**PHS Human Subjects and Clinical Trials Information Form**

**Narrative Instructions**

National Institutes of Health

Research (“R” Series) Instructions (e.g., R01, R03, R21)

*This document provides summarized instructions for completing the narrative attachments of the PHS Human Subjects and Clinical Trials Information form for NIH Research Grant (R series) proposals (e.g., R01, R03, or R21). While this document provides summarized instructions for narrative attachments, complete instructions for completing the form and its attachments can be found by reviewing the relevant Funding Opportunity Announcement (FOA) and the* [*SF424 (R&R) Research (R) Instructions – Forms Version I Series*](https://grants.nih.gov/grants/how-to-apply-application-guide/forms-i/general-forms-i.pdf)*.*

**Overall Instructions**

* All applicants must use the PHS Human Subjects and Clinical Trials Information form regardless of whether human subjects are involved, though the majority of sections and attachments are required only if human subjects are involved.
* Be especially careful to avoid redundancies with your Research Strategy.
* In the PHS Human Subjects and Clinical Trials Information form, you will add detailed information at the study level. Add a separate study record for each proposed study involving human subjects. Do not duplicate studies within your application. Each study within the application should be unique and should have a unique study title. Furthermore, the filename for each attachment within a study must be unique within the application (i.e., do not use the same filename in multiple study records). Each study record is divided into the following numbered sections:
	+ Section 1 – Basic Information
	+ Section 2 – Study Population Characteristics (includes Inclusion Enrollment Report)
	+ Section 3 – Protection and Monitoring Plans
	+ Section 4 – Protocol Synopsis
	+ Section 5 – Other Clinical Trial-related Attachments
* *Note on Grouping Studies into Study Records:* While there may be more than one way to split or group studies into Study Records, you are encouraged to group studies that use the same human subjects population and same research protocols into a single Study Record, to the extent that the information you provide is accurate and understandable to NIH staff and reviewers. If information in any attachment is identical across studies, include the complete information only in the first Study Record for which the information is relevant. In the subsequent Study Records for which the identical information is needed, upload an attachment that says, “See information for attachment X in Study Record entitled [include study title]." No other information is needed in the attachment. Do not submit attachments that are duplicated from one Study Record to another. Note that you should not name Study Records by number.
* There are no page limits for any attachments in the PHS Human Subjects and Clinical Trials Information form.
* For studies where the only involvement of human subjects is the use of identifiable biospecimens or data originally collected for another purpose, complete the PHS Human Subjects and Clinical Trials Information form with information specific to the current study and not the original collection unless the information associated with the original collection is pertinent to the proposed study. If information about the original collection is necessary, provide context and clearly distinguish between the current study and historical information.
* Projects involving public health surveillance activities described in 45 CFR 46.102(l)(2) must complete one or more Study Records describing those public health surveillance activities as if the exclusion does not apply.
* Note that R25 and R36 applications may have specific requirements. See the FOA and SF424 (R&R) Research (R) Instructions – Form Version I Series.
* Use of hyperlinks and URLs is not allowed unless specified in the funding opportunity announcement.

**PHS Human Subjects and Clinical Trials Information Form Checklist[[1]](#footnote-1)**

* Inclusion of Individuals Across the Lifespan (required for most human subjects studies)
* Inclusion of Women and Minorities (required for most human subjects studies)
* Recruitment and Retention Plan (required for most human subjects studies)
* Study Timeline (required for clinical trials, optional for other human subjects studies)
* Protection of Human Subjects (required for all human subjects studies)
* Single Institutional Review Board Plan (if applicable; only requested for AHRQ applications, not NIH applications)
* Data and Safety Monitoring Plan (required for clinical trials, optional for other human subjects studies)
* Overall Structure of the Study Team (optional)
* Statistical Design and Power (for clinical trials only)
* FDA-regulated Interventions (if applicable; for clinical trials only)
* Dissemination Plan (for clinical trials only)
* Human Specimens and/or Data Explanation (if applicable)
* Other Requested Information (if applicable; renewal or resubmission of a renewal application only)
* Delayed Onset Study(ies) Justification (if applicable)

**Section 1 – Basic Information**

This section is required for all studies involving human subjects; no attachments are required.

**Section 2 – Study Population Characteristics**

Section 2 is required for all studies involving human subjects unless your project is exempt from Federal regulation due to Exemption 4 and no other exemptions.

