

12. Clinical Research

Although the majority of studies reviewed by the CHS are social-behavioral in nature, some clinical research involving FDA approved drugs and devices, as well as clinical research involving the use of investigational new drugs or devices are undertaken at Harvard Medical School or Harvard School of Dental Medicine facilities or elsewhere where review by the CHS is necessary.

Clinical Research. NIH defines human clinical research as: (1) Patient-oriented research, that is 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. Patient-oriented research includes: (a) study of mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. (2) Epidemiologic and behavioral studies. (3) Outcomes research and health services research.

Clinical Trial. The NIH defines a *clinical trial* as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial. Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects. Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

- **Phase I** clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
- **Phase II** clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- **Phase III** studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- **Phase IV** studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

In such cases where FDA regulated investigational drugs and devices are being studied:

1. If the research is to be conducted anywhere other than the Veteran's Affairs-Boston Healthcare System (VA-Boston), then the CHS will rely on the review of the Partners Healthcare IRB (Partners IRB), or the IRB of the medical facility where the research will take place.
2. If research is to be conducted at the VA-Boston, then the CHS will not review the research unless and until it has been approved by the VA-Boston IRB. Once the VA-Boston IRB has approved the research, the CHS will review the research for compliance with DHHS regulations and will rely on the VA-Boston IRB for compliance with FDA requirements.

For studies involving approved drugs/biologics and devices the following additional state and federal regulations, and CHS policies and procedures apply:

12.1. Studies Involving Drugs in Research

12.1.1. Massachusetts Requirements

Studies Involving Schedule II Narcotics. The Massachusetts Controlled Substances Act (M.G.L. c. 94C) and the regulations of the Massachusetts Department of Public Health (DPH) implementing that Act (105 CMR 700.001 et seq), contain provisions relating to “research projects and studies” involving controlled substances. Those provisions (M.G.L. c. 94C, § 8, and 105 CMR 700.009) impose certain requirements on individual researchers planning to conduct any “research project or study involving any narcotic drug in Schedule II or the investigational use of any ‘new drug’ as defined in [21 USC § 321(p)]” (hereinafter “covered studies”). Specifically, researchers planning to conduct covered studies must register with the DPH and provide the agency with information relating to the study drug, including descriptions of how the drug will be used in the study and how it will be stored and secured. The researcher is also required to provide DPH with copies of the IRB approval letter for the study, and in appropriate cases the FDA Form 1572 (for IND studies) and the researcher’s DEA Researcher Registration. [Note: any use of investigational new drugs in research must follow the policy as outlined in Section 12 (above) regarding the review of such research.]

The Investigator may also be required to submit, upon the specific request of the DPH, a copy of the study protocol and such further related information that DPH may reasonably require. Requests for additional information by the DPH should be reviewed and approved by the CHS Chair and Administrator, and ORSP Director. The Director should be copied on all correspondence to the Commissioner of DPH, and the correspondence will remain in the study file.

The statute and the DPH implementing regulations also impose the following substantive requirements in addition to what is required by 45 CFR§ 46 and the FDA regulations:

- A parent or guardian may not, under any circumstance, “override a minor’s refusal of consent.”
- The IRB must document how it will monitor the Investigator on the project and how it will notify the Commissioner about proposed protocol changes or “emergent problems” (e.g. unexpected side effects of the drug) that arise in the course of the research.

- At least one-third of IRB members approving the study “must be independent of the research institution and must not be health care professionals.”

The statute also authorizes the Commissioner of Public Health to order that a study within Massachusetts be “terminated” when, after giving Investigators notice and an opportunity to be heard, he or she concludes that: (1) the drug is unsafe under the conditions of use, (2) the Investigators lack the knowledge and experience to conduct or complete the study, or (3) the Investigators made a material misstatement in the materials they furnished to the DPH. A further provision authorizes the Commissioner to “discontinue” a study if s/he finds (1) that the Investigators are not maintaining an adequate reporting system or (2) the study methodology does not adequately insure against “diversion” of the subject drug. Any suspension or termination of the study by the MA DPH must be reported to the CHS Office, reviewed by the convened CHS, and be reported to the FDA and OHRP as outlined in Section 15 of this policy document.

