U.S. Department of Health and Human Services
Public Health Service
Supplemental Grant Application Instructions
For All Competing Applications and Progress Reports
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PART II

Supplemental Instructions for Preparing the Protection of Human Subjects Section of the Research Plan
1. Introduction

A Protection of Human Subjects section of the Research Plan is required for all applications submitted using the PHS 398 and SF424 (R&R) instructions and forms. The information provided in the section on Protection of Human Subjects should be consistent with the information provided on the face page of the application.

For all research involving human subjects, the Scientific Review Group (SRG) will assess the adequacy of protections for research participants against research risks, and the scientifically appropriate inclusion of women, minorities, and children, based on the information provided in the application.

To assist in preparing the section on Protection of Human Subjects, six possible scenarios are provided in Section 2 below. All research projects will fall into one of these six scenarios. (To help determine whether research that involves the use of human data or biological specimens is human subjects research, refer to this Web site: http://grants.nih.gov/grants/policy/hs/) Determine which scenario the proposed research falls into, then go to the specific instructions applicable to that scenario in Section 3. Where appropriate, Section 3 provides instructions on addressing the Inclusion of Women and Minorities, the Planned Enrollment Reports(s), and the Inclusion of Children. All definitions related to human subjects research are linked to text found in Part III.3 under Human Subjects Research Definitions and Terms. Section 5 of this Part includes descriptions of and links to the DHHS Human Subjects Protections regulations and NIH policies that apply to clinical research.

Do not use the human subjects section to circumvent the page limit of the Research Strategy.

While this information is written primarily for competing applications, guidance here may also be applicable to interim progress reports.

2. Scenarios

Scenario A. No Human Subjects Research

If no human subjects research is proposed in the application, you will have designated “No” in response to Human Subjects Research on the PHS 398 face page (or on the SF424 (R&R) Other Project Information Form). If your proposed research involves the use of human data and/or biological specimens, you must provide a justification for your claim that no human subjects are involved in the Protection of Human Subjects section of the Research Plan.

See the instructions for Scenario A.

Unless you are providing a special justification as described above, no additional information is necessary if no human subjects are involved.

Scenario B. Non-Exempt Human Subjects Research

If research involving human subjects is anticipated to take place under the award, you will have designated “Yes” in response to Human Subjects Research on the PHS 398 face page (or on the SF424 (R&R) Other Project Information Form where you will have entered your assurance number). In the Protection of Human Subjects section of the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR part 46), and (2) the requirements of NIH policies on inclusion of women, minorities, and children. Research involving a clinical trial will fall under either Scenario E or F below.

See the instructions for Scenario B.
Scenario C. Exempt Human Subjects Research

If all of the proposed human subjects research meets the criteria for one or more of the exemptions from the requirements in the DHHS regulations (46.101(b), “yes” should be designated in response to Human Subjects Research as well as Research Exempt on the PHS 398 face page (or Yes should be designated in response to “Are Human Subjects Involved?” on the SF424 (R&R) Other Project Information Form, the appropriate exemption number should be checked, and “NA” should be entered for the Human Subject Assurance Number since no OHRP assurance number is required for exempt research). In the section on Protection of Human Subjects in the Research Plan (or on the PHS Fellowship Supplemental Form for Fellowship applicants), provide a justification for the exemption(s) containing sufficient information about the involvement of the human subjects to allow a determination by peer reviewers and NIH staff that claimed exemption(s) is/are appropriate.

The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. When in doubt, consult with the Office for Human Research Protections (OHRP), Department of Health and Human Services by accessing their Web site http://www.hhs.gov/ohrp/ for guidance and further information.


Unless the research meets the requirements for Exemption 4, the investigator(s) must address the requirements of NIH policies on the inclusion of women, minorities, and children.

Please note: if the proposed research involves only the use of human data or biological specimens, you should first determine whether the research involves human subjects. The exemptions do not apply if the research does not involve human subjects. For help determining whether research that involves the use of human data or biological specimens is human subjects research, please refer to this Web site: http://grants.nih.gov/grants/policy/hs/.

See the instructions for Scenario C.

Scenario D. Delayed-Onset Human Subjects Research

If human subjects research is anticipated within the period of the award but plans for involvement of human subjects cannot be described in the application as allowed by the DHHS regulations (45 CFR part 46.118), you will have designated “Yes” to Human Subjects Research on the PHS 398 face page (or you will have designated Yes in response to “Are Human Subjects Involved?” on the SF424 (R&R) Other Project Information Form and entered your OHRP assurance number). In the section on Protection of Human Subjects in the Research Plan (or on the PHS Fellowship Supplemental Form for Fellowship applicants), you should either include an explanation of anticipated protections for human subjects or an explanation of why protections cannot be described.

Examples of delayed-onset of human subjects research include:

- Human subjects research is dependent upon the completion of animal or other studies; or
- Human subjects research protocols to be included will undergo an independent decision-making process (often defined by a FOA).

See instructions for Scenario D.

Scenario E. Human Subjects Research Involving a Clinical Trial

If research involving human subjects is anticipated to take place under the award, and you intend to conduct a clinical trial during the project period, you will have designated “Yes” in Human Subjects Research on the PHS 398 face page, “No” in in response to Research Exempt on the PHS 398 face page, and “Yes” in response to Clinical Trial on the PHS 398 face page (or you will have designated Yes in response to “Are Human Subjects Involved?” on the SF424 (R&R) Other Project Information Form, entered your OHRP assurance number, and
checked “Yes” to Clinical Trial on either the PHS 398 Cover Page Supplement Form or on the PHS Fellowship Supplemental Form).

In the section on Protection of Human Subjects in the Research Plan (or on the PHS Fellowship Supplemental Form for Fellowship applicants), you must provide sufficient information for reviewers to determine that the proposed research meets:

1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR part 46);
2) NIH policy requirements for Data and Safety Monitoring for Clinical Trials;
3) the ClinicalTrials.gov requirements if applicable;
4) the requirements of NIH policies on inclusion of women, minorities, and children; and
5) the requirements of NIH policy on reporting race and ethnicity data for human subjects in NIH-defined clinical research.

See instructions for Scenario F.