**Inclusion of Individuals Across the Lifespan**

* Exclusion of any specific age or age range group (e.g., children or older adults) should be justified in this section. In addition, address the following points:
	+ Individuals of all ages are expected to be included in all NIH-defined clinical research unless there are scientific or ethical reasons not to include them. Discuss whether individuals will be excluded based on age and provide a rationale for the minimum and maximum age of study participants, if applicable. Additionally, if individuals will be excluded based on age, provide a scientific or ethical rationale for their exclusion.
	+ Include a description of the expertise of the investigative team for working with individuals of the ages included, the appropriateness of the available facilities to accommodate individuals in the included age range, and how the age distribution of participants will contribute to a meaningful analysis relative to the purpose of the study.
* Note, 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 must be addressed in the Protection of Human Subjects attachment (discussed below).
* If you will use an existing dataset, resource, or samples that may have been collected as part of a different study, you must address inclusion, following the instructions above. Generally, you must provide details about the sex/gender, race, and ethnicity of the existing dataset/resource and justify the details as appropriate to the scientific goals of the proposed study.

**Inclusion of Women and Minorities**

* Address the following points:
	+ Describe the planned distribution of subjects by sex/gender, race, and ethnicity.
	+ 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.
	+ Describe proposed outreach programs for recruiting sex/gender, racial, and ethnic group members.
	+ Inclusion and Excluded Groups: 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.
* If you will use an existing dataset, resource, or samples that may have been collected as part of a different study, you must address inclusion through the points identified immediately above. Generally, you must provide details about the sex/gender, race, and ethnicity of the existing dataset/resource and justify the details as appropriate to the scientific goals of the proposed study.
* If the proposed research includes a NIH-Defined Phase III Clinical Trial, this document must address plans for how sex/gender, race, and ethnicity will be taken into consideration in the design and valid analysis of the trial. For NIH-Defined Phase III Clinical Trials only, include the following two sections:

*Valid Analysis:* 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 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.
	+ 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.

*Plan to Test for Differences in Effect among Sex/gender, Racial, and/or Ethnic Groups:* Address whether you plan to test for differences in effect among sex/gender, racial, and/or ethnic groups and why such testing is or is not appropriate.This plan 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.

**Recruitment and Retention Plan**

* Describe 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.

**Study Timeline**

* This document is required if you answered “Yes” to all the questions in the Clinical Trial Questionnaire; it is optional for all other human subjects research.
* Provide a description or diagram describing the study timeline. The timeline should be general (e.g., “one year after notice of award”) and should not include specific dates.

**Section 3 – Protection and Monitoring Plans**

Section 3 is required for all studies involving human subjects, unless otherwise noted.

**Protection of Human Subjects**

* For any proposed non-exempt study involving human subjects, NIH requires a Protection of Human Subjects attachment that is commensurate with the study’s risks, size, and complexity. Organize this document into the four specified headings in the specified order and discuss each of the points listed.
* If you are claiming that your human subjects research falls under any exemptions, instead of providing the information below, justify why the research meets the criteria for the exemption(s) that you have claimed. Do not merely repeat the criteria for or definitions of the exemptions themselves.
* Do not use this document to circumvent the page limits of the Research Strategy.

***1. Risks to Human Subjects***

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

* Briefly describe the overall study design.
* Describe the subject population(s) to be included in the study; the procedures for assignment to a study group, if relevant; and the anticipated numbers of subjects for each study group.
* 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.

*b. Study Procedures, Materials, and Potential Risks*

* Describe all planned research procedures (interventions and interactions) involving study subjects; how research material, including biospecimens, data, and/or records, will be obtained; and whether any private identifiable information will be collected in the proposed research project.
* For studies that will include the use of previously collected biospecimens, data, or records, describe the source of these materials, whether these can be linked with living individuals, and who will be able to link the materials.
* Describe all the potential risks to subjects associated with each study intervention, procedure, or interaction, including physical, psychological, social, cultural, financial, and legal risks; risks to privacy and/or confidentiality; or other risks. Discuss the risk level and the likely impact to subjects.
* Where appropriate, describe alternative treatments and procedures, including their risks and potential benefits. When alternative treatments or procedures are possible, make the rationale for the proposed approach clear.

***2. Adequacy of Protection Against Risks***

*a. Informed Consent and Assent*

* Describe the process for obtaining informed consent. 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 the plans for obtaining consent from a legally authorized representative for adult subjects not able to consent.
* If the proposed studies will include children, describe the process for meeting HHS regulatory requirements for parental permission and child assent (45 CFR 46.408).
* If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Do not submit informed consent document(s) with your application.

*b. Protections Against Risk*

* Describe planned strategies for protecting against or minimizing all potential risks identified, including strategies to manage and protect participants’ privacy and research data confidentiality.
* Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects on participants.
* Describe plans for handling incidental findings, such as those from research imaging, screening tests, or paternity tests.