In order to comply with the federal and state regulations pertaining to the use of controlled substances, the University has developed the *Harvard University Researchers’ Guide for Use of Controlled Substances* (appendix 49a).

12.1.2. Use of FDA-Approved Drugs in Research

When the research activities involve the administration of an FDA-approved drug or biologic, dietary supplement or food additive (hereafter, “Drug”), Investigators are required to complete CHS Form C (Appendix 49b) to provide the CHS with information about the Drug, how it will be used in the research, and to confirm the FDA approval status of the Drug.

If the Drug requires an IND the research must be reviewed as indicated in Section 12 above, and stated again below:

1. If the research is to be conducted anywhere other than the Veteran’s Affairs-Boston Healthcare System (VA-Boston), then the CHS will rely on the review of the Partners Healthcare IRB, or the IRB of the medical facility where the research will take place.
2. If research is to be conducted at the VA-Boston, then the CHS will not review the research unless and until it has been approved by the VA-Boston IRB. Once the VA-Boston IRB has approved the research, the CHS will review the research for compliance with DHHS regulations and will rely on the VA-Boston IRB for compliance with FDA requirements.

The CHS may review and approve research involving approved drugs, as long as the Drug meets the following criteria, which confirm that an IND is not required:

- (i) the drug is lawfully marketed in the United States;
- (ii) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling;
- (iii) it is not intended to support a significant change in the advertising;

- (iv) it does not involve a route of administration or dosage level, use in a participant population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with its use;
- (v) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR §§ 56 and 50, respectively];
- (vi) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR § 312.7]; and
- (vii) it does not intend to invoke 21 CFR § 50.24 (Exception from informed consent requirements for emergency research).

In addition to providing information about the Drug and its use, the CHS must determine whether the Investigator has the appropriate expertise and knowledge to conduct the research. The CHS may require one or more of the following:

- A meeting with the CHS Administrator and/or ORSP Director to assess the knowledge of the Investigator in terms of the requirements to conduct the research, document informed consent, has the appropriate facilities for the research (including Drug storage), and record keeping, prior to CHS approval;
- A department mentor or advisor to help oversee the research activities and requirements;
- Regular monitoring (which could involve verification of study records and control of the Drug, as well as monitoring of informed consent) by a member of the CHS, the CHS staff, or the QA Coordinator; and
- Regular progress reports submitted to the CHS.

For CHS reviews of studies involving Drugs, the composition of the Committee will include reviewers with experience in reviewing such research, and may also include consultants with appropriate expertise in the field of research under review. The confirmation that an IND is not required will be recorded in the minutes of the convened CHS meeting in which the study is reviewed.

12.2. Use of Devices in Research

When the research activities involve the use of a device, Investigators are required to complete CHS Form D (Appendix 50a) to provide the CHS with information about the device, how it will be used in the research, its FDA approval status, and whether the FDA considered it a Significant Risk (SR) or a Non-Significant Risk (NSR) device.

When a medical device is being evaluated for safety or effectiveness, the device is considered “investigational” and is subject to the requirements of the IDE regulations (21 CFR § 812). **If the device requires an IDE from the FDA (meaning it is not exempt from the IDE regulations and does not qualify for an abbreviated IDE), then the study involving its use will be reviewed as noted above in Section 12 above, and stated again below:**

1. If the research is to be conducted anywhere other than the Veteran’s Affairs-Boston Healthcare System (VA-Boston), then the CHS will rely on the review of the Partners Healthcare IRB, or the IRB of the medical facility where the research will take place.

