University of Virginia

IRB-HSR Board Member's Guidance

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Introduction to the Institutional Review Boards (IRBs) Structure at UVa and Your Role as a Member

Preface

The guide is based on the IRB-HSR Standard Operating Procedures, applicable federal regulations, Virginia state statutes, and University of Virginia policy as they pertain to the conduct of human research at the University of Virginia.

The IRB Administrative Office

Office Location

The IRB-HSR Administrative Office is located on the 4th floor at One Morton Drive, Charlottesville Virginia in the Morton Building. The IRB administrative staff is available to assist you in your role as an IRB Member.

Contact Lists

The contact lists for the IRB-HSR administrative staff may be found on the IRB-HSR website Contact List.

Organizational Structure for Research Oversight

For an organizational chart of the human subject research offices see the Organizational Charts on the IRB-HSR Website.

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IRB Administrative Staff

The administrative staff for the IRB consists of paid professionals who write procedures and guidance, handle correspondence with relevant federal agencies, process applications for review, request progress reports from researchers, conduct training for researchers and IRB members, arrange IRB meetings, and generally provide support services needed for the oversight of research at UVA. The IRB, not the professional staff, makes final decisions regarding a research project that has been submitted for consideration. Thus, the IRB and the administrative staff have differing roles and responsibilities, and their relationship with researchers will therefore differ.

The IRB and Protection of Human Research Subjects

What is an Institutional Review Board (IRB)?

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The IRB is an oversight committee, administratively independent of the institution it serves. It is charged with reviewing all research involving human subjects to ensure the research complies with institutional policies and state, local and federal laws. The IRB has the authority to approve, require changes to the study procedures, or disapprove proposed research projects.

The IRB functions as a surrogate "human subject advocate." Its role is to safeguard the rights and welfare of research subjects by evaluating the risks and benefits of the research to assure an acceptable balance.

National and international communities have adopted ethical principles to guide the use of human subjects in

research. The most important of these are the Belmont Report, the Nuremberg Code and the Declaration of Helsinki. These ethical principles have been incorporated into regulations that provide for the protection of human subjects in research.

The IRB was created by federal regulations as the institutional body charged with implementing the regulations on a local level. IRB activities are subject to review by a variety of groups including the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) in the Department of Health and Human Services (DHHS). The University negotiates with OHRP to provide a document called a Federal-wide Assurance (FWA), which acts as a guide for its human subject's research protections. There are other federal agencies that oversee or provide guidance for research.

OHRP may audit IRB activities on a random basis or when a particular problem or set of problems has been identified. The FDA may also audit for cause, but they primarily conduct periodic on-site "not for cause" audits. These audits can include any FDA-regulated areas, such as the pharmacy and investigator files, as well as all IRB activities. The audits from both OHRP and the FDA may include review of IRB policies, handbooks and standard operating procedures, meeting minutes, agendas, protocol files and other pertinent materials.

The Vice-President for Research (VPR) at the University of Virginia serves as the Institutional Official (IO) for issues related to the protection of human subjects. The IRB and the institutional official are responsible for ensuring compliance with federal, state and other applicable regulations; for interpreting those regulations and determining local policy and procedures; and for developing new policy as science and its ethical implications change.

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The IRB and Protection of Privacy (HIPAA)

The Health Insurance Portability and Accountability Act of 1996: (HIPAA) from the federal Office of Civil Rights (OCR), provides additional guidance and restrictions on privacy and the use of protected health information (PHI). These regulations require institutions to name a privacy board, whose primary responsibility is to ensure that research protocols comply with the HIPAA Privacy Rule. At the University of Virginia, the IRB-HSR serves as the Privacy Board in addition to its IRB duties. They are responsible for ensuring that the institution is in compliance with the regulations and serves as a point of contact for any questions or concerns regarding HIPAA. For additional information see HIPAA.

IRB Purview

The primary role of the IRB is to ensure that human subjects are protected. For this reason, the IRB is responsible for reviewing all research in which humans participate as research subjects at the University of Virginia BEFORE it begins.

Per federal regulations, 45 CFR Part 46.111 (DHHS) and 21 CFR Part 56.111 (FDA), in order to approve research the IRB-HSR must determine that all of the following requirements are satisfied:

1. **Risks to subjects are minimized:**
   By using consistent review procedures, the IRB verifies that a sound research design is in place. This prevents subjects from being exposed to risk unnecessarily.

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2. **Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.**
   In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).
   The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
   The IRB should take into account that while a study may not be of benefit to the individual participant it may be of help to others in the future.
3. **Selection of subjects is equitable.**
   In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
4. **Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45CFR Part 46.116.**
5. **Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR Part 46.117.**
6. **When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.**
7. **When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.**
   When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Types of studies that the IRB may review

- Healthy volunteer subjects in behavioral and medical research
- Patients recruited as subjects in clinical trials of new drugs and devices.
- Surveys, questionnaires and interviews,
- Use of tissue and body fluids and other materials both with and without identifiers,
- Use of individual and aggregate data, patient charts, x-rays, etc.

Federal regulations recognize differences between types of research and provide three categories of review. Those categories are Full Board, Expedited and Exempt.

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While the default is review by the full board at a scheduled meeting, certain minimal risk projects may be eligible for expedited review or may be exempt from review requirements. Only the IRB can make the

determination that the research meets exempt criteria, meets expedited criteria or will require approval of the full board.

OO18 Just as the IRB has the authority to approve research, the IRB has the authority to suspend or terminate research involving human subjects which does not conform to the approved protocol, where compliance issues are suspected or documented, and where the risk benefit ratio is or becomes unacceptable.

Composition of IRBs

The University of Virginia has a single Federal Wide Assurance (FWA) from OHRP that covers the operation of two IRBs to review biomedical and behavioral research. Besides the IRB-HSR, the IRB for Social and Behavioral Sciences (IRB-SBS) reviews studies that are non-invasive and focus on research in the behavioral sciences.

The current roster of members of the IRB-HSR may be found on the IRB-HSR Membership List

IRBs are made up of reviewers constituted according to the rules set forth in the federal regulations (The Common Rule). Each IRB is appointed with at least five members including a chair and vice chair.

IRB members will have varying backgrounds necessary to promote complete and adequate review of human research activities commonly conducted by the institution. An IRB usually includes individuals drawn from the following groups:

OO19 (1) Faculty affiliated with the institution representing diverse academic disciplines that typically engage in research with human participants;

(2) Non-scientist faculty affiliated with the institution;

OO18 (3) Community representatives with no formal institutional affiliation whose role is to represent the interests of the community and to bring an independent perspective; and

(4) On occasion if the IRB reviews research with prisoners, a community representative who has the sole responsibility to ensure that rights of prisoners are protected (for example, a public defender or a representative of a prisoner advocacy group) is required to be present.

(5) The boards may also include members who can represent the interests of special and vulnerable populations, such as children, pregnant women and fetuses and neonates.

OO19 (6) On occasion, additional individuals with expertise in a particular field may be invited to a meeting to provide consultation on specific protocols; such individuals are not included in the quorum nor do they have voting rights.

IRB Member Term Duration

Most IRB members serve 3 years. The exceptions are:

- Medical Students serve for 1 year and are nominated to serve by the Mulholland Society. The board may have 2 medical students that share a position.
- Study coordinator representative is nominated by the School of Medicine-Clinical Trials Office. The study coordinator representative serves for 1 year.
- Residents serve 1-2 years as they are able

Role as a Member or Alternate of the IRB

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Types of Members who May Serve on the IRB and Vote:

1. **Affiliated members**. Individuals associated with the University of Virginia in a variety of capacities.
2. **Nonaffiliated members**. Nonaffiliated members are not currently affiliated with the institution and are not part of the immediate family of a person who is currently affiliated with the institution. They are expected to provide input regarding the local community (research context) and be willing to discuss issues and research from that perspective as well as to comment on the comprehensibility of the consent document.

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3. **Scientific members**. Scientific members are expected to assess whether risks to subjects are reasonable in relation to anticipated benefits. These members should also be able to advise the IRB if additional expertise in a nonscientific or other scientific area is required to assess if the protocol adequately protects the rights, safety, and welfare of subjects.
4. **Nonscientific members**. Nonscientific members are expected to provide input on areas germane to their knowledge, expertise, and experience, professional and otherwise. Nonscientific members should advise the IRB if additional expertise in a nonscientific area is required to assess if the protocol adequately protects the rights, safety, and welfare of subjects, and/or to comment on the comprehensibility of the consent document.

   **Individual members of the IRB may meet more than one type as described above (i.e a non scientific member may be either affiliated or unaffiliated with UVA)

In addition to the roles as described above, members may be asked to serve on subcommittees of the IRB. Although the board has a chair and vice chair to provide leadership, from time to time, members may also be asked to serve as ad hoc chair, if they are a scientific member of the board.

