

All requirements of 45 CFR § 46 and subparts A (Protection of Human Subjects), B (Additional Protections for Pregnant Women, Human Fetuses and Neonates involved in Research), C (Additional Protections Pertaining to Biomedical and Behavioral Research involving Prisoners as Subjects), and D (Additional Protections for Children Involved as Subjects in Research) will be met for all research, regardless of sponsorship, except if otherwise noted in the CHS FWA.

Any studies that fall under the jurisdiction of the FDA will be conducted in accordance with applicable FDA administered statutes and regulations, including the Code of Federal Regulations 21 CFR § 50 (Protection of Human Subjects), 21 CFR § 56 (Guidance for IRBs and Clinical Investigators), 21 CFR § 312 (Investigational New Drug/IND), and 21 CFR § 812 (Investigational Device Exemptions/IDE), as applicable.

In addition to federal regulations, the CHS follows certain Commonwealth of Massachusetts requirements relating to the ethical conduct of research. Where state regulations differ from federal regulations, the more stringent regulations shall be followed. This is noted in the appropriate policy sections.

2. Roles and Responsibilities

2.1. Responsibilities of the Institution

The Faculty of Medicine bears responsibility for the performance of research involving human research participants covered by its FWA, including compliance with previously noted federal and state laws as they may relate to such research.

The Faculty of Medicine, including all its named components (Appendix 9), acknowledges and accepts its responsibilities for protecting the rights and welfare of research participants covered by its FWA, including:

- Ensuring that CHS and University policies are in compliance with evolving laws and regulations.
- Publicizing policies and requirements regarding research with human participants for the research community.
- Establishing and maintaining an appropriately qualified CHS.
- Providing both meeting space and sufficient staff and resources to support the CHS, its review and record-keeping responsibilities.

2.1.1. Resources for the CHS

The Faculty of Medicine provides appropriate staff, office space, computer equipment, finances, materials and other resources for the CHS. The budgets supporting the CHS are reviewed annually as part of the budget review cycle. The budget reviews include annual assessments of staffing and salary levels, and of non-salary resources, including equipment, materials and training needs. The Dean for Faculty and Research Integrity (the CHS Institutional Official, or IO) and the ORSP Director undertake the budget review with the HMS Budget Director from Financial Operations and Analysis (FOA).

As part of the provision of sufficient resources to the CHS, the Faculty of Medicine provides written materials and training opportunities to CHS members and to CHS staff, including policy and procedure manuals, checklists to assist research reviewers, continuous updated educational material relating to recent developments in human subjects research, opportunities to attend training sessions, and other guidance. The resources provided are sufficient to assure timely review of research projects, comprehensive meeting minutes, timely notifications and useful assistance to Investigators.

The IO has the responsibility to ensure that the CHS is provided with sufficient resources. Each quarter, the CHS Administrator provides the IO and the ORSP director with a spreadsheet of protocols reviewed by the CHS staff. Included with this list are the type of reviews (exempt, expedited, full committee and designated) and the approximate time from submission of the protocol to the office to the time the protocol is approved. Given the volume of the workload and the nature of the reviews performed in a thorough and timely manner, the IO has determined that the present single CHS for the Faculty of Medicine is sufficient to meet the needs of the research program.

2.2. Responsibilities of the Institutional Official

The Dean for Faculty and Research Integrity, who serves as the Institutional Official (IO), is responsible for the implementation and maintenance of the HRPP and the CHS (Appendix 10). The IO has direct access to the Dean for Academic and Clinical Programs and to the Dean of the Faculty of Medicine. The budgets for the CHS, Office for Research Issues, and Office for Research Compliance, each of which supports the HRPP, are under the IO's supervision. In addition to the Dean of the Faculty of Medicine, the Dean for Academic and Clinical Programs, and members of the Office of the General Counsel, the IO has direct access to the Dean of the HSDM and the University Provost's Office.

