

# **POLICIES AND PROCEDURES**

Of the

**Harvard Medical School  
Harvard School of Dental Medicine  
Committee on Human Studies**

**Post-Study Approval Monitoring Program (P-StAMP)**

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**HMS/HSDM Committee on Human Studies  
Post-Study Approval Monitoring Program (P-StAMP)  
Policies and Procedures**

**1. Purpose**

The HMS/HSDM Committee on Human Studies (CHS) post-Study Approval Monitoring Program (P-StAMP) was established through the Office for Research Subject Protection (ORSP) and the Office for Research Compliance (ORC). The mission of the program is to help the CHS carry out the University's commitment to a rigorous Human Research Protection Program (HRPP) that will comply with federal and state regulations governing research with human subjects and help ensure that research is conducted within accepted ethical standards.

**2. Aims**

- The post-Study Approval Monitoring Program aims to educate and foster a research culture in which studies involving human participants will be conducted according to the highest standards of ethical conduct and within the regulatory framework.
- Through post-approval reviews, P-StAMP aims to monitor investigator compliance with the approved research protocol and all federal, state, and institutional policies, thus ensuring that all research activities, especially those relating to the safety and well being of human research participants, are carried out according to the highest standards.
- As part of its work, P-StAMP also will confirm that the CHS complies with all federal, state, and institutional policies as they relate to the approval of research protocols through monitoring of meetings, minutes and office records, in this way providing "full circle" protection of human research participants.

The over-arching intent of the Post Study Approval Monitoring Program is to help protect the interests of all parties involved in research with human subjects. The goal is to achieve this standard by helping researchers conduct their study protocols in accordance with the highest scientific and ethical standards.

**3. Review Criteria**

To help verify that research activities are carried out according to the highest standards, P-StAMP will aim to monitor at least one to two active research studies per month. Research studies will be assessed in two separate stages: 1) Review of the CHS files; and 2) Review of the research site and files maintained by the Principal Investigator (PI). The review of the CHS files hopefully will capture any areas of the CHS record keeping or review process that may require corrective action to fully comply with federal, non-federal or institutional regulations or policies. The PI and Study Protocol Review component will provide an individual evaluation of the study's strengths and areas that may require corrective action to fully comply with regulations and institutional policies or Good Clinical Practices in the case of FDA regulated studies. By evaluating both the CHS files and the way in which the PI is conducting the study, the institution

ensures consistency across its HRPP, eliminating confusion and potential conflicts regarding issues of non-compliance.

#### **4. Selection of Research Studies for Review**

Research Studies will be selected for review from two categories: Not For Cause and For Cause.

##### **4.1. Not For Cause Review**

Protocols chosen for a Not For Cause review are selected equitably based on computer generated random prioritization that incorporates weighted risk factors.

All studies that have been approved to enroll human participants and have been active for at least six months may be selected from each of the review categories (Full Committee, Expedited, Exempt, and Designated) for a Not For Cause review. As a model, random selection will be from the group of all studies that were approved six months prior to the audit month (e.g., the studies to be audited in January will be randomly selected from the group of all studies that were approved the previous June).

Weighted risk factors may include:

- The degree of risk the protocol poses to human participants as determined by category of review the protocol received by the CHS (Full Committee, Expedited, Exempt, Designated); and
- The inclusion of vulnerable populations covered under 45 CFR § 46 Subparts B, C, or D (pregnant women, human fetuses and neonates; prisoners; and children).

Following the computer generated random prioritization, “fair distribution” factors may influence the final selection of studies chosen for review. “Fair distribution factors” may include:

- The inclusion of other populations considered vulnerable, but not covered under 45 CFR § 46 Subparts B, C, or D (e.g., low literate; non-English speakers; decisionally impaired; economically disadvantaged; employees, students, fellows or faculty; international study; persons with stigmatized health condition; inpatients or outpatients);
- The complexity or difficulty of the protocol;
- The degree to which the study is controversial or likely to engender the scrutiny of the government or other external parties;
- The number of previous Quality Assurance (QA) reviews (either For Cause or Not For Cause) involving the PI, and the findings resulting from those reviews; and
- Principles of fairness and balance, with the goal of ensuring that post-approval monitoring reviews are apportioned throughout the various departments such that no department, researcher or category of protocol is singled out for inappropriately greater attention, and that all departments and researchers receive roughly equivalent levels of review appropriate to the nature of their research.