Scenario F. Human Subjects Research Involving an NIH-Defined Phase III Clinical Trial

If research involving human subjects is anticipated to take place under the award, and you intend to conduct an NIH-defined Phase III clinical trial during the project period, you will have designated “Yes” in response to Human Subjects Research on the PHS 398 face page, “No” in response to Research Exempt on the PHS 398 face page, and “Yes” in response to NIH-defined Phase III Clinical Trial on the PHS 398 face page (or you will have designated Yes in response to “Are Human Subjects Involved?” on the SF424 (R&R) Other Project Information Form, entered your OHRP assurance number, and checked “Yes” to Agency-Defined Phase III Clinical Trial on the PHS 398 Cover Page Supplement Form on the PHS Fellowship Supplemental Form). In the section on Protection of Human Subjects in the Research Plan (on the PHS Fellowship Supplemental Form for Fellowship applicants), you must provide sufficient information for reviewers to determine that the proposed research meets:

1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR part 46);
2) NIH policy requirements for Data and Safety Monitoring for Clinical Trials;
3) the ClinicalTrials.gov requirements if applicable;
4) the requirements of NIH policies on inclusion of women, minorities, and children;
5) the requirements of NIH policy on reporting race and ethnicity data for subjects in NIH-defined clinical research; and
6) additional requirements for NIH-defined Phase III clinical trials.

See instructions for Scenario F.

3. Instructions for Preparing the Section on Protection of Human Subjects

Scenario A. No Human Subjects Research Proposed

Criteria

| Human Subjects Research | No |
| Exemption Claimed       | No |
| Clinical Trial          | N/A |

Supplemental Instructions for PHS 398 and SF424 (R&R)
NIH-Defined Phase III Clinical Trial

Instructions and Required Information

If proposed studies using human data or biological specimens do not involve human subjects, provide an explanation of why the proposed studies do not constitute research involving human subjects.

In the application narrative for paper PHS398 applications, 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.” For electronic SF424 (R&R) applications, save this explanation as a .pdf file entitled “Human Subjects Research.pdf” and attach at the “Protection of Human Subjects” item of the PHS 398 Research Plan (for K applicants, this is located on the PHS 398 Career Development Award Supplemental Form; for F applicants, on the PHS Fellowship Supplemental Form – Research Training Plan).

The explanation could include: a description of the source of the data/biospecimens and whether there is any intervention or interaction with the subjects in order to obtain the specimens and data; what identifiers will be associated with the human specimens and data and who has access to subject identities; the role(s) of providers of the data/biological specimens in the proposed research; and the manner by which the privacy of research participants and confidentiality of data will be protected.

Research that does not involve intervention or interaction with living individuals, or identifiable private information, is not human subjects research (see Definitions in Part III.3). 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 (http://www.hhs.gov/ohrp/policy/cdebiol.html).

Research that only proposes the use of cadaver specimens is not human subjects research because human subjects are defined as “living individuals.” The use of cadaver specimens is not regulated by 45 CFR part 46, but may be governed by other Federal, State or local laws.

Scenario B. Non-Exempt Human Subjects Research

Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Subjects Research</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exemption Claimed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIH-Defined Phase III Clinical Trial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Instructions and Required Information

Although no specific page limitation applies to this section of the application, be succinct.

In the application narrative for paper PHS398 applications, create a section entitled “Protection of Human Subjects” and create a subheading for each of the following items. For electronic SF424 (R&R) applications, provide the required information as a separate file. For applications using Forms B application packages, save each of the four files as a .pdf file and attach in of the Human Subjects Sections of the PHS 398 Research Plan (for K applicants, the PHS 398 Career Development Award Supplemental Form; for F applicants, the PHS Fellowship Supplemental Form – Research Training Plan). For applications using Forms C application packages, Protection of Human Subjects, Inclusion of Women and Minorities, and Inclusion of Children remain an upload in the Research Plan Form. However, the Planned Enrollment Report is now a separate Form in the application package.

Follow the instructions that are identified for each of the following topics and provide the required information:

Protection of Human Subjects - Section 4.1 - 4.1.4

Supplemental Instructions for PHS 398 and SF424 (R&R)
Inclusion of Women and Minorities - Section 4.2
Planned Enrollment Reports(s) - Section 4.3
Inclusion of Children - Section 4.4

If the research involves collaborating sites or subprojects, provide the information identified above for each participating site.

Scenario C: Human Subjects Research Claiming Exemption 1, 2, 3, 4, 5, or 6

Criteria

<table>
<thead>
<tr>
<th>Human Subjects Research</th>
<th>Exemption Claimed</th>
<th>Clinical Trial</th>
<th>NIH-Defined Phase III Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>1, 2, 3, 4, 5, or 6</td>
<td>Yes or No</td>
<td>No</td>
</tr>
</tbody>
</table>

Instructions and Required Information

Although no specific page limitation applies to this section of the application, be succinct. The exemptions appear in Part III under Human Subjects Research Definitions and Terms.

Although the research may be exempt from the DHHS regulatory requirements, it is still research involving human subjects and the application must follow the instructions that are identified for each of the following topics and provide the information that is requested.

In the application narrative for paper PHS398 applications, provide the required information for each of the following topics below. For electronic SF424 (R&R) applications, provide the required information for each of the following topics below as a separate files. For applications using Forms B application packages, save each of the four files as a .pdf file and attach in the Human Subjects Sections of the PHS 398 Research Plan (for K applicants, the PHS 398 Career Development Award Supplemental Form; for F applicants, the PHS Fellowship Supplemental Form - Research Training Plan). For applications using Forms C application packages, Protection of Human Subjects, Inclusion of Women and Minorities, and Inclusion of Children remain an upload in the Research Plan Form. However, the Planned Enrollment Report is now a separate Form in the application package.

Protection of Human Subjects - Include the following statement: “This Human Subjects Research falls under Exemption(s) ...” Clearly identify which exemption(s) (1, 2, 3, 4*, 5, or 6) you are claiming and justify why the research meets the criteria for the exemption(s) that you have claimed.

If the research will include a clinical trial, even if exempt, include a Data and Safety Monitoring Plan – Section 4.1.5, and address the ClinicalTrials.gov requirements if applicable – Section 4.1.6.

