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VA Investigator Assurances

Human Research Protection Program

Investigator Manual

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What is the purpose of this manual?

This document is designed to guide you through policies and procedures related to the conduct of human research that are specific to OHSU.

Documents referenced in this manual, as well as additional information, can be found on the IRB's Policies and Forms website.

General information regarding human research protections and relevant federal regulations and guidance is incorporated into the required human protections training. For additional information, see below: "What training does my staff and I need in order to conduct human research?"

What is Human Research?

"POLICY: Definitions (HRP-001)" defines the activities that this organization considers to be "Human Research." An algorithm for determining whether an activity is human research can be found in the "WORKSHEET: Human Research (HRP-421)." Use this document for guidance, keeping in mind that the IRB makes the ultimate determination in questionable cases as to whether an activity constitutes human research subject to IRB oversight.

You are responsible not to conduct human research without prior IRB review and approval. If you have questions about whether an activity is human research, Request a Determination from the IRB Office via the eIRB.

Because of state or local laws or policies that mandate additional protections, some activities, like genetic research or embryonic stem cell research, may require IRB review even if the activity is not human research. If you have questions about whether an activity requires IRB review, contact the IRB Office.

What is the Human Research Protection Program?

A Human Research Protection Program or HRPP is an organization-wide system to protect human subjects in research. It is described in "POLICY: Human Research Protection Program (HRP-010)."

When am I engaged in Human Research?

You are considered "engaged" in human research when you 1) intervene or interact with living individuals for research purposes; 2) obtain individually identifiable private information for research purposes; or 3) obtain the informed consent of a subject for a research study. Further, an institution is considered to be engaged in human research when it receives a direct federal award to support the research, regardless of the institution's role in conducting the research. See "WORKSHEET: Engagement (HRP-422)."

What training do my staff and I need to conduct human research?

All members of the research team involved in the design, conduct, or reporting of the research must complete training.

OHSU-required human research protections training can be completed by logging into the Big Brain system and completing all required education modules based on the types of research activities you will be conducting.

Alternatively, non-OHSU investigators and research staff may complete the Collaborative Institutional Training Initiative (CITI) human subjects online training program. The CITI site can be accessed at http://www.citiprogram.org/.

On a case-by-case basis, the IRB can approve alternative training.

OHSU Big Brain re-training and refresher courses must be completed when prompted by the system. CITI training is valid for a three-year period.

This section describes the training requirements imposed by the IRB. You may have additional training imposed by other federal, state, or organizational policies.

Members of the research team who have not completed human research protections training may not take part in aspects of the research that involve human subjects.

How do I know what regulations apply to my research?

Your research may be regulated by more than one federal agency, depending on the project funding and type of project. Regardless of the funding source, all non-exempt human research must meet the regulatory criteria for approval stated in "WORKSHEET: Criteria for Approval (HRP-400)." State laws and regulations may also apply. Some examples of common laws and regulations that apply to human research include.

- If your research is funded by a federal agency, you are required to follow Department of Health and Human Services regulations at 45 CFR 46.
- If your research involves drugs, devices, or other FDA regulated products, you are required to follow Food and Drug Administration regulations at 21 CFR 50 and 21 CFR 56. Refer to "INVESTIGATOR GUIDANCE - Additional FDA Obligations (HRP-815)" for more information. The Oregon Clinical and Translational Research Institute (OCTRI) offers a Clinical Research Coordinator Training Workshop that covers these topics in detail. Information about the workshop is available here: http://www.ohsu.edu/xd/research/centers-institutes/octri/education-training/crc-workshop.cfm
    - If your research involves the use of a drug with an active Investigational New Drug (IND) application, you are required to follow FDA regulations at 21 CFR 312. If you are the IND holder, you are required to follow BOTH the Investigator Responsibilities and Sponsor Responsibilities at 21 CFR 11, 21 CFR 54, 21 CFR 210, 21 CFR 312, 21 CFFR 314, 21 CFR 320, 21 CFR 330, and 21 CFR 601. See "INVESTIGATOR GUIDANCE - Additional FDA Obligations (HRP-815)" for details.
    - If your research involves the use of a device with an active Investigational Device Exemption (IDE), you are required to follow FDA regulations at 21 CFR 812. If

you are the IDE holder, you are required to follow BOTH the Investigator Responsibilities and Sponsor Responsibilities at 21 CFR 11, 21 CFR 54, 21 CFR 812, 21 CFR 814, 21 CFR 820, and 21 CFR 860. See "INVESTIGATOR GUIDANCE - Additional FDA Obligations (HRP-815)" for details.