The responsibilities of the Institutional Official include:

- Ensuring that research participants are protected;
- Ensuring that HMS/HSDM Investigators comply with University and CHS policies and Federal regulations protecting human research participants;
- Selecting a qualified CHS Chair;
- Selecting qualified CHS members in accordance with OHRP guidance;
- Assuring that the CHS Administrator and CHS staff demonstrate appropriate knowledge and experience for their roles;
- Reviewing periodically the qualifications, knowledge and experience of the CHS Chair, members and staff.
- Assuring adequate resources for the CHS office (including office and meeting space, staff, supplies, and training);
- Assuring adequate compensation and/or recognition of the CHS Chair, members and staff;
- Providing appropriate educational opportunities to the CHS Chair, members and staff;
- Assuring independent actions of the CHS; including freedom from undue influence or coercion by University officials;
- Ensuring access for the CHS to legal counsel with expertise in human subjects protection issues;

- Providing guidance with complex issues, such as faculty or CHS member conflict of interest; Investigator non-compliance with federal regulations; and serious adverse events/unexpected problems, privacy, confidentiality and emergency issues involving research participants.

2.3. Responsibilities of the CHS

The CHS must understand and apply the University's rules, and federal, state and local regulations on the use of human participants in research. The CHS will ensure effective knowledge of participant populations, institutional constraints, differing legal requirements, and other factors which can foreseeably contribute to a determination of risks and benefits to participants, and can properly judge the adequacy of information to be presented to participants in accordance with requirements of 45 CFR §§ 46.103(d), 107(a), 111, and 116. Additionally, the CHS will assure equitable selection of research participants, respect the autonomy of the participants and seek knowledge of the local research context.

The CHS will review and have the authority to approve, require modification to, disapprove, suspend or terminate research activities (including proposed changes to previously approved research) of the faculty, staff and students under the jurisdiction of the CHS.

Scheduled meetings of the CHS occur on a monthly basis. The CHS may hold interim review sessions, called by the Chair at the request of any CHS member or IO, to consider matters regarding the rights and welfare of any participant, or participant population. Additionally, CHS members will serve as reviewers for minimal risk studies meeting expedited and exempt research category requirements.

CHS reviews are in accordance with the basic ethical principles (respect for persons, beneficence, and justice) articulated in *The Belmont Report* to determine that:

- Risks to participants are minimized.
- Risks to participants are reasonable in relation to anticipated benefits, if any.
- Selection of participants is equitable.
- Informed consent is adequately obtained in accordance with federal regulations.
- Informed consent is appropriately documented, in accordance with federal regulations.
- Adequate provisions have been made for monitoring data collected, when appropriate.
- Adequate provisions have been made to protect privacy of participants and maintenance of confidential data, when appropriate.
- Additional safeguards are in place to protect vulnerable participants and others likely vulnerable to coercion, when appropriate.
- Timely continuing review of approved research is conducted as appropriate to each study.
- The CHS application is in concordance with the grant application funding the research.

The CHS will also, in accordance with federal regulations and institutional policies, perform continuing reviews of all approved studies, and review and consider all reported adverse events,

and unanticipated problems, as required, which it receives from the Investigator, from data and safety monitoring committees, or from Investigators at other sites in multi-center studies. The CHS will also, in appropriate cases, based on an adverse event or other relevant information it receives after commencement of the study, terminate, suspend, or require modifications to a study, or take other appropriate steps to protect participants, such as requiring changes in the informed consent form, requiring re-consent, or requiring the provision of information to current participants or those who have already completed the study. In addition, the CHS, in many cases with the assistance or support of the CHS staff, the Office for Research Compliance or other Harvard offices or officials, will investigate and review instances of actual or alleged noncompliance, and will take appropriate action based on the results of its review and deliberations.