Inclusion of Women and Minorities - Section 4.2
Planned Enrollment Report(s) - Section 4.3
Inclusion of Children - Section 4.4

*NOTE: If all of the proposed research meets the criteria for Exemption 4, then the requirements for inclusion of women and minorities, planned enrollment report(s), and inclusion of children, do not need to be addressed.
Scenario D: Delayed-Onset Human Subjects Research

Criteria

<table>
<thead>
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</tr>
<tr>
<td>Exemption</td>
<td>Yes or No</td>
</tr>
<tr>
<td>Clinical Trial</td>
<td>Yes or No</td>
</tr>
<tr>
<td>NIH-Defined Phase III Clinical Trial</td>
<td>Yes or No</td>
</tr>
</tbody>
</table>

Instructions and Required Information

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 the institution's responsibility, research training grants, and projects in which the involvement of human subjects depends upon completion of instruments, animal studies, or purification of compounds.

If the involvement of human subjects cannot be fully described, create a heading entitled “Protection of Human Subjects” and provide a detailed explanation why it is not possible to develop definite plans at this time. The explanation should be specific and directly related to the Specific Aims in the application. If the involvement of human subjects depends upon information that is not presently available (e.g., completion of instruments, animal studies, purification of compounds), be explicit about the information and the factors affecting the availability of the information. Describe the information that will be necessary in order to develop definite plans for the involvement of human subjects, why that information is not currently available, and when the information is expected to become available during the course of the project.

If an award is made, prior to the involvement of human subjects the grantee must submit to the NIH awarding office for prior approval either (1) detailed information as required in the Research Plan, Protection of Human Subjects (addressing risks to the subjects, adequacy of protection against risks, potential benefits of the proposed research, importance of the knowledge to be gained, and data and safety monitoring plan if applicable) and certification of IRB approval, OR (2) if all of the research meets the criteria for one or more exemptions, identification of which exemption(s) is/are applicable to the research, and a justification for the exemption with sufficient information about the involvement of human subjects to allow a determination that the claimed exemption is appropriate. For NIH-defined clinical research, the request for prior approval must also address plans for the inclusion of women and minorities, the inclusion of children, and provide completed Planned Enrollment Report(s) as required in the Research Plan.

Under no circumstance may human subjects be involved in research until approval is granted by the awarding entity, and certification of IRB approval has been accepted by the agency.

In the application narrative for paper PHS398 applications, create a section entitled Protection of Human Subjects and a subheading for each of the following items. For electronic SF424 (R&R) applications, provide the required information for each of the following topics below as a separate file. For applications using Forms B application packages, save each of the four files as a .pdf file and attach in the Human Subjects Section of the PHS 398 Research Plan (for K applicants, the PHS 398 Career Development Award Supplemental Form; for F applicants, the PHS Fellowship Supplemental Form - Research Training Plan). For applications using Forms C application packages, Protection of Human Subjects, Inclusion of Women and Minorities, and Inclusion of Children remain an upload in the Research Plan Form. However, the Planned Enrollment Report is now a separate Form in the application package.

Follow the instructions that are identified for each of the following topics and EITHER provide as much of the information that is requested as possible, OR describe why it is not possible to provide the information due to delayed-onset of human subjects research:
Protection of Human Subjects - Section 4.1 - 4.1.4
If the research will include a clinical trial, include a Data and Safety Monitoring Plan - Section 4.1.5, and address the ClinicalTrials.gov requirements if applicable – Section 4.1.6.
Inclusion of Women and Minorities - Section 4.2
Planned Enrollment Report(s) - Section 4.3
Inclusion of Children - Section 4.4

Scenario E: Clinical Trial

Criteria

Human Subjects Research: Yes
Exemption: Yes or No
Clinical Trial: Yes
NIH-Defined Phase III Clinical Trial: No

Instructions and Required Information

In the application narrative for paper PHS398 applications, create a section entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research meets the definition of a clinical trial.” (See definition of “clinical trial” under Part III.3.) Create a subheading for each of the following items below. For electronic SF424 (R&R) applications, provide the required information for each of the following topics below as a separate file. For applications using Forms B application packages, save each of the four files as a .pdf file and attach in the Human Subjects Sections of the PHS 398 Research Plan (for K applicants, the PHS 398 Career Development Award Supplemental Form; for F applicants, the PHS Fellowship Supplemental Form - Research Training Plan). For applications using Forms C application packages, Protection of Human Subjects, Inclusion of Women and Minorities, and Inclusion of Children remain an upload in the Research Plan Form. However, the Planned Enrollment Report is now a separate Form in the application package.

Follow the instructions that are identified for each of the following topics and provide the required information:

Protection of Human Subjects - Section 4.1 - 4.1.6
Inclusion of Women and Minorities - Section 4.2
Planned Enrollment Report(s) - Section 4.3
Inclusion of Children - Section 4.4

If the research involves collaborating sites or subprojects, provide the information identified above for each participating site.

Scenario F: NIH Defined Phase III Clinical Trial

Criteria

Human Subjects Research: Yes
Exempt: No
Clinical Trial: Yes
NIH-Defined Phase III Clinical Trial: Yes
Instructions and Required Information

In the application narrative for paper PHS398 applications, create a section entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research involves an NIH-Defined Phase III Clinical Trial.” (See definition of "NIH defined Phase III Clinical Trial" in Part III.3.). Create a subheading for each of the items below. For electronic SF424 (R&R) applications, provide the required information for each of the following topics below as a separate file. For applications using Forms B application packages, save each of the four files as a .pdf file and attach in the Human Subjects Sections of the PHS 398 Research Plan (for K applicants, the PHS 398 Career Development Award Supplemental Form; for F applicants, the PHS Fellowship Supplemental Form - Research Training Plan). For applications using Forms C application packages, Protection of Human Subjects, Inclusion of Women and Minorities, and Inclusion of Children remain an upload in the Research Plan Form. However, the Planned Enrollment Report is now a separate Form in the application package.

Follow the instructions that are identified for each of the following topics and provide the required information:

- Protection of Human Subjects - Section 4.1 - 4.1.6
- Inclusion of Women and Minorities - Section 4.2
- Additional Instructions and Requirements when NIH-Defined Phase III Clinical Trials are Proposed - Section 4.2.1
- Planned Enrollment Report(s) - Section 4.3
- Inclusion of Children - Section 4.4

If the research involves collaborating sites or subprojects, provide the information identified above for each participating site.

