Monitoring and Maintaining Compliance

203.1 Assurance of Compliance

The UH System and its affiliates covered by the HRPP maintain its FWA under OHRP (45 C.F.R. § 46.103), and is filed and searchable to Investigators and others involved in human participant research on the OHRP website.

203.2 Access to Policies, Procedures, and Other Resources

The HSP has primary responsibility for ensuring the HRPP GPM and related materials are available to the entire UH research community, including:

- Investigators
- Research support staff (e.g., study coordinators, research assistants, etc.)
- HSP staff
- IRB members
- UH administrators, faculty, staff, and students
- Collaborating research sites and their administrators

The HSP maintains the HSP website which provides access to:

- HRPP GPM
- HRPP SOPs
- Links to relevant federal regulations and guidelines, and ethical principles from various disciplines (e.g., American Psychological Association, American Sociological Association, etc.)
- Links to collaborative research institutions and non-UH IRBs
- Links to other UH departments and offices involved in human participant research
- Information and instructions on required and elective training for human participant research
- Templates and guidelines for consent forms, recruitment material, and other study material
- HSP educational presentations
- Application and report forms and reviewer checklists and worksheets (based on eProtocol application)
- Alerts and updates on revised or new policies and procedures pertaining to human research protection
- Frequently Asked Questions
- Guidelines and checklists to assist Investigators on human participant research determination (e.g., review type, quality improvement vs. research, etc.)
- Information for research participants
203.3 Independence of the UH IRBs

Organizational Structure to Maintain Independence

The IRB operates independently, with HSP administrative support. The duties of the Vice President for Research and Innovation relate to establishing policy for research and oversight of research compliance, particularly as it relates to human participant research.

Delegation to the IRB

The UH IRBs have the authority to:

- Review, approve, disapprove, require to modify research involving human participants;
- Suspend or terminate the enrollment and/or ongoing involvement of human participants in research, as necessary for the protection of those participants (e.g., cases where research has been associated with unexpected serious harm to participants), or
- Suspend or terminate an Investigator’s privilege to conduct human participant research (e.g., in situations where research is not being conducted in accordance with IRB requirements),
- Observe or delegate a third party to observe the consent process
- Observe or delegate a third party to observe the conduct of research.

Prohibiting External Entities from Assuming IRB Approval Authority or Using Undue Influence

Officials/administrators, investigators, faculty, staff, students, and sponsors contracting with UH for research are prohibited from:

- Maintaining or claiming IRB approval of research that has been disapproved or not yet been reviewed by the IRB. A decision of any IRB to disapprove a research protocol or proposal cannot be overridden by the State or Institutional Official.
- Attempting to use or using undue influence with the IRB, any of its members or staff, an Investigator or any other member of the research support staff to obtain a particular result, decision or action.

In preventing undue influence of or threat to IRB members, the HSP and the UH IRBs preserve the anonymity of its members. IRB Rosters are kept confidential from Researchers, faculty, staff, students, and contracted sponsors. Only redacted rosters are provided for individuals requesting a copy for purposes of reporting to regulatory departments, funding agencies, etc.

203.4 Regulatory Definition of “Human Subject Research”

Human subject research is defined under 45 C.F.R. §§ 46.102(d) and (f), 21 C.F.R. §§ 50(c), (e), and (j), specifically:
“Human Subject” as defined by DHHS is a living individual about whom an Investigator (whether professional or student) conducting research obtains (1) data through Intervention or Interaction with the individual, or (2) information that is both Private Information and Identifiable Information.

For the purpose of this definition:
- “Intervention” means physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.
- “Interaction” means communication or interpersonal contact between Investigator and subject.
- “Private Information” means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
- “Identifiable Information” means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the Investigator or associated with the information).

“Human Subject” as defined by the FDA is an individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. A human subject includes an individual on whose specimen a medical device is used.

“Research” as defined by the DHHS is a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

“Research” as defined by the FDA is any experiment that involves a test article and one or more Human Subjects, and that meets any one of the following:
- Must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act meaning any use of a drug other than the use of an approved drug in the course of medical practice;
- Must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act meaning any activity that evaluates the safety or effectiveness of a device; OR
- Any activity the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.

The HSP, as designated by its IRB, retain ultimate authority to determine whether an activity meets the definition of “human subject research.” All protocols and proposals involving both “research” and “human subjects” (except those determined to be exempt) must be reviewed and approved by the IRB before any research activity involving human participants commence.

See SOP 101: Human Subject (Participant) Research Determination for procedures for making determinations on UH projects.

Exempt Research Determination

As defined per the Common Rule, Subpart A of 45 C.F.R. part 46, exempt research encompasses categories of research that do not require IRB approval and continuing review (see SOP 111: Exempt Review and Determination).
Exempt status cannot be granted when:

- Categories (1) through (5) apply and research is subject to FDA regulations.
- The research involves significant physical invasions or intrusions upon the privacy of its participants.
- The research involves prisoners as participants.
- Category (b)(2) applies and research involves children as participants, except for research involving observation of public behavior or when the Investigator(s) do not participate in the activities being observed.