Members may be asked to assist in providing educational seminars to the local and research community or to serve as a resource to those within and outside your department or community as they develop protocols or have questions regarding IRB-related issues.

Members of the IRB, may have access to research ideas, confidential information of companies, pre-marketing data and many other kinds of confidential and sensitive personal and business materials. At the beginning of the member's term, a confidentiality agreement will be signed. Access to this information is for IRB purposes only, and members are reminded that any use of such information for any other purpose would be a violation of federal law and the ethical principles by which the university is bound

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Duties of IRB-HSR Members

Duties of members include reviewing human subject application materials in advance of meetings and being prepared to discuss issues related to human subject's protections, and having an understanding of the specific requirements of human subject's regulations. Overall duties include:

- Attending IRB meetings and actively participating in the review of research, unless arrangements have been made for the alternate's attendance.
- Completing initial training in human subjects protection for IRB members prior to voting on any research, with continuing education every three years and as provided
- Understanding and applying the principles of the Belmont report and the federal regulationsrelated to the protecting the rights and welfare of research subjects.

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- Providing timely written comments on research undergoing IRB review.
- Review meeting minutes for accuracy and promptly notify the IRB administrative staff or IRB Chair of any corrections or additions.
- Maintaining confidentiality of IRB related information.
- Maintaining a current knowledge of relevant regulations, laws, and policies related to the protection of human subjects.
- Working with investigators to resolve matters relating to research approval.

Duties of IRB-HSR Alternates:

An alternate is an individual appointed to the IRB to serve in the same capacity as the specific IRB member(s) for whom the alternate is named, who substitutes for the member at convened meetings when the member is not in attendance. *Note: IRB members and alternates have equal responsibilities in terms of required education, service, and participation.*

1. Federal regulations allow organizations to appoint an alternate(s) to substitute for an IRB member(s) who is unable to attend so that IRB business may move forward in a timely manner. Alternates are appointed by the same process and for the same length of time as IRB members.

2. IRB alternates function as regular board members when they are in attendance. An alternate may substitute for the primary IRB member for an entire meeting or at any time during a meeting. Alternates and IRB members have equal responsibilities (i.e., "job-share") in terms of required education, service and time commitments, and participation.

3. Each alternate member is paired with one or more regular members with comparable experience and expertise, as possible. The IRB roster identifies the primary member(s) for whom each alternate may substitute. Minimally, alternates and members are paired by scientific "class," as physician scientists (when applicable), other scientists, and non-scientists. The IRB roster will identify the member(s) for whom each alternate can substitute.

4. When an alternate substitutes for a regular IRB member, the alternate receives and reviews the same materials that the regular member received (or would have received), and IRB minutes document that an alternate replaced a primary member.

Duties of Consultants/Ad hoc Reviewers

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For research that requires expertise beyond or in addition to that available on the IRB, or involves a vulnerable population where no IRB member knowledgeable about or experienced in working with these participants will be present at the meeting, the IRB may invite scientists or non-scientists from within or outside the University of Virginia, who have special expertise, to function as consultants and ad hoc reviewers.

IRB Director/appointed staff may identify the need for review by a consultant during the prereview submission process. The IRB Director/staff member will work with IRB Chair to invite an individual with the necessary expertise to serve as a consultant and assist the IRB in its review.

The primary reviewers or IRB board may identify the need for a consultant during their review of a new study or at the time of a modification to an existing study. The primary reviewer(s) will work with an IRB Director/staff member and/or IRB Chair to invite an individual with the necessary expertise to serve as a consultant and assist the IRB in its review.

Any individual asked to participate, as a consultant/ad hoc reviewer, will be required to sign a confidentiality agreement and declare in writing that they have no conflict of interest or financial conflict of interest in research for each consultation that relates to the protocol that they are asked to review.

The use of a consultant and the result of the consultant's review will be shared with the IRB Full Board by either having the consultant attend and present to the convened IRB or by having the consultant provide a written report to the IRB.

- If the consultant presents at a convened meeting, the IRB minutes will document key information provided by the consultant. The consultant will not vote with the IRB.
- If the consultant provides a written report, the report will be included in the protocol records.

Meeting Attendance and Quorum

When and Where

The IRB-HSR Meetings take place **every second and fourth Tuesday** of each month, except for December when only the first meeting is held. The meetings are slated to run from **12:00 to 4:00**. They rarely run until 4:00 but it is important to note that they could. Lunch is served starting at noon.

A schedule of meeting dates is available on the IRB-HSR website.

Requirement for Review of Research by the IRB at Convened Meetings

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In order to approve a protocol, the study must meet the approval criteria found in 45CFR45.111/ 21CFR56.111. The IRB member review checklists provide additional information regarding these criteria.
In accordance with HHS regulations at 45 CFR 46.108(b), initial and continuing reviews of research, which are more than minimal risk, must be conducted by the IRB at convened meetings at which a majority of the members (at least half) of the IRB are present, including at least one member whose primary concerns are in nonscientific areas (i.e., a quorum). "Presence" at a meeting means the person must participate by being at the

meeting in person or participating by conference call. Any actions taken at a meeting without the presence of a nonscientist or more than half of the IRB-HSR voting members are considered invalid.

OO19 Meeting attendance is one of the most critical services of board members and alternates. Full time board members are expected to attend each scheduled board meeting. If the full board member is unable to attend, their alternate will be asked to attend. It is crucial that members and alternates notify the administrative staff of their availability for meetings. This is important to allow appropriate assignment of protocols to available reviewers and that a quorum of members will be present. This is generally accomplished via e-mail or a phone call with administrative staff.

OO19 No legally valid IRB action may be taken without a properly constituted quorum. Approval of research is by a majority vote of this quorum. A quorum consists of more than half the number of regular members, including at least one non-scientist. If a quorum is lost during a meeting,(e.g., loss of a majority through recusal of members with conflicting interests or early departures, or absence of a nonscientist member), then the board cannot conduct official business until the quorum is restored. If the quorum is not restored, the meeting is concluded and remaining business continues at the next scheduled meeting.

If a situation arises where the board member cannot attend, and the member has been assigned as a primary reviewer for the meeting, the member should contact the IRB-HSR and request that the project be reassigned to another primary reviewer. If the board member has reviewed the submission, they may submit their comments to the IRB-HSR Chair who will review them. The IRB Chair will determine if he/she will present the protocol at the IRB meeting or table it to a future meeting when the IRB reviewer can be present. . A primary reviewer unable to attend and failing to notify the IRB-HSR will cause the study review to be delayed until the following meeting.

Member Conflict of Interest

OO18 Members of the IRB play multiple roles and may have potentially overlapping relationships. This is also true of members of the IRB who participate in research projects and who are members of departments and sections whose faculty colleagues may be submitting protocols for IRB review. As an ethics, privacy and regulatory committee, it is essential that the IRB avoid even the appearance of conflict of interest.

No IRB-HSR member or consultant/ad hoc reviewer may participate in the IRB-HSR initial or continuing review of any project in which the member/consultant has a conflict of interest, except to provide information requested by the IRB-HSR. In cases where the assigned initial reviewer has a conflict of interest, the reviewer must declare that conflict of interest and the study application will be re-assigned to another reviewer. When the member with a conflict has a protocol for review before the IRB-HSR (investigator-member), the member may be present at the IRB-HSR meetings, like any investigator, only to provide information requested by the IRB-HSR. The investigator-member may not vote on the study. If the researcher is listed as personnel on a new protocol they must be absent from the room during the final discussion and vote. The absent member is not counted towards a quorum when the vote on the study in question is taken.

The following defines the circumstances under which an IRB-HSR member or consultant/ad hoc reviewer is considered to have a conflicting interest:

"Conflict of interest" refers to a divergence between an individual's personal financial, relational, or other interests and his/her professional obligations to the University of Virginia – whether through teaching,

involvement in research, contracting, purchasing, or performing other administrative duties -- such that an independent observer might reasonably determine that the individual's professional actions or decisions are, or potentially could be adversely affected, distorted or otherwise compromised by the individual's personal interest.

The term conflict of interest is broader and encompasses more professional activities than the term financial conflict of interest in research, defined below.

"Financial conflict of interest in research" is the existence of a significant financial interest that an independent observer might reasonably determine affects or compromises, or appears to affect or compromise, the design, conduct, reporting or management of research.

Interests of IRB-HSR members, consultants/ad hoc reviewers and their immediate families with the same financial interest as an investigator would trigger consideration by the IRB-HSR.

"Immediate Family Member" means any individual having a relationship to a person (whether by blood, law or marriage) as spouse, parent, child, grandparent, grandchild, stepchild, or sibling.

