

Guidance: Provision of Clinical and Medical Services During Clinical Research

Guidance Statement

Clinical care, the treatment of patients, is outside the mission of the University when it is pursued for its own sake, with two established exceptions: the provision of clinical care at Harvard School of Dental Medicine, and Harvard University Health Services. However, Harvard supports its faculty members in pursuing clinical research, recognizing that some clinical research projects may have a clinical care component. Harvard faculty members may submit grant applications to support such projects, but additional steps are required for the University to assure itself that risks to human subjects are minimized, that the University has sufficient and appropriate resources to support these activities and that the research project will comply with the complex sets of regulations relating to clinical activities.

Reason for Guidance

This guidance is intended to provide Harvard faculty who conduct clinical research and those who administer and oversee research projects uniform criteria for the conduct of research with a clinical care component.

Clinical research is reviewed and approved by **Institutional Review Boards** (IRBs) whose responsibility is to protect research subjects. When a **clinical research** project involves **clinical care**, it is also subject to [Provost's Review](#), to consider the range of risks that may be associated with the project beyond the human subject risks identified by an IRB. The scope of Provost's Review varies according to the risk profile of the particular project, as described in the Procedures below. For example, research with more intensive clinical interventions, higher risk of adverse events, or invasive procedures may undergo an intensive review to ensure that regulatory, contractual, and administrative requirements are satisfied.

Unlike Harvard, universities that operate their own teaching hospitals are well positioned to manage the interplay between clinical research and clinical care because the treatment of patients is inherently within their mission, and they have the practical means to administer the entire range of clinical research: their teaching hospitals have policies, procedures and administrative offices to ensure compliance with applicable FDA regulations, state and local licensure requirements, and other obligations associated with patient treatment. Harvard does not operate its own teaching hospital, does not include clinical care within its mission, and does not maintain the same capacities as part of its regular operations, so it must pay particular attention to be sure it is providing proper support and oversight for the clinical research its faculty members perform.

Of course, Harvard’s faculty members have unparalleled opportunities for clinical research. Harvard Medical School has longstanding ties to its seventeen clinical and research affiliates. Harvard Catalyst draws together all Harvard’s Schools, the HMS affiliate hospitals and research centers, and a growing number of other universities and research institutions, including MIT, “enabling collaboration and providing tools, training, and technologies to clinical and translational investigators.” Newer Harvard---associated entities, such as the Broad Institute, Harvard Stem Cell Institute, the Ragon Institute, and the Wyss Institute provide additional clinical research opportunities and support.

Clinical research may include **clinical trials**, a broad term used to identify a variety of studies involving patient care and treatment (e.g. surgical, medical or psychological interventions,). Because clinical trials are intended to answer questions about biomedical or behavioral interventions, clinical trial projects often have a clinical care component that triggers [Provost’s Review](#). If a substantial portion of the budget of a proposed research project is allocated for clinical care---related costs, the Provost’s Review will consider whether the University possesses appropriate facilities and support infrastructure for the project. The outcome of such a review may be a determination that the grant proposal instead should be submitted through an affiliated hospital.

Procedures

This guidance describes how existing Harvard policies apply to proposals for clinical research projects that include clinical care components to ensure that Harvard either has the means to carry out the work and oversee and manage the project, or is able to make arrangements with outside entities to do so. One aspect of these reviews is assessing whether the environment in which a research activity will take place is appropriate in terms of minimizing risk. Links to research---related policies and general guidance for researchers are included in Related Resources.

Clinical Research With No Clinical Care Component

Ordinarily, if clinical research does not involve clinical care, then there are no special policies or procedures to be followed apart from Institutional Review Board (IRB) review.

However, in some cases, clinical research projects without a clinical care component may meet [Provost’s Review](#) criteria, such as certain international human subjects research (Criterion 4); projects where more than half of Harvard’s primary award is allocated to sub awards (Criterion 6); or proposals for “a scope, scale, or type of work that is beyond the University's teaching and research mission or is especially unusual or complex” (Criterion 10).

