HUMAN RESEARCH PROTECTION PROGRAM PLAN

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Purpose

The Harvard University Faculty of Medicine comprised of Harvard Medical School and the Harvard School of Dental Medicine – HMS/HSDM is committed to protecting the rights and welfare of participants in Human Research. The purpose of this document is to describe HMS/HSDM's plan to comply with ethical and legal requirements for the conduct and oversight of Human Research.

HMS/HSDM's Human Research Protection Program (HRPP) is a comprehensive system to ensure the protection of the rights and welfare of participants in Human Research. It is comprised of the institutional leadership, Office of Human Research Administration that includes the Institutional Review Board (IRB) and Quality Improvement Program (QIP), investigators and their study staff, and other relevant offices including Office of Sponsored Programs Administration (SPA), Office of Research Compliance (ORC), Office of Technology Development (OTD), Office of Information Technology (IT), Office of General Counsel (OGC), the Academy at Harvard Medical School, and Scholars in Medicine Office (SMO). The HRPP is based on all above-mentioned parties fulfilling their roles and responsibilities described in this plan.

Agent

An individual who is an employee or student is considered an agent of HMS/HSDM for purposes of engagement in Human Research when that individual is on-duty in any capacity as an employee or student of HMS/HSDM. Specifically, an agent is an individual who, by agreement or otherwise, may act on behalf of the School and bind it by words or actions; a person who represents the School by its authority or delegated authority.

An individual who is not an employee is considered an agent of HMS/HSDM for purposes of engagement in Human Research when that individual has been specifically authorized to conduct Human Research on behalf of HMS/HSDM.

The Office of Human Research Administration (OHRA) will consult with the Office of the General Counsel (OGC) to determine whether someone is acting as an agent of HSPH when it is unclear whether the individual meets this definition.

Clinical Trial

Human Research intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of an investigational product(s), to identify any adverse reactions to a drug, device, or biologic, to evaluate the safety or effectiveness of a drug, device, or biologic, or to study absorption, distribution, metabolism, and excretion of a drug with the object of ascertaining its safety or efficacy.

Engaged in Human Research

In general, HMS/HSDM is considered engaged in Human Research when its employees or agents, for the purposes of the Human Research, obtain: (1) data about the participants of the research through intervention or interaction with them; (2) identifiable private information about the participants of the research; or (3) the informed consent of human participants for the research. HMS/HSDM follows OHRP guidance on "Engagement of Institutions in Research"[1] to apply this definition and exceptions to this definition.

[1] http://www.hhs.gov/ohrp/policy/engage08.html

Human Research:

Any activity that either:

- Is "Research" as defined by DHHS and involves "Human Subjects" as defined by DHHS ("DHHS Human Research"); or
- Is "Research" as defined by FDA and involves "Human Subjects" as defined by FDA ("FDA Human Research").

Human Subject as Defined by DHHS

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 (for example, survey administration).
- **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 FDA

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 (identified or unidentified) a medical device is used.

Investigator

The person responsible for the conduct of the Human Research at one or more sites. If the Human Research is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Research as Defined by DHHS

A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.[2]

Research as Defined by FDA

Any experiment that involves a test article and one or more human subjects, and that meets any one of the following:

[2] For research conducted within the Bureau of Prisons: Implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.

- 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.

Mission

The mission of the HRPP is to protect the rights and welfare of research participants in Human Research that is reviewed and approved by HMS/HSDM IRB.

HMS/HSDM aims to promote a culture of compliance with the highest legal and ethical standards for the conduct of human research. It is also committed to education of the HMS/HSDM research community and outreach to collaborating institutions participating in global health research.

Ethical Requirements

The Faculty of Medicine follows the ethical principles outlined in the April 18, 1979 report of The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research titled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," also known as "The Belmont Report:"

- Respect for Persons
- Beneficence
- Justice

In addition, when engaged in international research, HMS/HSDM follows applicable international and local ethical guidelines.

Legal Requirements

The Faculty of Medicine commits to apply its ethical standards to all Human Research regardless of funding.

When HMS/HSDM is engaged in DHHS Human Research that is conducted, funded, or otherwise subject to regulations by a federal department or agency, who is a signatory of the Common Rule, the organization commits to apply the regulations of that agency relevant to the protection of Human Subjects.