Financial and non-financial conflict criteria may include but are not limited to:

- Is a member of the research team;
- Has a financial interest in the research with value that cannot be readily determined;
- Has a financial interest in the research with value that exceeds a specified monetary threshold ($10,000);
- Has received or will receive compensation with value that may be affected by the outcome of the study;
- Has a proprietary interest in the research, such as a patent, trademark, copyright, or licensing agreement;
- Has received payments from the sponsor that exceed a specified monetary threshold ($10,000) in the past year;
- Is an executive or director of the agency or company sponsoring the research; or
- Has an interest that the IRB-HSR member believes conflicts with his or her ability to objectively review a protocol;
- Has an interest that the IRB-HSR member or others perceive may conflict with his or her ability to objectively review a protocol.

How are conflicting interests identified?

- It is the responsibility of the member to declare any real or perceived conflicts of interest he/she may have.
- It is the responsibility of the consultant/ad hoc reviewer to declare any real or perceived conflicts of interest he/she may have.

Member Liability

IRB members function as employees and/or agents of the University of Virginia. As such, when acting in accordance with the University of Virginia IRB's Standard Operating Procedures, their actions are covered by the University of Virginia general liability coverage. Community members when acting in accordance with the

University of Virginia's IRB Standard Operating Procedures are covered by the University of Virginia's general liability coverage.

Member Training Requirements

Once an IRB-HSR member has been appointed, the IRB-HSR member will meet with the IRB-HSR staff to learn about IRB-HSR process. IRB-HSR members must fulfill the CITI modules required for IRB-HSR members at the University of Virginia prior to being appointed as scientific or non-scientist reviewer on a protocol. On an ongoing basis, members will receive information about educational opportunities that are available.

IRB-HSR members are provided educational reading material and opportunities for discussion at IRB-HSR meetings. Materials are circulated to the members, discussed during the meeting and documented in the minutes.

The IRB-HSR also maintains a small library of materials that includes the OHRP Institutional Review Board (IRB-HSR) Guidebook, the Belmont Report, and other books and videotapes discussing ethical and regulatory issues relating to human subjects research. These materials are available to the entire UVa community.

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Initial Training:

- New IRB members are required to complete the CITI Training Modules
- Members who are not researchers at UVa will select the training for IRB for Health Sciences Research (IRB-HSR): STAFF/BOARD MEMBER
- Attend training with IRB Office Staff to answer any questions and to review procedures for reviewing new and ongoing protocols that are being modified.
- New IRB members are required to attend an IRB meeting as a guest prior to being assigned as a reviewer.
- New members are encouraged to view Learning Shots for IRB Members regarding the review of IRB submissions found on the IRB-HSR Education Website Page

Continuing Education for IRB Members/Alternates

The following continuing education opportunities will be offered to current members of the IRB

1. A copy of the IRB related publications.
2. Periodic short educational sessions held at regular IRB Meetings.
3. Periodic outside speakers may provide a presentation on a topic of interest.

Removal of Member

When a board member consistently fails to attend IRB meetings or fails to meet expectations, the Director, and/or chair will meet with the board member to determine the cause. If the IRB member indicates an inability to continue to function effectively as an IRB member, IRB chair, Director, or designee will work with the Dean and/or department chair in obtaining a replacement member to serve on the IRB. Members who do not adequately fulfill their responsibilities, as judged by the IRB chair, may be asked to step down from IRB membership by the VPR.

Notification of Meetings and Distribution of Materials

The agenda and application materials for all full board activities are distributed via email to IRB-HSR members in advance of the meeting date to allow time for review. The agenda indicates the date, time, and place of the meeting.

Reviewer Assignments

There are two reviewers assigned to each new protocol or Five Year update:

1) **Primary or Scientific Reviewer**

2) **Secondary or Non-Scientific Reviewer**

One Primary or Scientific Reviewer is assigned to each additional type of review such as modifications or continuations.

The Primary/Scientific Reviewer is typically a physician or scientist with experience and expertise in the type of research under consideration, though this is not an absolute requirement, depending upon the type of study.

The Secondary/Non-Scientific Reviewer is typically an individual who can provide another perspective, for example, lay person, genetic counselor, lawyer, nurse or parent. The secondary reviewer, therefore, complements the scientific expertise of the primary reviewer.

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Both the primary and secondary reviewers are expected to fully and carefully review all aspects of the protocol, consent form and associated materials.

Members who are not assigned to specific protocols on the agenda are expected to review the protocol summary, consent forms and any study specific items such as questionnaires or survey materials, as well as advertisements for subject recruitment. After the primary and secondary reviewer have presented the study and review comments, the protocol is opened up for discussion.. The Chairperson may direct specific questions to the assigned reviewers or other members of the IRB with specific expertise or viewpoints (e.g., a layperson, nurse or other member who may bring a different perspective to the discussion).

When assigning primary and secondary reviewers, consideration is given to the reviewer's area of experience and expertise (e.g., pediatrics, obstetrics, neonatology, neurology, psychiatry) and representative capacity (i.e., physician scientist, nonscientist, other scientists). Scientific reviewer assignments are made based on the member's knowledge and expertise. When the agenda includes protocols that involve vulnerable populations, the IRB Chairpersons or designated alternate(s) are responsible for ensuring that at least one member attending the meeting has knowledge and experience in working with the study population. The UVa IRB reserve the right to reschedule protocols for review based on the experience and expertise of the members attending the IRB meeting.

Each reviewer will receive hard copies or packets of study documents about one week before the meeting. The packet will contain all the materials that will be reviewed at the upcoming meeting. These materials are placed in a bag and made available about a week before the meeting. Members are encouraged to obtain their review packets promptly. Complete file documentation will also be available through the memory sticks.

Included with each of the packets for the assigned reviewers is a Reviewer Checklist for both the scientist and

non-scientist to complete for each the assignments. Many sections of this form will be pre-filled by the staff prereviewer, including the Protocol Number, PI Name, and Meeting Date. Each section of this form should be completed and the form should be printed, signed, and returned at the IRB Meeting. The forms can be handwritten or filled out electronically.

General Guidelines for Reviewing the Assigned Material

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The designated reviewer will conduct an in-depth, comprehensive review of each assigned protocol or amendment prior to the meeting. This review will look at the many detailed aspects of the protocol and consent form but also ensure that the core principles of research with human subjects are upheld. These key issues include:

- **Respect for persons**: each individual is treated as autonomous, and any persons with diminished autonomy are entitled to special protections;
- **Justice:** selection of subjects should be scrutinized to ensure that some groups are not being systematically selected or excluded; and
- **Beneficence:** do no harm, minimize risk, and maximize benefit.

A review will determine if the:

- Risk level (minimal to significant).
- Risks have been reduced to the maximum extent possible.
- Risk have been disclosed and benefits outweigh the risks of the project.
- Subject selection is equitable.
- Consent process and document is sufficient to allow for "informed consent."
- Equipoise is present.
- Members are expected to review all materials, however are expected to review very carefully the items for which they are assigned the role of reviewer. Members will know what documents they are assigned by checking the Assignments document that is sent with the agenda.

IRB members are encouraged to contact the investigator or study team member if there are questions or concerns. If issues cannot be resolved in this discussion, the member can invite the study team members to attend the meeting. (Make sure to inform the administrative staff if study team members are invited so they can insure that there is adequate seating and food.)

IRB members are encouraged to contact the administrative staff or other IRB members if there are questions that need to be discussed prior to the meeting.

Key Points to Remember as a Reviewer:

1. **Read the assigned materials at least 2-3 days in advance of the meeting.**
   If you are assigned as the scientific or non-scientific reviewer, it is your responsibility to thoroughly review the IRB application materials in advance of the meeting. If you wait until the day before the meeting, you may not have time to contact the researcher with your questions.

2. **Get all questions answered before the meeting.** IRB Members are not expected to be the absolute experts about the protocols they are assigned to review. Talk with others as needed. Feel free to contact the:
    - IRB Chair
    - Co- reviewer
    - Informal Consultant (e.g., colleague w/ expertise)
    - Furthermore, do not hesitate to contact the Primary Investigator if you have questions. Collegial interaction between researchers and IRB members facilitates the IRB review process and research compliance as well as fosters respect for human subject's protection.
3. **Contact the IRB Chair if you have serious concerns about the protocol.**
4. **Decide whether the investigator should attend the meeting to discuss any problems or concerns noted with the project.** Determine if specific changes are needed in the application, protocol or consent form, and come to the meeting with recommended wording to be transmitted to the investigator.

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5. **Write comments and recommendations on the Reviewer's checklist** and be prepared to present them to the Board. You will submit this form to the IRB administrative staff during the IRB meeting. Please make sure you have answered all questions and signed and dated the form(s) before turning it in. In many cases, the documentation on the reviewer's checklist is the only place certain regulatory reviews are documented.
6. **Be organized** (bring packet materials to the meeting).
Informal verbal consultation is encouraged. However, IRB members must be respectful of maintaining all board proceedings and documents that contain personal, confidential and proprietary information in strict confidence. Such information may not be used for any purpose other than the IRB review and may not be disclosed to anyone outside of the IRB.

