



INSTRUCTIONS FOR THE NIH RESEARCH GRANT APPLICATION

Updated January 2018 (includes revised directions for "FORM E" applications due on or after January 28, 2018).

(NOTE: While these guidelines are specific to the NIH application, the principles stated here are also applicable for scientific proposals to other major research funders)

This document describes the basic sections of an investigator-initiated R01 NIH research grant application. Note that if you submit a proposal responding to a different grant mechanism or in response to a specific Funding Opportunity Announcement (FOA), make sure to read the FOA carefully; instructions in the FOA will supersede instructions in the NIH Grant Application Guide.

This guide includes NIH instructions for the new Forms E, effective January 28, 2018. You will also find tips and guidance on how best to write the application, primarily taken from NIH online resources.

This document is provided by the MMCRI Grants and Contracts Office.

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Identifying a Funding Opportunity Announcement (FOA)

All NIH applications must be submitted in response to an FOA. To browse through current FOAs, go to <http://grants.nih.gov/funding/index.htm>. NIH has Parent FOAs for use by applicants who wish to submit unsolicited investigator initiated R01 applications and other common grant mechanisms. In addition, NIH publishes FOAs for specific Request for Applications (RFA) and Program Announcements (PA) that identify special research opportunities. If you are submitting to a specific RFA or PA, read the announcement in detail to be sure your application is appropriate for the announcement. Deadlines for common grant mechanisms are as follows:

New R01s	February 5, June 5, October 5
Renewals and Resubmissions of R01s	March 5, July 5, November 5
New R21s (Exploratory Development Awards) and R03s (Small Research Grant Program)	February 16, June 16, October 16
Renewals and Resubmission of R21s, R33s and R03s	March 16, July 16, November 16
New K Awards (Research Career Development Awards)	February 12, June 12, October 12
Renewal and Resubmission of K Awards	March 12, July 12, November 12
F Awards (Fellowships)	April 8, August 8, December 8

The deadlines for applications in response to special RFAs and Program Announcements with special receipt (PAR), may differ. Always check the FOA for the receipt date. In addition, **it is MMC's policy to submit NIH proposals at least two days prior to the due date, to ensure there is time to correct any problems with electronic submission.**

Format

Your documents should all be in Arial 11 point font, with ½" margins all around. There should be no page numbers, headers or footers.

Title

Title should be short and descriptive of the proposed research.

Abstract (30 line limit)

The Project Summary is meant to serve as a succinct and accurate description of the proposed work when separated from the application. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the mission of the agency). Describe concisely the research design and methods for achieving the stated goals. This section should be informative to other persons working in the same or related fields and insofar as possible understandable to a scientifically or technically literate reader. Avoid describing past accomplishments and the use of the first person. Finally, please make every effort to be succinct.

The abstract should be a self-contained description of the project. Information should include significance, broad objectives, hypotheses, specific aims, and methods to be employed. Do not include proprietary or sensitive information, as the abstract will become publicly available if the grant is funded. Do not include graphs or images in the abstract. The maximum length is 30 lines of text. All abstracts for funded applications are available through the NIH Reporter. To see examples of successful abstracts, search on terms associated with your research area at <https://projectreporter.nih.gov/reporter.cfm?frs>. Avoid describing past accomplishments and the use of the first person. **Write the abstract last so that it reflects the entire application.**

You may wish to consider the following questions when writing your abstract. Did you state the overall objective of the proposed research? Did you succinctly state the specific aims? Did you briefly describe the

methods? Did you indicate the long-term goal of the research? Does your abstract provide a snapshot of the whole proposal?

Health Relevance/ Project Narrative (2-3 sentence limit)

Using no more than two or three sentences, describe the relevance of this research to public health. For example, NIH applicants can describe how, in the short or long term, the research would contribute to fundamental knowledge about the nature and behavior of living systems and/or the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. If the application is funded, this public health relevance statement will be combined with the project summary (above) and will become public information.

Be succinct and use plain language that can be understood by a general, lay audience.

Key Personnel/Biosketches (5 page limit)

Mandatory review criteria include an assessment of key personnel. Choose key personnel whose training and experience match the science proposed in the application. Senior/Key Personnel are defined as all individuals who contribute in a substantive, meaningful way to the scientific development or execution of the project, whether or not salaries are requested. All senior/key personnel must commit “measurable time” – a defined per cent effort greater than zero. Consultants should be included if they meet this definition. Do not include technicians or junior investigators unless they are providing specific expertise or skills needed to complete the proposed research. If you are awarded the grant, any changes in key personnel must be approved by the NIH program officer assigned to your grant. Additionally, all senior/key personnel must be compliant with MMC’s Financial Conflict of Interest policy. Your application should indicate to reviewers that the key personnel on the application are very well suited to conduct the research. This is reflected in their training and publication record. It is not necessary to name each person working on the project as key personnel. If collaborators from other institutions are part of key personnel, you will need to include letters of commitment in your application that clearly spell out their roles and commitment to the project. For consultants, letters should include rate/charge for consulting services.

Each person listed as Senior/Key must submit an NIH Biosketch form which requires a personal statement describing relevant experience and qualifications that make this person well suited for the role to be played in the project. It also includes up to five sections detailing “contributions to science” which can include up to four publications each. Finally, it may include a link to the full bibliography of the key personnel, which is found on the public NIH website My NCBI. Click <http://grants.nih.gov/grants/forms/biosketch.htm> for a link to biosketch instructions and sample.

In selecting key personnel, consider the following questions. Are the PI and other key personnel appropriately trained and well-suited to carry out this work? Is the work proposed appropriate to the experience level of the PI and other researchers? Do the PI and investigative team bring complementary and integrated expertise to the project?

Other Significant Contributors (OSCs)

OSCs are scientists who have agreed to consult or collaborate on the project, usually to contribute a particular area of expertise, but who are not giving measurable time to the project. Instead, they will be available on an “as needed” basis. Biosketches are required for OSCs, as well as letters agreeing to advise on the project.