When HMS/HSDM is engaged in FDA Human Research, the organization commits to apply the FDA regulations.

When Human Research is conducted or funded by the following Departments, HMS/HSDM commits to comply with relevant regulations:

Departments	Regulations
Department of Justice (DOJ)	28 CFR §22
Federal Bureau of Prisons (DOJ)	28 CFR §512

Department of Defense (DOD)	DOD Directive 3216.02, which includes the requirement to apply 45 CFR §46 Subparts B, C, and D[3]. DFARS clause or comparable language used in the agreement with the DOD Component supporting the research involving human subjects
Department of Education (ED)	34 CFR §97 Subpart D (equivalent to 45 CFR §46 Subpart D), 34 CFR §98.3, 34 CFR §98.4, 34 CFR §356.3, and 34 CFR §99
Department of Energy (DOE)	DOE O 443.1A and to use "Checklist for IRBs to Use in Verifying that HS Research Protocols are in Compliance with the Department of Energy (DOE) Requirements."
Environmental Protection Agency (EPA), or when the results of research are intended to be submitted to or held for inspection by EPA	40 CFR §26, which includes the requirement to apply 45 CFR §46 Subparts B and D.

Other Requirements

When reviewing research that involves Community-Based Participatory Research (CBPR), HMS/HSDM considers the following core principles:

- Facilitates collaborative, equitable partnerships in all phases of research
- Integrates & achieves balance between research and action for benefit of all partners
- Recognizes community as unit of identity
- Builds on community strengths/resources
- Promotes co-learning and capacity building among all partners
- Involves a long-term process and commitment
- Emphasizes local relevance of Public Health problems and multiple determinants of health
- Disseminates findings and knowledge gained to all partners and involves all partners in that process

For clinical trials, when required by the sponsor, HMS/HSDM commits to apply the "International Conference on Harmonisation – Good Clinical Practice E6." (ICH-GCP)

HMS/HSDM prohibits payments to professionals in exchange for referrals of potential participants ("finder's fees") and payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments").

[3] Quick applicability table for DHHS Subparts:

	DHHS	DOD	ED	EPA	VA
Subpart B	X	X		X	
Subpart C	X	X			X
Subpart D	X	X	X	X	X

Sponsor Human Research

For both sponsored and non-sponsored Human Research, HMS/HSDM abides by its ethical principles, regulatory requirements and its policies and procedures.

Scope Of Human Research Protection Program

The categories of research conducted at HMS/HSDM include:

- Research involving human subjects
- Research involving pregnant women as subjects
- Research involving non-viable neonates
- Research involving neonates of uncertain viability
- Research involving fetuses
- Research involving in vitro fertilization
- Research that plans to or is likely to involve prisoners as subjects
- Research involving children as subjects
- Research involving children, pregnant women, fetuses, or neonates that is not otherwise approvable without approval of an agency secretary or director
- FDA-regulated research
- Research involving drugs that require an IND
- Research involving devices that require an abbreviated IDE
- Research involving devices that require an IDE issued by FDA
- International research
- Community-Based Participatory Research (CBPR)
- Research conducted or funded by the Department of Defense (DOD)
- Research conducted or funded by the Department of Justice (DOJ)
- Research conducted or funded by the Department of Education (ED)
- Research conducted or funded by the Department of Energy (DOE)

The categories of research not reviewed by HMS/HSDM IRB include:

- Research involving a waiver of consent for planned emergency research
- Emergency use of a test article in a life-threatening situation
- Activities involving humanitarian use devices
- Classified research

Policies and Procedures for Conducting Human Research at HMS/HSDM

Policies and procedures for the Human Research Protection Program are available on OHRA website: http://www.hsph.harvard.edu/ohra

Human Research Protection Program Components

Institutional Official

The Chief Research Operations Officer (CROO) is designated as the Institutional Official (IO) for HMS and HSDM.

The IO has the authority to take the following actions or delegate these authorities to a designee:

- Sign federal assurances.
- Appoint and remove IRB members and IRB chairs.
- Suspend or terminate IRB approval of research.

- Place limitations or conditions on an investigator's or research staff's privilege to conduct Human Research.