4. Instructions Pertaining to Non-Exempt Human Subjects Research

In your application narrative for paper PHS398 applications, create a section entitled “Protection of Human Subjects.” For electronic SF424 (R&R) applications using Forms B application packages, include attachments in the Human Subjects Sections in the PHS398 Research Plan Form (for F applicants, the PHS Fellowship Supplemental Form - Research Training Plan), if required. For applications using Forms C application packages, Protections of Human Subjects, Inclusion of Women and Minorities, and Inclusion of Children remain an upload in the Research Plan Form. However, the Planned Enrollment Report is now a separate Form in the application package. Although no specific page limitation applies to this section of the application, be succinct. Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the protection of human subjects. DHHS regulations and policies governing human subjects research are described and referenced in Section 5 below. Use subheadings to address the issues listed under items 4.1-4.4 below. If your research includes a clinical trial, include a subheading "Data and Safety Monitoring Plan" and follow the instructions in 4.2 below. If your research includes an NIH-Defined Phase III Clinical Trial, follow the additional instructions in 4.2.1 below.

4.1 Protection of Human Subjects

4.1.1 Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

- Describe and justify the proposed involvement of human subjects in the work outlined in the Research Strategy section.
• Describe the characteristics of the subject population, including their anticipated number, age range, and health status if relevant.

• Describe and justify the sampling plan, as well as the recruitment and retention strategies and the criteria for inclusion or exclusion of any subpopulation.

• Explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.

• If relevant to the proposed research, describe procedures for assignment to a study group. As related to human subjects protection, describe and justify the selection of an intervention’s dose, frequency and administration.

• List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.

b. **Sources of Materials**

• Describe the research material obtained from living individuals in the form of specimens, records, or data.

• Describe any data that will be collected from human subjects for the project(s) described in the application.

• Indicate who will have access to individually identifiable private information about human subjects.

• Provide information about how the specimens, records, and/or data are collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.

c. **Potential Risks**

• Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects.

• Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

4.1.2 **Adequacy of Protection Against Risks**

a. **Recruitment and Informed Consent**

• Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.

• Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. **Protections Against Risk**

• Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
• Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections. Refer to DHHS regulations, and OHRP guidance:
  o Additional Protections for Pregnant Women, Human Fetuses and Neonates: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb
  o Additional Protections for Prisoners: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc
  o OHRP Subpart C Guidance: http://www.hhs.gov/ohrp/policy/index.html#prisoners
  o Additional Protections for Children: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd
  o OHRP Subpart D Guidance: http://www.hhs.gov/ohrp/policy/index.html#children

• Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a general description of the plan for data and safety monitoring of the clinical trials and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.

4.1.3 Potential Benefits of the Proposed Research to Human Subjects and Others

• Discuss the potential benefits of the research to research participants and others.

• Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

4.1.4 Importance of the Knowledge to be Gained

• Discuss the importance of the knowledge gained or 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.

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

4.1.5 Data and Safety Monitoring Plan

The NIH Data and Safety Monitoring Policy is described and referenced in Section 5.3.

• If the proposed research includes a clinical trial, create a heading entitled "Data and Safety Monitoring Plan."

• Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (http://www.fda.gov/) and also see the following Web sites for more information related to IND and IDE requirements:
The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:

a. PD/PI (required)

b. Institutional Review Board (IRB) (required)

c. Independent individual/safety officer

d. Designated medical monitor

e. Internal Committee or Board with explicit guidelines

f. Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of Data and Safety Monitoring Boards (DSMBs) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also need DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.

A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. For additional guidance on creating this Plan see [http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html).

### 4.1.6 ClinicalTrials.gov Requirements

Public Law 110-85 (also known as the FDA Amendments Act (FDAAA) of 2007) mandates registration and results reporting of "applicable clinical trials" in ClinicalTrials.gov. Under the statute these trials generally include: (1) **Trials of Drugs and Biologics**: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) **Trials of Devices**: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. Review the statutory definition of applicable clinical trial to identify if registration is required to comply with the law (See [PL 110-85](https://www.congress.gov/bill/110th-congress/house-bill/85), Section 801(a), adding new 42 U.S.C. 282(j)(1)(A)).

NIH encourages registration of ALL clinical trials whether required under the law or not.

Registration is accomplished at the ClinicalTrials.gov Protocol Registration System Information Web site ([http://prsinfo.clinicaltrials.gov/](http://prsinfo.clinicaltrials.gov/)). A unique identifier called an NCT number, or ClinicalTrials.gov registry number, will be generated during the registration process.

The NIH implementation of FDAAA requires:

- the registration of applicable clinical trials in ClinicalTrials.gov no later than 21 days after the first subject is enrolled,

- the reporting of summary results information (including adverse events) no later than 1 year after the completion date for registered applicable clinical trials involving drugs that are approved under section 505 of the Food, Drug and Cosmetic Act (FDCA) or licensed under section 351 of the PHS Act, biologics, or of devices that are cleared under section 510k of FDCA, and

- if an "applicable clinical trial" is funded in whole or in part by an NIH grant or cooperative agreement, grant and progress report forms shall include a certification that the responsible party has made all required submissions to ClinicalTrials.gov.

For competing new and renewal applications that include applicable clinical trials which require registration and results reporting under FDAAA, provide the NCT number/s in the human subjects section of the Research Plan under a section heading entitled ClinicalTrials.gov.
The entity responsible for registering the trial is the “responsible party”. The statute defines the responsible party as:

(1) the sponsor of the clinical trial (as defined in 21 CFR 50.3) (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.3), or

(2) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee (provided that “the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements” for submitting information under the law) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)(ix)).

For the complete statutory definitions of "responsible party" and "applicable clinical trial," refer to Elaboration of Definitions of Responsible Party and Applicable Clinical Trial.

The signature on the application of the Authorized Organization Representative assures compliance with FDAAA.

Additional information can be found on the ClinicalTrials.gov Web site (http://grants.nih.gov/ClinicalTrials_fdaaa/).

### 4.2 Inclusion of Women and Minorities

Create a section heading entitled "Inclusion of Women and Minorities" and place it immediately following the "Protection of Human Subjects" section. Although no specific page limitation applies to this section of the application, be succinct. The NIH Policy on the Inclusion of Women and Minorities in Clinical Research is described and referenced in Section 5.6. Additional information and guidance can be found at: http://grants.nih.gov/grants/funding/women_min/women_min.htm.

Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the scientifically justified inclusion (or exclusion) based on sex/gender, race, and ethnicity in NIH-defined clinical research.

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

1. Describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study and complete the format in the Planned Enrollment Report. (Instructions for completing this table are provided below in Section 4.3.)

Additional guidance for research utilizing existing datasets:

- If using existing datasets or specimens that meet the NIH definition for clinical research and information about sex/gender, race, and ethnicity is available, this information should be described as with any other type of study.
- If using existing datasets or specimens that meet the NIH definition for clinical research but without access to information on the distribution by sex/gender, race, and/or ethnicity, so state and explain the impact on the goals of the research as part of the rationale that inclusion cannot be described.
- For an existing dataset or specimens, use the Cumulative Inclusion Enrollment Report rather than the Planned Enrollment Report. Additional guidance is available under Section 4.3.

2. Describe the subject selection criteria and rationale for selection of sex/gender, racial, and ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.

3. Provide a compelling rationale for proposed sample specifically addressing exclusion of any sex/gender, racial, or ethnic group that comprises the population under study (see examples below).
4. Describe proposed outreach programs for recruiting sex/gender, racial, and ethnic group members as subjects.

Below are examples of acceptable justifications for the exclusion of:

A. **One sex/gender:**
   1. One sex/gender is excluded from the study because:
      - inclusion of these individuals would be inappropriate with respect to their health;
      - the research question addressed is relevant to only one sex/gender;
      - evidence from prior research strongly demonstrates no difference between sexes/genders; or
      - sufficient data already exist with regard to the outcome of comparable studies in the excluded sex/gender, and duplication is not needed in this study.

   2. One sex/gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by sex/gender (e.g., uniquely valuable stored specimens or existing datasets are single sex/gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).

   3. Sex/gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete sex/gender documentation are used), and this does not compromise the scientific objectives of the research.

B. **Racial and/or ethnic groups or subgroups:**
   1. Some racial and/or ethnic groups or subgroups are excluded from the study because:
      - inclusion of these individuals would be inappropriate with respect to their health;
      - the research question addressed is relevant to only specific racial or ethnic groups;
      - evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
      - a specific racial or ethnic group(s) study is proposed to fill a research gap; or
      - sufficient data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.

   2. Some racial or ethnic groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:
      - the size of the study;
      - the relevant characteristics of the disease, disorder or condition; or
      - the feasibility of making a collaboration or consortium or other arrangements to include representation. In general, cost is not an acceptable justification for exclusion.

   3. Some racial or ethnic groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant’s selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited racial and/or ethnic representation, very small numbers of subjects are involved, or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens), and this does not compromise the scientific objectives of the research.

   4. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial and/or ethnic documentation are used) and this does not compromise the scientific objectives of the research.
4.2.1 Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

If the proposed research includes an NIH-Defined Phase III Clinical Trial, the section on Inclusion of Women and Minorities also must address whether clinically important sex/gender, racial, and/or ethnic differences are expected from the intervention effect. The discussion may include supporting evidence and/or data derived from animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies as well as observational, natural history, epidemiology and/or other relevant studies. The discussion of expected sex/gender, racial, and ethnic differences in intervention effect must include selection and discussion of one of the following analysis plans:

- Plans to conduct valid 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 subgroups, or
- Plans to include and analyze sex/gender, racial, and/or ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender, racial, and ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), or
- Plans to conduct valid analyses of the intervention effect in sex/gender, racial, and/or ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect among subgroups.

4.3 Instructions for Completing the Enrollment Report(s) for Sex/Gender, Race, and Ethnicity

The NIH Policy on the Inclusion of Women and Minorities in Clinical Research is described in Part II, Section 5.6. The NIH Policy on Reporting Race and Ethnicity Data for Subjects in Clinical Research is described and referenced in Section 5.8.

Instructions for Completing Planned Enrollment Reports

[Link to NIH website for paper applications](http://grants.nih.gov/grants/funding/phs398/phs398.html) for paper applications, [Link to NIH website for electronic applications](http://grants.nih.gov/grants/funding/phs398-phs398.html) for electronic applications using Forms B: SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section 5.8 for electronic applications using Forms C)

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by sex/gender, racial, and ethnic categories using the Planned Enrollment Report(s). See below for additional guidance when working with a study(s) involving an existing dataset or specimens. If the application includes more than one study, provide separate Planned Enrollment Reports for each. At a minimum, studies including foreign subjects (even if part of the same study with domestic subjects) must be reported separately from domestic studies (or studies including domestic subjects). See below for additional guidance under “Research Conducted with Foreign Participants.”

When completing each Planned Enrollment Report:

- Provide a unique study title that will facilitate identification of each Planned Enrollment Report.
- Select whether the study involves domestic or foreign subjects.
- Provide the information as numbers of subjects, not percentages.
- The Total Field on the Planned Enrollment Report (bottom right) means the number of subjects that are expected to be enrolled in the study, consistent with the definition in ClinicalTrials.gov.
• Provide the numeric distribution of individuals on the basis of their sex/gender, ethnicity, and race. Note
that Hispanic/Latino is an ethnic category, not a racial category, and subjects should identify both
ethnicity and race. Subjects are permitted to select more than one race. If the sample is likely to include
individuals who identify with more than one race, they should be accounted for in the “More than one
race” category on the Planned Enrollment Report(s). If including individuals identifying as more than
one race is not expected, enter zeroes in that category.

• Any proposed racial or ethnic subpopulations may be listed in the comment field.

Where to Attach Planned Enrollment Report(s)
For electronic SF424 (R&R) applications using the Forms C package, if your application includes Planned
Enrollment Reports, these will be entered into a structured data form(s). For electronic SF424 (R&R)
applications using the Forms B package, if your application inclusion Planned Enrollment reports, these will be
attached as PDFs after the section describing plans for the inclusion of women and minorities. For paper PHS
398 applications, if your application inclusion includes Planned Enrollment Report(s), these will be inserted
after the section describing plans for the inclusion of women and minorities.