Provost's Review of Clinical Research Projects Having a Clinical Care Component

If a clinical research project “*involves, or is allied with, the direct provision of medical or clinical services*” then it is subject to Provost’s Review (Criterion 5). In this Guidance, “medical or clinical services” is also referred to as “clinical care.” Researchers employed by Harvard must not, *under the aegis of Harvard University itself*, engage in direct clinical care (outside the Dental School), including the operation of a clinical laboratory or pharmacy. Other than in the Dental School, in no event should Harvard researchers take on the responsibilities of a Covered Entity under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) vis a vis research subjects.

The intensity of the Provost’s Review of studies that have a clinical care component will depend in part on whether the IRB has determined that a project is “minimal risk” or “greater than minimal risk.”

- Minimal risk research with a clinical care component: When a research project “involves, or is allied with, the provision of medical or clinical services” but has been found by an IRB to be “minimal risk,” the Provost’s Review typically would specify only that the researcher meet the following requirements (though other requirements could be specified in particular cases):
 - Researcher must possess requisite training and malpractice insurance as appropriate;
 - Harvard University must have the proper facilities for the activity; and
 - The research team must have the necessary licenses or credentials to conduct the clinical activity.
- Greater than minimal risk research with a clinical care component: When a research project “involves, or is allied with, the provision of medical or clinical services” and has been found by an IRB to be “greater than minimal risk,” the Provost’s Review will be more robust and, in addition to the basic criteria for minimal risk research, these criteria must be satisfied (though other criteria could be specified in particular cases):
 - i) In order for the clinical research to be sited at Harvard, the Harvard University investigator must be particularly well suited for some significant aspect of the clinical research activity. The review may include asking questions about the investigator’s clinical experience, specialty training, board certifications and the like.
 - ii) All clinical research and clinical care must be conducted in accordance with applicable regulatory requirements; and
 - iii) Researchers must be appropriately covered by malpractice insurance, and the sponsor must have provided adequate indemnification and insurance coverage. In the event the sponsor does not provide adequate indemnification and insurance, the study must obtain additional insurance coverage.

Greater than minimal risk clinical research projects with a clinical care component require a Dean's approval as well as Provost's Review and approval, to ensure that these basic criteria (and any other requirements that may be imposed) are satisfied, and to specify additional oversight and management measures, including but not limited to those set forth in Appendix A. Deans may define categories of clinical research projects and specify conditions for their conduct, instead of making case-by-case decisions.

A description of categories of clinical research that an IRB typically finds to be greater than minimal risk is set forth in Appendix B. A researcher may seek preliminary guidance about risk level from the cognizant IRB office before completing and submitting a research proposal, in order to proceed with Dean's and Provost's Review at the earliest appropriate time, although nothing in this guidance is intended to limit an IRB's discretion in determining risk level when it formally reviews a project.

Infrastructure Concerns:

- i) Where Harvard lacks the appropriate infrastructure, clinical care activities that underlie and are required by clinical study protocols must be subcontracted to another institution or entity that has capacity and local licensure to provide such care. See Appendices C and D.
- ii) Clinical research studies must comply with all applicable record keeping laws.
- iii) The research budget must be adequate to cover the costs associated with the research, unless the School has approved cost sharing for the project. The cost share component may not include indemnification costs not covered by the sponsor or the additional insurance policy.

During Dean's review and Provost's review of clinical research projects, other offices may be consulted or involved; examples include Sponsored Programs reviewing affiliate agreements and new subrecipient entities; Office of Technology Development reviewing industry agreements; Global Support Services assisting with international staffing; Risk Management and Audit Services advising on liability insurance and other matters, and the Office of the General Counsel reviewing legal, policy and contracting issues.

Contacts

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Definitions

Clinical care: health care services for the purpose of evaluating, diagnosing or treating an illness, injury or disease

Clinical research (*National Institutes of Health*):

Research with human subjects that is:

1. Patient---oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes:
 - mechanisms of human disease
 - therapeutic interventions
 - clinical trials
 - development of new technologies
2. Epidemiological and behavioral studies.
3. Outcomes research and health services research.

Studies falling under 45 CFR part 46.101(b) (4) (Exemption 4) are not considered clinical research by this definition.

Clinical Trial (*National Institutes of Health*): A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Human Subject: 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.

Institutional Review Board (IRB): Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. *Note: Internationally, some countries use the term Ethics Review Committee or Ethics Committee for an IRB.*

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.

Investigational Device---ID (FDA): Investigational device is a device, including a transitional device that is the object of an investigation.