2. If research is to be conducted at the VA-Boston, then the CHS will not review the research unless and until it has been approved by the VA-Boston IRB. Once the VA-Boston IRB has approved the research, the CHS will review the research for compliance with DHHS regulations and will rely on the VA-Boston IRB for compliance with FDA requirements.

If the device is deemed a non significant risk (NSR) device, which is considered to have an abbreviated IDE or is exempt from the requirements for an IDE, then the study involving its use will be reviewed by the CHS.

In addition to reviewing information about an FDA determined NSR device and its proposed use, prior to any study protocol approval, the CHS may require one or more of the following:

- A meeting with the IRB Administrator and/or ORSP Director to assess the knowledge of the Investigator in terms of the requirements to conduct the research, document informed consent, has the appropriate facilities for the research (including Drug storage), and record keeping, prior to CHS approval;
- A department mentor or advisor to help oversee the research activities and requirements;
- Regular monitoring (which could involve verification of study records and control of the device, as well as monitoring of informed consent) by a member of the CHS, the CHS staff, or the QA Coordinator; and
- Regular progress reports submitted to the CHS.

The determination that a device is a non-significant risk and does not require an IDE will be recorded in the minutes of the convened CHS meeting in which it is reviewed.

12.2.1. Significant/Non-Significant Device Determinations by the CHS

- a) A study involving an NSR device may be submitted directly to the CHS with documentation from the FDA supporting the NSR status. The study is then reviewed by the CHS with the FDA NSR status noted, and the study evaluated as per CHS review processes for participant safety.
- b) If a study involving a device comes before the CHS and there is no risk status documentation from the FDA about the device, then the CHS will evaluate the risk status of the device based on the regulations noted below in (c). If the CHS determines that the study device is in fact a significant risk device, it notifies the Investigator and, where appropriate, the sponsor (21 CFR § 812.66), ordinarily within 5 business days of the CHS meeting, that an IDE is required by the FDA and **therefore, the CHS cannot further review or approve the study, and the review must take place in accordance with the policy outlined in Section 12.**
- c) If the convened CHS makes an independent determination based on the criteria set forth below that the device is NSR, the investigation may proceed only when approved by the CHS. In order to find that the device is NSR, the CHS must find that it does not fall into any of the following categories:
 - i. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a participant (21 CFR § 812.3(m)(1)).

- ii. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a participant (21 CFR § 812.3(m)(2).
- iii. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a participant (21 CFR §812.3(m)(3).
- iv. Otherwise presents a potential for serious risk to the health, safety, or welfare of a participant (21 CFR § 812.3(m)(4).

If the device does fall into any of the above categories, then the CHS must determine that an investigation in fact involves a significant risk device. In such cases, it notifies the Investigator and, where appropriate, the sponsor (21 CFR § 812.66), ordinarily within 5 business days of the CHS meeting, that an IDE is required by the FDA and **therefore, the CHS cannot further review or approve the study, and the review must take place in accordance with the policy outlined in Section 12.**

If the device does not fall into any of the above categories, then CHS may make an NSR determination. If the risk to participants is determined to be minimal in accordance with 21 CFR § 56.102(i), then the CHS may vote to conduct continuing review through the expedited review procedure (21 CFR § 56.110).

12.2.2. Exemption from the Requirement for an IDE

Research that falls into one or more of the following categories is exempt from the requirement for an IND: [21 CFR 812.2(b)]

1. Exemption #1: A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
2. Exemption #2: A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR §807 in determining substantial equivalence. (I.e., “FDA-approved device”)
3. Exemption #3: *(All must be true)*
 - 3.1. A device is a diagnostic device.
 - 3.2. The sponsor complies with applicable requirements in 21 CFR §809.10(c).
 - 3.3. The testing is noninvasive.
 - 3.4. The testing does not require an invasive sampling procedure that presents significant risk.
 - 3.5. The testing does not by design or intention introduce energy into a subject.
 - 3.6. The testing is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

4. Exemption #4: A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
5. Exemption #5: A device intended solely for veterinary use.
6. Exemption #6: A device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR §812.5(c).
7. Exemption #7: A custom device as defined in 21 CFR §812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