New or Early Stage Investigator

If you are a new or early stage investigator, be sure to note this when you register for eRA Commons and in the personal statement. To determine whether you qualify, go to the NIH website and read the definition (http://grants.nih.gov/grants/new_investigators/). Not only are new and early stage investigators eligible for specific funding opportunities, but reviewers must take this status into consideration as well. Reviewers will give greater consideration to the proposed approach, rather than the research track record. Early stage applicants may have less preliminary data and fewer publications than more seasoned investigators, and NIH reviewers understand this. Reviewers instead place more emphasis on how the investigator has demonstrated that he or she is truly independent of any former mentors, whether he or she has his or her own resources and institutional support, and whether he or she is able to independently lead the research.

Facilities and Other Resources (no page limit)

Describe how the scientific environment in which the research will be done contributes to the probability of success (e.g., institutional support, physical resources, and intellectual rapport). In describing the scientific environment in which the work will be done, discuss ways in which the proposed studies will benefit from unique features of the scientific environment or subject populations or will employ useful collaborative arrangements. For Early Stage Investigators (ESIs), describe institutional investment in the success of the investigator, e.g., resources for classes, travel, training; collegial support such as career enrichment programs, assistance and guidance in the supervision of trainees involved with the ESI's project, and availability of organized peer groups; logistical support such as administrative management and oversight and best practices training; and financial support such as protected time for research with salary support. If there are multiple performance sites, describe the resources available at each site. Describe any special facilities used for working with biohazards or other potentially dangerous substances.

This section provides information to indicate that the environment can support the proposed research. Resources should include laboratory, animal facility, computer, office, clinical, or other facilities. Provide information on capacities, relative proximity, and extent of availability of resources to the project. Describe only those resources that are directly applicable to the proposed research.

You may wish to consider the following questions. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support? The MMC grant administrator has templates for the MMC and MMCRI resources and scientific environment which you may use and modify for your own proposal.

Important Note: A template for Maine Medical Center Facilities and Other Resources is available at the Grants and Contracts office. The grant administrator will provide assistance in updating and editing this section.

Equipment (no page limit)

List major equipment available to the project (if applicable). The grant administrator has a template that includes all equipment available at MMCRI. If appropriate, use the template and modify it to include only what you will use for the project. If your work will not be done on the MMCRI Scarborough campus, you will need to list the equipment available at your lab at clinical facility, if applicable.

Budget

The amount of money requested should reflect the scope of the science proposed. The budget includes such items as investigator and research staff time, equipment, supplies, travel expenses, research clinical procedures animal care and purchase, core facility fees, and the like. Salaries generally account for 60% to 80% of direct costs. Begin to work with the grant administrator early. All costs must be allowable, reasonable, and necessary and NIH has salary caps and other rules regarding budgets. If you ask for too little money given the work proposed, reviewers will see the application as naïve. If you ask for too much, reviewers will cut the budget. The budget also includes a Budget Justification. There are two types of budgets: 1) a modular budget, which must not be over \$250,000 per year in direct costs (for an R01) and only requires personnel justification, and 2) a detailed non-modular budget, for requests over \$250,000 or specific RFAs, which require detailed line items and detailed justifications for all items. You cannot go above \$500,000 per year in direct costs without NIH Institute approval. The FOA and your own budgetary needs will determine the budget you decide to use. Plan to spend time thinking through the budget and justification. If the budget is getting too high for the grant mechanism or your stage of career development, consider cutting back the specific aims or experiments. There are no page limits for this section. The grant administrator will work with you to construct a budget which is compliant with MMC fringe rates and indirect costs, to draft and edit a budget justification and to interpret the budget guidelines. If collaborating institutions are involved, the grant administrator will work with them to receive appropriate budgets and institutional approvals.

THE RESEARCH PLAN

Specific Aims (one page limit)

State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved.

List succinctly the specific objectives of the research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology.

*A strong proposal is driven by a strong hypothesis (es) that leads to clear research objectives. The Specific Aims section should encapsulate these concepts. It typically begins with a narrative paragraph or two that concisely states the issue or problem to be addressed, describes the long-term goals or objectives of the project and clearly states the hypothesis to be tested. This is followed by a numbered list of the Specific Aims. The aims test different aspects of the hypotheses, operationalize the objectives and provide a rationale for the experimental approach to be described later. For clarity, **each aim should consist of only one sentence**. Use a brief paragraph under each aim if detail is needed. Most successful applications have 2-4 specific aims. Make sure the aims are logical, achievable, and clearly relate back to the hypothesis. Depending on the goals of the application, the Specific Aims section may take on a somewhat different form if, rather than testing a specific hypothesis, the goal is to create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology.*

In crafting the Specific Aims section, consider the following questions. Do your specific aims address the research goals and objectives? Did you state your hypotheses and link them appropriately to your specific aims? Are the specific aims clearly related to each other? Do the specific aims represent an achievable amount of work? An unrealistic and overly ambitious set of specific aims is a common pitfall of many applications. This section is by far the most important page of the application. Many applications are won or lost depending on how precisely stated and how compelling the hypothesis and specific aims are presented!

Research Strategy (12 pages for an R01; 6 pages for an R21)

The research strategy is organized into three sections: **Significance, Innovation, and Approach.**

Significance

- Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses.
- Describe the scientific premise for the proposed project, including consideration of the strengths and weaknesses of published research or preliminary data crucial to the support of your application.
- Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.
- Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.

Innovation

- Explain how the application challenges and seeks to shift current research or clinical practice paradigms.
- Describe any novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, and any advantage over existing methodologies, instrumentation, or interventions.
- Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation, or interventions.

Approach

Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Describe the experimental design and methods proposed and how they will achieve robust and unbiased results. State how the data will be collected, analyzed, and interpreted and describe statistical techniques that will be used. If applicable, for clinical trials that randomize groups or deliver interventions to groups, describe how your methods for analysis and sample size are appropriate for your plans for participant assignment and intervention delivery. These methods can include a group- or cluster- randomized trial or an individually randomized group-treatment trial.

- Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.
- If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work.
- Explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans. For example, strong justification from the scientific literature, preliminary data, or other relevant considerations, must be provided for applications proposing to study only one sex.
- Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be exercised.
- If research on Human Embryonic Stem Cells (hESCs) is proposed but an approved cell line from the NIH hESC Registry cannot be identified, provide a strong justification for why an appropriate cell line cannot be chosen from the Registry at this time.

Additionally, if applicable, include the following information in the Research Strategy, keeping within the three sections (Significance, Innovation, and Approach) listed above.

Preliminary Studies for New Applications

For new applications, include information on preliminary studies in your research strategy. Discuss the PD/PI's preliminary studies, data, and or experience pertinent to this application. Except for Exploratory/Developmental Grants (R21/R33), Small Research Grants (R03), and Academic Research Enhancement Award (AREA) Grants (R15), preliminary data can be an essential part of a research grant application and can help to establish the likelihood of success of the proposed project. Early stage investigators should include preliminary data.

Progress Report for Renewal and Revision Applications.

Note that the Progress Report falls within the Research Strategy and is therefore included in the page limits for the Research Strategy. For renewal/revision applications, provide a Progress Report. Provide the beginning and ending dates for the period covered since the last competitive review. In the Progress Report, you should:

- Summarize the specific aims of the previous project period and the importance of the findings, and emphasize the progress made toward their achievement.
- Explain any significant changes to the specific aims and any new directions, including changes resulting from significant budget reductions.
- Discuss previous participant enrollment (e.g., recruitment, retention, inclusion of women, minorities, children, etc.) for any studies meeting the NIH definition for [clinical research](#). Use the Progress Report section to discuss, but not duplicate information collected elsewhere in the application.

NOTE: Do not include a list of publications, patents, or other printed materials in the Progress Report. That information will be included in the "Progress Report Publication List" attachment.

*Consider the following questions when drafting the Research Strategy Section: Does the background provide a clear statement of the general problem being addressed? Have you compared, contrasted, and critiqued what others have done? Have you shown how existing work lays the groundwork for the research you propose? Have you cited the literature appropriately? Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well-integrated, well-reasoned, and appropriate to the aims of the project? Did you provide an overview of the experimental design before giving details of the methods? Did you relate the design and methods back to each specific aim? Did you use diagrams or flow charts to explain complex protocols? Did you give enough detail to show that you know what you're talking about? Does the applicant acknowledge potential problem areas and consider alternative tactics? **NOTE:** If an applicant has multiple Specific Aims, then the applicant may address Significance, Innovation and Approach for each Specific Aim individually, or may address Significance, Innovation and Approach for all of the Specific Aims collectively.*

Resource-Sharing Plan (no page limit)

This section is required for all applications. If applicable, include plans to share resources developed with the scientific community (NOTE: publication of the findings is not considered resource-sharing). The Grants Office has a template available for this section which can be modified for your particular project.

Data Sharing Plan: All investigator-initiated applications with direct costs of \$500,000 or greater (exclusive of consortium F&A) in any single year are expected to address data-sharing in their application. Applicants are encouraged to discuss data-sharing plans with their program contact at the time they negotiate an agreement with the Institute/Center (IC) staff to accept assignment of their application. Instructions related to the data-sharing policy as it is applied to applications and proposals responding to a specific Request for Application (RFA) or Request for Proposals (RFP) will be described in the specific FOA. In some cases, other Funding Opportunity Announcements (FOAs) may request data-sharing plans for applications that are less than \$500,000 direct costs in any single year. NIH recognizes that in some cases data-sharing may be complicated or limited by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the HIPAA Privacy Rule. The rights and privacy of individuals who participate in NIH-sponsored research must be protected at all times. Thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects. When data-sharing is limited, applicants should explain such limitations in their data-sharing plans.

Sharing Model Organisms: Regardless of the amount requested, all applications where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms or state why such sharing is restricted or not possible.

Genomic Data Sharing (GDS): Applicants seeking funding for research that generates large-scale human or non-human genomic data are expected to provide a plan for sharing of these data. Examples of large-scale genomic data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data. Supplemental Information to the NIH GDS provides examples of genomic research projects that are subject to the Policy.

Bibliography and References Cited (No page limit)

Provide a bibliography of any references cited in the project narrative and any other parts of your application. This section shows your breadth of knowledge in your field. There is no page limit for this section. Each reference must include the names of all authors (in the same sequence in which they appear in the publication), the article and journal title, book title, volume number, page numbers, and year of publication. When citing articles that fall under the Public Access Policy (i.e., arose from NIH support), provide the NIH Manuscript Submission reference number (e.g., NIHMS97531) or the Pubmed Central (PMC) reference number (e.g., PMCID234567) for each article. If the PMCID is not yet available because the journal submits articles directly to PMC on behalf of their authors, indicate "PMC Journal – In Process." Citations that are not covered by the Public Access Policy, but are publicly available in a free, online format may include URLs or PMCID numbers along with the full reference. The following is an example of an appropriate citation in the bibliography: Pillai SK, Good B, Pond SK, Wong JK, Strain MC, Richman DD, Smith DM. Semen-specific genetic characteristics of human immunodeficiency virus type 1 env. J Virol. 2005 79(3):1734-1742. PMCID: PMC544119. Copies of publicly available publications are not accepted as appendix material. The references

should be limited to relevant and current literature.

ADDITIONAL SECTIONS (IF APPLICABLE)

The following sections do not count against the Research Strategy page limits and are uploaded in separate sections. They may or may not be applicable to your application.