Investigational Device Exemption---IDE (FDA): IDE refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 are met.

Investigational New Drug---IND (FDA): Investigational New Drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of FDA regulations.

FDA: United States Food and Drug Administration

Minimal Risk: Means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Related Resources

[OSP Policies and Guidance](#)

[Provost's Review Criteria](#)

[Longwood IRB Office](#) (HMS, HCSPH, HSDM)

[University Area IRB Office, CUHS](#)

[Harvard Catalyst](#)

[Vice Provost for Research: Policies, Guidance](#)

Revision History

Appendices

Appendix A

Oversight and Management Measures for Greater than Minimal Risk Clinical Research Having a Clinical Care Component

For clinical research with a clinical care component that is greater than minimal risk, there must be a School Dean's approval as well as Provost's Review (Criterion 5).

The following measures inform planning of studies and their budgets, assist sponsored research staff in reviewing proposals before submission to funding agencies, and provide School Deans and the Provost's office a set of specific criteria for reviewing these proposals.

These measures are intended to approximate the infrastructure supporting clinical research programs that is in place at other institutions that undertake clinical care. The measures are to be invoked or deployed as appropriate, on a case by case basis, based on an assessment of the degree of risk. Studies involving less intense clinical interventions may not be required to carry out as many of these measures, and may be more likely to be approved.

- a) ***Selection of Qualified Subcontractors or Vendors:*** Selection of qualified subcontractors or vendors to undertake clinical research or clinical trials that is greater than minimal risk to subjects is vital to assure subject safety and minimize risk. Selection of a subcontractor or vendor must be careful and deliberate and must be justified in writing, with information as to other potential subcontractors that were considered and rejected.
 - i) Harvard---affiliated hospitals are considered to be qualified subcontractors or vendors.
 - ii) Clinical subcontractors or vendors that are not affiliated with Harvard must be assessed before a subcontract or agreement is signed and before the study commences, to ensure that there is clinical competency, adequate clinical staff, adequate training in the study protocol, appropriate provision for the detection and reporting of adverse events/unanticipated risks that might arise in the course of the study, and financial and administrative capacity. Each subcontract or vendor agreement for clinical services should include the template provisions (see Attachment 1A and 1B) to ensure that major risks are foreseen and addressed.
 - iii) Assessment of potential clinical subcontractors or vendors must be performed impartially. *Harvard may appoint a standing committee of respected and un---conflicted clinical researchers who could perform these site reviews for the University and its IRBs.*

- iv) Continuing reviews of previously---approved subcontractors or vendors should be undertaken with a defined periodicity or on a for---cause basis.
- b) **Study Budgets:** As a general matter, budgets for clinical research or trials that are greater than minimal risk must include adequate provision for clinical care costs that are required by the protocol and that are not being paid from other sources. This is necessary to assure that a study is not approved and launched with inadequate funding for clinical care. In addition, federal regulations require that study subjects must be given an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Thus, budgets for such studies must include provision for payment for clinical care provided to subjects injured as a direct result of their participation; this may take the form of an explicit commitment by a school or department to pay such costs from its own funds even if no specific funding for the cost of care for subject injuries is made in a study budget.
- c) **Indemnification:** A clinical research or clinical trials study sponsored by a company or industry---affiliated foundation may not begin unless and until there is written assurance in the sponsored research agreement that the sponsor will pay the costs of any claims brought against Harvard and/or its researchers as a result of the clinical research or clinical trial and will defend any lawsuits brought against Harvard and/or its researchers. This indemnification can be either: in the clinical research or clinical trials agreement signed by Harvard; in a separate statement addressed to Harvard on company letterhead and signed by an authorized official of the company; or in the form of additional liability insurance paid for by the sponsor, obtained commercially or through Harvard University Risk Management & Audit Services (RMAS).
- d) **Regulatory Requirements:** Clinical research must be conducted in compliance with all applicable regulatory requirements. These may include requirements for researchers to obtain IRB or Ethics Committee approval; follow an approved consent process; comply with any reporting and registration requirements (e.g. ClinicalTrials.gov); make all required financial conflict of interest disclosures and resolve any identified conflicts; and comply with requirements governing the protection of personally identifiable information.
- e) **Studies in which Intervention/Treatment is indicated (incidental findings):** Studies in which Harvard researchers or subcontractors may detect clinical findings for which some intervention or treatment is indicated but not provided as part of the research protocol must have a process for informing subjects of such conditions and referring them to appropriate local clinical care providers. The study protocol and informed consent process must address specifically the possibility that a clinical condition might be identified for which care is needed but is not provided by the study. Studies to which this standard applies may include, for example, studies of diagnostic technologies, genetic studies, sero---surveys, other health surveys, and brain imaging studies.
- f) **Reporting Requirements:** All serious adverse events reports, reports of unanticipated risks to subjects or others, and reports of regulatory deviations in clinical research must be promptly reported by the investigators to the IRB(s) of applicable jurisdiction,