2.4. Responsibilities of the CHS Office

The CHS office is responsible for ensuring that the institution, its investigators, and its members follow the guidelines set forth in the following policies and procedures, and adhere to federal regulations regarding the protection of human research participants, as set forth in 45 CFR § 46, its subparts, and the ethical principles of *the Belmont Report*.

The CHS office is responsible for facilitating constructive communication among the CHS, investigators, department heads, administrators, institutional officials, and research participants, as a means of maintaining a high level of awareness regarding the safeguarding of the rights and welfare of research participants.

Responsibilities of the CHS office include:

- The application of and compliance with federal regulations, state/local laws and institutional policies regarding CHS procedures.
- Supporting and facilitating the CHS processes.
- Developing and implementing institutional CHS policies and procedures.
- Protection of human participants involved in research activities conducted at HMS and HSDM.
- Ensuring compliance with the institution's FWA and other assurance processes.
- Developing and conducting training and education programs for CHS staff, CHS members, and research staff.

2.5. Responsibilities of the Investigator

The Investigator bears primary responsibility for the protection of human participants in research studies. Research Investigators must adhere to federal regulations regarding the protection of research participants as set forth in 45 CFR § 46, the ethical principles of the Belmont Report, and the guidelines set forth by the CHS and the Institution. Investigators must communicate with the CHS office, and submit timely applications and continuing renewal forms, as well as other required documentation on a yearly basis (or more frequently, if determined by the CHS). All researchers under the aegis of the CHS will:

1. Take personal responsibility for their actions in pursuit of individual and organizational excellence.

2. Uphold the highest standards of ethical and professional conduct in accordance with the Belmont Report, and Faculty of Medicine and University policies governing research.
3. Complete periodic training to remain up-to-date on federal regulations, CHS policies and procedures and compliance expectations. In addition, direct key personnel involved in their research projects to do the same.
4. In consultation with the CHS, determine whether their research requires CHS approval.
5. Ensure the CHS application and protocol contain the same information as the funding proposal for extramural or intramural support. Provide accurate human studies approval information when corresponding with sponsoring agencies.
6. Receive CHS approval before commencing research activities.
7. Submit continuing review form, current informed consent forms, and associated study material for renewal at least annually to the CHS for review and approval.
8. Obtain (and document, as required) informed consent from all participants, unless the CHS has issued a waiver of such.
9. Ensure the confidentiality of participant data.
10. Report problems to the CHS according to CHS policies and procedures, and report adverse events to sponsors and appropriate federal agencies as applicable and required by those entities.
11. Apply to the CHS for approval of changes to the study or study materials prior to implementing the changes.
12. Maintain applications, protocols, approved informed consent forms, surveys and associated material related to the study as required by federal, state and HMS policies/procedures.
13. Adhere to federal regulations, state and local laws, institutional and CHS policies and procedures regarding the safety and protection of human subjects.
14. In conducting studies involving investigational drugs and devices, adhere to all requirements of FDA regulations, including reporting adverse events and unanticipated problems to the study sponsor as required by the protocol, and properly storing, using and documenting the receipt, use or disposal of controlled articles.
15. Participate and cooperate in quality assurance reviews, investigations and other oversight, monitoring and investigative activities of HMS, HSDM or their designated representatives or personnel.

2.6. Responsibilities of Unaffiliated Investigators and Unaffiliated Institutions

Each unaffiliated Investigator at an unaffiliated research site (e.g., a private practice physician not otherwise an employee or appointee of HMS or HSDM or who otherwise would not ordinarily be bound by the provisions of the CHS FWA or any other applicable institutional policies) involved in human studies research of this institution must request from the CHS office either an Agreement for an Independent Investigator or a Non-institutional Investigator Agreement, as appropriate, depending on the nature of the research activity.

Performance sites that are legally separate from the Faculty of Medicine are not authorized to cite the CHS FWA unless agreed to by the CHS and documented in an IRB Authorization Agreement citing this institution as the IRB of record.