- If your research involves funding by a federal agency other than DHHS and NIH, such as the Department of Defense, Department of Energy, or Department of Education, you are required to follow regulations pertaining to those agencies. See the INVESTIGATOR GUIDANCE documents below for more information.
- If your research involves the use or disclosure of Protected Health Information (PHI), you must follow the applicable HIPAA regulations at 45 CFR 160, 45 CFR 162, and 45 CFR 164.
- If you are conducting genetic research, you must follow the Oregon Genetic Privacy Law at ORS 192.529 – 549; 659A.300 and 303; 743.730; 746.135; and 746.632, and associated regulations at OAR 333-025-0100 through 333-025-0165.

What are the obligations of individuals who conduct human research?

The obligations of individuals who conduct human research can be found in these documents:

- INVESTIGATOR GUIDANCE - Investigator Obligations (HRP-800)
- INVESTIGATOR GUIDANCE - Prompt Reporting Requirements (HRP-801)
- INVESTIGATOR GUIDANCE - Informed Consent (HRP-802)
- INVESTIGATOR GUIDANCE - Documentation of Informed Consent (HRP-803)
- INVESTIGATOR GUIDANCE - Additional DOD Obligations (HRP-810)
- INVESTIGATOR GUIDANCE - Additional DOE Obligations (HRP-811)
- INVESTIGATOR GUIDANCE - Additional DOJ Obligations (HRP-812)
- INVESTIGATOR GUIDANCE - Additional ED Obligations (HRP-813)
- INVESTIGATOR GUIDANCE - Additional EPA Obligations (HRP-814)
- INVESTIGATOR GUIDANCE - Additional FDA Obligations (HRP-815)
- INVESTIGATOR GUIDANCE - Additional ICH-GCP Obligations (HRP-816) (*Generally, ICH-GCP applies to all Clinical Trials.*)

In addition, Principal Investigators must follow OHSU's "Roles and Responsibilities in the Conduct of Research and Administration of Sponsored Projects."

How do I submit new human research to the IRB?

Complete a New Study submission in the eIRB and attach all requested documents. The Principal Investigator must submit the study to the IRB for review. If you are unsure if the project is human research, choose the "Request a Determination" option instead of New Study.

Can a different IRB review my human research?

The IRB may, in some cases, agree to rely on the review of another IRB. This arrangement must be approved by both parties, and a written agreement must be in place. Refer to the "Help Sheet – Collaborations with Non-OHSU Institutions and Investigators" for further guidance. If you

think it is appropriate for your study that another IRB provide review for the activities of OHSU investigators, submit a Request for Waiver of Oversight to Another IRB in the eIRB system. The IRB is more likely to permit this if your research is not greater than minimal risk.

Can the OHSU IRB review human research for non-OHSU investigators?

In some cases, yes. This arrangement must be approved by both parties, and a written agreement must be in place. Refer to the "Help Sheet – Collaborations with Non-OHSU Institutions and Investigators" for further guidance. If you are requesting this, clearly state this in your IRB application and describe the involvement of the non-OHSU investigators.

How do I write a Protocol?

You may use any format or style as long as the required information is included for the IRB to evaluate the Criteria for Approval. The IRB Policies and Forms website provides templates that serve as a starting point for drafting a new Protocol and instructions in italic text regarding the information the IRB requires for its review.

You may not include any individuals who are known at the time of enrollment to be members of the following potentially vulnerable populations, unless your protocol specifically states that they will be included and describes how they will be protected, as appropriate:

- Adults unable to consent (decisionally impaired)
- Children
- Neonates
- Pregnant women
- Prisoners
- OHSU employees or students (only if targeted for enrollment)

If a subject's status as a member of a vulnerable population is not relevant to your study and belonging to that vulnerable population would not affect the risk to the subject for that study, you are not required to determine whether each subject is a member of the vulnerable population. (For example, you would not need to ask each female subject if she is pregnant in order for her to participate in a minimal risk phone survey about a topic unrelated to pregnancy.)

If you are conducting research with decisionally impaired adults, children, prisoners, or OHSU students, please see the IRB Policies and Forms website for additional information and guidance.

How do I create a consent document?

Select the appropriate Consent and Authorization, Information Sheet, Short Form, or Telephone Script template from the IRB Policies and Forms website and follow the instructions within the template to include both required standard language and study-specific information.

Use of the appropriate OHSU template is required for all studies. Industry sponsor, cooperative group, or similar multi-site consent documents must be transferred onto the OHSU template, with all OHSU standard language included where applicable.