A plan and schedule for Not For Cause monitoring visits will be developed and updated periodically by the QA Coordinator, Director of ORSP, and Director of ORC.

Once a research study has completed a full Not For Cause review, it will no longer be eligible for another Not For Cause review during the current grant funding cycle. If funding is renewed, if a no-cost extension is approved, or if there is a major change in the research activities, the research study will again become eligible for another review through Not For Cause selection process.

#### **4.1.1. PI Requested Review – Not For Cause Review**

A PI may request a complete research study review to make sure that the research project is in full compliance with regulations, policies or Good Clinical Practices, if FDA regulated. A requested full review will not differ from a Not For Cause review in terms of scope or educational opportunities. If a study review is requested by the PI, the study will not be included in the Not For Cause selection process.

A PI may also request a partial review of the study in order to concentrate on the area(s) of the PI's choosing. If a partial review is requested by the PI, the research study may still be selected for a full study review (at a later date) as part of the Not For Cause selection process.

#### **4.2. For Cause Review**

The CHS, Office of Research Compliance, or Faculty Affairs may request a For Cause audit of research involving human participants where 1) compliance concerns have been raised based upon information provided in continuing review reports, adverse events or other sources; or 2) investigators or study staff have serious or continuous issues of non-compliance with federal, state, or institutional policies or regulations, or Good Clinical Practices.

### **5. Review Personnel**

The QA Coordinator is primarily responsible for performing the research study reviews. However, at times, the QA Coordinator may be accompanied by staff or members from the CHS or the ORC.

### **6. Review Materials and Observations**

A research study review will include study files maintained by the PI and his or her research staff. Additionally, post approval monitoring will include a review of the study files maintained by the office for the CHS and records relevant to the CHS approval process. If the study involves multiple departments or data collection sites, they may be reviewed separately and the findings included in the report to the PI.

A PI and Study Review may include any or all of the following:

- Discussion with investigators and other study personnel
- Review of the CHS application and other relevant documents
- Review of research study participant records

- Tour of the research offices and/or laboratory
- Observation of the recruitment or consent process
- Observation of the research activity
- Examination of consent forms from enrolled participants
- Interview with screened or enrolled participants
- Educational information or recommendations for investigators and study personnel

## **7. Notification and Scheduling**

### **7.1. Not For Cause Review**

When a study has been identified for Not For Cause review, the PI and the study coordinator (if identified) will be notified by e-mail, with follow up by telephone. The review will be scheduled for a mutually convenient date that will be no later than three weeks from the initial notification of selection.

### **7.2. For Cause Review**

When a study has been identified for For Cause review, the PI and the study coordinator (if identified) will be notified by e-mail, with follow up by telephone. The review will be take place within five working days of the initial notification.

## **8. Review Process**

The review process for a study chosen for a Not For Cause review is essentially the same as that for a study identified for a For Cause review. However, if a study is reviewed as the result of a For Cause request by the CHS, ORC, or ORSP, additional documents or contact with relevant participants or personnel may be required. In all cases, the PI or designated staff member will be informed in advance. Please Note: the For Cause review of the QA Coordinator does not replace the authority of the CHS to conduct separate or additional For Cause reviews of the PI, or study(ies).

### **8.1 CHS Assessment**

As soon as a study has been identified for review (For Cause or Not For Cause) the QA Coordinator will notify the Director of the ORSP, the CHS Administrator, and the CHS Coordinator assigned to the study and the review may begin immediately.

#### **8.1.1. CHS Documents for Review**

The QA Coordinator will review all CHS office records relevant to that study. This includes, but is not limited to paper and electronic files of the application and all associated materials, protocol documentation, correspondence, and records including information maintained in HIRBERT, the Harvard IRB Reporting Tool, which is the database for human studies protocols. If there are questions about the study or study materials, the QA Coordinator may consult with the CHS

Coordinator or CHS Administrator, although this is not intended to be a routine part of the review.

