Human Subjects and Clinical Trials Information

Applicants to RM18-019, SPARC Partnership Funding Opportunity: Custom Arrangements for Device Trials with Flexible Data and Intellectual Property Rights, may refer to this guidance document when developing the "Human Subjects Research Plan" section of their proposal(s).

Section 1 – Basic Information

NIH requires this information for all studies involving human subjects.

1.1. Study Title - Each study title should be distinct

1.2. Federal Regulations Exemption - Is this study Exempt from Federal Regulations? "Yes" or "No"

- 1.2.a. If the research is exempt from federal regulations regarding human subjects, as defined by 46.101(b) of 45 CFR 46, provide the category of exemption and justify why the research meets the criteria for the exemption(s) that you have claimed. This justification should explain how the proposed research meets the criteria for the exemption claimed. Do not merely repeat the criteria or definitions themselves.
- 1.2.b. Exemption Number:

1.3. Clinical Trial Questionnaire - If the answers to all four questions below are yes, this study meets the definition of a Clinical Trial.

- 1.3.a. Does the study involve human participants? "Yes" or "No"
- 1.3.b. Are the participants prospectively assigned into an intervention? "Yes" or "No"
- 1.3.c. Is the study designed to evaluate the effect of the intervention on the participants? "Yes" or "No"
- 1.3.d. Is the effect that will be evaluated a health-related, biomedical, or behavioral outcome? "Yes" or "No"

1.4. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable.

Section 2 – Study Population Characteristics

NIH requires this information for all human subjects studies, unless the study is exempt because it involves the use of existing data or specimens that are publicly available or de-identified (Exemption 4 under 46.101(b) of 45 CFR 46).

2.1. Conditions or Focus of Study - Identify the name(s) and disease(s) or condition(s) you are studying, or the focus of the study. If available, use appropriate descriptors from NLM's Medical Subject Headings (MeSH).

2.2. Eligibility Criteria - List the study's inclusion and exclusion criteria.

- 2.2.a. Age Limits - Provide the minimum and maximum age a potential participant can be to be eligible for the study, or indicate if there is no lower or upper limit, or no lower or upper limit is known.

2.3. Inclusion of Women, Minorities, and Children – Please see Section 5.

2.4. Recruitment and Retention Plan – You should include a description of how you will recruit and retain participants in your study. You should address both planned recruitment activities as well as proposed engagement strategies for retention.

2.5. Recruitment Status (Not yet recruiting, Recruiting, Enrolling by invitation, Active-Not Recruiting), Completed, Suspended, Terminated-Halted Prematurely, Withdrawn-No Participants Enrolled)

2.6. Enrollment Timeline – You should include the information requested below.

- 2.6.a. Enrollment of First Subject:
  - 2.6.a.1. Date
  - 2.6.a.2. Anticipated or Actual
- 2.6.b. Enrollment of Last Subject:
  - 2.6.b.1. Date
  - 2.6.b.2. Anticipated or Actual

2.7. Inclusion Enrollment Report – You should include the information requested below. Please note that multiple U.S. sites can be reported in one report, and multiple foreign countries can be submitted in one enrollment report but U.S. and non-U.S. enrollment sites should be reported separately. See the NIH FAQs on Monitoring Inclusion When Working with Existing Datasets and/or Resources for more information.

- 2.7.a. Does the proposed study use an existing dataset, resource or samples collected as part of a different study?
  - 2.7.a.1. If yes, provide details about the sex/gender, race, and ethnicity of the existing dataset/resource/samples and justify the details as appropriate to the scientific goals of the proposed study.
- 2.7.b. Are participants based at a U.S. (domestic) or non-U.S. (foreign) site?
- 2.7.c. Provide cumulative/actual or planned enrollment by Racial category, ethnic category, and by sex/gender in the format of the PHS Inclusion Enrollment Report form.

Section 3 – Protection and Monitoring Plans

NIH requires this information for all studies involving human subjects, unless otherwise specified.

3.1. Protection of Human Subjects – You should include the information requested below. If the proposed studies will include children, See the HHS page on Research with Children FAQs and the NIH page on Requirements for Child Assent and Parent/Guardian Permission.