Introduction (Required for resubmission applications only – one page limit)

- summarizes substantial additions, deletions, and changes to the application
- responds to the issues and criticism raised in the summary statement
- is limited to one page in length, unless specified otherwise in the FOA

Progress Report Publication List (Applicable for renewal applications only) (no page limit)

List the titles and complete references to all appropriate publications, manuscripts accepted for publication, patents, and other printed materials that have resulted from the project since it was last reviewed competitively. When citing articles that fall under the Public Access Policy, were authored or co-authored by the applicant and arose from NIH support, or arose from AHRQ funding provided after 2/19/16 (see <https://grants.nih.gov/grants/guide/notice-files/NOT-HS-16-008.html>), provide the NIH Manuscript Submission reference number (e.g., NIHMS97531) or the PubMed Central (PMC) reference number (e.g., PMCID234567) for each article. If the PMCID is not yet available because the Journal submits articles directly to PMC on behalf of their authors, indicate “PMC Journal – In Process.” A list of these journals is posted at: http://publicaccess.nih.gov/submit_process_journals.htm. Citations that are not covered by the Public Access Policy, but are publicly available in a free, online format may include URLs or PubMed ID (PMID) numbers along with the full reference (note that copies of these publications are not accepted as appendix material. Also note that if your article was peer-reviewed and was supported by the NIH grant, it MUST be compliant or it can affect future funding.

Vertebrate Animals (No page limit)

If vertebrate animals are involved, address each of the three points below. If all or part of the proposed research involving vertebrate animals will take place at alternate sites (such as collaborating sites), identify those sites and answer the three points for those sites as well.

1. **Description of Procedures.** Provide a concise description of the proposed procedures to be used that involve vertebrate animals in the work outlined in the “Research Strategy” section. Identify the species, strains, ages, sex, and total numbers of animals by species, to be used in the proposed work. If dogs or cats are proposed provide the source of the animals.
2. **Justifications:** Provide justification that the species are appropriate for the proposed research. Explain why the research goals cannot be accomplished using an alternative model (e.g. computational, human, invertebrate, in vitro).
3. **Minimization of Pain and Distress:** Describe the interventions including analgesia, anesthesia, sedation, palliative care and humane endpoints to minimize discomfort, distress, pain, and injury.
4. **Euthanasia:** describe the method of euthanasia if applicable.

Each of the criteria must be addressed. Failure to adequately address the criteria may negatively affect the application’s impact score. In addition to the 3 criteria above, you should also:

- Identify all project performance (or collaborating) sites and describe the proposed research activities with vertebrate animals that will be conducted at those sites.
- Explain when and how animals are expected to be used if plans for the use of animals have not been finalized.

NOTE: You will also be asked if the method of euthanasia used is consistent with American Veterinary Medical

Association (AVMA) guidelines. If “No,” you will need to describe the method and provide a scientific justification.

Multiple PI Leadership Plan (No page limit)

For applications designating multiple PD/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PD/PIs and other collaborators. Do not submit a leadership plan if you are not submitting a Multiple PD/PI application. If budget allocation is planned, the distribution of resources to specific components of the project or the individual PD/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote on the Notice of Grant Award. *NOTE: The Grants Office has several templates for the multiple PI plan.*

Consortium/Contractual Arrangements (No page limit)

If your application includes consortium arrangements with collaborative institutions, explain the programmatic, fiscal, and administrative arrangements to be made between the applicant organization and the consortium organization(s). If consortium/contractual activities represent a significant portion of the overall project, explain why the applicant organization, rather than the ultimate performer of the activities, should be the grantee. The signature of the Authorized Organization Representative on the (Section R.200 - SF 424 (R&R), Item 19) signifies that the applicant and all proposed consortium participants understand and agree to the following statement: *The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.*

NOTE: The grant administrator will write this section for you as she will be assembling consortium documents.

Letters of Support

Attach all appropriate letters of support, including any letters necessary to demonstrate the support of consortium participants and collaborators such as Senior/Key Personnel and Other Significant Contributors included in the grant application. Letters are not required for personnel (such as research assistants) not contributing in a substantive, measurable way to the scientific development or execution of the project. Letters should stipulate expectations for co-authorship, and whether cell lines, samples or other resources promised in the letter are freely available to other investigators in the scientific community or will be provided to the particular investigators only. For consultants, letters should include rate/charge for consulting services and level of effort/number of hours per year anticipated. In addition, letters ensuring access to core facilities and resources should stipulate whether access will be provided as a fee-for-service. Do not place these letters in the Appendix.

Authentication of Key Biological and/or Chemical Resources (One page limit)

If applicable to the proposed science, briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies. No more than one page is suggested. Key biological and/or chemical resources may or may not be generated with NIH funds and: 1) may differ from laboratory to laboratory or over time; 2) may have qualities and/or qualifications that could influence the research data; and 3) are integral to the proposed research. These include, but are not limited to, cell lines, specialty chemicals, antibodies, and other biologics. Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals

Appendix

Refer to the FOA to determine whether there are any special appendix instructions for your application. See the updated NIH Guide Notice on the [Appendix Policy](#).

Format: A maximum of 10 PDF attachments is allowed in the Appendix. If more than 10 allowable appendix attachments are needed, combine the remaining information into attachment #10.

Use file names for attachments that are descriptive of the content.

A summary sheet listing all of the items included in the Appendix is encouraged but not required. When including a summary sheet, it should be included in the first appendix attachment.

Content: The only allowable appendix materials are:

- Blank data collection forms, blank survey forms, and blank questionnaire forms - or screenshots thereof
- Simple lists of interview questions

Note: In your blank forms and lists, do not include items such as: data, data compilations, lists of variables or acronyms, data analyses, publications, manuals, instructions, descriptions or drawings/figures/diagrams of data collection methods or machines/devices.

- Blank informed consent/assent forms
- Other items *only* if they are specified in the FOA as allowable appendix materials

No other items are allowed in the Appendix. Simply relocating disallowed materials to other parts of the application will result in a noncompliant application. Some FOAs may have different instructions for the Appendix. Always follow the instructions in your FOA if they conflict with these instructions.

