

**PARTNERS HEALTHCARE SYSTEM, INC.
BRIGHAM AND WOMEN'S HOSPITAL
MASSACHUSETTS GENERAL HOSPITAL**

Partners Human Research Protection Program (HRPP) Plan

1.0 THE HRPP

The HRPP of Partners HealthCare System, Inc. (Partners) is the integrated program with overall responsibility for the protection of the rights and welfare of human subjects in research for The Brigham and Women's Hospital, Inc. (BWH) and The General Hospital Corporation (also known as Massachusetts General Hospital) (MGH). The HRPP includes specific protocol review and oversight as conducted by these institutions' institutional review boards (collectively, the Partners IRB(s) or the IRB); management of funding negotiations as conducted by their Offices of Grants and Contracts and the Partners Office of Corporate Sponsored Clinical Research; provision and development of training and policies for researchers; coordination of interactions with potential as well as enrolled human subjects; conduct of quality improvement and assurance activities; and the support of the compliance responsibilities of the covered institutions and investigators.

2.0 MISSION

A core mission of BWH, MGH and Partners is to advance care through excellence in biomedical research. Consistent with that, the HRPP's mission is to help ensure that in being a leader in research, Partners and its hospitals protect human subjects participating in research conducted or sponsored by BWH or MGH, or in which BWH or MGH are otherwise engaged, in accordance with legal requirements and ethical guidelines. The HRPP fosters a culture of compliance with the highest legal and ethical standards for human subject protection among the institutions, their investigators and all members of the broad research community. The Partners HRPP is also committed to education of and outreach to persons interested in research.

3.0 ETHICAL PRINCIPLES

The Partners HRPP is guided by the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, generally known as the "Belmont Report," as well as the *Partners Guiding Principles for Human Studies* as outlined in the *Responsible Conduct of Human Studies*.

4.0 APPLICABLE LAWS

Federal Regulations:

DHHS Regulations 45 CFR Parts 46 and 164
FDA Regulations 21 CFR Parts 11, 50, 54, 56, 312, 812

State Statutes and Codes:

M.G.L. c. 94C §8 (Controlled Substances in Research)
M.G.L. ch. 111L (Human Embryonic Stem Cell Research)
M.G.L. ch. 111, §70E (Patients Rights/Informed Consent)
M.G.L. c.111 § 70F (Consent to HIV/AIDS Testing)
M.G.L. c.111 § 70G (Genetic Privacy)
M.G.L. c.112, §12F (Consent by Minors)
M.G.L. c.112, §12J (Experimentation on Fetuses)
M.G.L. c.201, §§6-6B (Guardianships)
M.G.L. c.201D,6; 2-1-2 to 201-4 (Health Care Proxies)
104 C.M.R. 31.00 (Department of Mental Health Research)
105 C.M.R. 700.009 (Controlled Substances in Research)
105 C.M.R. 960.000 (Human Embryonic Stem Cell Research)
115 C.M.R. 10.00 (Department of Mental Retardation Research)

5.0 SCOPE

The Partners HRPP is responsible for all human-subjects research and clinical investigations conducted by BWH or MGH investigators or under the auspices of the hospitals, or in which the hospitals are otherwise engaged, regardless of the source of funding. This includes:

- ❑ Research sponsored by BWH or MGH;
- ❑ Research conducted by or under the direction of employees or agents of BWH or MGH in connection with their institutional responsibilities;
- ❑ Research conducted by or under the direction of any employee or agent of BWH or MGH using any property or services of BWH or MGH; or
- ❑ Research involving the use of BWH's or MGH's private information to identify or contact subjects.

BWH and/or MGH are engaged in human-subjects research whenever employees or agents (e.g., professional staff) of the institution intervene or interact with living individuals for research purposes or the institutions receive a direct HHS award to support such human-subjects research.

6.0 DEFINITIONS

For the purposes of the HRPP, human-subjects research encompasses activities that meet the Department of Health and Human Services (DHHS) definitions of *research* and *human subject* or the Food and Drug Administration (FDA) definitions of *human subject* and *clinical investigation*. The DHHS definitions of *research* and *human subject* and the FDA definitions of *human subject* and *clinical investigation* are provided below.

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. [45 CFR 46.102(d)]

Human subject means 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) Identifiable private information. *Intervention* includes both 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* includes communication or interpersonal contact between investigator and subject. *Private information* includes 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). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. [45 CFR 46.102(f)(1)(2)]

Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical studies. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous... [21 CFR 50.3(c) and 21 CFR 56.102(c)]

Human subject means an individual who is or becomes a participant 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. [21 CFR 50.3(g) and 21 CFR 56.102(g)]

7.0 GOVERNANCE

Governance of the Partners HRPP is coordinated among Partners Corporate and BWH and MGH.