- 3.1.a. Human Subjects Involvement, Characteristics, and Design – Describe the overall study design, subject population(s) to be included in the study, anticipated numbers of subjects for each study group, and the role of any collaborating sites where human subjects research will be performed, and the role of collaborating investigators in performing the proposed research.
- 3.1.b. Study Procedures, Materials, and Potential Risks – Describe all planned research procedures (interventions and interactions) involving study subjects, how research material (e.g., biospecimens, data, and/or records) will be obtained and source of these materials if previously collected, whether previously collected material can be linked to living individuals, whether any private identifiable information will be collected, potential risks and associated impact to subjects (e.g., physical, psychological, social, cultural, financial, and legal risks), and rationale for alternative treatments and procedures where appropriate (e.g., risks and potential benefits).

3.1.c. Adequacy of protections against risk – Describe the process for obtaining informed consent (e.g., how to determine a potential adult subjects' capacity to consent and plans for obtaining consent from a legally authorized representative), circumstances under which consent will be sought and obtained, nature of the information to be provided to prospective subjects, method of documenting consent, justification for waiving some or all of the informed consent elements if applicable, and the process for meeting HHS regulatory requirements for parental permission and child assent (45 CFR 46.408) if applicable.

3.1.d. Protections Against Risk – Describe the planned strategies for protecting against or minimizing all potential risks identified, strategies to manage and protect the privacy of participants and confidentiality of research data, plans for ensuring necessary medical or professional intervention in the event of adverse effects on participants, and plans for handling incidental findings (e.g., those from research imaging, screening tests, or paternity tests).

3.1.e. Vulnerable Subjects - If relevant to your study, explain the rationale for the involvement of special vulnerable populations (e.g., fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations), provide a clear description of the risk level and additional protections necessary to meet the HHS regulatory requirements (e.g., Subparts B, C and D), and plans to obtain OHRP certification.

3.1.e.1. HHS' Subpart B - Additional Protections for Pregnant Women, Fetuses, and Neonates

3.1.e.2. HHS' Subpart C - Additional Protections Pertaining to Prisoners as Subjects

3.1.e.3. OHRP Subpart C Guidance on Involvement of Prisoners in Research

3.1.e.4. HHS' Subpart D - Additional Protections for Children

3.1.e.5. OHRP Guidance on Subpart D Special Protections for Children as Research Subjects and the HHS 407 Review Process

3.1.f. Potential Benefits of the Proposed Research to Research Participants and Others – Discuss the potential benefits of the research to research participants and others, and why the risks to subjects are reasonable in relation to these anticipated benefits. *(Note: financial compensation should not be presented as a benefit of participation in research.)*

3.1.g. Importance of Knowledge to be Gained - Discuss the importance of the knowledge to be gained as a result of the proposed research, and why the risks to subjects are reasonable in relation to the importance of this knowledge.

3.2. Multi-site Study - Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site? "Yes", "No" or "N/A"

3.2.a. If yes, describe the single Institutional Review Board (sIRB) plan – You should include the information requested below.

3.2.a.1. Describe how you will comply with the NIH Policy on the Use of sIRB for Multi-Site Research?

3.2.a.2. Provide the name of the IRB that will serve as the sIRB of record.

3.2.a.3. Indicate that all identified participating sites have agreed to rely on the proposed sIRB and that any sites added after award will rely on the sIRB.

3.2.a.4. Briefly describe how communication between sites and the sIRB will be handled.

3.2.a.5. Indicate that all participating sites will, prior to initiating the study, sign an authorization/reliance agreement that will clarify the roles and responsibilities of the sIRB and participating sites.

3.2.a.6. Indicate which institution or entity will maintain records of the authorization/reliance agreements and of the communication plan.

3.2.a.7. If your human subjects study meets the agency definition of "Delayed Onset," include information regarding how the study will comply with the sIRB policy prior to initiating any multi-site study in the delayed onset study justification.

3.2.a.8. For sites requesting an exception based on compelling justification, indicate which site(s) is requesting an exception to the use of the sIRB and provide compelling justification based on ethical or human subjects protection issues or other well-justified reasons. *(Note: Do not account for this exception in your proposed budget. The proposed budget should reflect any necessary sIRB costs without an exception.)*

3.3. Data and Safety Monitoring Plan – NIH requires a data and safety monitoring plan (DSMP) that is commensurate with the risks of the trial, its size, and its complexity. A data and safety monitoring plan is not required by the NIH, but is optional for human subjects studies that are not defined as clinical trials.