*Emergency use of a test article* is exempt from prospective IRB review per 21 C.F.R. § 56.104.

See SOP 111: Exempt Review and Determination

Managing Conflict of Interest When Making Exempt Determinations

IRB members and HSP staff involved in reviewing and approving the exempt determination of protocol or proposal applications refrain from participating in the review of the research in which they have a conflicting interest (see SOP 102 IRB Member Conflicts of Interest).

203.5 Conflicts of Interest

Executive Policies and Administrative Procedures

The University has the following policies and procedures on reporting and managing significant financial and other conflicts of interest for UH research:

- [Executive Policy 12.214](#) on Conflicts of Interest and Commitment
- [Administrative Procedures A5.504](#) on Conflicts of Interest and Commitment
- [Administrative Procedures A8.956](#) on Financial Conflicts of Interest (FCOI) for Public Health Services Grants, Cooperative Agreements and Contracts


Investigator’s Conflict of Interest -- Role of the IRB

Investigators’ Conflicts of Interest regarding research are managed by the ORS, Compliance Section.

See SOP 107: Investigators’ Conflicts of Interest (COI) for IRB role and procedures involving Investigator’s conflict of interest in research.

Recordkeeping

Records on all disclosures of financial interests and all decisions to manage, mitigate, or eliminate COI for a particular research protocol or proposal are maintained for three (3) years from that study’s
institutional conflict of interest.

Institutional Conflict of Interest

An institutional conflict of interest (ICOI) occurs when an Investigator at UH undertakes human participant research on a drug, device, biologic or other item on which UH has a patent, has licensed the intellectual property, or receives royalties or other fees.

All new human participant research protocols submitted for IRB review must indicate the source(s) of all funding to be used in supporting the research, including unrestricted school, department or individual accounts, as well as the name of the manufacturer when applicable. In addition, the Investigators are required to answer questions about the relationship of their research to their administrative duties. When a protocol lists a manufacturer, or when other information indicates a potential conflict, the issues are handled as outlined in accordance with Executive Policy 12.214. Documentation and reporting is to be conducted in accordance with APM A5.504 and APM A8.956. Decisions are communicated to the IRB and to the relevant academic departments within the University so that the recommendations can be implemented at the level of the individual schools as appropriate.

203.6 Non-Compliance

Any situation of perceived or actual serious or continuing non-compliance jeopardizes the UH’s commitment to human participant research protection. It is essential to report any possible non-compliance for accountability and education purposes, correcting non-compliance, and attempting to prevent reoccurrences mitigate any adverse effects on research participants.

In general, “non-compliance” is defined as an action or activity in human participant research that does not follow the IRB-approved protocol or proposal, other requirements and determinations of the IRB, the HRPP GPM and other applicable UH policies and procedures, or relevant state or federal laws. Protocol violations (PVs) or protocol deviations (PDs) are considered non-compliance instances, and need to be reported to the IRB or HSP.

Obligation to Report Non-compliance

The following individuals, or entities, have the responsibility to report observations, evidence or allegations of non-compliance of human participant research to the Human Studies Program:

- Investigators (i.e., Principal Investigator, Co-Investigator, Sub-Investigator)
- Research support staff
- UH administrators, faculty, staff, or students
- IRB member
- HSP staff
- Study monitor, auditor or sponsor either directly or through the Investigator

Research participants and individuals not directly involved with conducting or overseeing the research are also encouraged to report suspected non-compliance to the Human Studies Program.
Reports of possible non-compliance may also be directed to the following individuals, who in turn forward them to the HSP staff:

- Principal Investigator
- The Vice President for Research and Innovation (Institutional Official)
- The Office of Research Compliance

HSP staff may also uncover possible non-compliance or evidence of non-compliance during the course of their normal duties.

**Non-Compliance – Allegations or Findings**

Reports of noncompliance are received in one of two forms: (1) allegations or (2) findings. Allegations of noncompliance have yet to be proven and are reviewed and investigated. Once an allegation is determined to be true based on the preponderance of the evidence, it is then considered to be a finding. Generally, self-reported incidents of non-compliance incidents by the Investigators via appropriate forms (e.g., protocol violation report, continuing review, etc.) will be accepted as findings of noncompliance.

**Handling Non-Compliance**

The HSP handles non-compliance in the following order: (1) receipt of an allegation, (2) inquiry, (3) formal investigation, (4) appeals, (5) dissemination of findings, and (6) reporting to IOs and general agencies.

See [SOP 108: Determining and Reporting Non-Compliance and Protocol Violations](#) for definitions and reporting procedures.