*c. Populations that are vulnerable to coercion or undue influence and pregnant women, fetuses, and neonates (if relevant to your study)*

* If relevant, explain the rationale for the involvement of populations that are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons or others who may be considered vulnerable populations.
* If relevant, explain the rationale for the involvement of pregnant women, human fetuses, and neonates.
* If the study involves pregnant women, fetuses, and neonates or children, provide a clear description of the risk level and additional protections necessary to meet the HHS regulatory requirements.
* If the study involves prisoners, describe how proposed research meets the additional regulatory requirements, protections, and plans to obtain Office for Human Research Protections (OHRP) certification for the involvement of prisoners in research. ‘Prisoners’ includes all subjects involuntarily incarcerated (for example, in detention centers).

***3. Potential Benefits of the Proposed Research to Research Participants 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.
* *Note: Financial compensation of subjects should not be presented as a benefit of participation in research.*

***4. 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.

**Single Institutional Review Board (sIRB) Plan**

* **For NIH applicants**, the single IRB plan is no longer required. Do not provide an attachment. The applicant must provide a statement naming the sIRB of record in the Just-in-Time submission prior to award.
* **For AHRQ applicants**, for research projects that involve more than one institution and that will be conducted in the United States, applicants are expected to use a single Institutional Review Board (sIRB) to conduct the ethical review required by HHS regulations for the Protections of Human Subjects Research. Such applicants must include a single IRB plan (unless review by a sIRB would be prohibited by a federal, tribal, or state law, regulation, or policy) that includes the following elements:
* Describe how you will comply with the single IRB review requirement under the Revised Common Rule at 45 CFR 46.114 (b) (cooperative research).
	+ If available, provide the name of the IRB that will serve as the sIRB of record.
	+ 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.
	+ Briefly describe how communication between sites and the sIRB will be handled.
	+ 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.
	+ Indicate which institution or entity will maintain records of the authorization/reliance agreements and of the communication plan. *Note: Do not include the authorization/reliance agreement(s) or the communication plan(s) documents in your application.*
	+ For studies with legal-, regulatory-, or policy-based claims for exception as described by the sIRB Policy, indicate that review by an sIRB will not be possible for all or some sites (specify which sites) because local IRB review is required by an existing federal/state/tribal law or policy. Include a specific citation to the relevant law, policy, or regulation.
* *Note: If you anticipate research involving human subjects but cannot describe the study at the time of application, include information regarding how the study will comply with the single Institutional Review Board (sIRB) requirement prior to initiating any multi-site study in the Delayed Onset Study Justification (see below).*

**Data and Safety Monitoring Plan (DSMP)**

* This document is required if you answered “Yes” to all the questions in the Clinical Trial Questionnaire; it is optional for all other human subjects research.
* **For AHRQ Applicants,** DSMPs are required in all non-exempt research applications when support is sought to study the effect of a health-related intervention on outcomes in human subjects where there is greater than minimal risk. If you seek AHRQ support to conduct non-exempt research to study the effect of a health-related intervention on outcomes in human subjects where there is greater than minimal risk, a DSMP attachment is required.
* For any proposed clinical trial, NIH requires a DSMP that is commensurate with the risks of the trial, its size, and its complexity. Provide a description of the DSMP, including:
	+ - Indicate how many people and what type of entity will provide the monitoring. Include such details as whether a single person, multiple people, or a data safety monitoring board will provide monitoring. Also indicate what type of entity will provide the monitoring (e.g., PD/PI, Independent Safety Monitor/Designated Medical Monitor, Independent Monitoring Committee, Safety Monitoring Committee, Data and Safety Monitoring Board, etc.).
		- 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, including Serious Adverse Events such as deaths, hospitalizations, and life-threatening events and Unanticipated Problems, will be managed and reported, as required, to the IRB, the person or group responsible for monitoring, the awarding IC, and the Food and Drug Administration.
		- The individual(s) or group that will be responsible for trial monitoring and advising the appointing entity. Because the DSMP 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 approved 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 experts.
			* 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 all Phase III clinical trials, although Phase I and Phase II clinical trials may also need DSMBs. If a DSMB is used, please describe the general composition of the Board without naming specific individuals.
* *Note: For human subjects research that does not involve a clinical trial, your study, although it is not a clinical trial, may have significant risks to participants, and it may be appropriate to include a DSMP. If you choose to include a DSMP, you may follow the content criteria listed above, as appropriate.*

**Overall Structure of the Study Team**

* This document is optional.
* Provide a brief overview of the organizational/administrative structure and function of the study team, particularly the administrative sites, data coordinating sites, enrollment/participating sites, and any separate laboratory or testing centers.
* The attachment may include information on study team composition and key roles (e.g., medical monitor, data coordinating center), the governance of the study, and a description of how study decisions and progress will be communicated and reported.
* Do not include study team members’ individual professional experiences (i.e., biographical sketch information).