3.3.a. Overall framework for safety monitoring – You should include the information requested below.

3.3.a.1. The frequency of monitoring, including any plans for interim analysis and stopping rules (if applicable).

3.3.a.2. 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 IRB, the person or group responsible for monitoring, the awarding IC, the NIH Office of Biotechnology Activities, and the Food and Drug Administration.

3.3.a.3. The individual(s) or group that will be responsible for trial monitoring and advising the appointing entity. Options for monitoring include, but are not limited to, monitoring by a PD/PI, independent safety monitor/designated medical monitor, Independent Monitoring Committee or Safety Monitoring Committee, or Data and Safety Monitoring Board (DSMB). (*Note: NIH requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally, for all Phase III clinical trials, although Phase I and Phase II clinical trials may also need DSMBs.)*

3.3.a.4. A brief overview of the organizational structure of the study team, particularly the administrative sites, data coordinating sites, enrollment/participating sites, and any separate laboratory or testing centers. (*Note: Do not include study team members' individual professional experiences.)*

3.3.b. Will a Data and Safety Monitoring Board be appointed for this study? “Yes” or “No”

3.3.b.1. If yes, please describe the general composition of the Board without naming specific individuals.

Section 4 – Protocol Synopsis

NIH requires this information for all proposed studies meeting the NIH definition of a clinical trial. You should include the information requested below.

4.1. Brief Summary – Discuss the objectives of the protocol, including the primary and secondary endpoints.

4.2. Study Design – Include the information requested below.

4.2.a. Narrative Study Description - Describe your plans for assignment of participants and delivery of interventions, show that your methods for sample size and data analysis are appropriate given these plans. Special methods are required for trials that randomize groups or deliver interventions to groups (see the Research Methods Resources webpage).

4.2.b. Primary Purpose - Select the best single description of the clinical trial and provide a description if you select “Other”. (Treatment, Prevention, Diagnostics, Supportive Care, Screening, Health Services Research, Basic Science, Device Feasibility, Other)

4.2.c. Interventions - Complete this section for each intervention to be used in your proposed protocol, even if the study includes more than one intervention.

4.2.c.1. Type – Drug (including placebo), Device (including sham), Biological/Vaccine, Procedure/Surgery, Radiation, Behavioral (e.g. Psychotherapy, Lifestyle Counseling), Genetic (including gene transfer, stem cell and recombinant DNA), Dietary Supplement (e.g. vitamins, minerals), Combination Product, Diagnostic Test, and Other

4.2.c.2. Name

4.2.c.3. Description

4.2.c.4. Model (Single Group, Parallel, Cross-Over, Factorial, Sequential, or Other)

4.2.d. Study Phase - Indicate one of the following that best describes the phase of the clinical trial. (Early Phase 1 or Phase 0, Phase 1, Phase 1/2, Phase 2, Phase 2/3, Phase 3, Phase 4, or Other)

4.2.d.1. Is this an NIH-defined Phase III clinical trial? “Yes” or “No”

4.2.e. Masking/blinding: “Yes” or “No”

4.2.e.1. If yes, select one or more of the following that will be masked/blinded. (Participant, Care Provider, Investigator, and Outcomes Assessor)

4.2.f. Allocation - Select the best single description of the clinical trial. (N/A, Randomized, Non-randomized)

4.2.g. Outcome Measures - Indicate the following for each primary, secondary, and other important measures to be collected during your proposed clinical trial.

4.2.g.1. Name

4.2.g.2. Type (Primary, Secondary, Other)

4.2.g.3. Time Frame

4.2.g.4. Brief Description

4.2.h. Statistical Design and Power - Specify the number of subjects you expect to enroll, the expected effect size, the power, and the statistical methods you will use with respect to each outcome measure identified above. You will need to show that your methods for sample size and data analysis are appropriate. Special methods are required for trials that randomize groups or deliver interventions to groups (see the Research Methods Resources webpage).