Note: Applications will be withdrawn and not reviewed if they do not follow the appendix requirements in these instructions or in your FOA. Information that expands upon or complements information provided in any section of the application – even if it is not required for the review – is not allowed in the Appendix unless it is listed in the allowed appendix materials above or in your FOA. For example, do not include material transfer agreements (MTA) in the appendix unless otherwise specified in the FOA.

ASSIGNMENT REQUEST FORM (Optional)

This section of the form is optional. You may request up to three institutes/centers for assignment of your application. Instructions are below.

Assign to Awarding Component:

Enter preferences for NIH IC assignment in the boxes in the “Assign to” row. Use the column labeled “1” to enter your first choice.

Do Not Assign to Awarding Component:

You may request that your application not be assigned to a specific NIH IC by entering that information in the boxes in the “Do Not Assign To” row.

In most cases, you will only want to make one or two requests; there is no need to make an entry in all six boxes. To facilitate accurate communication of your request to NIH referral and review staff, please use the short abbreviation for the requested NIH IC (e.g., NCI for the National Cancer Institute). Please click <http://mmcri.org/ns/wp-content/uploads/2014/08/Awarding-Component-Assignment-Request1.pdf> for the Assignment Form.

HUMAN SUBJECTS AND CLINICAL TRIAL SECTION

Protection of Human Subjects: Does your research involve human subjects? According to DHHS regulations, the answer is “yes” if you obtain data or biological specimens through intervention or interaction with a living individual or you obtain identifiable private information about a living individual. If you answer “yes” to human subjects’ involvement, there are required sections of the application that must be written and a number of questions that must be answered. NIH does not require that you have IRB approval at the time of submission; however, you will need to have an IRB approval letter before the proposal is funded. The human subjects section of the NIH application has become more complex and detailed. Instructions are below.

Scenario A: No Human Subjects Research Proposed but specimens or data are used

Research that does not involve intervention or interaction with living individuals, or identifiable private

information, is not considered human subjects research. Research involving the use of coded private information or biological specimens may not constitute human subjects research if the conditions of the OHRP Guidance on Research Involving Coded Private Information or Biological Specimens have been met. OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. To help determine whether your research is classified as human subjects research, refer to the [Research Involving Private Information or Biological Specimens](#) flowchart.

If proposed studies involve the use of human data or biological specimens, you must provide an explanation of why the proposed studies do not constitute research involving human subjects. Your explanation must be in line with the OHRP guidelines. For guidance, OHRP does not consider research involving **only** coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are **both** met:

1. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
 - a. the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);
 - b. there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
 - c. there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

This guidance applies to existing private information and specimens, as well as to private information and specimens to be collected in the future for purposes other than the currently proposed research. The following are examples of private information or specimens that will be collected in the future for purposes other than the currently proposed research: (1) medical records; and (2) ongoing collection of specimens for a tissue repository.

What you need to write for Scenario A: Create a heading labeled “Protection of Human Subjects” and include the following statement below the heading: “No Human Subjects Research is proposed in this application” plus the justification for why the research is deemed “not human subjects. This justification should 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.

Scenario B: Exempt Human Research:

The most common exemption used for biomedical human research is exemption 4, defined below:

Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The Office of Human Research Protections (OHRP) guidance states that appropriate use of exemptions described in 45 CFR 46 should be determined by an authority independent from the investigators (for more information, see [OHRP's Frequently Asked Questions](#)). Institutions often designate their Institutional Review

Board (IRB) to make this determination. Because NIH does not require IRB approval at the time of application, the exemptions designated often represent the opinion of the PD/PI, and the justification provided for the exemption by the PD/PI is evaluated during peer review.

What you need to write for Scenario B: If your research is exempt under exemption 4, then in the section entitled “Protection of Human Subjects” include the following statement: “This Human Subjects Research falls under Exemption 4.” Justify why the research meets the criteria for the exemption that you have claimed based on the definition provided above. Explain how the proposed research meets the criteria for the exemption claimed and do not merely repeat the criteria or definitions themselves.
(NOTE: If you claim Exemption 4, you do not need to fill out section 2)

Scenario C: Non-Exempt Human Research. If you are conducting non-exempt human research, you will need to fill out a detailed study record for each protocol you propose. MMCR1 has a pdf of this study record here (PUT LINK). There are four sections:

Section 1: Basic Information:

Title: maximum 600 characters; each human subjects study must have a unique title.

Note: When registering a clinical trial in ClinicalTrials.gov, all study titles across your organization must be unique.

Is the study a clinical trial? Answer “Yes” or “No” to the following questions to determine whether this study involves a clinical trial. If you answer “Yes” to all questions, then your study is a clinical trial.

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

If your study is a clinical trial:

- provide the clinicaltrials.gov identifier number, if applicable. (NOTE: this is optional at submission time).
- fill out all questions in sections 2- 4 (and 5, if applicable)
-

If your study is not a clinical trial:

- fill out sections 2-3 only. (NOTE: If your study is exempt under exemption 4, do not fill out section 2).

Section 2: Study Population Characteristics

2.1: Identify the names of the diseases or conditions you are studying, or the focus of the study. If available, use appropriate descriptors from [NLM's Medical Subject Headings](#) (MeSH) so the application can be categorized. Include an entry for each condition. You must provide at least one entry, and may provide up to 20 entries.

2.2: Eligibility Criteria (15,000 character limit): List the study’s inclusion and exclusion criteria. To provide a bulleted list, use a dash (or other character) followed by a space (“- “) at the start of each bullet. Be sure to check the formatting in the assembled application image. Further explanation or justification should be included in the Recruitment and Retention plan.

2.3: Age Limits: Enter the numerical value for the minimum age a potential participant can be to be eligible for

the study. Provide the relevant units of time (i.e., years, months, weeks, days, hours, or minutes). If there is no age lower age limit or no lower limit is known, enter “N/A”. Also enter the numerical value of the maximum age a potential participant can be to be eligible for the study. If there is no upper limit, enter “N/A.”