Some cases of non-compliance may involve other allegations, such as academic misconduct or financial mismanagement. The HSP and the IRBs cooperate with other entities in their review of those allegations to avoid duplicated effort and minimize competition for resources. The HSP may also report those allegations to appropriate institutional officials.

IRB members, and other individuals involved in the review process of a non-compliance case must recuse themselves from the review if they have a conflict of interest in the matter.

It is against UH policy to retaliate against good faith whistle-blowers. Prompt reporting of non-compliance and fair review of allegations are critical for the HSP to protect human participants, and require a climate free of fear from retaliation. Generally, the Investigator under review will have access to the identities of the persons who have filed an allegation against the Investigator or provided information on the allegation. However, for those individuals subordinate to the Investigator who wish to maintain anonymity, the HSP strives to protect their identities while providing the Investigator access to relevant information regarding the allegations. Note, that the HSP cannot guarantee absolute anonymity.

**IRB Actions to Protect Human Participants in Research**

At any time during the review of an allegation, the IRB may take one or more of the following actions to ensure the safety and welfare of human participants in research:
1. Suspending the study;
2. Requiring the Investigator to submit a corrective action plan;
3. Requiring the Investigator or Research Support Staff to complete additional training;
4. Requiring that currently- or previously-enrolled subjects to be contacted and provided with additional information or be re-consented;
5. Requiring more than one review annually;
6. Initiating an audit of the study;
7. Reporting to UH IOs and federal agencies;
8. Initiating sanctions against the Investigator; and
9. Terminating the study.
10. Any administrative action that is appropriate under the circumstances.

203.7 Unanticipated Problems and Other Reportable Information

Both DHHS and FDA regulations require Unanticipated Problems (UPs) to be reported to the IRB.

See SOP 116: Reporting and Reviewing Unanticipated Problems for further information on procedures regarding UPs.

Reporting UPs to the IRB

When reporting UPs to the UH IRB, the Investigator shall:
- notify the IRB of each event that qualifies as a UP by contacting HSP within 24 hours of when the Investigator becomes aware of the event,
- report the event to the IRB using the appropriate form on reporting unanticipated problems no later than ten (10) working days after the Investigator becomes aware of the event, and
- file a follow-up report to the HSP if appropriate.\(^\text{17}\)

An Investigator shall report UPs to the IRB, regardless of whether it is an internal or external event. The UH IRB only reviews a UP report on internal events, and external events where UH IRB is the IRB of record.

However, an Investigator is not required to report every adverse event to the IRB unless the event qualifies as a UP. Information on the distinction between “unanticipated problems” and an “adverse event” can also be found in the SOP 116: Reporting and Reviewing Unanticipated Problems.

The HSP fulfills the reporting requirements to institutional administrators, the sponsor and/or to the appropriate regulatory agency (FDA or OHRP) on UPs within two (2) months after the IRB or the IRB Chair recognizes that the event is an unanticipated problem.

Reviewing UPs

Unanticipated Problems are always reviewed by a convened IRB.

In the process of reviewing a UP report, the IRB may take the following actions to address the problem:

\(^\text{17}\) See OHRP Guidance on UPs, supra note Error! Bookmark not defined. at V.
• accept the report as submitted;
• request additional information from the Investigator;
• require modifications to the risk section of the consent form;
• require that a written communication be sent to all enrolled participants about the newly-recognized risk;
• require provisions of additional information to past participants;
• require current participants to re-consent to participation;
• modify the schedule of continuing review;
• require changes to the protocol initiated by the Investigator before obtaining IRB approval to eliminate apparent immediate hazards to participants;
• require a change in the study inclusion or exclusion criteria;
• require additional education and/or training for the research team;
• require the research site to develop procedures designed to prevent the reoccurrence of the UP;
• require changes to the protocol designed to reduce or eliminate the risk;
• require temporary or permanent suspension of enrollment of participants;
• require more than one review annually;
• suspend or terminate the research;
• suspend or terminate funding;
• notify the sponsor of action taken;
• require that the Investigator report the event to the sponsor, regulatory agency, or both; or
• other action determined to be appropriate by the IRB.

