Protocol Templates & Vulnerable Populations
Agenda

1. Protocol Templates
   - HRP-503 – Template Protocol (clinical/biomedical)
   - HRP-503a – Template SBS Protocol
   - HRP-508 – Site Supplement

2. Vulnerable Populations
   - Pregnant Women, Fetuses and Neonates (HRP-412, HRP-413, HRP-414)
   - Children (HRP-416)
   - Prisoners (HRP-415)
   - Cognitively Impaired (HRP-416)
Session Goals

• Understand proper use and application of the HRPP Toolkit protocol templates
• Describe additional considerations and approval criteria for enrolling vulnerable populations in research: pregnant women, fetuses, neonates, children, prisoners, and cognitively impaired adults
• Understand considerations for inclusion of students or employees and how to mitigate undue influence and coercion
• Additional federal agency criteria for research funded or conducted by Veterans Administration, Department of Justice, Environmental Protection Agency, Department of Energy, Department of Education and Department of Defense
Protocol Templates
HRPP Toolkit Protocol Templates

HRP-503, HRP-503a, & HRP-508

The HRPP Toolkit includes a variety of templates designed to assist study teams with providing all relevant information to facilitate the IRB’s review.

Brown HRPP Leadership are prioritizing the implementation of HRPP Toolkit protocol templates to minimize administrative burden for researchers and increase efficiency.

The Templates include:

- HRP-503 – TEMPLATE – Protocol (biomedical/clinical)
- HRP-503a – TEMPLATE – Protocol SBS (social/behavioral)
- HRP-508 – TEMPLATE – Site Supplement (supplement to industry-sponsored protocols)
HRPP Toolkit Protocol Templates

HRP-503, HRP-503a, & HRP-508

The use of protocol templates will minimize burden by:

- Reducing the number of fields investigators need to complete in the IRB system; and
- Enable study teams to more easily prepare for reliance on external IRBs

Brown rolled out these templates to study teams for use on June 3rd – Use of new protocol templates will be required for all new studies beginning July 1st
HRPP Toolkit Protocol Templates

HRP-503 & 503a

- Includes prompts for the information that study teams need to provide to the IRB for review
- References out to HRPP Toolkit documents, as applicable

Table of Contents

1.0 Study Summary .............................................................. 3
2.0 Objectives* .................................................................. 4
3.0 Background* ................................................................. 4
4.0 Study Endpoints* ........................................................... 4
5.0 Study Intervention/Investigational Agent .......................... 4
6.0 Procedures Involved* ...................................................... 5
7.0 Data and Specimen Banking* ............................................ 5
8.0 Sharing of Results with Subjects* ..................................... 6
9.0 Study Timelines* ............................................................ 6
10.0 Inclusion and Exclusion Criteria* ..................................... 6
11.0 Vulnerable Populations* .................................................. 6
12.0 Local Number of Subjects ............................................... 7
13.0 Recruitment Methods .................................................... 7
14.0 Withdrawal of Subjects* .................................................. 7
15.0 Risks to Subjects* .......................................................... 7
16.0 Potential Benefits to Subjects* ........................................ 8
17.0 Data Management* and Confidentiality ......................... 8
18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects* .................................................. 8
19.0 Provisions to Protect the Privacy Interests of Subjects .................................................. 9
20.0 Compensation for Research-Related Injury ...................... 9
21.0 Economic Burden to Subjects ......................................... 9
22.0 Consent Process ........................................................... 9
23.0 Process to Document Consent in Writing ....................... 13
24.0 Setting ................................................................... 13
25.0 Resources Available....................................................... 13
26.0 Multi-Site Research* ...................................................... 14
PROTOCOL TITLE:

INSTRUCTIONS:

- Use this template to prepare a document with the information from following sections.
- Depending on the nature of your study, some sections may not be applicable to your research. If so, mark as “NA”. For example, research involving a retrospective chart review may have many sections with “NA.” For subsections, like 1.x or 8.x, you can delete it if it’s not applicable.
- When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.
- As you are writing the protocol, remove all instructions in italics so that they are not contained in the final version of your protocol.
- Omit starred (*) items if this is the activation of a protocol at a new site or sites that will be overseen by a principal investigator who will take separate and full responsibility for that site or those sites. Complete by describing information specific to the site(s). Do not repeat information in the approved protocol that applies to all site(s).
Vulnerable Populations
Considerations for Vulnerable Populations

When reviewing submissions, the IRB is tasked with verifying certain regulatory requirements are fulfilled when study teams propose enrolling vulnerable populations:

- Research with Pregnant Women, Fetuses and Neonates *(HRP-412 CHECKLIST)*
- Research Involving Children *(HRP-416 CHECKLIST)*
- Research Involving Prisoners *(HRP-415 CHECKLIST)*
- Research with Cognitively Impaired Adults *(HRP-417 CHECKLIST)*
Research Involving Pregnant Women, Fetuses and Neonates