Most consent documents must include the required and additional appropriate elements in Section 4 of "WORKSHEET: Criteria for Approval (HRP-400)." Combined Consent and Authorization documents must include all required elements of HIPAA authorization in "WORKSHEET: HIPAA Authorization (HRP-427)." The OHSU templates are designed to include all required elements.

Always start with a template directly from the website, rather than one saved to your computer, to ensure that you are using the most recent template version.

What if I want to enroll non-English speaking participants in my study?

Participants who have limited English proficiency should be presented with informed consent documents in a language understandable to them that includes all the required and additional elements for disclosure. Either the long form of the consent document needs to be translated in writing into the subject's language or the short form of consent documentation may be used. With the short form of consent documentation, the long form consent may be translated orally and only a small portion of the information translated in writing into the subject's language.

See the "Quick Reference Guide – Limited English Proficiency" for more information.

When can a consent waiver be used?

The IRB may approve a consent procedure that does not include, or that alters, some or all of the required elements of informed consent. Refer to "CHECKLIST: Waiver of Consent (HRP-300)." Also, the IRB may approve a consent procedure that waives the requirement to obtain written informed consent. Refer to "CHECKLIST: Waiver of Documentation of Consent (HRP-303)."

When can a HIPAA waiver be used?

The IRB can waive or alter the requirement to obtain HIPAA authorization if certain criteria are met. See "WORKSHEET: Waiver of HIPAA Authorization (HRP-428)."

What are the different regulatory classifications that research activities may fall under?

Submitted activities may fall under one of the following five regulatory classifications:

- Not "Human Research": Activities that do not meet the definition of "Human Research" do not fall under IRB oversight. The criteria for whether an activity is human research is in "WORKSHEET: Human Research (HRP-421)." Submit a Request for Determination via the eIRB if you are uncertain whether an activity is human research.

- "Human research that does not engage the institution": Some human research requires review by an IRB, but not the OHSU IRB because OHSU investigators are not "engaged" in the human research activities. The criteria for this determination is in "WORKSHEET: Engagement (HRP-422)." Submit a Request for Determination via the eIRB if you are uncertain whether human research is the responsibility of the organization.
- Exempt: Certain categories of human research may be exempt from regulation but still require a limited form of IRB review. The IRB, not the investigator, must determine whether human research is exempt. See "WORKSHEET: Exemption (HRP-423)" for the categories of research that may be exempt.
- Review Using the Expedited Procedure: Certain categories of human research are not exempt but may qualify for review using the expedited procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review "WORKSHEET: Expedited Review (HRP-424)" for the categories of research that may be reviewed using the expedited procedure. The IRB will determine if a study may be reviewed using the expedited procedure.
- Review by the Convened IRB: Non-exempt human research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

What are the decisions the IRB can make when reviewing proposed research?

The IRB may approve research, require modifications to the research to secure approval, defer research, or disapprove research:

- Approve as Presented: Made when all criteria for approval are met. See "How does the IRB decide whether to approve human research?" below.
- Approve with Changes: Made when IRB members require specific modifications to the research before approval can be finalized.
- Defer: Made when the IRB determines that the board is unable to approve research, and the IRB suggests modifications the might make the research approvable and/or requests more information. The IRB describes the recommended modifications and their reasons and gives the investigator an opportunity to respond to the IRB by resubmitting the study for re-review.
- Disapprove: Made when the IRB determines that it is unable to approve research and there are not modifications that might make the research approvable. The IRB describes its reasons for this decision and gives the investigator an opportunity to respond.

How does the IRB decide whether to approve human research?

The criteria for IRB approval for exempt research can be found in "WORKSHEET: Exemption (HRP-423)," and for non-exempt research in "WORKSHEET: Criteria for Approval (HRP-400)." The latter worksheet references other checklists that might be relevant. All checklists and worksheets can be found on the IRB Policies and Forms website.

These checklists are used for initial review, continuing review, and review of modifications to previously approved human research.

You are encouraged to use the checklists to write your protocol in a way that addresses the criteria for approval.

What will happen after IRB review?

The IRB will provide you with a written decision indicating that the IRB has approved the human research, requires modifications to secure approval, has deferred the research, or has disapproved the research.

- If the IRB has approved the human research: The human research may commence once all other organizational approvals have been met. IRB approval is usually good for a limited period of time (3 years for exempt research and 364 days for non-exempt research), which is noted in the approval letter.
- If the IRB approved your research with changes and you agree to the modifications: Make the requested modifications and submit them to the IRB. If all requested modifications are made, the IRB will issue a final approval. Research cannot commence until this final approval is received. If you do not accept the modifications, explain in a written response why the requested modifications cannot or should not be made, propose alternative modifications to ensure that the study meets the criteria for approval, and re-submit to the IRB.
- If the IRB deferred the human research: The IRB will provide a statement of the reasons for deferral and suggestions to make the study approvable, and give you an opportunity to respond in writing. The IRB will re-review the research along with your response.
- If the IRB disapproved the human research: The IRB will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing.