Partners HealthCare System, Inc. (PHS) is the corporate parent of BWH, MGH, as well as a number of other health care provider entities. Partners has a Board of Directors, which generally manages and directs the overall health care system. BWH and MGH are legally separate corporate entities, and as such, have their own Boards of Trustees, which carry out core responsibilities with respect to the hospitals. BWH and MGH are each distinct recipients of all external funding. BWH and MGH each have their own Federalwide Assurances (FWAs) signed by their own Institutional Officials (IOs), who are legally authorized to represent each institution. The IOs at MGH and BWH provide assurance that the IRBs designated in the FWAs are knowledgeable about the local research context and will comply with the terms of the FWAs.

Partners provides some centralized services (e.g., research management, legal, information systems and human resources): The individual entities carry out most other operations.

In 1996, BWH and MGH combined the operation and management of their respective IRBs into a single integrated IRB system, known as the Partners IRB(s) or the IRB (also known as the Partners Human Research Committee(s) or the PHRC). Cooperative Amendments were filed with the Office for Human Research Protections (OHRP) to codify this agreement, and the current FWAs reflect this arrangement.

The integrated IRB operation is managed by staff of Partners Research Management, which is a centralized department responsible for supporting research services for BWH and MGH investigators. These services include among others, administrative IRB support, grants and contracts, and research finance. In addition to centralized Research Management, other key centralized functions for the HRPP include: the Office of General Counsel; Information Systems; and Corporate Sponsored Clinical Research.

Although the ultimate responsibility for the protection of human subjects of research resides with the individual institutions, the Partners HRPP coordinates and carries out review and oversight activities on behalf of BWH and MGH and reports directly to the designated Institutional Official of each institution.

8.0 KEY ROLES AND RESPONSIBILITIES

8.1 Partners Chief Academic Officer

Daniel K. Podolsky, M.D., the Chief Academic Officer (CAO) reports to the President and Chief Executive Officer of Partners. The CAO is responsible for providing the necessary resources for those components of the HRPP that are under his authority. Corporate components of the HRPP that report to the CAO include:

- Partners Research Administration, which includes:
 - Grants and Contracts
 - Research Finance
 - Human Research Affairs, consisting of the IRB and Quality Improvement Program
- Research Compliance Office
- Research Ventures and Licensing (RVL) that supports all interactions with corporate sponsors via the following four distinct Departments:
 - Corporate Sponsored Clinical Research (CSCR)
 - Corporate Sponsored Research and Licensing
 - Business Development
 - Center for Innovative Ventures

8.2 Institutional Officials

BWH and MGH each have an approved Federalwide Assurance (FWA) on file with the DHHS Office for Human Research Protections (OHRP). The FWAs are executed by a senior official of the institution, referred to as the Institutional Official.

The IO understands the institution's responsibilities under the FWA, assures the protection of human subjects of research, and assures that the designated IRBs are knowledgeable about the local research context and will comply with the terms of the FWA. The IO ensures that the IRB is the sole entity that can grant approval for a human research protocol. The FWAs have been approved by OHRP and are updated as necessary when information changes.

The IO for each institution is responsible for:

- Setting the "tone" for an institutional culture of respect for human subjects;
- Ensuring effective institution-wide communication and guidance on human subjects issues;
- Ensuring that investigators fulfill their responsibilities;
- Facilitating participation in human subject education activities;
- Serving as a knowledgeable point of contact for OHRP, FDA, the Office of Research Integrity (ORI) and other relevant federal and state agencies;
- Submitting required reports to OHRP, FDA, ORI and other relevant federal and state agencies; and

- Serving as the institutional Research Integrity Officer.

Administratively, the IO is responsible for:

- Providing the IRB with the necessary local resources, such as meeting space; and
- Supporting the authority and decisions of the Partners IRB(s).

The Institutional Official for the Brigham and Women's Hospital is Barbara Bierer, M.D., Senior Vice President for Research.

The Institutional Official for the Massachusetts General Hospital is F. Richard Bringhurst, M.D., Senior Vice President for Research and Technology.