Fetus: Product of conception from implantation until delivery

Neonate: A newborn

Viable: Being able, after delivery, to survive to the point of independently maintaining heartbeat and respiration (given the benefit of available medical therapy)

Nonviable neonate: After delivery, although living, is not viable
Research can only be conducted in pregnant women or fetuses if **all** the following conditions are met:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>When scientifically appropriate, preclinical studies (on pregnant animals) and clinical studies (on non-pregnant women) have been conducted</td>
<td></td>
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<tr>
<td>Risk to the fetus is caused solely by interventions or procedures that hold out prospect of direct benefit for the woman or the fetus; if there is no prospect of direct benefit, the risk to the fetus is not greater than minimal</td>
<td></td>
</tr>
<tr>
<td>Any risk is the least possible for achieving the objectives of the research</td>
<td></td>
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<tr>
<td>Any individual providing informed consent is fully informed of the reasonably foreseeable impact of the research on the fetus or neonate</td>
<td></td>
</tr>
<tr>
<td>Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy</td>
<td></td>
</tr>
<tr>
<td>Individuals engaged in the research will have no part in determining the viability of a neonate</td>
<td></td>
</tr>
<tr>
<td>For children who are pregnant, assent and permission are obtained according to Subpart D</td>
<td></td>
</tr>
<tr>
<td>No inducements, monetary or otherwise can be offered to terminate a pregnancy</td>
<td></td>
</tr>
</tbody>
</table>
Research can only be conducted in pregnant women or fetuses if all the following conditions are met (cont.):

| • If the research holds out prospect of direct benefit for the pregnant woman, both the pregnant woman and fetus, or no prospect of direct benefit to pregnant woman or fetus, risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means, informed consent must be obtained from the pregnant woman subject in accord with the regulations | • If the research holds out the prospect of direct benefit solely to the fetus, informed consent must be obtained from the pregnant woman and father; the father’s consent is not necessary if the father is unavailable, incompetent, incapacitated, or if pregnancy is result of rape or incest |
Research can only be conducted in nonviable neonates and neonates of uncertain viability if all the following conditions are met:

- When scientifically appropriate, preclinical studies and clinical studies have been conducted

- Each individual providing informed consent is fully informed of the foreseeable impact of the research on the neonate

- Individuals engaged in the research will have no part in determining the viability of a neonate
After delivery, a nonviable neonate cannot be in research unless the previous common conditions and these following conditions are met:

• Vital functions of the neonate will not be artificially maintained;
• The research will not terminate heartbeat/respiration of the neonate;
• No added risk to the neonate from the research;
• The purpose of the research is to develop important biomedical knowledge that cannot be obtained by other means; and
• Legally effective informed consent is obtained from both of the parents....(cannot have an LAR)
Neonates of uncertain viability—until it has been ascertained whether a neonate is viable, a neonate may not be involved in research unless the previous conditions and these following conditions are met:

- The IRB determines that (1) the research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability... OR (2) the purpose of the research is to develop important biomedical knowledge that cannot be obtained by other means and there is no added risk to the neonate resulting from the research
- Legally effective informed consent is obtained from either of the parents or an LAR
- Viable neonates: a neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted and in accordance with the requirements of 45 CFR 46 Subparts A and D
IRB Considerations

Prior preclinical research and if feasible, research with non-pregnant women should form the basis of the risk/benefit assessment.

The research should seek information that cannot be obtained any other way.

If abortion is involved, the PI may have no part in the decision or timing of it; no inducement may be made for terminating a pregnancy for research.
Research Involving Children

Children: persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of jurisdiction in which the research will be conducted.

Rhode Island age of majority = 18

IRB duties involved in reviewing research with children include:

Pediatric risk determination

§46.404/ §50.51 - Research not involving greater than minimal risk.

§46.405/ §50.52 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

§46.406/ §50.53 - Research involving greater than* minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. *risk is a minor increase over minimal risk.

§46.407/ §50.54 - Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
Research Involving Children – Requirements for Assent

Adequate provisions are made to solicit assent of children who are capable of providing assent

In determining capability, IRB must consider age, maturity, psychological state of the children involved

Assent is not a necessary condition if the IRB determines that:

- Capability is limited, OR
- The research holds out prospect of direct benefit that is important to the health and well being of the children and is only available in the research context

Even when the IRB determines subjects are capable to assent, the IRB can still waive assent requirement if:

- No more than minimal risk to the subject;
- Waiver will not adversely affect rights and welfare of subjects;
- Research could not be practicably carried out without waiver; and
- When appropriate, subjects are provided with additional information after participation
Research Involving Children – Requirements for Parental Permission

Where parental permission is to be obtained, the IRB may find:

Permission of one parent/guardian is sufficient

- The IRB may find that permission of one parent is sufficient for studies that meet the risk criteria at 46.404/50.51 or 46.405/50.52 but the IRB may at any given time require both parents to sign

Permission of both parents is required unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility

- Permission of two parents is required for 46.406/50.53 and 46.407/50.54 studies
DHHS Carveout for Obtaining Parental Permission when Enrolling Children

46.408

If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.
Research Involving Children – Wards of the State

Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

• Related to their status as wards; or

• Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards

The IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis

• One individual may serve as advocate for more than one child
• The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and
• Who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.
Research Involving Prisoners

**Prisoner**: any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

**Minimal Risk**: the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

- This is different than the definition of minimal risk in Subpart A: the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
Research Involving Prisoners

Requirements for approval of prisoner research:

• The research represents one of the categories of research permissible under 46.306(a)(2)

• Any possible advantages to the prisoner participating in the research study are not of such a magnitude that his or her ability to weigh the risks against the benefits of the research is impaired

• Risks to prisoners in the research study are comparable to risks that would be accepted by non-prisoner subjects

• Procedures for selection of subjects are fair

• Information is presented in a language understandable to the subject population

• Adequate assurance that parole boards will not take research participation into account when making decisions regarding parole

• Any follow-up care needed after research participation will be provided
Research Involving Prisoners

**Subpart C applies whenever any human subject in a research protocol subject to 45 CFR part 46 becomes a prisoner at any time during the study.**

- When a previously enrolled research subject becomes a prisoner and the relevant research protocol was NOT reviewed and approved by the IRB in accordance with the requirements of HHS regulations at 45 CFR part 46, subpart C, the principal investigator should promptly notify the IRB of this event. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until the requirements of subpart C have been satisfied with respect to the relevant protocol.
  - **NOTE:** OHRP has allowed one important exception. In special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.

- Upon receipt of notification that a previously enrolled research subject has become a prisoner, the IRB should promptly re-review the protocol in accordance with the requirements of subpart C if the principal investigator wishes to have the prisoner subject continue to participate in the research.
Research Involving Cognitively Impaired Adults

ICH-GCP
AAHRPP Requirements

HHS and FDA regulations do not identify individuals with impaired decision-making capacity as a vulnerable population.

It is the responsibility of the IRB to ensure additional protections are in place and documented for research that is planned to include the participation of persons, other than children, who may have impaired decision-making capacities. When reviewing greater than minimal risk research involving individuals with questionable capacity to consent, IRBs should discuss and document the potential value of an independent monitor.

It is the responsibility of the Principal Investigator (PI) to plan for obtaining ongoing, legally valid informed consent of all research participants. To respect autonomy, assent should be obtained whenever possible.
IRB considerations for research involving Cognitively Impaired Adults with anticipated direct benefit to subjects

- Subjects have a disease or condition for which the procedures involved in the research hold out a prospect of direct benefit to the individual subject that is unavailable outside the research context, OR
- The objectives of the trial cannot be met by means of study of subjects who can give consent personally
- Risks to subjects are reasonable in relation to the anticipated benefits to subjects
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches
- The trial is not prohibited by law
- Subjects will be particularly closely monitored
- Subjects will be withdrawn if they appear to be unduly distressed
- The proposed plan for the assessment of the capacity to consent is adequate
- The subject will be informed about the research to the extent compatible with the subject’s understanding
- Assent will be obtained from all subjects, unless not possible, in which case the study team provides an explanation of who assent will and will not be obtained from along with an adequate rationale
- The consent document includes a signature line for a Legally Authorized Representative (LAR)
- If capable, the subject will sign and personally date the written informed consent
IRB considerations for research involving Cognitively Impaired Adults with NO anticipated direct benefit to subjects

- Subjects have a disease or condition for which the procedures involved in the research are intended
- The objectives of the trial cannot be met by means of study of subjects who can give consent personally
- The foreseeable risks to the subjects are low
- The negative impact on the subject’s well-being is minimized and low
- The trial is not prohibited by law
- Subjects will be particularly closely monitored
- Subjects will be withdrawn if they appear to be unduly distressed
- The proposed plan for the assessment of the capacity to consent is adequate
- The subjects will be informed about the research to the extent compatible with the subject’s understanding
- Assent will be obtained from all subjects, unless not possible, in which case the study team provides an explanation of who assent will and will not be obtained from along with an adequate rationale
- The consent document includes a signature line for a (LAR)
- If capable, the subject will sign and personally date the written informed consent
Next Steps

Researchers should now see all HRPP Toolkit documents in the IRB system

Effective July 1st, researchers **must** begin using the new protocol and consent templates

Important Dates
- **Monday, June 17th** – Protocol Templates and Vulnerable Populations
- **Thursday, June 27th** – Informed Consent
- **Monday, July 1st** – Reportable New Information
Questions?
Thank you!