely to include individuals who identify with more than one race, they should be accounted for in the "More than one race" category on the Planned Enrollment Report(s). If including individuals identifying as more than one race is not expected, enter zeroes in that category.
 - List any proposed racial or ethnic subpopulations in the comment field.
-

Inclusion of Children (separate document)

The NIH Policy on Inclusion of Children is referenced and described in Section 5.7. Instructions for this item of the Research Plan (for F applicants, the PHS Fellowship Supplemental Form – Research Training Plan) are as follows:

- Create a section entitled "Inclusion of Children" and place it immediately following the section on the Inclusion of Women and Minorities.
- For the purpose of implementing these guidelines, a *child* is defined as an individual under the age of 18 years (for additional information see <http://grants.nih.gov/grants/funding/children/children.htm>).
- Provide either a description of the plans to include children, including the particular age ranges to be included, or, if children (or a subset) will be excluded from the proposed research, present an acceptable justification for the exclusion (see below).

- If children are included, the description of the plan should include a rationale for selecting a specific age range of children. The plan also must include a description of the expertise of the investigative team for working with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.
- Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the age-appropriate inclusion or exclusion of children in the proposed research project.
- When children are involved in research, the Additional Protections for Children Involved as Subjects in Research (45 CFR part 46 Subpart D) apply and must be addressed under the Protections Against Risk subheading (4.1.2.b).

Justifications for Exclusion of Children

For the purposes of this policy, all individuals under 18 are considered children; however, exclusion of any specific age group, should be justified in this section. It is expected that children will be included in all NIH-defined clinical research unless one or more of the following exclusionary circumstances apply:

1. The research topic to be studied is not relevant to children.
2. Laws or regulations bar the inclusion of children in the research.
3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
4. A separate, age-specific study in children is warranted and preferable. Examples include:
 - a. The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or
 - b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
 - c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.
5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.
6. Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).
7. Other special cases can be justified by the investigator and found acceptable to the review group and the Institute/Center Director.