The Institutional Review Board Review Process

The IRB-HSR has sole authority at University of Virginia for the approval of research with human subjects.

The review of research at University of Virginia is conducted in accordance with the:

- Office of Human Research Protections (OHRP)
- National Institutes of Health (NIH)
- Federal regulations as published by Department of Health and Human Services (DHHS)
- Food and Drug Administration (FDA)

In the case of a decision by the IRB-HSR to disapprove, suspend, or terminate a project, the AVRPGS or any other officer or agency of the University of Virginia, state government, or federal government may not reverse the decision.

IRB-HSR review applies to research conducted by faculty, students, staff, or agents of the University utilizing facilities or resources of UVA, as well as research conducted elsewhere by UVA personnel in connection with their institutional responsibilities.

The review requirements apply to all research conducted under the auspices of UVA, regardless of the funding source or University support or any research determined by the Institutional Official (IO).

UVa IRB-HSR Board Member's Guidance

The IRB-HSR is responsible for ensuring that all approved research complies with the letter and spirit of the human subject protections regulations, as well as the three principles previously defined in the Belmont Report:

- respect for persons
- beneficence
- justice

The review will help ensure that:

- Investigators recruit subjects in an equitable, non-coercive manner,
- Subjects are fully informed about the risks and benefits in participation, and
- Subjects are not exposed to disproportionate risks.

The IRB-HSR has the authority to:

- Approve
- Require modifications
- Defer actions when additional information is needed before approval can be given
- Disapprove proposed human subjects research.

The IRB-HSR also has the authority to suspend or revoke its approval of on-going research.

In order to maintain a review process that is responsive to the concerns of all involved Federal regulations require that the IRB-HSR membership reflect:

- experience,
- expertise and diversity in academic, research and professional background,
- racial and cultural heritage
- sensitivity to community attitudes

When the IRB-HSR reviews research involving a vulnerable category of subjects, such as cognitively impaired individuals or prisoners, it is required to include one or more individuals qualified to represent that group, either through personal experience or experience working with that population.

Protocols are reviewed by IRB-HSR members whose knowledge best matches the expertise required for review of the protocol. If no IRB-HSR member has adequate knowledge or experience to review a given protocol, the IRB-HSR chair may elect to engage a consultant to conduct the review.

Failure to comply with IRB-HSR requirements is considered serious non-compliance (and may be misconduct) and may be subject to sanctions, including possible termination of all approved research.

<u>Sequence of Events at IRB Meetings</u>

The format for discussion of protocols at the full board meeting is not set by federal regulations or guidance documents. Thus, IRBs are able to develop a routine that works for their institution and membership.

What follows is a basic order of IRB-HSR meetings held at UVA.

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- The Chair/Vice-Chair calls the meeting to order once quorum is established.
- Any relevant announcements are made prior to presenting new studies for review.
- The Scientific or Primary reviewer presents new study applications to the board.
- The primary reviewer summarizes important issues they noted related to research ethics, safety, and/or science. The presentation ends with a summary of unresolved issues and/or issues requiring revision. The reviewer makes a recommendation for how the committee should vote on the protocol.
- The Non-scientific or Secondary reviewer comments on the protocol. The secondary reviewer does not repeat the information presented by the first reviewer, but indicates where he or she agrees or disagrees with the issues as outlined by the first reviewer. The secondary reviewer adds or clarifies information and ends with a recommendation that may or may not agree with the primary reviewer's recommendation.
- It is the responsibility of the chair to open the discussion, make sure every issue and question is addressed, and to ensure the meeting is carried out in a courteous and productive manner. The chair ends the discussion and calls for a vote to approve, accept with modifications, withhold pending major modifications, table, or disapprove. The Chair will ask for an IRB member to second the vote
- An ideal environment is one that promotes an open discussion and encourages all members to express their views in a warm atmosphere, and all IRB members participate in identifying and discussing the issues. There is no formula for this process so it is essential that the IRB chair manage this aspect of the meeting.
- Questions of regulatory or policy matters are often addressed by the Chair or IRB Director as IRB members are not expected to be as expert in these areas.

<u>Issues Considered by the Institutional Review Board when reviewing a New Protocol</u>

OO18 What follows is guidance regarding what factors should be considered when performing review of a new full board study.

1. **Determining whether the risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.** In making this assessment, please consider the following:
    - Whether adequate safeguards have been adopted to reduce risk exposure as much as possible.
    - Whether adequate measures have been taken to ensure that the occurrence of illness or injury will be detected and treated.
    - Whether the study procedures have been piggybacked onto procedures that would be performed for clinical purposes when possible.
    - Whether there are adequate means in place (e.g., data and safety oversight committee) such that if the research protocol needs to be modified, or changes in the risk level occur, they will be appropriately and timely brought to the attention of the IRB for review and approval.

- Whether the data to be collected are adequately protected against the risk of break of confidentiality.
- Whether the eligibility criteria will adequately reduce risks to subjects by excluding those who may be at higher risk from the study procedures.

2. **Determining whether the risks of the research are reasonable in relation to the benefits (i.e., the study has a reasonable risk/benefit ratio).** In making this assessment, please consider the following:
   - The purpose of the research.
   - Whether the research design is sufficiently robust to warrant the risks to the subject.
   - Whether the objectives of the study are appropriate and that study endpoints are clearly defined and likely to be met.
   - Whether the study design is sound such that the study will result in useful knowledge.
   - Whether the potential benefits to the subject and/or society outweigh the risks being incurred.
   - Whether there is reasonable justification for the protocol, especially if it presents more than minimal risk to subjects.
   - The types of risks the study may involve: physical, psychological, sociological, economic, or legal.
   - Potential risks to others, such as the risks related to disclosure of genetic information.
   - Potential reproductive risks.
   - Potential long-term effects.
   - Whether the potential risks and benefits have been clearly and accurately identified.
   - Qualifications of personnel to conduct research.
   - The setting in which the research will be conducted, including the adequacy of the facilities at which the research is conducted and the adequacy of the procedures in place should an emergency arise.
   - Whether the protocol should include a counseling or referral plan and, if so, whether these resources are adequate.
   - UW and national standards, especially in terms of institutional standards of care.
   - Whether additional protections are needed to ensure the protection of vulnerable populations.
   - How subject privacy and confidentiality are protected and whether this is adequate.

- Data and tissue disposition (e.g., who will see the study data or receive samples, whether the data or samples with be destroyed or kept long-term, whether data/samples will be used for unspecified future research, whether the data/samples will leave this institution).

3. **Determining whether subject selection is equitable.** In making this assessment, please consider the following:

   - Whether inclusion or exclusion criteria are appropriate.
   - Whether a group will be targeted for inclusion or exclusion and whether this is justifiable.
   - Whether there is an adequate rationale or justification for sample size.
   - Whether recruitment methods are reasonable and will not bias subject selection or unduly influence subjects.

4. **When some or all of the subjects are likely to be vulnerable to coercion or undue influence,** such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. In making this assessment, please consider the following:

   - Assess whether any of the following are included in the protocol: children, prisoners, pregnant women, mentally disabled persons, economically or educationally disadvantaged persons, VA subjects, critically ill patients, or others who may be vulnerable (which may include situationally vulnerable).
   - Whether vulnerable populations will be included and whether this is warranted.
   - Are additional measures needed to protect these subjects in terms of the recruitment process, payment, informed consent process, where the research occurs, how information is managed and protected and who conducts study procedures?
   - Is consent monitoring required or the presence of a subject advocate or witness during the consent procedure?

5. **Informed Consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116, and, if applicable, 38 CFR 16.116 and 21 CFR 50.20 and 21 CFR 50.25.** In making this assessment, please consider the following:

   - Is the investigator requesting a waiver or alteration of informed consent? If so, are the following conditions of a waiver or alteration of informed consent met: (1) research represents an emergency use of FDA-regulated drug or device; OR (2) the research presents no more than minimal risk to subjects; (3) the waiver or alteration will not adversely affect the rights and welfare of subjects; and (4) the research could not practicably be carried out without the waiver or alteration? NOTE: With few exceptions a waiver of informed consent cannot be granted for FDA-regulated research.