If the application includes a study recruiting subjects at more than one site/location, investigators may create one
Planned Enrollment Report or separate Planned Enrollment Reports (per site), depending on the scientific goals
of the study and whether monitoring of inclusion enrollment would benefit from being combined or separated.

If you are preparing a multi-project application, include the Planned Enrollment Report(s) with the component
that involves the study unless otherwise directed by the FOA. Should your study span more than one subproject,
include the Planned Enrollment Report(s) with only one subproject and insert a comment in the comment field
to indicate what other subprojects it is associated with.

For paper PHS398 applications or electronic SF424 (R&R) Forms B package, if your application involves
subprojects, attach the Planned Enrollment Reports to the relevant component immediately after the section
describing the plans for the inclusion of women and minorities.

NOTE: It is important that the Planned Enrollment Report(s) for a given study only be associated with one
application and provided only once in a given application. If you are submitting a single application as part of a
network or set of linked applications, please provide the Planned Enrollment Report(s) with the individual site
applications unless otherwise directed by the FOA.

Additional Guidance
For additional guidance and FAQs related to inclusion policy and inclusion data forms, please
see: http://grants.nih.gov/grants/funding/women_min/women_min.htm.

Renewal, Resubmission, and Revision Applications
For Renewal applications, investigators should provide information on cumulative enrollment from the
previous funding period(s) as part of the progress report section of the application. The Cumulative
Inclusion Enrollment Report must be used for reporting actual accrual data to the NIH. Where possible,
include the Study Title that is associated with inclusion data from the previous funding period. If
inclusion enrollment from the previous funding period was reported on separate cumulative inclusion
enrollment reports, provide them in the same way. In addition, if a given study will continue with the
same enrollment or additional enrollment, or if new studies are proposed, provide a new Planned
Enrollment Report for each.

For Resubmission applications, if Enrollment Report(s) (Planned or Cumulative) were provided in the
initial submission application and those studies will be part of the resubmission application, please
submit again with the revision application, regardless of whether the enrollment has changed or not.
Also, any new (additional) Planned Enrollment Report(s) should be provided.
For Revision applications, investigators should provide a Planned Enrollment Report(s) if new studies are planned as part of the Revision and they meet the NIH definition for clinical research.

**Research Conducted with Existing Datasets**

Any application (New, Renewal, Resubmission, Revision) using existing datasets or specimens that meet the NIH definition for clinical research, you should complete the Cumulative Inclusion Enrollment Report(s) rather than the Planned Enrollment Report, even if the entire sample is unknown/not reported. Please note in the Comment field that you are working with an existing dataset. For additional guidance on working with existing datasets see: [http://grants.nih.gov/grants/funding/women_min/women_min.htm](http://grants.nih.gov/grants/funding/women_min/women_min.htm).

**Research Conducted with Foreign Participants**

If proposed studies involve foreign participants, investigators are encouraged to design culturally sensitive and appropriate data collection instruments that allow research participants to self-identify their racial and/or ethnic affiliation. However when reporting these data to NIH, these items should be designed in a way that they can be aggregated by the investigator into the OMB-required categories which are defined in Section 5.8. Also, the investigator can report on any racial or ethnic subpopulations or culturally relevant descriptors by listing this information in the comments section of the Planned Enrollment Report(s). This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied. Also, as previously instructed, foreign and domestic subjects must be provided on separate Planned Enrollment Report(s) even if part of the same study.

**Delayed-Onset Human Subjects Research**

If the proposed research includes studies that meet the definition for delayed-onset human subjects research described in Section 2, Scenario D in the Human Subjects section of the instructions, and it is not possible to describe the proposed study and provide planned enrollment on sex/gender, race, and ethnicity, then enter a comment on the Planned Enrollment Report(s) indicating this is a delayed-onset study. For study title, you may enter the Project Title along with the words “Delayed Onset Study.” If you expect that more than one study will be delayed onset, it is acceptable to provide only one Planned Enrollment Report indicating delayed onset, but you may wish to indicate in the comments section of the Planned Enrollment Report that more than one study is anticipated under this scenario.

### 4.4 Inclusion of Children

The NIH Policy on Inclusion of Children is referenced and described in Section 5.7. Instructions for this item of the Research Plan (for F applicants, the PHS Fellowship Supplemental Form – Research Training Plan) are as follows:

- Create a section entitled “Inclusion of Children” and place it immediately following the section on the Inclusion of Women and Minorities.

- For the purpose of implementing these guidelines, a *child* is defined as an individual under the age of 21 years (for additional information see [http://grants.nih.gov/grants/funding/children/children.htm](http://grants.nih.gov/grants/funding/children/children.htm)).

- Provide either a description of the plans to include children, including the particular age ranges to be included, or, if children (or a subset) will be excluded from the proposed research, present an acceptable justification for the exclusion (see below).

- If children are included, the description of the plan should include a rationale for selecting a specific age range of children. The plan also must include a description of the expertise of the investigative team for working with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.
• Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the age-appropriate inclusion or exclusion of children in the proposed research project.

• When children are involved in research, the Additional Protections for Children Involved as Subjects in Research (45 CFR part 46 Subpart D) apply and must be addressed under the Protections Against Risk subheading (4.1.2.b).

Justifications for Exclusion of Children

For the purposes of this policy, all individuals under 21 are considered children; however, exclusion of any specific age group, such as individuals under 18, should be justified in this section. It is expected that children will be included in all NIH-defined clinical research unless one or more of the following exclusionary circumstances apply:

1. The research topic to be studied is not relevant to children.

2. Laws or regulations bar the inclusion of children in the research.

3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.

4. A separate, age-specific study in children is warranted and preferable. Examples include:
   a. The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or
   b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
   c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.

5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.

6. Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).

7. Other special cases can be justified by the investigator and found acceptable to the review group and the Institute/Center Director.