8.3 Partners Institutional Review Boards

The Partners IRB(s) are registered with DHHS/OHRP. The IRB registrations are updated and submitted to OHRP as needed when there are any changes to the membership of the IRBs. Within Partners HRA, it is the Partners IRB(s) specifically that are responsible for review and oversight of human-subjects research under its scope of authority.

As noted above, the activities of the BWH and MGH IRBs have been integrated to improve operational efficiency, minimize redundancy of review and foster collaboration among the institutions' investigators. The BWH and MGH IRBs exercise their responsibilities for protection of human research subjects with independence of decision-making. Only the IRBs are allowed to grant approval for any research protocol.

Partners Human Research Quality Improvement Program

The QI Program is responsible for assisting the institutions and investigators in fulfilling their human-subjects research responsibilities through compliance with Federal and State regulations governing human research and for promoting an environment in which human-subjects research will be conducted according to the highest legal and ethical standards. The QI Program accomplishes these goals through on-site assessments, review of self-assessments completed by investigators, and education.

The QI program is responsible for and has the authority to:

- Perform routine (not for-cause) audits that focus on compliance with all relevant regulations. These audits may be conducted on any study that has been approved by the Partners IRB;
- Conduct directed (for-cause) audits at the request of the Partners IRB or the Institutional Officials;
- Review responsibilities of IND or IDE holders with investigators; and

- Review standard operating procedures for control of investigational drugs or investigational devices.

8.4 Partners Office of Grants and Contracts and Research Finance

The Partners Offices of Grants and Contracts and Research Finance are responsible for the programmatic, administrative and financial monitoring of all awards made to BWH and MGH, as well as to sub-recipients, under federally and non-federally sponsored projects. Partners has the obligation, throughout the life of an award, to monitor the activities of awardee institutions and sub-recipients to make certain that project objectives are completed and all funds are used for authorized purposes in compliance with applicable, laws, regulations, and provisions of the prime contracts or grant agreements.

When the research proposal involves human subjects, the Office of Grants and Contracts is responsible for certifying to federal and non-federal sponsors that the research proposal has been reviewed and approved by the Partners IRB(s). The staff has access to the integrated research management database that associates sponsored grants and contracts to protocols reviewed by the Partners IRB(s). The PHRC provides additional information as needed.

8.5 Corporate Sponsored Clinical Research

The primary office within Research Ventures & Licensing that interfaces with human-subjects issues is the Partners Office of Corporate Sponsored Clinical Research (CSCR). This office is responsible for developing, negotiating and executing agreements and associated budgets for industry-sponsored clinical research on behalf of MGH, BWH, and certain other entities within the Partners system (Newton-Wellesley Hospital, Faulkner Hospital, Spaulding Rehabilitation Hospital Corporation, and Partners Community HealthCare, Inc). In negotiating these agreements, CSCR agreement associates pay particular attention to issues related to freedom to publish, rights to use and control data including confidentiality of study data, patient confidentiality, compliance with the Common Rule and HIPAA Privacy Rule, and subject injury and indemnification. Of note, CSCR, in collaboration with the senior research leadership at BWH and MGH, the Partners Office of General Counsel, and the Office of Human Research Affairs, has developed standard terms and policies for acceptable provisions in clinical trial agreements. Executed agreements are made available to the PHRC for review for consistency with the informed consent documents.

When the research is corporate-sponsored, the clinical trial agreement must be executed between the sponsor and Partners CSCR and the protocol must be approved by the IRB before the research may begin.

8.6 Department Chairs/Chiefs

Department chairs/chiefs are responsible for ensuring that investigators conducting human-subjects research are qualified by training and experience to conduct the proposed research. In addition, department chairs/chiefs are responsible for ensuring that investigators have sufficient resources (time, research personnel, and access to appropriate populations) and facilities to conduct the proposed research. For each protocol submitted to the IRB for approval, the department chair/chief must certify that s/he accepts responsibility for assuring adherence to federal and state research regulations and institutional policies governing the protection of human subjects, including applicable institutional credentialing requirements.

The department chair/chief is also responsible for compliance with the requirements of Massachusetts General Laws (M.G.L.) 94C Controlled Substances Act Section 8 governing research projects and studies. Department chairs/chiefs must fulfill annual registration and reporting requirements with the Commonwealth of Massachusetts Department of Public Health. The Commonwealth of Massachusetts works through the PHRC to register all chairs/chiefs of departments and obtain annual reports on clinical investigations involving IND drugs, controlled substances or schedule II drugs that are being conducted at the institution by members of the registered department.