- Will subjects or their legally authorized representatives be given sufficient time to consider the risks, benefits and alternatives to participation and whether they wish to participate?
- Is consent monitoring warranted?
- Are the individuals conducting the consent process the appropriate people to do so?
- Are the consent documents written at an adequate reading level, is the length of the form appropriate for the complexity of the study, and is clear, concise, non-technical language used throughout?
- Will the circumstances of the consent process minimize the potential for undue influence or coercion?
- If potential subjects are unable to provide informed consent on their own behalf, are additional safeguards needed to protect their rights and welfare?
- Is the consent language provided to potential subjects and/or their legally authorized representatives in language that is understandable to them?
- Is the information being communicated to potential subjects or their representatives during the consent process free of exculpatory language (i.e., language that suggests the subjects or their legally authorized representatives are made to waive or appear to waive any of the subjects' legal rights or has released or appeared to release the investigator, the sponsor, the organization, or its agents from liability for negligence?)
- Do the consent (not assent) documents contain the required information, including:
    - A statement that the protocol involves research
    - Explanation of the purpose of the research
    - The expected duration for subject's participation
    - The procedures to be followed
    - Identification of the experimental parts or procedures of the study
    - A description of the reasonably forseeable invasive or non-invasive risks or discomforts
    - Any potential benefits to subjects
    - Disclose appropriate alternative procedures, if any, that might be advantageous to the subject
    - Describe how confidentiality of the records identifying the subject will be maintained
    - A statement, if research is more than minimal risk, whether any compensation is available

- Indicate whom to contact for questions about the research itself
- Include a statement that participation is *voluntary*, that there are no penalties if one refuses to participate, and subjects can withdraw at any time without penalty

- Are any of the following additional elements of consent appropriate and/or required?
  - A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
  - Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
  - Any additional costs to the subject that may result from participation in the research
  - The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
  - A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject
  - The approximate number of subjects involved in the study
- If adults with impaired decision-making capacity will be enrolled, are there mechanisms for obtaining consent of surrogates?
- If minors will be enrolled:
  - Is an assent process and form needed? Please take into account the ages, maturity, and psychological state of the children involved.
  - If an assent process is required, is the proposed assent process appropriate and does assent need to be documented?
  - How many parents need to provide permission for their participation according to the requirements of Subpart D?
  - Does parental permission need to be documented?
  - If parental/guardian permission needs to be waived because it is not a reasonable requirement to protect the subjects, what is an appropriate substitute mechanism for protecting the children who will participate as subjects in the research?
  - Can documentation of parental/guardian permission be waived and is it appropriate?
  - Are any children to be enrolled wards of the State?

- If individuals who do not speak English will be included, does the consent process address this situation adequately?
- Does the protocol involve deception? If so, is this warranted and is there adequate debriefing planned?

6. **Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117, and, if applicable, 38 CFR 16.117 and 21 CFR 50.27.**

   - Is the investigator asking for a waiver of written consent? If so, does the protocol meet one of the following criteria: (1) the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (NOTE: this criterion cannot be applied to FDA-regulated research); or (2) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.
   - Will an oral consent process be used? If so:
     - Will the entire consent form be read to the subject or the subject's LAR or will a short form be used that is accompanied by a summary that contains the required elements of consent?
     - Will there be a witness to the oral presentation as required by the regulations, who is conversant in the language of the present and potential subject, and will witness sign and date the short form and copy of the summary presented to the subject?
     - Will a copy of the signed and dated summary be given to the subject or the subject's LAR?
   - Will the consent form(s) be signed? If so:
     - Will they be signed by the subject or the subject's LAR?
     - Will the subject or the subject's LAR be asked to date the consent document(s)?
     - Will the person obtaining informed consent sign and date the consent document(s)?
     - Will copies of the signed and dated consent form(s) be given to the subject or the subject's LAR?

The IRB-HSR will also carefully review the informed consent/assent process; when, where and how consent is obtained, and any provisions for the on-going consent of subjects. Generally, the IRB-HSR will not dictate the procedure to be used to obtain informed consent, but reserves the right to do so if deemed necessary.

7. **When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.** In making this assessment, please consider the following:

    - If the study presents minimal risk to subjects, a data and safety monitoring plan may not be required.
    - For research that presents more than minimal risk to subjects, consider whether the following are adequate:
        - How adverse events and unanticipated problems are defined in the protocol
        - How adverse events and unanticipated problems are monitored and whether they meet institutional and federal reporting requirements
        - Whether adverse events will be reviewed by an appropriate person/entity to ensure that new information that arises will be recognized and disseminated to relevant individuals (e.g., sponsor, investigators, subjects) promptly
        - Whether a formal Data Safety Monitoring Board or Data Monitoring Committee is required
        - If Data Safety Monitoring Board or Data Monitoring Committee is proposed, whether its composition adequate, meets sufficiently frequently, and reviews the appropriate information
        - Does the protocol outline sufficient monitoring of subject to ensure adequate safeguards are in place to prevent or identify and mitigate adverse effects of the study procedures?
        - For multisite research, whether the management of information relevant to the protection of subjects is adequate.

8. **When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.** In making this assessment, please consider the following:

    - *Privacy* can be defined in terms of having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.
    - *Confidentiality* pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding of the original disclosure without permission.
    - Are research procedures conducted in a setting that helps ensure subject privacy?
    - Are the individuals accessing protected health information involved in their health care or have subjects given explicit permission for this information to be shared?
    - Is all information collected in the study or accessed by researchers necessary to answer the research question?

- Is the plan for protecting the confidentiality of the data adequate?
- When does the investigator plan on de-identifying the data? Is this soon enough?
- Do the application, protocol, and consent documents clearly identify all individuals or entities that may receive identifiable subject data?
- If identifiable subject data will be shared with others, is this warranted and are the confidentiality protections sufficient?
- How and where will the data be stored? What mechanisms are used to secure the data?
- Are any sensitive data collected such that additional protections (e.g., a Certificate of Confidentiality) are needed?

- Is the rationale for the study clearly stated and is the rationale scientifically sound?
- Are the aims and corresponding hypothesis clearly stated?
- Is the primary outcome (and secondary outcomes, as appropriate) clearly defined?
- Are there adequate preliminary data in the literature (or from the investigator) to justify the proposed research? Has an adequate literature review been done to support this study?
- Is the question or hypothesis being tested providing important knowledge to the field?
- Is the design of the study appropriate for the questions that are posed?
- Have the validity and reliability of measures been established or are there methods proposed for establishing validity and reliability?
- Is the proposed subject population appropriate?
- Are statistical considerations, including sample size and justification, estimated accrual and duration, and statistical analysis clearly described and adequate to meet the study objectives?
- Are all the proposed tests or measurements requested necessary to answer the scientific question?
- Are the investigators well qualified to conduct this study?

9. When appropriate, the IRB-HSR will determine whether a project requires more than annual review and may require an appropriate monitoring procedure that could include monitoring of the consent process, observation of the research procedures and review of research related records. In some instances, the IRB-HSR may refer review of the research to an additional committee. However, final authority for additional review lies with the IRB-HSR.

10. When appropriate, the IRB-HSR will assess whether there is a potential for a conflict of interest. Conflict of interest refers to a divergence between an individual's personal financial, relational, or other interests and his/her professional obligations to the University of Virginia whether through teaching,

involvement in research, contracting, purchasing, or performing other administrative duties such that an independent observer might reasonably determine that the individual's professional actions or decisions are adversely affected, distorted or otherwise compromised by the individual's personal interest. The term conflict of interest is broader and encompasses more professional activities than the term financial conflict of interest in research, defined below.

Financial conflict of interest in research is the existence of a significant financial interest that an independent observer might reasonably determine could affect or compromise, or appears to affect or compromise, the design, conduct, reporting or management of research. The effect or compromise contemplated might relate to the collection, analysis, and interpretation of data, the hiring of staff, the procurement of materials, the sharing of results, the choice of protocol, the involvement or consenting of human participants, and/or the use of statistical methods.

11. The IRB-HSR will review the recruitment methods outlined by the study team.

The IRB-HSR is required to review the method for prospective identification and recruitment of subjects. They will examine the means of identifying and contacting potential subjects and the methods for ensuring the subjects' privacy and confidentiality. Investigators are required to submit plans for ensuring the privacy and confidentiality of subjects.

A recruitment tool informs potential subjects of a research activity and provides them with an opportunity to contact the researcher. A recruitment tool may include, but is not limited to, post-cards, flyers, advertisements, press releases, brochures, and postings on the Internet. Investigators are required to use the following guidelines when developing recruitment tools:

- Name and address of the clinical investigator and/or research facility (letterhead is acceptable)
- Condition under study and/or the purpose of the research
- Summary form, the criteria that will be used to determine eligibility for the study
- Brief list of the benefits of study participation, (if any) i.e. a free health examination
- Time or other commitments required
- Location of the research and the person or office to contact for further information
- Drug or device studies, no claim should be made as to the superiority , safety or effectiveness of the drug or device. Proprietary names of study products may not be used.
- Excessive monetary or other incentives that could be interpreted as inappropriate or coercive are not included
- Are consistent with the protocol.

Due to contractual obligations, recruitment tools should not include any proprietary identifiers, contain therapeutic or outcome claims or mention the corporate sponsor by name.

12. When appropriate, the IRB-HSR will review all surveys, questionnaires, interview material and other testing instruments to ensure that they adequately reflect the purpose and procedures in the study and handle sensitive issues appropriately.