5. Human Subjects Research Policy

Human Subjects Research Policy includes DHHS regulations for the protection of human subjects and the following NIH policies related to human subjects research.
5.1 Protection of Human Subjects

The Department of Health and Human Services (DHHS) regulations for the Protection of Human Research Subjects provide a systematic means, based on established, internationally recognized ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the DHHS. The regulations stipulate that the awardee organization, whether domestic or foreign, bears responsibility for safeguarding the rights and welfare of human subjects in DHHS-supported research activities. The regulations require that all organizations engaged in nonexempt human subjects research supported or conducted by the DHHS hold a Federalwide Assurance (FWA) with the Office for Human Research Protections (OHRP), and establish appropriate policies and procedures for the protection of human subjects. These regulations, 45 CFR part 46, Protection of Human Subjects, are available from OHRP, Department of Health and Human Services, The Tower Building, 1101 Wootton Parkway, Suite 200, Rockville, MD; telephone: 1-866-447-4777 (toll-free) or (240) 453-6900; e-mail: ohrp@osophs.dhhs.gov. In general, OHRP considers organizations that receive direct support from DHHS for the conduct of nonexempt human subjects research to be engaged in human subjects research. (For more information on whether an institution is engaged in human subjects research, refer to: http://www.hhs.gov/ohrp/policy/engage08.html). When a research project is conducted by multiple organizations, each organization that is engaged in nonexempt human subjects research must hold an FWA and comply with the regulations at 45 CFR 46.

Nonexempt research involving human subjects may only be conducted under a DHHS award if the engaged organization(s) is operating in accord with an approved FWA and provides verification that an Institutional Review Board (IRB) that is registered under the specific FWA has reviewed and approved the proposed activity in accordance with the DHHS regulations. No award to an individual will be made unless that individual is affiliated with an approved organization that accepts responsibility for compliance with the DHHS regulations. Foreign applicant organizations must also comply with the provisions of the regulations unless a determination of equivalent protections is made in accord with 45 CFR 46.101(h).

Under DHHS regulations to protect human subjects, certain research areas are exempt. However, if an applicant makes inappropriate designations of the noninvolvement of human subjects or of exempt categories of research, this may result in delays in the review of an application or an application not being reviewed. The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. With the exception of research projects that meet the criteria for Exemption 4, studies that are exempt from the human subjects regulatory requirements must still address the inclusion of women, minorities, and children in the study design.

Regulations of the Food and Drug Administration (21 CFR 50, 21 CFR 56) generally apply to biomedical research involving an unapproved drug, device or biologic and may apply to certain studies of approved products. Additional information on FDA regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfsearch.cfm. If work falls under FDA’s regulatory requirements, the grantee must follow both DHHS and FDA human subject protection regulations.

The National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) apply to all projects (NIH-funded and non NIH-funded) involving recombinant DNA molecules that are conducted at or sponsored by an institution that receives NIH support for recombinant DNA research. See Part III, 2.9, Research Involving Recombinant DNA, including Human Gene Transfer Research.

Federal requirements to protect human subjects apply to most research on human specimens (such as cells, blood, and urine), residual diagnostic specimens, and medical information. Research involving existing data, documents, records, pathological specimens, diagnostic specimens, or tissues that are individually identifiable is considered “research involving human subjects.” The NIH Office of Extramural Research Human Subjects Web site contains additional information and Frequently Asked Questions to help investigators understand how these federal requirements apply to their research. See: http://grants.nih.gov/grants/policy/hs/index.htm.

The DHHS regulations require the NIH to evaluate all applications and proposals involving human subjects (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.120). This independent evaluation is conducted at the NIH through the peer review system and NIH staff review, and, as required, will take into
consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the NIH may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

5.2 Vulnerable Populations

Investigators who conduct research involving pregnant women, human fetuses and neonates, prisoners (or subjects who become prisoners after the research has started), or children, must follow the provisions of the regulations in Subparts B, C, and D of 45 CFR part 46, respectively. The subparts describe the additional protections required for conducting research involving these populations. Relevant information may be obtained at the OHRP Web site (http://www.hhs.gov/ohrp/policy/index.html).

Exemptions 1-6 do not apply to research involving prisoners or subjects who become prisoners (see Subpart C). Although Exemptions 1 and 3-6 apply to research involving children (see Subpart D). Exemption 2 can only be used for research involving educational testing or observations of public behavior when the investigator(s) do not participate in the activities being observed.

5.3 Data and Safety Monitoring Plans for Clinical Trials

For each proposed clinical trial, NIH requires a data and safety monitoring plan that describes oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. Prior to the accrual of human subjects, a detailed data and safety monitoring plan must be submitted to the applicant’s IRB and to the funding entity for approval. Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other appropriate offices or agencies. This policy requirement is in addition to any monitoring requirements imposed by 45 CFR part 46. NIH policy specifically requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials. See also Part III, 2.1 Human Subjects Research.

5.4 IRB Approval

NIH does not require certification of IRB approval of the proposed research prior to NIH peer review of an application. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html.

Following NIH peer review, applicants and their institutions will be notified of the need for review and approval of the proposed research by an IRB that is registered under the institutional assurance with OHRP. See http://www.hhs.gov/ohrp/ to register an IRB. Certification of IRB approval must be sent to the Grants Management Office through eRA Commons the Just-in-Time module (Part III, Section 1.7). Certification of IRB review and approval must include: the PHS application number, title of the project, name of the program director/principal investigator, date of IRB approval, and appropriate signatures. Grantees may also use the optional form “Protection of Human Subjects - Assurance Identification/IRB Certification/Declaration of Exemption (Common Rule)” (OMB Form No. 0990-0263 http://www.hhs.gov/ohrp/assurances/forms/of310.pdf) to meet this requirement.

According to OHRP policy, in general an institution is considered to be engaged in human subjects research when it receives an NIH award to support nonexempt human subjects research. See http://www.hhs.gov/ohrp/policy/engage08.html. All institutions engaged in human subjects research must obtain a Federal Wide Assurance (FWA) from OHRP. Instructions for applying for a Federal Wide Assurance (FWA) are available from the OHRP Web site at http://www.hhs.gov/ohrp/assurances/index.html.

DHHS human subject regulations at 45CFR46.103(f) require that each application for non-exempt HHS-supported human subject research be reviewed and approved by an IRB (see also http://www.hhs.gov/ohrp/policy/conditionalapproval2010.html). Only the date of approval of the application should be submitted to NIH. However, the IRB must ensure that any corresponding protocol(s) are
consistent with the application, and must maintain documentation of IRB approval of all corresponding protocols, including those reviewed by consortium participants. For multi-site research, the primary grantee is expected to collect the certification from each subrecipient.