including to a Harvard IRB. *The Harvard IRB must notify the Vice Provost for Research and the Chief Research Compliance Officer as soon as it receives such a report.*

- g) **Clinical Research Monitoring:** All greater than minimal risk clinical research or clinical trials conducted under the aegis of Harvard University must have a monitoring plan in place before they are undertaken. If the sponsor of the project does not have a Clinical Research Organization (CRO) to perform monitoring, Harvard will issue a RFP for these services. Each study that involves a clinical intervention that exceeds minimal risk will therefore include, and each study budget must accommodate expenses for, such an external monitor.

Appendix B

Clinical Research or Clinical Trials with Greater than Minimal Risks

When an IRB determines that the risks of harm anticipated in the proposed research are greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests, the IRB will classify the research protocol as posing “greater than minimal risk”. Broadly, the range of such studies include:

- i) Research with intensive clinical interventions or that poses higher risk for adverse clinical events.
- ii) Clinical drug studies if:
 - (1) an investigational new drug application¹ is required; or
 - (2) the research significantly increases the risks or decreases the acceptability of the risks associated with the use of a marketed drug (e.g. off label use).
- iii) Research on medical devices if:
 - (1) an investigational device exemption application² is required; or
 - (2) the medical device is not cleared/approved for marketing, and the device is being used for purposes other than its cleared/approved labeling.
 - (3) *Note: Studies intended to evaluate the safety and effectiveness of a medical device, including studies of cleared medical devices for new indications are considered “greater than minimal risk.”*
- iv) Prospective collection of biological specimens for research purposes by invasive means.
- v) Collection of data through invasive procedures (e.g. involving general anesthesia or sedation).
- vi) Procedures involving X-rays or microwaves.

¹ As defined by 21 CFR Part 312.

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312> ²

As defined by 21 CFR Part 812

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812>

Appendix C

Checklist for Selection of Vendors for Clinical Research or Clinical Trials That Involve the Provision of Clinical or Medical Services (U.S. Based Entities)

The following guidelines are provided to assist with the selection of qualified subcontractors or vendors to undertake clinical research or clinical trials for which Harvard does not have the appropriate infrastructure to conduct the clinical care component in Harvard facilities. This is not intended to be a comprehensive and all-inclusive list; rather it is intended to identify critical issues that need scrutiny. The pre-qualification may require a site visit to assess the site's qualifications for the study such as the ability of the Principal Investigator and his/her staff, and its document management system and other systems. *If a site visit is required the Vice Provost for Research, or designee, must be a member of the site visit team.*

At a minimum, evaluators should ascertain the following information:

- 1) Does the entity have the necessary licenses (Federal, State and local, as appropriate), registrations, and accreditations (e.g. from The Joint Commission) for the proposed work?
- 2) Does the entity have the necessary facilities (e.g. laboratories, imaging facility, etc.) and equipment necessary to conduct the study?
- 3) Does the entity have a history of conducting such studies?
- 4) Does the entity have the appropriate infrastructure (e.g. clinical trials office, regulatory office) for oversight of such studies?
- 5) Does the entity have a good history of regulatory compliance for the conduct of such studies?
- 6) Is the entity financially capable of conducting the study?
- 7) Does the entity have a registered Institutional Review Board (IRB) and a Federalwide Assurance (FWA)?
- 8) Is the entity's IRB accredited (e.g. by The Association for the Accreditation of Human Research Protection Programs, Inc. AAHRPP)?
- 9) Does the entity have a clinical research or clinical trials monitoring program?
- 10) Are the individuals who will be conducting the study qualified to do so?
- 11) Does the Principal Investigator have previous experience in clinical research or clinical trials being subcontracted?
- 12) Do the individuals who will be conducting the study have adequate time to dedicate to the conduct of the study?**