### **8.1.2. Quality Assurance Assessment – Primary Information Form**

This form is used to record basic information regarding the study such as PI name, protocol title, funding source, CHS approval information, and forms submitted to the CHS.

### **8.1.3. CHS Component - Initial Detailed Findings Form**

This form is used to document the comprehensive results of the review.

### **8.1.4. CHS Component – CHS Response Form**

Immediately following the Research Study Review the QA Coordinator will complete the *CHS Component – CHS Response Form*. This report summarizes the areas reviewed, most notable best practices, required corrective actions, and recommendations for improvement. The *CHS Response Form* will be distributed to the CHS Coordinator, CHS Administrator, and Director of ORSP. The CHS Office must review, address and respond to each *Required Corrective Action* and *Recommendation* as outlined.

- Required Corrective Actions: *all actions must be addressed promptly* to meet federal regulations and guidelines and institutional policies. If the required action is not possible or cannot be completed, a reason must be provided. The following actions can be used to respond to required actions:
  - Action accepted and implemented: Recommendation deemed useful and action has been implemented. Please explain how.
  - Action accepted and will be implemented as soon as possible: Recommendation deemed useful and action will be implemented ASAP. Please explain reason for delay in implementation.
  - Action Disputed: Required action is disputed and additional clarification or consultation with the reviewer is requested. Please provide explanation.
- Recommendations: While responses to recommendations are not mandatory, it is strongly encouraged that all recommendations be considered and evaluated in terms of OHRP, CHS and IRB best practices to be incorporated as deemed helpful. The following actions can be used to respond to recommendations:
  - Action accepted and implemented: Recommendation deemed useful and action has been implemented. Please explain how.
  - Action accepted and will be implemented as soon as possible: Recommendation deemed useful and action will be implemented ASAP. Please explain reason for delay in implementation.
  - Action Disputed: Recommendation deemed impractical or unfeasible for this protocol. Please provide reason and/or provide an alternative.
  - Observation acknowledged - No action needed: As applicable, an observation may be noted in which no follow-up action is necessary. The CHS Coordinator is asked to acknowledge the observation, or provide clarification.

After all *Required Corrective Actions* and *Recommendations* have been addressed (optimally within one month of receipt) the completed *CHS Response Form* will be returned to the QA Coordinator. All responses will be reviewed and noted in the file. The Director of ORSP will review the CHS response and will sign the form acknowledging that all actions have been appropriately taken or considered. All forms completed for the CHS Component of the assessment will be kept in the Study Review file maintained by the QA Coordinator.

## **8.2. Site Assessment**

### **8.2.1. Preparing for the Site Review**

At least one week prior to the initial meeting and study review, the PI will be asked to submit a list of all investigators, consultants, and research staff working on the project. The PI also will be asked to submit a complete list of Subject/Participant IDs for all participants enrolled in the study. If more than 5 participants have been enrolled, a percentage of the research participant files will be randomly selected for a detailed review. The PI will also be asked about any particular areas of concern or topics, so that educational materials can be prepared prior to the initial meeting.

The PI will be asked to assure available space (desk, office/cube) for the reviewer(s) during the review process, and access to all study and participant documents, binders, and files.

#### **8.2.1.1. Site Documents for Review**

- CHS Documentation
  - CHS application submissions, CHS Report on Action (ROA) letters, PI Responses, and Final ROA Letters
  - Continuing Renewals and Amendments
  - CHS correspondence with the PI
  - All approved protocol versions, informed consent versions, recruitment materials, and other study materials
  - Serious Adverse Event or Unanticipated Problem Reports, Non-Compliance Reports, and information on unanticipated risks to participants
- All study materials and relevant correspondence not with CHS (e.g. correspondence with the sponsor, Data Safety Monitoring Board Reports, additional IRB reviews)
  - Study Drug or Medical Device forms
  - Participant Informed Consent Forms
  - Participant research files
  - Participant Medical Records (if applicable)

### **8.2.2. Initial Meeting**

The QA Coordinator will meet with the PI and any designated research staff to explain the review process. This time will be used as an opportunity for the QA Coordinator to ask study related questions prior to the review, and for the PI and staff to ask questions about the process and/or express any concerns or ideas. Information from this meeting will be recorded on the *Site Component – Initial Interview Form*.