If the materials ask for information that, according to local law, would require reporting (e.g., elder or child abuse), the consent form should explain this exception to the promise of subject confidentiality. There are, however, a variety of psychological and other measures which are considered "standard" and, while they cannot be modified, reviewers should still indicate if use of a given measure is appropriate for a particular study. In particular, reviewers should consider if survey answers, if known, would impact a subject's reputation,

insurability, etc.

The No Child Left Behind Act of 2001(Public Law 107-110) identified 8 categories of protected information for survey responses:

- political affiliations of student or student's parent;
- mental or psychological problems of student or student's family;
- sex behavior or attitudes;
- illegal, anti-social, self-incriminating or demeaning behavior;
- critical appraisals of others with whom students have close family relationships;
- legally recognized privileged or analogous relationships;
- religious practices, affiliations or beliefs of student or student's parent; and
- income.

Research involving any of the eight identified categories requires written parental informed consent prior to participation of a child, even if the research meets the exempt criteria.

OO19 **13. The IRB-HSR will review the qualifications of the investigators.** Procedures requiring special skills on the part of the investigators, licensure, accreditation, and/or experience in qualifying the investigator for the performance of the proposed procedures are reviewed by the IRB-HSR. In addition, the IRB-HSR will consider the facilities and equipment used to conduct the research and maintain the rights and welfare of subjects.

14. When appropriate, the IRB-HSR will assess whether the study includes <u>Deception or Withholding Information</u>.

The basic principles that guide the ethical conduct of research, as previously outlined in Chapter 1, Introduction "The Foundations of 45 CFR 46: The Belmont Report" are (1) respect for subjects, (2) beneficence; and (3) justice. The requirements for complete informed consent strongly favor comprehensive, honest, and understandable disclosure of all elements of the subject's participation in research. There are times, however, especially in behavioral research, when investigators plan to withhold information about the real purpose of the study or purposely give subjects false information about some aspect of the research. As a result, the subject cannot give prospective fully informed consent. The use of deception or incomplete disclosure imposes special responsibilities on the investigator and the IRB-HSR. Occasionally, a study will involve degrees of deception. Minor deception, such as withholding specific points of interest in an attempt to prevent a bias in the results, can be acceptable, provided the subject is fully debriefed after participation. Risks stemming from major deception, such as leading the subject to believe that she/he has committed a crime or has a disease, must be clearly counterbalanced by the benefits of the research.

The Federal regulations do not allow the IRB-HSR to waive some or all of the elements of informed consent, including a fair and comprehensive description of all elements of the research, if the study involves more than minimal risk. In addition, the waiver of the elements of consent must not adversely affect the rights and welfare of subjects, and must be essential to the ability to carry out the research.

Incomplete disclosure or the use of deception cannot be used as a means to secure the participation of subjects in research. The IRB-HSR may not approve research that entails more than minimal risk and withholds information that is material to the subject's decision to participate in the study. The IRB-HSR is required to consider whether the withheld information would influence the decision of potential subjects to participate in the research. The IRB-HSR cannot approve a study that presents more than minimal risk where subjects are deceived or not given complete information that they would consider material to the decision to participate.

Use of Deception

The employment of deception by an investigator(s) for the purpose of securing subject participation and/or to prevent potentially biased reporting of data/information by the subject is permissible provided all of the following conditions exist:

- Deception is necessary due to the lack of alternative procedures for data collection not involving deception;
- The deceptive procedures will not place subjects at significant financial, physical, legal, psychological, or social risk;
- The data collection/experiment will be followed by careful debriefing sessions whereby the subjects are fully informed of the nature and purpose of the deception; and
- The procedures for deception must meet the guidelines established by the discipline of the investigator through its professional code of ethics.

Debriefing

In order for the IRB-HSR to adequately review the research, investigators should justify, in detail, in the protocol, the reasons for deceiving or withholding information from subjects, including an explanation of:

- the necessity for deceiving subjects;
- how potential benefits of the research justify the use of deception; and
- how the investigators will conduct the debriefing.

In addition, investigators should include a debriefing script or statement that indicates the information subjects will receive regarding their participation in the research.

The IRB-HSR in collaboration with the investigator will determine whether subjects should be debriefed either after unwittingly participating in the research or after knowingly participating in research that involved deception.

The IRB-HSR may require debriefing when it contributes to the subject's welfare, i.e.,

- when it corrects painful or stressful misperceptions, or
- when it reduces pain, stress, or
- anxiety concerning the subject's performance.

For example, if a subject is lead to believe through participation in deception research that she/he has committed a crime or has a disease, a debriefing session may correct the induced stress, pain, and/or anxiety.

Establishing Continuing Review Parameters for Approved Protocols

In approving a protocol, the IRB determines how frequently the protocol should be submitted for continuing review or oversight. Federal regulations state that approvals may be granted for no longer than a one-year period, but the IRB may recommend more frequent review based upon time intervals or enrollment numbers for high-risk protocols. When determining the interval for continuing review, members should consider:

- studies that are pilot studies and for which little preliminary data exists.
- the experience of the investigator.
- studies that pose a special risk to the subject.
- studies where there may be little preliminary human data.
- emergency waiver of consent protocols.
- studies in which the subjects are gravely ill and the risk/benefit ratio is unclear (e.g. sepsis trials).
- studies in which the preliminary data indicate a special element of risk for the subject.

Performing Non-Scientist Review for a New Full Board Protocols

Additional Points to Consider When Reviewing a Protocol as a Non-Scientist:

1. Establish a review routine by using a systematic approach to review each new protocol in the same way.
2. Read the consent document to understand the important aspects of the study. The consent document should serve as a good introduction to the study protocol. It should also orient you to the overall design of the study.
3. Read the lay abstract in the IRB application which provides key aspects of the study.
4. Read the full protocol and supporting materials carefully. The investigator provides the IRB with detailed information such as the study background and rationale, methodology, inclusion/exclusion criteria for subject enrollment, and other documents. Funding documents provide additional information. Take notes as needed.
5. Reread the consent document. Record suggested corrections or questions for the investigator, and ensure that the consent form adequately describes the actual study design and procedures in a language that can be understood by the subject.
6. Being mindful of certain requirements will help you identify ethical and regulatory issues while reviewing the IRB application. Here are some additional points to consider:

- What are the subjects required to do? Will they take an investigational drug or receive an investigational device, fill out a survey, or be interviewed about criminal activity? Are the research activities potentially harmful or embarrassing?

- Would you participate in this study, or would you want your parents, children, spouse or other family members to participate?
- Does the study make sense as written? Is it overwhelming with too much jargon or too many details?
- Is the informed consent document easy to understand and an accurate reflection of the study procedures?
- Who are the subjects and are they vulnerable to coercion (e.g. children, prisoners)?
- Is it necessary to keep the private information? Is more information being requested than is needed?
- If private information is collected, is there a mechanism in place to protect the subjects' identities or other private information? If so, is it adequate?
- Is the information provided in the protocol, consent, and recruitment materials consistent?
- Are there adequate safeguards to protect the subjects if an untoward event occurs? What action will the PI/researchers take if something goes wrong?
- If the intervention/treatment proves beneficial, will those subjects not in the intervention/treatment group (i.e. control group) be able to partake in the intervention or receive the treatment once the study has been concluded?
- What "gut" feelings do you get after reading the protocol? Sometimes, something about the study seems questionable and may make you feel uneasy. Express this unease and attempt to get the issue resolved.

Reviewing Modifications

Changes (commonly called modifications or amendments) in protocols must be approved by the IRB prior to the initiation of such changes, except when necessary to eliminate apparent immediate hazards to subjects. Reviewers should assess the modification and determine if the modification changes the risk/benefit ratio for the subjects negatively or substantially changes the way the research is conducted. Amendments involving more than minor changes (major) or changes that pose more than minimal risk will be reviewed by the full board.

The essence of the study should be summarized by the primary reviewer and will include:

- how the modification will affect the conduct of the study,
- the risk/benefit ratio
- whether or not the modification should be approved as submitted

If a study requires approval from the Cancer Center Protocol and Review Committee (PRC) documentation from the Cancer Center Protocol and Review Committee (PRC) will accompany the modification.

What constitutes a MAJOR change?

Major changes are changes that may increase the research population's risk or are of questionable risk. In addition, numerous changes to study design are considered major changes.

- Examples of major changes that are considered to increase the risk to the study/individual:
- Increasing the length of time a study participant is exposed to experimental aspects of the study.
- Increasing the dose/strength of an investigational drug.
- Changing the originally targeted population to include a more at-risk population (example: previous exclusion for those with renal failure are now allowed to enroll, or adding children or pregnant women to the study.
- Adding additional procedures where the risk of the additional procedure is greater than minimal risk.

- Adding a blood draw such that the total amount of blood drawn or frequency of blood draws exceeds what is considered to be expeditable.
- Adding an element that may breech the confidentiality of the subject such as tissue banking or genetic testing.