2.7. Additional Institutional Support and Responsibility

There are many separate components of the Faculty of Medicine Human Research Protection Program (HRPP) that work with the CHS and the CHS office to ensure the protection of research participants and research compliance at HMS and HSDM, including the following Harvard offices and committees:

Financial Operations and Analysis (FOA) – provides budget support to the CHS and HMS/HSDM department administrators who manage grants/contracts/funding for Investigators. Responsibilities include providing the CHS budget and billing of other institutions that rely on the Faculty of Medicine for CHS review.

Sponsored Programs Administration (SPA) – provides pre- and post- grant award support for the Faculty of Medicine. SPA works with the CHS to ensure research projects have been approved before grant money is allocated for research purposes. SPA has access to the CHS database to confirm the study status and that Investigator training requirements have been met. SPA will also notify the funding sources when research is suspended or terminated by the CHS office. Faculty of Medicine policy is to not release research funds of a primary, supplemental, subcontract, or renewal award until current CHS approval is documented.

Office of Technology Development (OTD) – negotiates Clinical Trial Agreements (CTAs), Sponsored Research Agreements (SRAs) and Material Transfer Agreements (MTAs) with industry that may support human studies research at HMS/HSDM. OTD works closely with the CHS to ensure the proper language regarding scope of work, along with compensation (for the researchers and research participants), provision of equipment or medications, management of adverse events and unanticipated problems, responsibility in case of injury, confidentiality and privacy of participants and their data, and other protocol-specific issues are included in these Agreements. Responsibilities include ensuring that the terms and conditions of all negotiated CTAs, SRAs and other research related agreements with industry sponsors are consistent with all applicable guidelines, federal regulations and Harvard University/HMS/HSDM policies pertaining to the protection of participants in research and the integrity of science.

Committee on Microbiological Safety (COMS) – provides independent health and safety review of studies involving the use or manipulation of rDNA molecules and other etiological biological agents of concern to the CHS including but not limited to retroviral vectors and toxic or select agents used in human studies. Responsibilities include reviewing and registering studies involving recombinant DNA and agents pathogenic for animals, including humans, plants, and biological toxins. Two kinds of human studies are reviewed and approved by COMS - those involving gene transfer and those involving the transplantation of animal tissues into humans. These reviews by COMS are intended to ensure that all potentially hazardous biological materials used in a study will be properly contained and used, and to ensure the health and safety of researchers, employees, study participants and the public. Approval by COMS is required prior to final approval from the CHS for studies of this nature. Representatives from COMS regularly attend CHS meetings.

Countway Library of Medicine (Countway) – works with the CHS on access to faculty and medical research records housed in the library that are under the CHS and/or Privacy Board purview (such as waiver of HIPAA Authorization for Protected Health Information (PHI) contained in archived medical records). Responsibilities include referring researchers to the CHS for appropriate applications for review and final approval of projects.

Office of Research Compliance (ORC) – helps to ensure that sponsored funds are managed in a manner consonant with agency guidelines, serves as a resource for research administration in the resolution and enforcement of research compliance issues, facilitates and coordinates training, education, and outreach initiatives, helps design and implement various auditing, monitoring and quality assurance activities and programs, assists or leads non-compliance inquiries and investigations, collects non-compliance trending data and employee survey information to identify compliance risk areas, and helps to provide policy guidance and clarify roles and responsibilities within HMS and HSDM. The Director of the ORC regularly attends CHS meetings to observe practices and measure them against relevant standards. ORC will also perform its own risk analyses and compliance analyses concerning the CHS on a periodic basis.

Office of the General Counsel (OGC) – counsel in the OGC of Harvard University assists the CHS on complex matters including cooperative institutional amendments, policies and procedures, interpretation of state and federal regulations, federal audits, and official institutional communications. Responsibilities include working with the CHS on issues pertaining to federal guidelines, Harvard policies/guidelines, CHS policies/procedures and Commonwealth laws pertaining to research involving human studies and research participants.