In all cases, you have the right to address your concerns to the IRB directly at an IRB meeting. To request this, contact your Analyst and the IRB Chair.

How do I submit a Continuing Review?

Complete a New Continuing Review in the eIRB and attach all requested documents. The PI must submit the Continuing Review.

If the IRB does not approve your Continuing Review before the approval expiration date, you must stop all study activities until approval is obtained. To avoid this, ensure that Continuing Reviews are submitted 6-10 weeks before the expiration date.

How do I submit a Modification?

Complete a New Modification Request in the eIRB and attach all requested documents. The PI must submit the Modification. All modifications to research must be approved by the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the subject.

What do I do when I am done with a study?

Complete a Termination Request in the eIRB and attach all requested documents. The PI must submit the Termination Request. This will end IRB approval for your study. No additional study procedures, including data analysis, may continue.

How long do I keep records?

Maintain signed and dated consent documents for at least three years after completion of the research.

Maintain signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations for at least six years after completion of the research.

If your human research is sponsored, funded, or FDA-regulated there may be additional requirements. Contact the sponsor, funding agency, or IRB for additional information.

How do I get additional information and answers to questions?

This document and the policies and procedures for the Human Research Protection Program are available on the IRB Policies and Forms website at http://www.ohsu.edu/xd/about/services/integrity/policies/irb-policies-by-category.cfm.

You may contact the IRB Office at 503-494-7887, option 1, or irb@ohsu.edu.

VA Portland Health Care System (VAPORHCS) Institutional Review Board (IRB)

Investigator Assurances

1. I will conduct this study in accordance with the policies and procedures set forth in the VAPORHCS IRB P&P.
2. I will initiate this study, and any proposed changes in the research, only **after** receiving written approval from the IRB.
3. I will submit all unanticipated serious adverse events, unanticipated problems involving risk, all apparent serious or continuing non-compliance, and moderate or major protocol deviations within the reporting timeframe (generally five (5) days of notification, or within 24 hours for major deviations indicating harm.)
4. I take responsibility for maintaining IRB approval and will submit all required information according to required timelines.
5. Unless the IRB has granted a waiver of all informed consent/authorization requirements, or a waiver of documentation of informed consent and a waiver of the master list requirement, I assure that I or a qualified research staff member will:
   a. Complete the informed consent process and obtain signed informed consent documentation for each subject prior to initiating any study interactions or interventions.
   b. Create a progress note within 24 hours containing all required elements in the Computerized Patient Record System (CPRS).
   c. Give a copy of the signed informed consent form to each subject and assure that the subject initials the original signed consent form acknowledging receipt of the copy.
   d. Forward each original signed consent form and signed HIPAA authorization as soon as possible, preferably within three business days, of obtaining consent to the Research Administration Office for review and scanning into CPRS (if appropriate). I will keep a copy until the original is returned and will then maintain the original on file.
   e. Activate an electronic research flag for all subjects consented in this study, unless the IRB determines that this requirement does not apply to my study. If subjects do not meet enrollment criteria, the flag will be removed.
   f. Maintain a master list of all consented subjects; this list will include subject's names and the date(s) of their informed consent and, if applicable, reconsent.
6. I will promptly report any changes in PI or research staff and will obtain written IRB approval prior to implementing those staff changes. If I know I will be absent more than one month, I will notify the IRB at least two months prior and provide a mechanism to assure that the safety and treatment of human subjects will not be compromised.
7. I will maintain research files based on standards of good clinical practice.
8. I will report to the IRB when the study is completed. If this study includes investigational drugs, I will inform the Chief of Pharmacy Service when the study is terminated.
9. I will maintain an accounting of disclosures of PHI to all non-VA entities.
10. I am aware of how and to whom to report a suspected or confirmed loss of VA information and I take responsibility for the security of the information and who has access to it.
11. I am aware that, when scientifically appropriate, special efforts must be made to include women Veterans and Veterans who are members of minority groups in studies of diseases, disorders and conditions that disproportionately affect these Veteran groups.
12. I will be responsible for the ethical conduct of this project and for protecting the rights and welfare of the subjects.
13. As the PI/responsible Clinician, I assume responsibility for all study-related health care decisions related to this research project.
14. I affirm that all responses provided to the IRB, including information in all IRQ appendices, are true and that this study will be conducted according to the information provided here.