Appendix D

Checklist for Selection of Vendors for Clinical Research or Clinical Trials That Involve the Provision of Clinical or Medical Services (International Entities)

Harvard University researchers routinely partner with international collaborators in conduct of clinical research or clinical trials. The selection of an international site where such studies will be conducted may present additional challenges due to differences in the regulatory requirements and cultural norms; as a result, it is not possible to compile a comprehensive listing to cover specific requirements for all countries. The key issues listed below should be considered, and may have to be augmented by country specific requirements. *Selection of an appropriate international site may require a site visit to assess the site's suitability for the study, which may include evaluation of the ability of the Principal Investigator and his/her staff, and the site's document management system and other systems. If a site visit is required, the Vice Provost for Research, or designee, must be a member of the site visit team.*

1. General Requirements

- a. Human research conducted outside the United States must conform both to the United States' ethical and regulatory standards, and to applicable local laws and norms of the host country.
- b. Harvard University researchers must ensure that studies also are conducted in accordance with Harvard University policies for the conduct and review of human research.
- c. All research involving human subjects conducted outside the United States by Harvard University researchers, must receive approval from the Harvard University IRB (i.e. IRB or CUHS) with jurisdiction over the study, and, where available, from the IRB or the Ethics Committee (EC) used by the international site.
- d. The proposed study must have undergone a Provostial Review and received approval.

2. Site Specific Requirements

At a minimum, evaluators should ascertain the following information:

- a) Does the entity have the necessary licenses, registrations, and accreditations for the proposed work, as required by the country or other local authority?
- b) Does the entity have the necessary facilities (e.g. laboratories, imaging facility, etc.) and

equipment to conduct the study?

- c) Does the entity have a history of conducting such studies with international partners?
- d) Does the entity have a good history of regulatory compliance for the conduct of such studies?
- e) Does the entity have required policies and procedures in place?
- f) Is the entity financially capable of conducting the study?
- g) Are there plans for financial transactions between Harvard University and the international entity?
- h) Does the entity have a registered Institutional Review Board (IRB), or Ethics Committee, and a U.S. Federalwide Assurance (FWA)?
- i) Is the entity's IRB accredited (e.g. by The Association for the Accreditation of Human Research Protection Programs, Inc. AAHRPP)?
- j) Is there a plan for communication between the local IRB, or Ethics Committee, and Harvard University IRB regarding any findings, adverse events, concerns, continuing reviews, etc.?
- k) Does the entity have a clinical research or clinical trials monitoring program?
- l) Are the individuals who will be conducting the study qualified (e.g. do they have local licensure and certification, as applicable)?
- m) Does the Principal Investigator have previous experience in clinical research or clinical trials with international collaborators?
- n) Are the individuals familiar with the recommendations of the International Conference on Harmonization?
- o) Do the individuals who will be conducting the study have adequate time to dedicate to the conduct of the study?
- p) Have the entity and individuals conducting the research in the country been screened against Office of Foreign Assets Control (OFAC) lists, to ensure that they are not on any sanctioned or boycotted lists?
- q) Have the entity and individuals conducting the research in the country certified as to their compliance with the Foreign Corrupt Practices Act?

3. Other Requirements

- a) Will Harvard University researchers conduct any work at the international site? If yes have any licensure or certification requirements been addressed?
- b) Are Harvard University researchers participating in the project familiar with any country specific regulatory requirements for the research being proposed (e.g., export of biospecimens; import of test drugs or devices)? Where regulatory requirements exist, what is the plan for satisfying these requirements?
- c) If the project involves the importation of biospecimens, what is the plan for complying with transportation requirements and for safely handling specimens that may pose a risk of infection?
- d) The Principal Investigator is responsible for providing to the Harvard IRB any reports of correspondence with the foreign institution or site and appropriate documentation of

data and safety measures throughout the course of the study, including serious and unexpected adverse events and unanticipated problems to participants or others (e.g., a breach of participant confidentiality resulting in local ramifications).

- e) Have potential language barriers (e.g. communications between investigators, subjects, IRB, etc.) and accurate translation of study documents (e.g. informed consents) been addressed?