Instructions for Preparing the Section on the Protection of Human Subjects

Your document should contain ALL of these sections:

1. **Protection of Human Subjects**
2. **Data Safety Monitoring Plan**
3. **Inclusion of Women and Minorities**
4. **Inclusion of Children**

INSTRUCTIONS

1. 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, including retention strategies and the criteria for inclusion or exclusion of any subpopulation.
- If relevant, 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, provide details about all planned interventions such as 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 will be collected, managed, and protected, as well as whether any individually identifiable private information will be collected specifically for the proposed research project.

c. ***Potential Risks***

- Describe all the potential risks to subjects posed by participation in the research (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. When alternative treatments or procedures are possible, the rationale for the proposed approach should be clear.

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. When appropriate, describe how potential adult subjects' capacity to consent will be determined and plans for obtaining consent from a legally authorized representative for adult subjects not able to 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 all potential risks identified, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
- Describe how proposed research involving vulnerable populations meets the additional regulatory requirements described in the HHS regulations, Subparts B, C or D. Refer to HHS 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 (see definition of "clinical trial" here: https://grants.nih.gov/policy/clinical-trials/definition.htm)) must include a separate attachment describing the plan for data and safety monitoring of the clinical trials and adverse event reporting to the IRB, the DSMB (if one has been established for the trial), the NIH and others, as appropriate, to ensure the safety of subjects (see next section below).

- Where appropriate, describe plans for handling incidental findings that may be uncovered as a result of the research, such as incidental findings from research imaging, results of screening tests, or misattributed paternity.

NOTE: Test articles (investigational new drugs, devices, or biologics) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the FDA, and/or the status of requests for an Investigational New Drug (IND) or Investigational Device Exemption (IDE) covering the proposed use of the test article in the Research Plan.

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.
- Please note that financial compensation of subjects should not be presented as a benefit of participation in research.

Importance of the Knowledge to be Gained

- Discuss the importance of the knowledge 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.

2. DATA AND SAFETY MONITORING PLAN

If the proposed research includes a clinical trial (See definition here: https://grants.nih.gov/policy/clinical-trials/definition.htm), create a document entitled "Data and Safety Monitoring Plan." If your proposed project does NOT include a clinical trial, please include this section, but write "Not Applicable."

For all clinical trials, a data and safety monitoring plan (DSMP) that is commensurate with the risks of the trial and its size and complexity is required. 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 DRDC, and the CDC.
- 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.

3. INCLUSION OF WOMEN AND MINORITIES

Create a section heading entitled "Inclusion of Women and Minorities" and place it immediately following the "Data and Safety Monitoring Plan" section. Although no specific page limits apply to this section of the application, be succinct. This section does not take the place of considering relevant biological variables (such as sex) in the research strategy. The NIH Policy on the Inclusion of Women and Minorities in Clinical Research is described and referenced here: https://grants.nih.gov/grants/funding/women_min/guidelines.htm
Additional information and guidance can be found at:
http://grants.nih.gov/grants/funding/women_min/women_min.htm.

Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the scientifically justified inclusion (or exclusion) based on sex/gender, race, and ethnicity in NIH-defined clinical research. This section is required for all studies meeting the NIH definition for clinical research, not just clinical trials. It is important to provide a detailed plan of who will be included (and/or excluded) and how the distributions of individuals on the basis of sex/gender, race, and ethnicity are justified in the context of the scientific goals of the application. Simply stating that certain individuals will not be excluded or that individuals of either sex/gender or any race/ethnicity are eligible is not sufficient. Details about why the individuals are the appropriate individuals to accomplish the scientific goals of the study should be provided.

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

1. Describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study and complete the format in the PHS Inclusion Enrollment Report. Instructions for completing this form are found here: https://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general/g.500-phs-inclusion-enrollment-report.htm
2. Describe 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.