The IO is responsible to

- Approve Human Research Protection Program Plan for Harvard Faculty of Medicine.
- Approve budget for all HMS and HSDM research managed by OHRA.
- Appointment IRB members and chair of the HMS/HSDM panel.

Director, Office of Human Research Administration (OHRA) for Harvard Longwood Medical Area

The Director of OHRA for Harvard Longwood Medical Area has overall responsibility for the HRPP within HMS and HSDM.

The OHRA Director has the authority to:

- Create and approve policies and procedures related to the Human Research Protection Program that are binding on the HMS/HSDM.
- Determine what IRBs the HMS or HSDM will rely upon.
- Approve and rescind IRB authorization agreements.
- Create budget for all HMS and HSDM research managed by OHRA
- Allocate resources among each unit within the Human Research Protection Program.
- Institute a suspension or termination of IRB approval of research.
- Hire and fire OHRA staff.

The OHRA Director is responsible to:

- Oversee the review and conduct of Human Research under the jurisdiction of the Human Research Protection Program.
- Periodically review this plan to assess whether it is providing the desired results and recommend amendments as needed.
- Establish policies and procedures designed to increase the likelihood that Human Research will be conducted in accordance with ethical and legal requirements.
- Establish policies and procedures for collaborating international sites to increase the likelihood that Human Research will be reviewed and conducted in accordance with relevant US and local ethical the legal requirements.
- Institute regular, effective, educational and training programs for all individuals involved with the Human Research Protection Program, including research staff at international sites.
- Ensure that the research review process is independent and free of coercion or undue influence, and ensure that HMS/HSDM officials cannot approve research that has not been approved by the IRB.
- Implement a process to receive and act on complaints and allegations regarding the Human Research Protection Program.
- Implement a Quality Improvement Program (QIP) to monitor compliance, identify problem areas, and to assist investigators in improving study site performance.
- Investigate and remediate identified systemic problem areas, and where necessary remove individuals from involvement in the Human Research Protection Program.
- Ensure that the Human Research Protection Program has sufficient resources, including the number of IRBs appropriate for the volume and types of Human Research to be reviewed, so that reviews are accomplished in a thorough and timely manner.
- Fulfill educational requirements mandated by HMS/HSDM and OHRP.

- Report Unanticipated Problem Involving Risks to Participants or Others, Serious or Continuing Non-Compliance, and/or a Suspension or Termination of IRB Approval to Institutional Official within 5 business days and to applicable external agencies, including OHRP, within 20 business days.

All members of the Harvard Faculty of Medicine

All individuals within the research community have the responsibility to:

- Be aware of the definition of Human Research.
- Consult the IRB when there is uncertainty about whether an activity is Human Research.
- Not conduct Human Research or allow Human Research to be conducted without review and approval/Determination by an IRB.
- Report allegations of undue influence regarding the oversight of the Human Research Protection Program or concerns about the Human Research Protection Program to the HRPP Director or Institutional Official.
- Report allegations or finding of non-compliance with the requirements of the Human Research Protection Program to the IRB and/or Quality Improvement Program.

Individuals who are responsible for business development are prohibited from carrying out day-to-day operations of the review process.

IRB

The HMS/HSDM IRB, designated by the Dean of Harvard Faculty of Medicine, is the IRB relied upon by the Human Research Protection Program. The IRB is supported and managed by the Office for Research Subject Protection (ORSP). HMS/HSDM may rely upon the IRB of another organization provided that the organization has a current, unexpired Federalwide Assurance on file with OHRP and one of the following criteria is met:

- The IRB is the IRB of a participating institution of the Harvard Catalyst.
- The IRB is the IRB of an AAHRPP accredited organization.
- HMS/HSDM's investigator is a collaborator on Human Research primarily conducted at another organization and the investigator's role does not include interaction or intervention with subjects.
- HMS/HSDM is engaged in the Human Research solely because it is receiving federal funds. (The local HMS/HSDM investigator does not interact or intervene with subjects, gather or possess private identifiable information about subjects, nor obtain the consent of subjects.)