12.2.3. Requirements for Investigators using Drugs or Devices in Research

Whether FDA regulated or not, Investigators using Drugs and Devices in research are responsible for:

- i. Ensuring that the study is conducted according to the safety indications of administering the drug/device in manner outlined in the drug/device brochure, the grant and the research protocol;
- ii. Protecting the rights, safety, and welfare of participants under the Investigator's care;
- iii. Obtaining informed consent from all participants, as outlined in section 10.3 of this policy document;
- iv. The control of the drugs/devices, including appropriate storage, quantity released to study participants, returning or destroying any unused drugs/devices at the end of the study, for drugs - maintaining and dispensing only non-expired drugs, destroying any expired drugs, and. If the drug is a controlled substance, the Investigator will comply with the *Harvard University Researchers' Guide for Use of Controlled Substances* (Appendix 49a);
- v. Administering the drugs/devices only to participants in the study only by authorized study personnel approved for such administration by the CHS;
- vi. Maintaining accurate records and case histories of all participants receiving the drug/device, including any benefits they have experienced as well as side effects or adverse reactions. The records should be kept for a minimum of 5 years, as recommended by the Faculty of Medicine Guidelines for Investigators in Clinical Research (Appendix 53);
- vii. Reporting any serious adverse events and unanticipated problems to the CHS as outlined in Section 13 of this policy document;
- viii. Assuring that timely and thorough continuing review applications are conducted as outlined in Section 5 of this policy document;
- ix. Assuring that any changes in the research are reviewed and approved by the CHS as outlined in Section 6 of this policy document.

12.2.4. Clinical Research Requirements for Sponsored Programs Administrators (including Grant and Contract Officers and CHS Administrators)

Written Agreements with Sponsors shall clearly address:

- i. The responsibility of Faculty of Medicine Investigators to abide by applicable institutional policies, CHS policies, ethical standards, and applicable federal and state laws
- ii. The responsibility of Faculty of Medicine Investigators to conduct the research in accordance with the CHS-approved protocol
- iii. The publishing rights of the Faculty of Medicine Investigator, within Faculty of Medicine guidelines.
- iv. What medical care, if any, will be provided to participants in the event of a study related injury and how a participant will receive or be reimbursed for such care.
- v. What compensation or payments, if any, will be provided to participants who incur a study related injury
- vi. The responsibility of the Sponsor to promptly report to the Investigator any findings that could:
 - a. Affect the safety of participants
 - b. Affect the willingness of participants to continue with the research
 - c. Influence the conduct of the study
 - d. Alter the CHS approval
- vii. Mechanisms to communicate to participants any study results which may affect their safety or medical care.

13. Adverse Events and Unanticipated Problems

In the course of a research project, various problems arise some of which may affect the research participants in varying degrees of severity. It is important that the CHS be aware of any problems that arise so that a determination can be made by the CHS whether such problems are anticipated or unanticipated and involve risks to participants or others with resultant corrective actions. Investigators must contact the CHS office via phone or email as soon as possible but not more than 48 hours after learning of a problem within their research program. All calls and emails are handled confidentially by CHS staff. The convened CHS will decide, as described below, which of the problems are anticipated or unanticipated involving risks to participants or others and subsequently determine whether any corrective actions need to be taken including, in extreme cases, suspension of the research with notification to participants.

Definitions and examples are provided below. However, the Investigator must report the following to the CHS as soon as possible, but in all cases not more than 48 hours:

- Any adverse event (any harm experienced by a participant regardless of whether the event was internal (on-site) or external (off-site) and regardless of whether the event meets the FDA definition of “serious adverse event”) which in the opinion of the Investigator are both **unexpected and related**.
 - **“Unexpected”** is defined as an event whose specificity and severity are not accurately reflected in the human studies application, protocol, consent form, current investigational brochure or medical device/medication package insert.