2.4: Inclusion of Women and Minorities and Children: Your write-up should have two sections:

a. **Inclusion of Women and Minorities**

- 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. See the [Inclusion of Women and Minorities as Participants in Research Involving Human Subjects - Policy Implementation Page](#) for more information.

Existing Datasets or Resources. 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.

For more information about what is considered an existing dataset or resource for inclusion policy, see the NIH [FAQ on Monitoring Inclusion When Working with Existing Datasets and/or Resources](#).

b. **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:

- 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.
- 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.
- 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.

(NOTE: if your study is an [NIH-defined Phase III Clinical Trial](#), see instructions at end of this booklet for additional info needed in this section.

2.5 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.

2.6. Recruitment Status: From the dropdown menu, select a single "Recruitment Status" that best describes the proposed study, based upon the status of the individual sites. If any facility in a multi-site study has an individual site status of “recruiting,” then choose “recruiting” for this question. Only one

selection is allowed. Choose from the following options:

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

2.7 Study Timeline: 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.

Note: Additional milestones or timelines may be requested as just-in-time information or post-award.

2.8 Enrollment of First Subject: Enter the date (MM/DD/YYYY) of the enrollment of the first subject into the study. From the dropdown menu, select whether this date is anticipated or actual.

INCLUSION/ENROLLMENT REPORT

Each proposed study, unless it falls under Exemption 4, must contain at least one Inclusion Enrollment Report (IER). However, more than one IER per study is allowed.

Once you have added an IER for a given study, you may edit, remove, or view it.

Note: The IER format should NOT be used for collecting data from study participants.

Note: You can add a maximum of 20 IERs per study record. These can be a combination of planned and cumulative reports.

Multi-site studies: Generally, if the application includes a study recruiting subjects at more than one site/location, investigators may create one IER or separate, multiple IERs to enable reporting by study or by site, depending on the scientific goals of the study and whether monitoring of inclusion enrollment would benefit from being combined or separated. At a minimum, participants enrolled at non-U.S. sites must be reported separately from participants enrolled at U.S. sites, even if they are part of the same study. Please review the FOA to determine whether there are any other specific requirements about how to complete the IER.

Duplicative Inclusion Reports: It is important that the IER for a given study be associated with only one application and be provided only once in a given application (e.g., do not submit the same IER on both the data coordinating center and the research site). If submitting individual application(s) as part of a network or set of linked applications, please provide the IER with the individual site applications unless otherwise directed by the FOA.

Renewal applications: When preparing a renewal (or resubmission of a renewal), investigators should provide a narrative description regarding the cumulative enrollment from the previous funding period (s) as part of the progress report section of the research strategy attachment in the application. The IER should NOT be used for this purpose. If a given study will continue with the same enrollment or additional enrollment, or if new studies are proposed, provide a new IER for each as described in the instructions below.

Resubmission applications: If IERs were provided in the initial submission application, and if those

studies will be part of the resubmission application, complete the IER and submit again with the resubmission application, regardless of whether the enrollment has changed or not. Also, provide any new (additional) IERs.

Revision applications: Provide an IER if new studies are planned as part of the Revision and they meet the NIH definition for [clinical research](#).

Comments: In this section of the inclusion/enrollment report, you may enter information you wish to provide about this IER. This includes, but is not limited to, addressing information about distinctive subpopulations if relevant to the scientific hypotheses being studied. If inclusion monitoring is conducted on another study or NIH grant (e.g., data coordinating center or research site), please indicate here.

PLANNED ENROLLMENT TABLE

You must enter planned enrollment counts if your proposed study will **not** use an existing dataset or resource. Planned enrollment generally means that individuals will be recruited into the study and/or that individuals have already been recruited and continue to be part of the study.

For more information about what is considered an existing dataset or resource for inclusion policy, see the NIH [FAQs on Monitoring Inclusion When Working with Existing Datasets and/or Resources](#).

For more information on racial categories, see the NIH Glossary definition of [Racial Categories](#). For more information on ethnic categories, see the NIH Glossary definition of [Ethnic Categories](#).

CUMULATIVE (ACTUAL) ENROLLMENT TABLES

You must enter cumulative enrollment counts if your proposed study will use an existing dataset or resource.

For more information about what is considered an existing dataset or resource for inclusion policy, see the NIH [FAQs on Monitoring Inclusion When Working with Existing Datasets and/or Resources](#).

For more information on racial categories, see the NIH Glossary definition of [Racial Categories](#). For more information on ethnic categories, see the NIH Glossary definition of [Ethnic Categories](#).

Section 3: Protection and Monitoring Plans

For Human Subjects Research Claiming Exemptions: If you are claiming that your human subjects research falls under any exemptions, 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.

For Studies that involve Non-Exempt Human Subjects Research: For any proposed non-exempt study involving human subjects, NIH requires a Protection of Human Subjects write-up that is commensurate with the risks of the study, its size, and its complexity. Organize your attachment into four sections, following the headings and specified order below, and discuss each of the points listed below. Start each section with the appropriate section heading given below.

Risks to Human Subjects

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.

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.

Adequacy of Protection against Risks

- 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.
- **For research involving children:** 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](#)). See the HHS page on [Research with Children FAQs](#) and the NIH page on [Requirements for Child Assent and Parent/Guardian Permission](#).
- 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 unless you are requested to do so.

Protections against Risk

- Describe planned strategies for protecting against or minimizing all potential risks identified, including strategies to manage and protect the privacy of participants and confidentiality of research data.
- 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.

Vulnerable Subjects, if relevant to your study

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. 'Prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers).

Pregnant Women, Fetuses, and Neonates or Children

If the study involves vulnerable subjects subject to additional protections under Subparts B and D (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.

HHS' [Subpart B - Additional Protections for Pregnant Women, Fetuses, and Neonates](#)

HHS' [Subpart D - Additional Protections for Children](#)

OHRP Guidance on Subpart D [Special Protections for Children as Research Subjects](#) and the [HHS 407 Review Process](#)

Prisoners: If the study involves vulnerable subjects subject to additional protections under Subpart C (prisoners), describe how proposed research meets the additional regulatory requirements, protections, and plans to obtain OHRP certification for the involvement of prisoners in research.