What do you review?

- **Review ONLY what is being revised.** At this juncture, you are **not** responsible for reviewing the entire protocol. Refer to any attached memo from the PI and/or sponsor that explains the rationale behind the requested revisions. In addition review the tracked changes in the IRB protocol, consent/assent and the sponsor protocol, if applicable.
- Ask yourself: Does the modification pose any additional risks to the subjects or others? Is so, has this been addressed in the protocol and/or consent? Is the proposed change acceptable based on the current study plan?
- Are the revisions being made to the protocol consistent with those made to the consent?

What do you document?

Refer to the "Full Board Modification Review Checklist" that will be attached to your review packet for the particular study. Complete the checklist and make comments if you require additional clarification from the PI. After completing the checklist, you will indicate your summary recommendation and include any additional comments

Your signature and date will indicate you have completed your review and subsequent recommendation.

Reviewers Checklists

Links to the modification reviewer's checklists are found on the IRB –HSR website.

Review of Continuations

Protocol Continuation Process

The IRB is responsible for the continuing review of research to ensure that the rights and welfare of human participants are being protected. The IRB is required to reevaluate research projects at intervals appropriate to the degree of risk, but not less than once a year per 45 CFR 46.109(e). At the time of initial approval, the IRB should decide the frequency of continuing review for each protocol necessary to ensure the continued protection of the rights and welfare of research subjects.

Approximately sixty and thirty days before study expiration, a reminder email is sent to the investigator. The email includes the Protocol Status Form. The investigator is responsible for completing the Protocol Status Form according to the instructions on the form and providing all requested documents.

If the researcher wishes to close the protocol, they are instructed to submit a Closure Form instead of the Continuation Status Report.

Once completed continuing review materials are received by the IRB, a determination is made regarding the applicable review process (e.g expedited or full board) for the continuation. The continuing review will be scheduled for review within 30 days of the study expiration date.

Criteria for Continuation/Renewal
Continuing review must be substantive and meaningful, in that continuing review by the convened IRB, with recorded votes on each study, required unless the research is otherwise appropriate for expedited review under Section 46.110.

When considering whether or not to renew a study, the IRB revisits the same criteria used to grant initial approval. Therefore, the IRB (or the individual reviewers for continuation requests reviewed under an expedited procedure) must determine that:

- The risks to subjects continue to be minimized and reasonable in relation to the anticipated benefits;
- The selection of subjects continues to be equitable and reasonable in relation to anticipated benefits;
- Informed consent continues to be appropriately documented;
- Additionally, that there are:
    - Provisions for safety monitoring of the data,
    - Protections to ensure the privacy of subjects and confidentiality of data, and appropriate safeguards for vulnerable populations.

Because it may be only after research has begun that the real risks can be evaluated and the preliminary results used to compute the actual risk/benefit ratio; IRB can then determine whether or not the study can be renewed at the same risk/benefit ratio, or if new information has changed that determination.

The IRB Administrative staff assigned to continuations will review the Protocol Status form and associated documents to determine if the request qualifies for the expedited review procedure (as allowed by the federal regulations, 45 CFR 46.110) or requires review by the full, convened IRB.

A completed Protocol Status report form for each study includes:

- Status of the study
- Local subject enrollment
- Local serious advents, unanticipated problems, protocol violations
- Any grievances or complaints received
- Any change in conflict of interest of research team
- Summary of changes, amendments, revisions (including study staff)
- Summary of any significant information
- Summary of local study results to date
- Summary of study-wide results with any reports provide by sponsor (DSMB, annual reports, new literature)
- IRB staff comments.

Research originally reviewed at the exempt or expedited level will generally qualify for expedited review unless previous or proposed modifications change the risk level or include activities that do not meet the criteria for expedited review.

The expedited review procedure may be used for the continuing review of research previously approved by the full, convened IRB as follows:

- Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research –related interventions; and (iii) the research remains active only for long-term follow-up of subjects; **or**
- Where no subjects have been enrolled and no additional risks have been identified; **or**
- Where the remaining research activities are limited to data analysis.

The expedited review procedure may also be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption when the research does not meet the expedited review criteria or the exceptions listed above but the IRB has determined in a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

The continuing review provides an important opportunity to ensure that changes in federal or state policy or IRB practices and expectations are reflected in the protocol and especially the consent form.

DHHS regulations at 45 CFR.111 set forth criteria that must be satisfied in order for the IRB to approve the research. These include: determinations by the IRB regarding risk, potential benefits, informed consent, and safeguards for human participants. The IRB shall ensure that these criteria are satisfied at the time of both initial and continuing review.
Investigators are notified in writing of the decision of the IRB and any changes required. As an outcome of continuing review, the IRB may require that the research be modified or halted altogether. The IRB may need to impose special precautions or relax special requirements it had previously imposed on the research protocol. Continued approval is not granted until all required changes have been made and submitted for review and approval. Once approved, the investigator is sent a continuing approval form indicating the date of the next study expiration

If an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the expiration date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval.

When continuing review of a research protocol does not occur prior to the expiration date specified by the IRB, IRB approval expires automatically. Such expiration of IRB approval does not need to be reported to OHRP as a suspension of IRB approval under HHS regulations.

What do you review?
Reviewers receive the Protocol Status Report. The Status Report includes information such as number of subjects enrolled, adverse events and protocol violations. In addition to the Status Report, reviewers will receive the current protocol, consent form and other applicable documents (AE Report and Event Reports)

If the board member(s) reviewing continuations has questions after reviewing the documents provided they may review the entire protocol file located in the IRB office or contact the administrative staff in charge of continuations.

Reviewers should:

- Consider if new or additional risks have been identified (e.g. number of serious adverse reactions) which would require changes to the protocol, consent form, review frequency, etc.
- Determine that changes in research were reported to and approved by the IRB.
- Identify protocols that should be suspended or terminated because research is not being conducted in accordance with IRB requirements.
- Determine if new IRB policies might necessitate changes in the protocol.

The full board member assigned to continuations reviews will provide recommendations to the IRB at the convened meeting on issues for any study for which they determine do not meet the federal criteria for approval, IRB requirements, are controverted, need additional information, or concern compliance with the mandatory human research training requirements

The primary reviewer will give a motion to approve, approve pending minor modifications, withhold approval pending major modification, table or reject the continuation approval

Reviewers Checklists
Links to the Continuation Reviewer's Checklist is found on the IRB-HSR website on the IRB Members page.

Review of Notification of Adverse Events, Unanticipated Problems and Protocol Violations

The IRB is responsible for the reviewing of notifications for internal serious and unexpected adverse events for studies. These notifications will appear on the agenda for each meeting.

In addition, the board is responsible for reviewing the notifications for Protocol Violations and Unanticipated Problems. These notifications appear as such on the agenda for each meeting.

Board members are encouraged to review these items and resolve any issues or make recommendations regarding these notifications during each meeting.

Additional information on these types of issues may be found on the IRB-HSR Website:

- Adverse Events
- Protocol Violations
- Unanticipated Problems

Full Board Review Outcomes

The IRB may come to one of five determinations regarding an application:

APPROVED:

The study meets the regulatory criteria for IRB approval as defined by 45CFR 46.111 and/or 21CFR 56.111. The application has secured approval, thus the investigator is not required to make changes to the protocol or IRB application. IRB approval is valid for one year, unless the board designates a shorter period due to higher levels of risk. An approval notice called an assurance is sent to the investigator. The consent documents are stamped with the IRB approval dates. The investigator may start enrolling subjects.

APPROVED PENDING MINOR MODIFICATIONS:

Modifications are the IRB's requests for clarifications or additional information. The term "minor modifications" may be used for all levels of review and types of submissions. The investigator will receive an approval form stating conditions which need to be met in order to be able to enroll subjects in the study.

These conditions include minor changes to the consent and/or protocol and/or approvals from other committees. Once these documents are submitted the study does NOT need to go before the full board again. If these conditions have not been met within 6 months of submission the protocol would need to be resubmitted to the Full IRB.

In a continuing review, if the modifications are minor, the investigator may continue to enroll subjects using the previously IRB approved consent document (unless the board has stated otherwise). If modifications are minor and do not affect the consent form, they will need to be satisfactorily addressed fulfilled by the next continuing review. If modifications are major, the IRB requires a response and verification that these modifications were addressed before approval is granted and new subjects can be enrolled (see below)

WITHHELD APPROVAL PENDING MAJOR MODIFICATIONS:

This option is only used during initial full board review. The study has been approved for a period of one year, pending review of the investigators response to all issues and concerns noted by the board. A letter will be written to the Principal Investigator outlining the general concerns. The investigator needs to address these concerns and re-submit copies of the revised protocol and consent form per full board requirements. It will be clear to the investigator that the study may not begin enrollment until the IRB has reviewed the revisions at a future full board meeting. In addition, the investigator may be asked to attend a future IRB meeting to answer questions.