### **8.2.3. Study Review**

The QA Coordinator will request a tour of the research offices and/or lab facilities to verify that records are kept in a secure location or as specified in the study documentation. Afterwards, the QA Coordinator will be left alone to review the study and participant files in the selected location. While the PI does not need to be available during this time, the study coordinator or designated staff member familiar with the protocol and study and participant documents should be available to answer any questions if they arise. The length of the review is dependent on the study protocol and the materials to be reviewed. The *Site Component – Initial Detailed Findings Form* will be used to document the comprehensive results of the review.

#### **8.2.3.1. Observation**

In addition to the review of the study files and documents, a QA Review may include an observation of the recruitment process, consent process, and/or the research activity. This would be done with sensitivity to the research protocol and scientific issues as well as the confidentiality and comfort level of the research participant.

#### **8.2.3.2. Interview with screened or enrolled participants**

A QA Review may also include a brief interview or similar contact with selected screened or enrolled participants. If notified that this will be part of the review process, the PI will be asked to identify three to five screened or enrolled participants who will be willing to answer written questions and/or discuss their experience as a study participant. It is essential that, prior to releasing their names or contact information, the PI obtain permission from these study participants to be contacted by the QA Coordinator.

### **8.2.4. Debrief Meeting**

The QA Coordinator will meet with the PI and any designated research staff to review the process and discuss any areas of concern. One objective of the review process is to learn about the research team's interpretation and application of CHS policies as well as federal regulations and guidelines. The debriefing meeting provides an additional opportunity to evaluate and clarify the research team's standard in this area. At this meeting, the QA Coordinator will provide educational information as well as a general overview of the study's strengths and areas requiring action in order to fully comply with regulations, policies or Good Clinical Practices or recommend best practices.

### **8.2.5. Review Report**

Immediately following the Research Study Review the QA Coordinator will complete a preliminary report to document all review findings and observations. This report will take into account PI and research study staff clarifications discussed in the Debriefing Meeting and will summarize the areas reviewed, most notable best practices, required corrective actions, and recommendations for improvement. The preliminary report will be reviewed by the Director of the ORSP prior to distribution to the Principal Investigator. The report may be updated by the Director of the ORSP, but the content will remain consistent with the documented findings of the review. The final version of report will be sent to the PI and will be titled *Site Component – PI Response Form*. A letter from the QA Coordinator will accompany the report and will specifically outline all required and recommended actions. The CHS Administrator and Protocol Coordinator will be notified of any required or recommended actions that involve review and/or approval by a member of the IRB.

The PI must review, address and respond to each *Required Corrective Action* and *Recommendation* as outlined.

- Required Corrective Actions: *all actions must be addressed promptly* to meet federal regulations and guidelines and institutional policies. If the required action is not possible or cannot be completed, a reason must be provided. The following actions can be used to respond to required actions:
  - Action accepted and implemented: Recommendation deemed useful and action has been implemented. Please explain how.
  - Action accepted and will be implemented as soon as possible: Recommendation deemed useful and action will be implemented ASAP. Please explain reason for delay in implementation.
  - Action Disputed: Required action is disputed and additional clarification or consultation with the reviewer is requested. Please provide explanation.
- Recommendations: While responses to recommendations are not mandatory, it is strongly encouraged that all recommendations be considered and evaluated in terms of OHRP, CHS and IRB best practices to be incorporated as deemed helpful. The following actions can be used to respond to recommendations:
  - Action accepted and implemented: Recommendation deemed useful and action has been implemented. Please explain how.
  - Action accepted and will be implemented as soon as possible: Recommendation deemed useful and action will be implemented ASAP. Please explain reason for delay in implementation.
  - Action Disputed: Recommendation deemed impractical or unfeasible for this protocol. Please provide reason and/or provide an alternative.
  - Observation acknowledged - No action needed: As applicable, an observation may be noted in which no follow-up action is necessary. The CHS Coordinator is asked to acknowledge the observation, or provide clarification.