Refer to HHS regulations, and OHRP guidance:

HHS' [Subpart C - Additional Protections Pertaining to Prisoners as Subjects](#)

OHRP Subpart C Guidance on [Involvement of Prisoners in Research](#)

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.

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.

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?

Select "Yes" or "No" to indicate whether this is a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site.

Select "N/A" only if any of the following apply (do not select "N/A" if none of the following apply):

- You answered "Yes" to "[Question 1.2 Is this Study Exempt from Federal Regulations? \(Yes/No\)](#)"
- You are a career development applicant
- You are a training applicant
- You are a fellowship applicant

Applicants who check "Yes" 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.

Note: The NIH sIRB policy applies to participating domestic sites. Foreign sites participating in NIH-funded, multi-site studies are not expected to follow this policy.

What to write: If yes, describe the single IRB plan

Although one sIRB attachment per application is sufficient, you must include a file for each study within your application. All file names within your application must be unique. You may either attach the same sIRB plan (with different file names) to different studies or attach a file that refers to the sIRB plan in another study within your application. For example, you may attach a file that says "See sIRB plan in the 'My Unique Study Name' study."

Content: The sIRB plan should include the following elements:

- Describe how you will comply with the [NIH Policy on the Use of sIRB for Multi-Site Research](#).
- 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.

Note: If your human subjects study meets the agency definition of "[Delayed Onset](#)," include information regarding how the study will comply with the NIH single Institutional Review Board (sIRB) policy prior to initiating any multi-site study in the [delayed onset study justification](#).

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.

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. NIH will determine whether to grant an exception following an assessment of the need. **Note:** If you intend to request an exception to the sIRB policy based on compelling

justification, do not account for this exception in your proposed budget. The proposed budget must reflect any necessary sIRB costs without an exception (i.e., applicants should not assume that an exception will be granted when considering what sIRB costs to include in the budget).

Data and Safety Monitoring Plan: This plan is required if you answered “yes” to all the questions in the Clinical Trial Questionnaire and you are conducting a clinical trial. This write up is optional for all other human subjects research.

For any proposed clinical trial, NIH requires a data and safety monitoring plan (DSMP) that is commensurate with the risks of the trial, its size, and its complexity. Provide a description of the DSMP, 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 IRB, the person or group responsible for monitoring, the awarding IC, the NIH [Office of Biotechnology Activities](#), 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.

Will a data and safety monitoring board be appointed for this study:

This question is required if you answered “Yes” to all the questions in the “[Clinical Trial Questionnaire](#).” This question is optional for all other human subjects research.

3.5 Overall Structure of the Study Team: This is required if you are conducting a clinical trial. This is optional for other human subjects research.

Provide 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 (i.e., biosketch information).

Section 4: Protocol Synopsis: This section is required if you are conducting a clinical trial.

4.1 Brief Summary: Enter a brief description of objectives of the protocol, including the primary and secondary endpoints. The Brief Summary is limited to 5,000 characters.

4.2 Study Design

a. Narrative Study Description: Enter a narrative description of the protocol. Studies differ considerably in the methods used to assign participants and deliver interventions. Describe your plans for assignment of participants and delivery of interventions. You will also need to show that your methods for sample size and data analysis are appropriate given those plans. For trials that randomize groups or deliver interventions to groups, special methods are required; additional information is available at the [Research Methods Resources](#) webpage.

The narrative description is limited to 32,000 characters.

b. Primary Purpose: Enter or selection from dropdown menu a single “primary purpose” that best describes the clinical trial. Choose from the following options:

- Treatment
- Prevention
- Diagnostics
- Supportive Care
- Screening
- Health Services Research
- Basic Science
- Device Feasibility
- Other (If you select “Other,” provide a description in the space provided. Your response is limited to 255 characters.)

c. Interventions: Complete the “Interventions” fields for each intervention to be used in your proposed protocol. If an arm of the study to which subjects will be assigned (as discussed in [4.2.a. Narrative Study Description](#)) includes more than one intervention (e.g., drug plus educational intervention), complete this section for each intervention. You can add up to 20 interventions.

Intervention Type: Enter or select from the dropdown menu the intervention type the clinical trial will administer during the proposed award. Choose from the following options:

- 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
- Other

Name: Enter the name of the intervention. The name must be unique within each study record. The name is limited to 200 characters.

Description: Enter a description of the intervention. The description is limited to 1,000 characters.

d. Study Phase: Enter or select from the dropdown menu a "[Study Phase](#)" that best describes the clinical trial. If your study involves a device, choose “Other.”

Choose from the following options:

- Early Phase 1 (or Phase 0)
- Phase 1
- Phase 1/2
- Phase 2
- Phase 2/3
- Phase 3
- Phase 4
- Other (If you select “Other,” provide a description in the space provided. Your response is limited to 255 characters.)

e. Intervention Model: Enter or select from the dropdown menu a single "Intervention Model" that best describes the clinical trial. If you select “Other,” provide a description in the space provided. Choose from the

following options:

- Single Group
- Parallel
- Cross-Over
- Factorial
- Sequential
- Other (If you select “Other,” provide a description in the space provided. Your response is limited to 255 characters.)

f. **Masking:** Select “Yes” or “No” to indicate whether the protocol uses [masking](#). Note that masking is also referred to as “blinding.”

If you answered “Yes” to the “Masking” question, select one or more types of masking that best describes the protocol. Choose from the following options:

- Participant
- Care Provider
- Investigator
- Outcomes Assessor
- Allocation

Enter or select from the dropdown menu a single “Allocation” that best describes how subjects will be assigned in your protocol. If allocation is not applicable to your clinical trial, select “N/A” (e.g., for a single-arm trial). Choose from the following options:

- N/A
- Randomized
- Non-randomized

4.3 Outcome Measures: Complete the “Outcome Measures” fields for each primary, secondary, and other important measures to be collected during your proposed clinical trial. You may have more than one primary outcome measure, and you can add up to 50 outcome measures.