The HMS/HSDM IRB has the authority to:

- Determine whether an activity is Human Research.
- Determine whether Human Research is exempt.
- Approve, require modifications to secure approval, and disapprove all Human Research overseen and conducted by HMS/HSDM. All Human Research must be approved by an IRB designated by the Dean. HMS/HSDM Officials may not approve Human Research that has not been approved by the IRB.
- Suspend or terminate approval of Human Research not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to participants.
- Observe, or have a third party observe, the consent process and the conduct of the Human Research.
- Determine the data security category/level according to Harvard Data Security Policy.

- Evaluate financial interests of investigators and research staff and have the final authority to decide whether the financial interest and management plan, if any, allow the research to be approved.
- Make final determination as to whether a particular event constitutes unanticipated problem involving risks to participants or others.
- Make final determination as to whether a particular protocol violation constitutes serious or continuing non-compliance.

IRB chairs, members and staff are responsible to follow applicable HMS/HSDM Human Research Protection Program policies and procedures.

Quality Improvement Program (QIP)

The Quality Improvement Program (QIP) is a division within the OHRA for Longwood Medical Area. It is independent of the IRB. QIP It is independent of the IRB. QIP consists of three distinct units: Compliance, Education and Human Research Support.

QIP's Compliance and Education units are responsible and have the authority to:

- Perform routine onsite reviews of any study that has been approved by the HMS/HSDM IRB.
- Perform routine review and/or directed audit of IRB records.
- Conduct directed (for-cause) audits at the request of the IRB, OHRA Director, or, Institutional Official.
- Provide investigators with quality improvement recommendations to ensure that research is conducted in accordance with good clinical practice guidelines.
- Provide training and education to the research community.
- Recommend action to the IRB, based on onsite observations during directed (for-cause) audits.
- Investigate allegations and findings of non-compliance.
- Report potential serious or continuing non-compliance with applicable regulations or institutional policies to the IRB and/or OHRA Director.

QIP's Human Research Support unit offers the following services:

- Assist investigator with IRB submission
- Provide investigator/study staff with study management tools
- Serve as short or long term study coordinator on specific studies upon investigator's request
- Conduct routine/regular onsite monitoring
- Offer regular education and training opportunities, and as requested by investigators and their study staff.

Investigators and Research Staff

Investigators and research staff have the responsibility to:

- Follow the Human Research Protection Program requirements described in the INVESTIGATOR MANUAL (HRP-103).
- Comply with all determinations and additional requirements of the IRB, the IRB Administrative Chair/chair, OHRA Director, and the Institutional Official.

Office of Research Compliance (ORC)

HMS ORC has the responsibility to:

- Ensure that sponsored funds are managed in a manner consonant with agency guidelines.

- Serve as a resource for research administration in the resolution and enforcement of research compliance issues, facilitates and coordinates training, education, and outreach initiatives.

Office of Technology Development (OTD)

OTD has the responsibility to:

- Negotiate intellectual property (IP) issues in Clinical Trial Agreements (CTAs) and Sponsored Research Agreements (SRAs), and approve Material Transfer Agreements (MTAs) with institutions that may support human research at HMS/HSDM.

The Office of General Counsel (OGC)

OGC has the responsibility to:

- Provide advice upon request to the HRPP Director, IRB Chairs, Administrative Chair, QIP Director, and other individuals involved with the Human Research Protection Program.
- Assist in determining whether someone is acting as an agent of HMS/HSDM.
- Assist in determining who meets the definition of "legally authorized representative" and "children" when Human Research is conducted in jurisdictions not covered by policies and procedures.
- Assist in the resolution of conflicts among applicable laws.

The Academy at Harvard Medical School

The Academy has the responsibility to:

- Review research involving medical school students as research participants (including medical school curriculum studies) prior to IRB approval. The Academy approval is a requisite of IRB determination and/or approval.

Scholars in Medicine Office (SMO)

SMO has the responsibility to:

- Work with OHRA to ensure all SMO sponsored student Human Research projects are reviewed by the IRB.

Department Chairs

Department Chairs have the responsibility to:

- Review Human Research Initial Review Applications and certify the following
  - The Principal Investigator is qualified by education, training and experience to personally conduct and/or supervise the research described in the protocol.
  - The Principal Investigator has completed all applicable institutional credentialing processes to conduct this research.
  - The Principal Investigator has sufficient resources to carry out this research as proposed.
  - The protocol is scientifically valid and employs research procedures which are consistent with sound research design.
- Oversee the review and conduct of Human Research in their department.
- Forward complaints and allegations regarding the Human Research Protection Program to the OHRA Director and/or Institutional Official.