3. Provide a compelling rationale for proposed sample specifically addressing exclusion of any sex/gender, racial, or ethnic group that comprises the population under study.
4. Describe proposed outreach programs for recruiting sex/gender, racial, and ethnic group members as subjects. This is particularly important if difficulty recruiting certain groups is anticipated.

Additional Considerations for justifying inclusion:

There may be reasons why the proposed sample is limited by sex/gender, race, and/or ethnicity. This should be addressed as part of the four points detailed above.

- Inclusion of certain individuals would be inappropriate with respect to their health;
- The research question addressed is only relevant to certain groups or there is a gap in the research area;
- Evidence from prior research strongly demonstrates no difference on the basis of sex/gender, race, and/or ethnicity;
- Sufficient data already exist with regard to the outcome of comparable studies in the excluded group(s)
and duplication is not needed in this study;
- A certain group or groups is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects (e.g., uniquely valuable stored specimens or existing datasets are limited by sex/gender, race, and/or ethnicity; 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); and/or
- 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.
- In general, the cost of recruiting certain groups and/or geographic location alone are not acceptable reasons for exclusion of particular groups. This should be considered when developing outreach plans. Establishing collaborations or other arrangements to recruit may be necessary.

Additional guidance for research utilizing existing datasets or resources:

- Inclusion must be addressed when conducting NIH-defined clinical research, even if the samples or data have already been collected as part of a different study. Details about the sex/gender, race, and ethnicity composition of the existing dataset/resource should be provided and justified as appropriate to the scientific goals of the proposed study.
- For the purposes of inclusion policy, an existing dataset may be constructed of different types of data including but not limited to survey data, demographic information, health information, genomic information, etc. Also included would be data to be derived from existing samples of cells, tissues, or other types of materials that may have been previously collected for a different purpose or research question but will now be used to answer a new research question. In general, these will be studies meeting the NIH definition for clinical research with a prospective plan to analyze existing data and/or derive data from an existing resource and where no ongoing or future contact with participants is anticipated.

Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed. If the proposed research includes an NIH-Defined Phase III Clinical Trial, the section on Inclusion of Women and Minorities also MUST address plans for how sex/gender, race, and ethnicity will be taken into consideration in the design and valid analysis of the trial. Valid analysis means an unbiased assessment which 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.

Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the scientifically justified inclusion plans, including these additional requirements for NIH-defined Phase III clinical trials.

- 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.
- Applicants also 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, 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:
  - Plans to conduct 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 one or more 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 the 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.

4. INCLUSION OF CHILDREN

Create a section entitled “Inclusion of Children” and place it immediately following the section on the Inclusion of Women and Minorities. Although no specific page limits apply to this section of the application, be succinct. The NIH Policy on Inclusion of Children is referenced

and described here: https://humansubjects.nih.gov/children. For the purpose of implementing these guidelines, a *child* is now defined as an individual under the age of 18 years.

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. This section is required for all studies meeting the NIH definition for clinical research, not just clinical trials. It is important to provide a detailed plan of who will be included (and/or excluded) based on age. Details about why the individuals in the given age/age range are the appropriate individuals to accomplish the scientific goals of the study should be provided. Instructions for this item of the Research Plan including addressing the following points:

- Describe the age(s) or age range of all individuals to be included in the proposed study.
- Specifically discuss whether children under the age of 18 (as a whole or a subset of individuals under 18) will be included or excluded.
- 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.
- 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 in Section 1 above.

Justifications for Exclusion of Children

For the purposes of this policy, individuals under 18 are defined as a child; however, exclusion of any specific age or age range 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:

- The research topic to be studied is not relevant to children.
- Laws or regulations bar the inclusion of children in the research.
- 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.
- A separate, age-specific study in children is warranted and preferable. Examples include:
  - 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
  - The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
  - 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.

- 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.
- 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).
- Other special cases can be justified by the investigator and assessed by the review group and the Institute/Center Director to determine if acceptable.