Name: Enter the name of the individual outcome measure. The outcome measure must be unique within each study record.

Type: Enter or select from the dropdown menu the type of the outcome measure. Choose from the following options:

- Primary – select this option for the outcome measures specified in your protocol that are of greatest importance to your study
- Secondary – select this option for outcome measures specified in your protocol that are of lesser importance to your study than your primary outcomes
- Other – select this option for additional key outcome measures used to evaluate the intervention.

Time Frame: Indicate when a measure will be collected for analysis (e.g., baseline, post- treatment).

Brief Description: Describe the metric used to characterize the outcome measure if the metric is not already included in the outcome measure name. Your description is limited to 999 characters.

4.4 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 [4.3 Outcome Measures](#).

You will need to 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

4.5 Subject Participant Duration: Enter the time (e.g., in months) it will take for each individual participant to complete all study visits. If the participation duration is unknown or not applicable, write “unknown” or “not

applicable.” The subject participation duration is limited to 255 characters.

4.6 Will the study use an FDA-regulated intervention?

Select "Yes" or "No" to 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).

a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/Investigational Device Exemption (IDE) status:

This attachment is required if you answered "Yes" to the "Will the study use an FDA-regulated intervention?" question.

Describe the availability of study agents and support for the acquisition and administration of the study agent(s). Please indicate the IND/IDE status of the study agent, if applicable, and whether the investigators have had any interactions with the FDA. If the study agent currently has an IND/IDE number, provide that information. **Note:** The awarding component may request consultation with the FDA and the IND/IDE sponsor about the proposed clinical trial after peer review and prior to award.

4.7 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 [policy](#) 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; and
- 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 your application.

Section 5: Other Clinical Trial-related Attachments

This section is only required for proposed clinical trials whose FOA specifies additional requirements. If the FOA does not specify additional requirements, do not include any additional attachments.

Scenario D: Delayed-Onset Human Subjects Research

In rare situations, applications are submitted with the knowledge that human subjects will be involved during the period of support, but plans are so indefinite that it is not possible to describe the involvement of human subjects in the application. The kinds of activities that lack definite plans are often institutional awards where the selection of specific projects is made by the institution after award, research networks or multi-site studies where protocols to be conducted are determined after all sites have been selected, or projects in which the involvement of human subjects depends upon initial work in the award such as completion of instruments, animal studies, or purification of compounds.

If any of your human subjects studies meet the agency definition of "[delayed onset human subject study](#)," enter the information as instructed below. For any study that you include as a delayed onset study in this section, do not fill out a full [study record](#), as the delayed onset record is sufficient.

The definition of delayed onset is: ***Human subjects research is anticipated within the period of award but definite plans for this involvement cannot be described in the application.***

Notes on delayed onset studies:

- Delayed onset does NOT apply to a study that can be described but will not start immediately (i.e.,

delayed start).

- If you have multiple delayed onset studies, you can include them together in a single Delayed Onset Study.

Study Title of Delayed Onset Study: This field is required. (600 character limit)

Enter a brief, unique title that describes the study the participants will be involved in. Each study within your application must have a unique Study Title. The first 150 characters will display in the application image bookmarks.

Note on multiple delayed onset studies: If you are including multiple delayed onset studies in one delayed onset study entry, you may enter “Multiple Delayed Onset Studies” as the title of this record.

Anticipated Clinical Trial? Check this box if you anticipate that this study will be a clinical trial. (see four questions above).

Read your FOA carefully to determine whether clinical trials are allowed in your application.

Note on multiple delayed onset studies: If you are including multiple delayed onset studies in one delayed onset study entry, and you anticipate that any of these studies will be a clinical trial, check the “Anticipated Clinical Trial?” checkbox.

Justification for Delayed Onset: Write a justification that includes the following:

Explain why human subjects study information is not available at the time of application.

If [NIH'sSingleInstitutionalReviewBoard\(sIRB\)policy](#) will apply to your study, this justification must also include information regarding how the study will comply with the policy and state that you will provide a [singleIRBplan](#) prior to initiating any multi-site study.

If [NIH'sPolicyontheDisseminationofNIH-FundedClinicalTrialInformation](#) will apply to your study, this justification must also include the [disseminationplan](#).

Note on multiple delayed onset studies: 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.

ADDITIONAL INSTRUCTIONS FOR SPECIAL CIRCUMSTANCES

NIH-Defined Phase III Clinical Trials. If the proposed research includes an [NIH-Defined Phase III Clinical Trial](#), the “Inclusion of Women, Minorities, and Children” attachment MUST 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](#).
[Valid Analysis](#) (for NIH-Defined Phase III Clinical Trials only):

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; 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 such differences exist.

Plan to Test for Differences in Effect among Sex/gender, Racial, and/or Ethnic Groups (for NIH- Defined

Phase III Clinical Trials only):

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.

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 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.
- 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.

OVERALL CONSIDERATIONS AND WRITING TIPS

1. *Observe application guidelines strictly.*
2. *Use basic English and avoid jargon.*
3. *Make sure all acronyms are spelled out when used initially.*
4. *Observe the type size and page limitations; Arial 11 point font and margins .5" all the way around.*
5. *Include only those graphs, tables, etc., that are unpublished and essential to the narrative.*
6. *Make sure all citations are complete: title, authors, book or journal, volume number, inclusive pages, year of publication. When citing articles that fall under the Public Access Policy, provide the NIH Manuscript Submission reference number (e.g., NIHMS97531) or the PubMed Central (PMC) reference number (e.g., PMCID234567) for each article. Citations that are not covered by the Public Access Policy, but are publicly available in a free, online format may include URLs or PMCID numbers along with full ref.*
7. *Make sure you work with a mentor and/or peer reviewers; have an outside reader review the application for clarity and consistency. Editing and proofing services are available in the Grants and Contracts Office.*