Studies Regulated by FDA

Reporting Requirements for UPs in Investigational Drug (IND) Studies

Investigators must promptly report all UPs to the IRB\textsuperscript{18} and report to sponsors any Adverse Events (AEs)\textsuperscript{19} related to the study they are responsible. In a multicenter study, the Investigator may rely on the sponsor's assessment of AEs and provide the IRB with a UP report prepared by the sponsor.\textsuperscript{20}

Reporting Requirements for UPs in Investigational Device (IDE) Studies

The reporting requirements on IDE studies are different from those on IND studies.\textsuperscript{21} An Investigator must submit to the IRB and the sponsor any unanticipated adverse device effect occurring during an investigation as soon as possible, but no later than ten (10) working days after the Investigator first learns of the effect.\textsuperscript{22}

\textsuperscript{18} 21 C.F.R. §§ 312.66, 312.53(c)(1)(vii); 56.108(b)(1).
\textsuperscript{19} 21 C.F.R. § 312.64(b).
\textsuperscript{20} FDA Guidance Adverse Event Reporting to IRBs – Improving Human Subject Protection, Section III. Reporting AEs to IRBs in clinical trials of drug and biological products conducted under IND regulations.
\textsuperscript{21} FDA Guidance Adverse Event Reporting to IRBs – Improving Human Subject Protection, Section IV. Reporting AEs to IRBs in clinical trials of devices under IDE regulations.
\textsuperscript{22} 21 C.F.R. § 812.150(a)(1).
Internal and External Reporting

Reportable Decisions

If the convened IRB:

- determines that serious or continuing non-compliance has occurred as specified in Section 203.5, or
- determines than an unanticipated problem involving risks to participants or other (UP) or some other reportable event has occurred as specified in Section 203.6, or
- suspends or terminates the approval of a protocol or proposal pursuant to Section 206.5

The IRB Chair and the HSP Director will notify the determination and IRB actions to the Institutional Official. Written procedures for reporting unanticipated problems, non-compliance, suspension and termination follow the OHRP and FDA regulations (45 C.F.R. § 46.103(5); 21 C.F.R. § 56.108(b)).

203.8 HRPP Quality Improvement

The UH supports quality improvement activities to foster ethical research conduct and compliance with institutional policies and procedures, including applicable federal and state regulations and guidance. The HSP Quality Improvement Unit (QIU) assesses and improves the compliance, efficiency, and effectiveness of the UH HRPP.

The objectives of these quality improvement activities are to:

1. Improve compliance of Investigators with their responsibilities.
2. Improve compliance of IRB meeting minutes with regulatory compliance
3. Increase efficiency of recording and finalizing IRB meeting minutes.

The QIU conducts reviews of records, interviews and observation of activities and facilities, and conducts surveys and other assessments for the following groups:

1. Investigators and research personnel participating in the design, conduct, data collection and/or analysis of human participant research (exempt and non-exempt) on behalf of UH;
2. UH IRBs;
3. HSP staff; and
4. Individuals involved in HSP education and outreach on human research participant protection.

See SOP 110: Quality Improvement Activities for specific activities and procedures in conducting and assessing quality improvement activities.

Additional Requirements

See GUIDE 617: Other Federal Agencies – Additional Requirements for other requirements depending on the sources of support/funding.
External Compliance Monitoring

On-Site Visit

Pursuant to 45 C.F.R, 46.109(e), the IRB have the authority to observe or have a third party observe the consent process and the research. Delegated by the UH IRB, select UH research projects may be audited by the QIU to assess its compliance with HHS regulations. Research is selected based on the criteria listed under the SOP 110: Quality Improvement Activities and monitored based on one of four categories: (1) routine, (2) for-cause, (3) Investigator-requested, or (4) observation of the informed consent process.

Reporting Outcomes

Outcomes of compliance monitoring activities are documented and reported to the HSP Director, the UH IRB, the ORC Director, the Institutional Official and other units within UH, as appropriate. These findings, supplemented by other review results when available, provide a qualitative and quantitative measurement of compliance with the HRPP. The HSP Director prepares and submits an HSP Annual Report that includes a summary of the compliance monitoring outcomes to the Office of the Vice President for Research and Innovation each year.

Research Community Feedback

The QIU tracks comments, inquiries and concerns received from UH Investigators, research personnel and participants to identify areas for potential improvement in the effectiveness of HRPP policies and procedures and for ensuring the protection of human research participants.

There are a variety of mechanisms available to Investigators for contacting relevant individuals to bring concerns and suggestions, including:

- Reporting possible non-compliance
- Reporting possible unanticipated problems
- Making general comments and suggestions and expressing concerns about other matters, issues or processes involving the HRPP, including IRB review and operations to any person in the HSP or in the ORC.

Additionally, input from researchers are actively sought for each protocol or proposal review on a continuing basis, via an online anonymous feedback survey about the service provided by the HSP and its IRBs; researchers may comment or provide suggestions on any aspect of the IRB or HRPP, by emailing the HSP through their website ([https://manoa.hawaii.edu/researchcompliance/human-studies](https://manoa.hawaii.edu/researchcompliance/human-studies)), directly emailing to HSP (uhirb@hawaii.edu), or by making an appointment with the HSP.

The HSP Director receives and evaluates the input from any of these sources, with review by other individuals, as necessary (e.g., OGC). The researcher receives a direct response for the input submitted, unless the researcher wishes to remain anonymous.

The Assistant Vice Chancellor for Research Compliance handles any concerns or complaints related to the HSP Director.