4.2.i. Subject Participation Duration - Provide the time (e.g., in months) it will take for each individual participant to complete all the study visits. If the participation duration is unknown or not applicable, indicate “unknown” or “not applicable”.

4.2.j. FDA-regulated Intervention - Indicate whether the study will use an FDA-regulated intervention (see the definition of "FDA Regulated Intervention" under the Oversight section of the ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies page).

4.2.j.1. Will the Study use an FDA-regulated intervention? “Yes” or “No”

4.2.j.2. If yes, describe the availability of the Investigational Product(s) and support for the acquisition and administration of the Investigational Product (s).

4.2.j.3. If yes, indicate the Investigational Product and Investigational New Drug (IND)/Investigational Device Exemption (IDE) status of the Investigational Product(s).

4.2.j.4. Indicate whether the investigators have had any interactions with the FDA.

4.2.j.5. If available, provide the IND/IDE number.

4.2.k. Dissemination Plan - Explain briefly your plan for the dissemination of NIH-funded clinical trial information, address how the expectations of the policy will be met, that the plan assures the following:

4.2.k.1. The applicant will ensure that clinical trial(s) under the award are registered and results information is submitted to ClinicalTrials.gov as outlined in the policy and according to the specific timelines stated in the policy;

4.2.k.2. Informed consent documents for the clinical trial(s) will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov; and

4.2.k.3. The recipient institution has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.

Section 5 – Inclusion of Women, Minorities and Children

5.1. Describe the planned distribution of subjects by sex/gender, race, and ethnicity

5.2. Describe the 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.

5.3. Describe proposed outreach programs for recruiting sex/gender, racial, and ethnic group members.

5.4. Provide a reason for limiting inclusion of any group by sex/gender, race, and/or ethnicity. In general, the cost of recruiting certain groups and/or geographic location alone are not acceptable reasons for exclusion of particular groups. See the Inclusion of Women and Minorities as Participants in Research Involving Human Subjects - Policy Implementation Page for more information.

5.5. If the proposed research includes an NIH-Defined Phase III Clinical Trial, the "Inclusion of Women, Minorities, and Children" section should address plans for how sex/gender, race, and ethnicity will be taken into consideration in the design and valid analysis of the trial. See the instructions for "Valid Analysis" and "Plans to test for Differences in Effect among Sex/gender, Racial, and/or Ethnic Groups" below. Additional information about valid analysis is available on the NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research page.

5.6. Address the following issues for ensuring valid analysis (for NIH-Defined Phase III Clinical Trials only):

- 5.6.a. 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;
- 5.6.b. Allocation of study participants of both sexes/genders and from different racial and/or ethnic groups to the intervention and control groups by an unbiased process such as randomization;
- 5.6.c. Unbiased evaluation of the outcome(s) of study participants; and
- 5.6.d. 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 such differences exist.

5.7. Plan to Test for Differences in Effect among Sex/gender, Racial, and/or Ethnic Groups (for NIH-Defined Phase III Clinical Trials only):

- 5.7.a. Applicants also should address whether they plan to test for differences in effect among sex/gender, racial, and/or ethnic groups and why such testing is or is not appropriate.
- 5.7.b. This plan should include selection and discussion of one of the following analysis plans:
  - 5.7.b.1. 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
  - 5.7.b.2. 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
  - 5.7.b.3. 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.

5.8. Inclusion of Children - for the purposes of the Inclusion of Children, individuals under 18 are defined as a child; however, exclusion of any specific age or age range group (e.g., older adults) should be justified in this section. In addition, address the following points:

- 5.8.a. Children are expected to be included in all NIH-defined clinical research unless there are scientific or ethical reasons not to include them. Discuss whether children (as a whole or a subset of individuals under 18) will be included or excluded. If children will be included, include a rationale for selecting a specific age range of children, if relevant. If children will be excluded, provide a rationale for exclusion. See the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects for additional information about circumstances that may justify the exclusion of children.

5.8.b. Include a description of the expertise of the investigative team for working with children of 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.

5.8.c. When children are involved in research, the policies under HHS' 45 CFR 46, Subpart D - Additional Protections for Children Involved as Subjects in Research apply and should be addressed.

Section 6 – Other Clinical Trial-related Information

Provide any additional trial-related information and only if specified in the Funding Opportunity.