The PI must respond to the *Site Component – Final Report & PI Response Form* and letter from the QA Coordinator in writing within 30 days of receipt and must address all required and recommended actions as detailed. The PI is ultimately responsible for assuring that all actions are appropriately taken or considered, and that the signed response is returned to the QA Coordinator on time. Delays in response or other failure to address and resolve critical issues

may result in such information being forwarded to the CHS and more immediate action taken by the CHS to ensure compliance and the safety of participants including suspension of a research study.

The QA Coordinator will review the *PI response Form* when it is returned. If any deficiencies are not adequately addressed and resolved, the QA Coordinator will contact the PI for clarification or explanation and continued correspondence until all issues are adequately resolved. Once all required corrective actions have been appropriately completed, and all recommendations adequately addressed, the Director of ORSP will review the PI Response Form and any supplemental materials or supporting documentation. After this final review, the review file will be closed.

All forms completed for the Site Component of the QA assessment will be kept in the Study Review file maintained by the QA Coordinator. If supplemental materials or supporting documentation is submitted, a copy may be included in the CHS file, if necessary.

### **8.3. P-StAMP Review File Closure**

When a study review is closed, the QA Coordinator will complete the following administrative tasks:

- A Thank You e-mail will be sent to the PI within 5 days of the study closure.
- The P-StAMP Final Report and PI Response will be filed in the P-StAMP study file, with a copy to the Director of the ORSP.
- HIRBERT will be updated to reflect that the study underwent a QA Review.
- A memo documenting the P-StAMP review will be submitted to the CHS Administrator and IRB Coordinator to be filed in the CHS study files.

## **9. Student Projects**

Projects by student investigators are subject to all of the policies and procedures discussed above. Additionally, advisors and/or mentors will be included in any correspondence and may be consulted during the review process.

## **10. Other Reviews**

In addition to monitoring active research studies, the QA Coordinator may also review other broader aspects of the HRPP, including an annual review of the FWA to assure that all of the terms and conditions are met and that information is up to date.

## **11. Reporting**

If at any time during a P-StAMP audit or other QA and education activity, a significant research issue or concern is noted by the QA Coordinator or any member of the HMS/HSDM research community, the QA Coordinator will immediately notify the Director of the ORSP and/or the Director of Research Compliance to discuss the issue and determine the best course of action. The QA Coordinator will coordinate efforts with the CHS office, and document the issue in the

appropriate file, investigate and manage or assist in preparing required reports to regulatory agencies and implementing corrective actions, as necessary.

In addition to reporting to the Director of ORSP and the Director of ORC, the Coordinator of P-StAMP will also provide quarterly reports to the Leadership Team, and the CHS on a regular basis.

### **11.1. Leadership Team**

In order to monitor and measure the effectiveness of its human research protection program, the Faculty of Medicine has established a Leadership Team comprised of the IO, CHS Chair, ORSP Director, and CHS Administrator, as well as a representative from OGC, the Director of ORC, the Assistant Director of Research at HSDM, and representatives from other offices (such as SPA) as necessary. The purpose of this team is to meet on at least a quarterly basis (more often if necessary) to discuss any new federal regulations or guidance, state laws, University policies, incorporation of new best practices, as well as issues of policy and procedure, including common recurrent problems, and CHS management and operational issues.

The QA Coordinator will provide reports to the Leadership Team on a quarterly basis which will give an account of any common recurrent problems and general findings of the CHS and Investigator protocol reviews. The Leadership Team may use this information to inform decisions on the implementation of new/revised policies, best practices and improvements in the HRPP.

### **11.2. CHS**

The QA Coordinator will report to the CHS on a regular basis to give an account of any common recurrent problems and general findings of the CHS and Investigator protocol reviews.

The QA Coordinator may also report on the specific findings of a protocol review if those findings are directly relevant to a Committee discussion of that protocol, are the result of a for-cause review, or are the result of a review requested by the CHS. Issues or concerns discovered during a not-for cause review will be evaluated by the QA Coordinator and referred to the IRB Coordinator, CHS Administrator, Director of ORSP, or Director of ORC for appropriate action and follow-up. Issues that would normally be reviewed by the CHS will be reviewed according to CHS policies and procedures.