**Section 4 – Protocol Synopsis**

Section 4 is required if your study meets the definition of a clinical trial; if your study does not meet the definition of a clinical trial, do not provide information in Section 4.

**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 you listed in 4.2 Outcome Measures.
* Show that your methods for sample size and data analysis are appropriate given your plans for assignment of participants and delivery of interventions.
* For trials that randomize groups or deliver interventions to groups, special methods are required; additional information is available at the Research Methods Resources webpage (<https://researchmethodsresources.nih.gov/>).

**FDA-regulated Interventions** (typical length is approximately 3,000 characters)

* If the study will use a Food and Drug Administration (FDA)-regulated intervention, describe the availability of Investigational Product and Investigational New Drug (IND)/Investigational Device Exemption (IDE) status.
* Describe the availability of study agents and support for the acquisition and administration of the study agent(s).
* Indicate, if applicable, the IND/IDE status of the study agent, including whether a clinical investigation is exempt from the IND/IDE requirement. Also indicate whether the investigators have had any interactions with the FDA (e.g., indicate if the FDA has stated that research may proceed). If the study agent currently has an IND/IDE number, provide that information.
* Do not include the IND/IDE application, manufacturer’s product specifications, study protocol, or protocol amendments.

**Dissemination Plan**

* Explain briefly your plan for the dissemination of NIH-funded clinical trial information and address how the expectations of the policy will be met. The plan must contain sufficient information to assure the following:
	+ 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 NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information and according to the specific timelines stated in the policy.
	+ Informed consent documents for the clinical trial(s) will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov.
	+ The recipient institution has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.
* *Note: Do not include informed consent documents in this attachment.*
* *Note: If your human subjects study meets the definition of “Delayed Onset,” include the Dissemination Plan in the* Delayed Onset Study(ies) Justification *described below).*
* *Note: One Dissemination Plan per application is sufficient.*

**Section 5 – Other Clinical Trial-related Attachments**

Do not complete Section 5 unless instructed to do so in the FOA.

**Other Potential Human Subjects Documents**

**Human Specimens and/or Data Explanation**

* If you answer “Yes” to the question “Does the proposed research in the application involve human specimens and/or data?” on the PHS Human Subjects and Clinical Trials Information form but the research is not considered human subjects research, provide an explanation for any use of human specimens and/or data not considered to be human subjects research.
* Include information on who is providing the data/biological specimens and their role in the proposed research, a description of the identifiers that will be associated with the human specimens and data, a list of who has access to subjects’ identities, and information about the manner in which the privacy of research participants and confidentiality of data will be protected.

**Other Requested Information** *(renewal or resubmission of a renewal applications only)*

* When preparing a renewal (or resubmission of a renewal), you can provide a list of ongoing studies or ClinicalTrials.gov identifiers (e.g., NCT87654321).
* Hyperlinks and URLs are not allowed unless specified in the funding opportunity announcement.

**Delayed Onset Study(ies) Justification**

* If you anticipate conducting research involving human subjects but cannot describe the study at the time of application (i.e., your study is a delayed onset human subject study), provide a justification explaining why human subjects study information is not available at the time of application.
	+ *Note: Delayed onset does NOT apply to a study that can be described but will not start immediately (i.e., delayed start).*
* If NIH’s Policy on the Dissemination of NIH-Funded Clinical Trial Information will apply to your study, this justification must also include the dissemination plan (see instructions for completing this under *Dissemination Plan* above).
* If you are including more than one delayed onset study in any given delayed onset study entry, address all the included studies in a single justification attachment.
* Hyperlinks and URLs are not allowed unless specified in the funding opportunity announcement.
1. This checklist and the subsequent outline provide information on required attachments for the PHS Human Subjects and Clinical Trials Information Form. Additional information, provided within text boxes on the form, is required and is ***not*** reflected within this outline and checklist. Please refer to the [Annotated Form Set for NIH Grant Applications: FORMS-I Series](https://grants.nih.gov/grants/ElectronicReceipt/files/Annotated_Forms_General_FORMS-I.pdf) to review text box fields within the PHS Human Subjects and Clinical Trials Information Form. [↑](#footnote-ref-1)