8.7 Investigators

Primary responsibility for protecting the rights and welfare of human subjects participating in research rests with the principal investigator (PI). PIs may not commence human-subjects research prior to obtaining IRB and, as appropriate, other institutional approval of their protocols. The PI must have a staff appointment and may not be a resident or research fellow or trainee. For each protocol submitted to the Partners IRB for approval, the PI must certify that s/he accepts responsibility for assuring adherence to applicable federal and state research regulations and hospital policies relative to the protection of the rights and welfare of subjects enrolled in the research.

PIs must be qualified by training and experience to conduct the research and must be in compliance with the Harvard Faculty of Medicine Conflicts of Interest Policy (if they have a Harvard Medical School faculty appointment) and/or the Partners Conflicts of Interest Policy (all Partners investigators). The PI's department chair or chief or his/her designee must review and sign new protocol applications for any research that involves an intervention or interaction with human subjects prior to submission to the Partners IRB(s). When the research involves the administration of a drug or use of a device for research purposes, the PI must be a licensed physician. Exceptions to this requirement are made by the Partners IRB(s)

on a case-by-case basis: exceptions require a licensed physician co-investigator and approval of the department chair/chief.

PIs may delegate responsibilities to appropriately qualified co-investigators and research staff. However, co-investigators and research staff must be qualified by training and experience to perform these responsibilities. Additionally, co-investigators and research staff must be in compliance with the Harvard Faculty of Medicine Conflicts of Interest Policy and/or Partners Conflicts of Interest Policy, as applicable. The PI remains responsible for the conduct of all persons to whom s/he delegates tasks.

All investigators and research staff must complete the Collaborative IRB Training Initiative (CITI) program or an equivalent program accepted by Partners in order to participate in the conduct of human research and must sign a Statement of Commitment to Human Subject Protection. Continuing education requirements must be completed every two years.

8.8 Research Participants

Massachusetts has a patient rights law, which provides that a person has the right to refuse to serve as a research subject and to refuse care or examination when the primary purpose is educational or informational rather than therapeutic [M.G.L. ch.111 70E(i)]. This law is generally consistent with federal requirements for informed consent or assent to research. Information about Patient Rights and Responsibilities is available through the BWH and MGH Admitting and Registration Services Department and on the individual Hospital websites.

Information about being a participant in a research study and the rights of every individual asked to participate in a research study, along with contact information for PHRC staff, is available on the Partners Human Research Committee website.

The Partners Research Consent Form template provides the PHRC telephone number for individuals to call if they wish to speak to someone other than the investigator about their rights as a research subject, their concerns about the research, or a complaint about the research. Participants are encouraged to call if they feel they are being pressured to enroll in the research or, once enrolled, to continue with the research.

8.9 Partners Office of General Counsel

The Partners Office of the General Counsel (OGC) has overall responsibility for all legal work arising from the activities of Partners and its affiliated hospitals and entities.

Within the OGC, a Research and Technology Section focuses on research and related work. Five lawyers in this Section counsel the Partners system

on human research issues, policies, and legal requirements; research compliance matters; research integrity and related misconduct investigations; conflicts of interest; intellectual property; technology transfer and licensing; clinical trial agreements; HIPAA-related concerns and general research affairs. Their work relating to human subject protection includes, for example, drafting and reviewing institutional review board IRB and other institutional policies, reviewing consent form language and other templates, advising on protocol-specific issues (*e.g.*, informed consent, confidentiality), counseling on privacy requirements, assisting in investigations of alleged noncompliance, advising on liability issues, and generally interpreting new and existing legal requirements.

The OGC has a close working relationship with Partners Human Research Affairs and the IRBs. Frequent conversations, meetings, and e-mail exchanges take place on a wide range of research issues. In addition, the OGC closely advises several other research clients, including Corporate Sponsored Clinical Research, Corporate Sponsored Research and Licensing, and research leadership across the Partners system.

8.10 Partners Research Compliance Program

The Partners Research Compliance Program developed in 2006 supports the system-wide commitment to ensuring quality and integrity in research. The specifics of this Program are currently being formalized. The goals of this Program include: serving as a resource to entity as well as corporate level compliance activities; providing education and training in specific areas and facilitating communication. At this time, the focus of the Program is in research finance compliance.

8.11 Professional and Institutional Conduct Committee (PICC)

The Partners Professional and Institutional Conduct Committee (PICC) is charged with the oversight of institutional policies relating to scientific and professional conduct and institutional research activities and with the development and implementation of consistent standards across Partners-affiliated institutions.