Risk Management and Audit Services (RMAS) – provides the CHS, the Privacy Board, and the University with guidance on HIPAA regulations, internal policies, procedures and forms. Responsibilities include providing guidance on the HIPAA Privacy Rule policies and guidelines, and conducting routine and for-cause audits of departments which may include reviews of human studies research activities and recordkeeping throughout the University.

Office of the Provost – the Office of the Provost at Harvard University coordinates and supports IRB initiatives, such as the accreditation process, the creation of the IRB database HIRBERT (Harvard Institutional Review Board Electronic Reporting Tool, and the online human studies training program, HETHR (Harvard Ethical Training in Human Research; Appendix 11) and organizes the University-wide Human Subjects Research Committee meetings, comprised of officials at the three Harvard IRBs and the Harvard affiliated hospitals.

Center for Evaluation (CfE) – reviews and approves research involving medical school students as research participants (including medical school curriculum studies) prior to CHS review. Such research applications are submitted directly to CfE by Investigators and once approved by CfE, forwarded by CfE to the Dean for Medical Education (for review and signature) whose office forwards the research materials for CHS review.

Office of Educational Programs (OEP) – provides fellowships and funding for student research projects, community services projects and language immersion programs for HMS and HSDM students. OEP supports students and their faculty mentors and assists them in study design. OEP

assists with any communication issues between the CHS and the student or mentor and will not provide any funding to a student for a research project unless CHS approval is documented.

HSDM Office of Research – reviews HSDM faculty and student human studies proposals prior to CHS submission. The Assistant Director works closely with the CHS to support initiatives and training opportunities for faculty, masters and pre and post doctoral students.

Office for Research Issues (ORI) - is responsible for implementing the policies adopted by the Faculty of Medicine as well as the policies promulgated by the federal government in the areas of research integrity/scientific misconduct and conflict of interest. ORI works directly with two standing committees (Faculty Conduct Committee and Faculty Committee on Conflict of Interest) that review and make recommendations to the Dean (and to the President of a Harvard affiliated institution when appropriate).

ORI provides oversight and implementation of the Faculty of Medicine Conflict of Interest Policy applicable to all faculty and fellows at HMS and HSDM and also handles allegations of scientific misconduct under a policy that applies to all faculty and trainees. The ORI publishes *Faculty Policies on Integrity in Science*, which includes guidelines for investigators involved in clinical and scientific research, investigating allegations of faculty misconduct, conflict of interest and commitment, and authorship guidelines for the Faculty of Medicine. ORI works closely with the CHS on all issues relating to human studies research.

2.8. Quality Assurance

In order to monitor and measure the effectiveness of its human research protection program, the institution has established a Leadership Team as described below. This team will meet on a quarterly basis to review, evaluate and provide guidance on: reports from the Quality Assurance Coordinator (who will be assessing both Investigator compliance with human research protections as well as the work processes of the CHS and the CHS staff); the CHS outreach activities; current regulations and guidance related to human research policy as issued under OHRP, FDA or other federal agencies or any state or local legal or ethical issues involving human research; changes within the Faculty of Medicine and the University. The Leadership Team will decide how to implement new best practices and improvements in the HRPP.

2.8.1. Monitoring of the CHS

The CHS will be continuously monitored through the Quality Assurance Coordinator's actions in evaluating of study files and CHS proceedings as described below. Additionally, the effectiveness of the CHS will be assessed through the Leadership Team as well as by yearly assessment by the IO in collaboration with the Dean for Academic and Clinical Programs regarding membership and the ability of the Chair to fulfill their duties, and the ability of the CHS to deal effectively with issues of non-compliance, unanticipated problems and/or investigator conflict of interest.