REJECTED: The board may also decide to reject a protocol if the magnitude and or number of concerns, questions and problems is such that the board requests significant revisions be made to the protocol documents. The investigator may attend a future IRB meeting to defend the protocol if he/she wishes to pursue the study.

TABLED: This term is used when the IRB application lacks sufficient information to make an appropriate determination. A letter will be written to the Principal Investigator outlining the general concerns.
Studies that have previously been REJECTED by the Full Board **cannot be reopened or modified**. Rejected studies are considered permanently closed. These studies can only be reactivated by undergoing the New Study Submission Process and being assigned a new IRB-HSR number. All IRB-HSR new study pre-reviews and procedures will be required for these new submissions.)

At a future meeting, the investigator needs to address these concerns in written documentation or by attending a IRB meeting.

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The Meeting Vote

At the conclusion of the board's deliberations on each protocol, the chair conducts a vote of the members.. Alternates vote only in the absence of the member for whom they are an alternate. Board actions require a simple majority of the members present during the meeting. Members may vote against the recommendation of the reviewer

At the discretion of the chair, voting may be by written ballot, a show of hands, or voice vote. At UVA, this is done by a show of hands. The official meeting minutes record, without individual identification, the number of votes to approve, approve with minor modification, withhold approval pending major modifications, table or reject. The names of those members who abstain or who are absent from the room are included with the vote count for each protocol

The board vote is recorded, as well as an indication of how frequently continuing review should be conducted. Though other institutional committees share the responsibility for following guidelines in the collective effort to protect human subjects, ultimately the final authority for participation of human subjects in research falls on the IRB.

Abstain:

If an IRB member is listed in a study under IRB review or has any other conflicted interest, they may not participate in the initial or continuing review of the study except to provide information requested by the IRB. The IRB member must leave the room and abstain themselves for the discussion and vote. The meeting minutes will reflect this. The chair requests IRB members with a conflict of interest to leave the room and not participate in the vote or discussion. Conflicts of interest include financial interest, active participation in the trial as principal investigator or co-investigator, or any other issue for which the member feels his or her vote could be potentially conflicted.

If an IRB member does not have a "conflict" but is unable to vote (e.g., left the room during discussion, does not comprehend the study or the issues) the member may "abstain" from voting. A vote to "abstain" will be included as part of the voting quorum. The meeting minutes will reflect this.

Absent:

IRB members who are not at the meeting or have left the room during the vote, that person will be considered "absent" and this information will be included as part of the meeting minutes.

Payments or Funding Allocations for IRB-HSR Service

U.Va. employees serving as members of the Institutional Review Board for Health Sciences Research (IRB-HSR), except for such employees belonging to the Office of the Vice President for Research, will receive the use of funds allocated to a University-owned professional development account (PDA) set-up for each such member. Each PDA is to be managed by the Academic Division (i.e. Agency 207) home department or the Medical Center (i.e. Agency 209) to which the IRB-HSR member ("member") belongs subject to the applicable U.Va. policies and procedures of Agency 207 or Agency 209. The funds are to be used for expenses that further career-related knowledge, skills, qualifications and experience consistent with achieving U.Va's mission. Examples of allowable professional development-related expenses include travel to conferences, books, and computer equipment.

Board members who are not employed by U.Va. are provided with a lump sum payment for IRB-HSR service. Such payment may be used at the discretion of the board member.

Some U.Va. employees may serve as alternate members of the IRB-HSR or as consultant to the IRB-HSR. An alternate is not required to attend meetings more than a few times per year. Consultants are invited to attend specific meetings as needed. No payment or fund allocation is provided to either alternate members or consultants.

The amount of payment or fund allocation, as well as the most appropriate means of disbursement, is set by the Office of the Vice President for Research.

Board members who are U.Va. employees (except employees belonging to the Office of the Vice President for Research)

Funds are allocated on a fiscal year basis (i.e. for service from July 1-June 30 of each fiscal year) after each year of service on the Board. In most cases, PDAs are funded in the month of July for the immediately-preceding full fiscal year of service.

Board members must use the professional development funds within the fiscal year in which the funds were allocated. Funds from one fiscal year will not be carried over to the next fiscal year. Unspent funds revert back to the Office of the Vice President for Research at the end of the fiscal year in which the funds were allocated to the PDA. .

If a board member transfers from one department to another within the University, upon agreement by both departments, unspent funds in his or her PDA are to be transferred from the department of origin to the new department for continued use by the Board member within the allowable fiscal year. Should a Board member transfer between University departments, the Office of the Vice President for Research requires notification (notify Corky Miller at mjh3e@virginia.edu) of such transfer from both departments. Upon such notification, the Office of the Vice President for Research will work with both departments, as applicable, to transfer the unspent balance in the Board member's PDA in the department of origin to a newly-established PDA in the new department.

Should a board member resign or terminate employment with the University for any reason, all unspent funds in

his or her PDA will revert back to the Office of the Vice President for Research. In such a case, the Office of the Vice President for Research requires immediate notification from the employee and/or his/her home department to address any outstanding account-related matters or funds transfers that must then occur in a timely manner.

For Board members who are academic division (Agency 207) employees, an account (PTAO) is established within each employee's home department for the professional development funds awarded for IRB-HSR service. The responsibility for managing all activity relating to the PTAO, including the procurement of goods and services, the management of property purchased regardless of value, and the subsequent account reconciliation, resides with the home department. Board members should communicate directly with their home department fiscal contact(s) regarding the administration of PDA funds.

For Medical Center (Agency 209) employees, professional development fund allocations are transferred to the Medical Center for account management within the Medical Center. Medical Center employees must communicate directly with the Medical Center Controller regarding the administration of their respective professional development accounts.

All goods purchased by University employees with funds allocated to University PDAs, regardless of value, are the property of the University, and are to be managed as such by the employee's home department in accordance with all applicable University policies and procedures. Should an employee transfer from one department to another within the University, the goods may also transfer to the new department. Should an employee leave the University, the goods remain at the University and are to be managed by the employee's home department.

Board members belonging to the University's Academic Division (Agency 207) and their respective home department fiscal contacts are notified of the allocation of funds to their respective PDAs via e-mail by the Office of the Vice President for Research staff at the time the accounts are funded.

All applicable U.Va.policies and procedures regarding the purchase, ownership, use, transfer and surplus of goods and/or services must be addressed by the home department as administrator of the funds.

<u>Board members who are U.Va. Medical students</u>

Medical students who serve on the IRB-HSR will receive payments in two installments during the term of service (i.e. during a fiscal year) to facilitate the use of professional development funds prior to rotation off the Board or graduation. The first of two equal payments will be processed in December during the term of service. The second payment will be issued in June prior to the end of the term of service.

Medical students will be notified via e-mail by the Office of the Vice President for Research staff at the time the funds are released. Checks will be mailed to the home address on record in the University's Integrated (Oracle) System. Medical students who do not receive their checks in a timely manner should contact the e-mail author; however, please be aware that the process for instituting a stop payment and re-submission for a new check release will not occur until after 30 days from the date the original check was mailed.

Board members who are NOT employees of U.Va.

Board members who are not employed by the University are awarded funds at the same time as the U.Va. employees; however, the means of disbursement differs. Each Board member is required to register with the University as a vendor (a one-time online process); this allows the University to process a check for the lump sum payment which will be mailed to the individual's home address entered during the registration process. If the registrations are completed as required, checks are generally mailed in July for service during the immediately-preceding fiscal year. For example, if a board member serves a term from July 1, 2011 through June 30, 2012, the payment will generally be processed in the month of July 2012.

To access the online registration module, go to the UVA Procurement webpage http://www.procurement.virginia.edu/pagevendors, select "To Register as a New Vendor", and complete and submit the Vendor Registration Form as an individual. Questions about the registration process should be directed to Procurement Services at 434-924-4212.

Board members will be notified via e-mail by the Office of the Vice President for Research staff at the time the checks are mailed. Individuals who do not receive their checks in a timely manner should contact the e-mail author; however, please be aware that the process for instituting a stop payment and re-submission for a new check release will not occur until after 30 days from the date the original check was mailed.

Salary Support

Board members (except for the Chair and Vice Chair of the Board) who are University Academic Division (Agency 207) employees (i.e. this does not include Medical Center or Agency 209 employees, medical students, alternates and Office of the Vice President for Research employees serving on the IRB-HSR) receive salary support of 5% (for a full position on the Board) and 2.5% (for a shared position on the Board). Board members eligible to receive salary support as described above should direct any questions regarding salary support to their respective home department fiscal contacts. The amount of salary support for the Chair and Vice Chair is determined jointly by the Office of the Vice President for Research and the Chair's and/or Vice Chair's department.

Acronyms

CITI Training

Educational Offerings

Federal Regulations

Glossary

Useful Websites and Links

UVa Research Partner Offices