Any modifications to the Research Plan in the application, required by either NIH or by the IRB, must be submitted with follow-up certification of IRB approval to the NIH before the competing award is made. It is the responsibility of the PD/PI and the applicant organization to submit the follow-up documentation.

If more than a year will have elapsed between the initial IRB review date and the anticipated award date, the awarding unit staff shall require re-review by the IRB prior to award.

### 5.5 Required Education in the Protection of Human Research Participants

NIH requires education on the protection of human research participants for all individuals identified in PHS applications as senior/key personnel who will be involved in the design or conduct of human subjects research, before funds are awarded for applications or contract proposals involving human subjects. For information relating to this requirement, see the following notices [http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html) and [http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html), and Frequently Asked Questions at: [http://grants.nih.gov/grants/policy/hs_educ_faq.htm](http://grants.nih.gov/grants/policy/hs_educ_faq.htm). Prior to award, applicants will be required to provide a description of education completed in the protection of human subjects for all senior/key personnel involved in the design or conduct of human subjects research. Although NIH does not endorse specific programs, curricula are available and provide guidance or can be modified to provide training in this area. See [http://phrp.nihtraining.com/users/login.php](http://phrp.nihtraining.com/users/login.php) for computer-based training developed by NIH that can be downloaded at no charge. For information on facilitating education and developing curricula, see [http://www.nih.gov/sigs/bioethics](http://www.nih.gov/sigs/bioethics).

### 5.6 NIH Policy on the Inclusion of Women and Minorities in Clinical Research

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding IC Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The Research Plan should describe the composition of the proposed study population in terms of sex/gender, race, and ethnicity, and provide a rationale for selection of subjects. It is important to justify the planned sample on the basis of sex/gender, race, and ethnicity in the context of the scientific goals of the proposed study(s) with discussion of the demographics of the population under study and/or who is at risk for the disease/condition. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See [http://grants.nih.gov/grants/funding/women_min/women_min.htm](http://grants.nih.gov/grants/funding/women_min/women_min.htm).

In addition, as detailed in Section 4.2.1 of these instructions, when conducting an NIH-defined Phase III clinical trial, there are additional requirements and considerations related to valid analysis.
5.7 NIH Policy on Inclusion of Children

Research involving children (see definition of “child”) must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research.

NIH policy requires that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH unless there are clear and compelling reasons not to include them. Therefore, applications proposing clinical research must include a description of plans for including children. For additional details and guidance, please refer to Part II, Sections 4.4 and 5.7 of these instructions as well as http://grants.nih.gov/grants/funding/children/children.htm.

The involvement of children as subjects in research must be in compliance with all applicable subparts of 45 CFR part 46 as well as with other pertinent Federal laws and regulations.

IRBs have special review requirements to protect the well-being of children who participate in research. These requirements relate to risk, benefit, parental/guardian consent, and assent by children, and to research involving children who are wards of the state or of another institution. The local IRB approves research that satisfies the conditions set forth in the regulations.

5.8 NIH Policy on Reporting Race and Ethnicity Data for: Subjects in Clinical Research

The Office of Management and Budget (OMB) defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting agencies (including NIH) in OMB Directive 15: http://www.whitehouse.gov/omb/fedreg_1997standards. The standards were revised in 1997 and include two ethnic categories (Hispanic or Latino and Not Hispanic or Latino) and five racial categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White). The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. Investigators shall use these categories when collecting and reporting data on race and ethnicity. The collection of greater detail is encouraged, for example on racial or ethnic subpopulations. However, any collection that uses more detail must be designed in a way that data can be aggregated into these minimally required OMB categories. Use self-report or self-identification to collect this information from subjects by asking two separate questions – one on ethnicity and one on race. Collect ethnicity information first, followed by the question on race and provide participants with the option to select more than one racial category. Participants also have the option not to identify. When feasible, NIH encourages investigators to include information about individuals who select more than one racial category and consider that data in their analyses. Participants who self-identify with more than one racial category should be reported to the NIH under the “More than one race” category of the report. See NIH Policy on Inclusion of Women and Minorities and http://grants.nih.gov/grants/funding/women_min/women_min.htm.

The following definitions apply to the minimum standards for the ethnic and racial categories.

**Ethnic Categories:**

- **Hispanic or Latino:** A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, “Spanish origin,” can be used in addition to “Hispanic or Latino.”
- **Not Hispanic or Latino**

**Racial Categories:**

- **American Indian or Alaska Native:** A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.
Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Ethnic/Racial Subpopulations: In addition to OMB ethnic and racial categories, each ethnic/racial group contains subpopulations that are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self-identify with more than one race. These ethnic/racial combinations may have biomedical, behavioral, and/or socio-cultural implications related to the scientific question under study.

5.9 Research on Transplantation of Human Fetal Tissue

In signing the application Face Page, the Authorized Organization Representative of the applicant organization certifies that if research on the transplantation of human fetal tissue is conducted, the applicant organization will make available, for audit by the Secretary, DHHS, the physician statements and informed consents required by section 498A (b)(2) and (c) of the Public Health Service Act, 42 U.S.C. 289g (b)(2) and (c), or ensure DHHS access to those records, if maintained by an entity other than the applicant organization.

5.10 Research Using Human Embryonic Stem Cells

In signing the application Face Page, the Authorized Organization Representative of the applicant organization certifies that if research using human embryonic stem cells is proposed, the applicant organization will identify hESCs to be used from the NIH Registry (http://stemcells.nih.gov/research/registry/), or, if a specific cell line cannot be referenced at the time of application, certify that one from the NIH Registry will be used, in accord with the NIH Guidelines on Human Stem Cell Research (http://stemcells.nih.gov/policy/2009guidelines.aspx). See http://stemcells.nih.gov/info/Pages/default.asp for additional information on stem cells, Federal policy statements, and guidelines on federally funded stem cell research.

5.11 ClinicalTrials.gov Requirements

In signing the application Face Page (or for electronic applications, in checking the “I agree” box on line 17 of the SF424 (R&R) Cover Form), the Authorized Organization Representative of the applicant organization certifies that if the research is an applicable clinical trial under Public Law 110-85, the applicant organization will be in compliance with the registration and reporting requirements of Public Law 110-85 (see Part III, Section 2.1.6).