Office of Sponsored Programs Administration (SPA)

SPA has the responsibility to:

- Review contracts and funding agreements including data use agreements for compliance with OHRA policies and procedures.

Office of Information Technology (IT)

IT has the responsibility to:

- Assist investigators and IRBs to identify the data security categories appropriate for studies, as necessary.
- Assist investigators to implement the appropriate data security requirements.

Monitoring and Auditing

Quality Improvement Program (QIP) staff will conduct routine onsite review and/or monitoring, as well as directed (for-cause) audits. Audits will focus on areas of concern that have been identified by any entity, i.e., federal, state or institutional.

Education and Training

All new investigators and study staff and IRB members are to review this plan as part of their initial orientation. The Quality Improvement Program (QIP) offers frequent and regular educational sessions open to the entire HMS/HSDM research community throughout the academic year, as needed, and/or as requested.

IRB members, IRB staff, and others involved in the review of Human Research must complete the Collaborative IRB Training Initiative (CITI) modules every three years.

Investigators, research staff, and others involved in the conduct of Human Research are to complete the CITI modules or acceptable equivalent every three years.

The OHRA Director and QIP will identify and implement additional educational and training as needed.

Questions and Additional Information of the IRB

Contact OHRA during its business hours, Monday – Friday 8:30 am - 4:30 pm with questions, requests for additional information or to provide feedback relating to IRB Operations, compliance, education and/or research support activities. Additional information, along with IRB applications can be found on the OHRA website at: www.hsph.harvard.edu/ohra

Contact and location information for OHRA is as follows:

- Phone: 617-432-3071
- Fax: 617-432-2165
- Email: irb@hms.harvard.edu
- Address:

  Office of Human Research Administration, Harvard Longwood Medical Area
  90 Smith Street
  Boston, Massachusetts 02120

Reporting and Management of Concerns

Questions, concerns, complaints, allegations of undue influence, allegations or findings of non-compliance, or input regarding the Human Research Protection Program may be reported orally or in writing. Employees or students are permitted to report concerns on an anonymous basis. Concerns may

be reported to the QIP Director, IRB Chair/Administrative Chair, HRPP Director, Institutional Official, and or OGC.

The QIP has the responsibility to investigate allegations of non-compliance when requested by the IRB, IRB Chair, IRB Administrative Chair or HRPP Director. The IRB, IRB Administrative Chair, or the HRPP Director will evaluate and manage all allegations and findings of non-compliance.

Employees or students who report in good faith possible compliance issues should not be subjected to retaliation or harassment as a result of the reporting. Concerns about possible retaliation should be immediately reported to the Institutional Official. To make such reports, their contact information is as follows:

Contact information for OHRA Director:

- Name: Delia Wolf, MD, JD, MSCI, CIP
- Phone: 617-432-2148
- Address:

  Harvard School of Public Health
  Office of Regulatory Affairs & Research Compliance
  90 Smith Street, 3rd Floor – room 337
  Boston, MA 02120

- Email: dywolf@hsph.harvard.edu

Contact information for Institutional Official:

- Name: Pamela S. Caudill, Chief Research Operations Officer
- Phone: (617) 432-0017
- Email: pamela_caudill@hms.harvard.edu
- Address:

  Harvard Medical School
  25 Shattuck St
  Gordon Hall, Office 404
  Boston, MA 02115

Disciplinary Actions

The HMS/HSDM Institutional Official may place limitations or conditions on an investigator's or research staff's privilege to conduct Human Research whenever in the opinion of the IO such actions are required to maintain the Human Research Protection Program.

Approval and Revisions to the Plan

This Human Research Protection Program Plan is to be approved by the HMS/HSDM Institutional Official. This plan is intended to be flexible and readily adaptable to changes in regulatory requirements. The OHRA Director has the responsibility to review this plan to assess whether it is providing the desired results. At the request of the OHRA Director, the IO has the authority to amend this plan as deemed necessary.