2.8.1.1. Quality Assurance Coordinator

The HMS Quality Assurance (QA) Coordinator performs evaluations and assessments of Faculty of Medicine active human studies, Investigator study files and the files of the CHS to provide full-circle evaluations of compliance. The QA Coordinator reports to the ORSP Director, with a “dotted-line” relationship to the Director of Research Compliance (ORC). The duties and functions of the QA Coordinator include the following:

CHS Evaluation

The QA Coordinator provides a dual-role in ensuring CHS study files are in concordance with Investigator study files, such that the CHS has accurate records of study activities, and that the CHS and the Investigator have the same version of materials requiring CHS approval. Additionally, the QA Coordinator assesses CHS performance pertaining to compliance with applicable laws, regulations, and institutional policies relating to the CHS, and evaluates CHS files to ensure that the CHS review has been conducted appropriately (such as risk:benefit analysis, equitable selection of participants, safety and confidentiality of participants and their data, appropriate consent language, and extra protections for vulnerable populations) as well as any other legal or ethical consideration involved in a study.

Investigator Evaluation and Education

The QA Coordinator is responsible for the following core functions: development of appropriate review checklists and forms; conducting (or participating in) for cause and not for cause review of approved studies; reporting results of reviews to the CHS Leadership Team and other HMS/HSDM and Harvard University offices and officials as appropriate; providing education and technical assistance to Investigators and their staffs; preparing periodic reports of general findings and concerns, including recommendations for improvement or resolution or prevention of problems; and other duties and activities as assigned.

2.8.1.2. CHS Leadership Team

The CHS 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 and OTD) 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 Leadership Team will undertake activities aimed at implementing the standard elements of compliance found in government guidance documents as follows:

- The Leadership Team will advise the CHS regarding implementation of new federal/state regulatory mandates and communication of those mandates to the HMS/HSDM community.
- The Leadership Team will evaluate all new and existing policies to ensure that they are sufficiently detailed and clear and easily accessible by the CHS staff, members, and the HMS/HSDM community.
- The Leadership Team will evaluate the roles and responsibilities of the CHS (including the Chair, members and staff) and Investigators to insure that these roles

and responsibilities are well defined and understood by the CHS (Chair, members and staff) and the HMS/HSDM community.

- The Leadership Team will review appropriate reports of the QA Coordinator (described in the preceding section) and evaluate the necessity of policy changes or CHS actions as a result of the reports.
- The Leadership Team will present planned improvements to the institution's HRPP to the University wide Committees to evaluate where changes would be best implemented across the University.
- The Leadership Team will assist in the further development of the CHS's outreach activities to the community and evaluate its effectiveness.

2.8.1.3. Institutional Official

The HMS Dean for Faculty and Research Integrity, who serves as the IO of the CHS is responsible for the implementation and maintenance of the HRPP and the CHS.

2.8.1.4. University Level

Provost Office: Harvard's three IRBs operate independently, but all participate in a University-wide Human Subjects Research Committee, established and supported by the Office of the Provost.

2.8.1.5. Federal Level

OHRP is the federal agency overseeing the compliance of the IRB's in relation to the federal regulations and also provides assistance to the IRBs in the interpretation and enforcement of the federal regulations. OHRP occasionally performs site visits of IRBs.

2.8.2. Researcher Grievances, Comments, or Suggestions

Filing grievances, concerns and suggestions may be sent to the CHS Administrator (Pamela Richmond, PJG7@med.harvard.edu, 617-432-2597), the ORSP Director (Carolyn Connelly, carolyn_connelly@hms.harvard.edu, 617-432-0651), the IO of the CHS (Gretchen Brodnicki, Gretchen_brodnicki@hms.harvard.edu 617-432-2496) or to the Office of Research Compliance Hotline (617-432-5555). More contact information is listed on the CHS website: <http://www.hms.harvard.edu/orsp/human/human.html> (Appendix 12).

All grievances will be reported to the IO, who will determine the appropriate level of investigation (and by whom the investigation will be conducted). The person reporting the grievance will be contacted regarding resolution.

3. CHS Member and Staff Policies

3.1. CHS Chair