The specific PICC functions are:

- To develop and implement policies relating to research and other conflicts of interest, consulting relationships involving Partners-affiliated individuals, and scientific integrity, including the review and resolution of specific cases.
- To develop and implement policies relating to institutional conduct of research and related matters, including relations with industrial sponsors of research and the dissemination of results of research.
- To develop and implement policies relating to the institutional ownership of equity received in connection with research activities.

- To act as a forum for discussion to achieve consistency in the resolution of other professional conduct matters reviewed by Partners-affiliated institutions.
- To provide periodic reports to Partners-affiliated institutions on its activities.

9.0 RESEARCH COMMITTEES

Partners, BWH and MGH have several research committees that provide guidance to the institutions on research issues and serve as a forum for investigator feedback and input into institutional research-related policies and procedures.

9.1 Partners Research Council (PRC)

PRC brings together physician and scientific leaders from across the Partners HealthCare System to consider research policies and initiatives with system-wide implications. The group also serves as a forum for consideration of topics stemming from NIH activities and relations with industry. The Partners Research Council meets monthly and is chaired by the Partners Chief Academic Officer.

9.2 Brigham Research Institute (BRI)

BRI includes all members of the BWH research enterprise. The mission of the BRI is to facilitate inter-departmental and inter-disciplinary research, as well as to provide a clear internal and external voice of the entire BWH research community. The BRI has the following eight thematic centers:

- Cancer
- Cardiovascular
- Diabetes and Metabolism
- Musculoskeletal
- Neuroscience
- Stem Cell
- Regenerative Medicine and Tissue Engineering
- Women's Health

The Centers are supported by three Resource and Technology Research Programs, which provide general tools for research support in the areas of clinical investigation, imaging, and animal models. Each center and program has two or three co-chairs and a working group of 10-20 individuals. The working groups are generally teams of investigators working in common research areas. The working groups address the needs of their specific research communities.

The BRI leadership includes the Executive Committee (EC) and the Research Oversight Committee (ROC). The EC (three rotating center directors and the BWH Senior Vice President of Research) is responsible for directing the BRI and for representing the BWH research community inside and outside the institution.

9.3 MGH Executive Committee on Research (ECOR)

ECOR is the central planning and policy-making body of the MGH research enterprise. This committee meets every two weeks and reports to the MGH General Executive Committee (GEC). ECOR membership includes elected as well as appointed faculty members and senior management. ECOR's chair and vice-chair are faculty members. Non-voting members include: the Partners Directors of Human Research Affairs, Research Finance, and Grants and Contracts. The specific tasks of ECOR include:

- Developing a research plan congruent with the clinical mission of the MGH and the Partners-wide science enterprise;
- Evaluating and monitoring the quality of the science;
- Optimizing communication between administration and investigators;
- Representing the needs of the MGH scientists to the GEC;
- Formulating research policies within the framework established by the Trustees and the President; and
- Developing recommendations for the GEC and the President on resource allocation issues.

The Research Council, a subcommittee of ECOR, meets once a month as a "grassroots" town meeting of the investigator community. The meeting is chaired by the ECOR vice-chair and is attended by community-elected representatives, departmental representatives, and any investigators who wish to attend. The goal of these meetings is to provide communication between ECOR and the investigator community.

10.0 RELATIONSHIP OF THE PARTNERS HRPP TO OTHER INSTITUTIONS

10.1 Dana Farber Cancer Center

Partners routinely relies on the Dana Farber Cancer Center IRB for review of all pediatric and adult oncology and non-malignant hematology research conducted under the auspices of the Dana Farber/Partners Cancer Care joint venture. This reliance is reflected in the BWH and MGH FWAs and in an agreement executed by the parties.

10.2 Harvard School of Public Health

Partners relies upon the Harvard School of Public Health IRB for review of the occasional research proposal that involves prisoners. This reliance is reflected in an agreement executed by the parties.

10.3 Spaulding Rehabilitation Hospital

Partners occasionally relies upon the Spaulding Rehabilitation Hospital IRB for review of collaborative research. These are considered on a case-by-case basis. This reliance is reflected in an agreement executed by the parties.

10.4 McLean Hospital

Partners occasionally relies upon the McLean Hospital IRB for review of collaborative research. These are considered on a case-by-case basis. This reliance is reflected in an agreement executed by the parties.

10.5 Other Institutions

Partners will rely upon the IRB of another institution for review of collaborative research on a case-by-case basis. When this occurs, a single project reliance agreement is executed by the parties.