**Instructions for Human Subjects Narrative Components**

National Institutes of Health

*This document provides summarized instructions for completing the Human Subjects Section of the PHS 398 Research Plan Form for standard NIH grant proposals. This section is completed when the research involves human subjects; complete instructions can be found by reviewing the relevant FOA and the Department of Health and Human Services (DHHS) Supplemental Grant Application Instructions.*

The proposal components included in this document are:

* Protection of Human Subjects
* Data and Safety Monitoring Plan (only used if the proposed research includes a clinical trial)
* Inclusion of Women and Minorities
* Inclusion of Children

**Protection of Human Subjects**

**1. Risks to Human Subjects**

***1.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.

***1.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 projects(s) described in the application.
* Indicate who will have access to individually identifiable private information.
* 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.

***1.c. Potential Risks***

* Describe all potential risks to subjects posed by participation in the research (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness.
* Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants. When alternative treatments or procedures are possible, the rationale for the proposed approach should be clear.

**2. Adequacy of Protection Against Risks**

***2.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 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.

***2.b. Protections Against Risk***

* Describe planned procedures for protecting against or minimizing all potential risks, including those to the privacy of individuals or confidentiality of data, and assess their likely effectiveness.
* Research involving vulnerable populations, as described in the HHS regulations, Subparts B-D, must include additional protections. See the DHHS Supplemental Grant Application Instructions document for a list of these protections and associated hyperlinks.
* Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects.
* 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 those 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.*

**3. Potential Benefits of the Proposed Research to Human Subjects and Others**

* Discuss the potential benefits of the research to participants and others.
* Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to participants and others.
* *Note: Financial compensation of subjects should not be presented as a benefit of participation in research.*

**4. Importance of 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 may reasonably be expected to result.

**DATA AND SAFETY MONITORING PLAN**

If the proposed research includes a clinical trial, provide a data and safety monitoring plan (DSMP) that is commensurate with the risks, size, and complexity of the trial. Complete instructions from the DHHS Supplemental Grant Application Instructions should be reviewed prior to completing this document.

Provide a description of the DSMP 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 NIH Institute or Center, the NIH Office of Biotechnology Activities, and the Food and Drug Administration (FDA).
* 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. 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.

**ClinicalTrials.gov**

For competing new and renewal applications that include applicable clinical trials that require registration and results reporting under the FDA Amendments Act (FDAAA), provide the NCT number(s) (i.e., the ClinicalTrials.gov registry number[s]).

**Inclusion of Women and Minorities**

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. This section does not take the place of considering relevant biological variables (such as sex) in the Research Strategy. If the research will utilize existing human subjects datasets or resources or if the project is a NIH-defined Phase III Clinical Trial, see the DHHS Supplemental Grant Application Instructions for additional instructions.

Address, at a minimum, the following four points:

**Planned Distribution**

* 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.

**Subject Selection Criteria and Rationale**

* 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.

**Sample Rationale**

* Provide a compelling rationale for the proposed sample specifically addressing exclusion of any sex/gender, racial, or ethnic group that comprises the population under study.

**Recruitment**

* 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.

*Note: 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. Examples of relevant situations include when:*

* *The Inclusion of certain individuals who 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).*
* *Representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or datasets 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.*

**Inclusion of Children**

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. A child is now defined as an individual under the age of 18 years.

Address 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.
* Include a rationale for selecting a specific age range of children.
* 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.

*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 acceptability.*