

Massachusetts Institute of Technology

**OPERATIONAL POLICIES AND PROCEDURES OF THE
COMMITTEE ON THE USE OF HUMANS AS
EXPERIMENTAL SUBJECTS**

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Introduction

The Committee on the Use of Humans as Experimental Subjects (COUHES) was established to act as the Institutional Review Board (IRB) for the Massachusetts Institute of Technology (MIT). MIT has an Assurance of Compliance with Federal Regulations for the Protection of Human Subjects (45 CFR 46) as amended, approved by the Office for Human Research Protection (OHRP), in the Department of Health and Human Services.

Research is defined as a systemic investigation designed to add to the body of general knowledge. *Human subject* is defined as a living individual about whom an investigator conducting research obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimen; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Ethical Principles

COUHES is governed by the *Ethical Principles and Guidelines for the Protection of Human Subjects*, generally known as the “Belmont Report”.

Scope of Authority

COUHES is responsible for the review of all research activities that involve human subjects, whether directly or indirectly, that will be conducted by investigators at or from MIT.

COUHES has the authority to:

- approve, require modifications to secure approval of, defer action on or disapprove research protocols involving human subjects;
- require progress reports from the investigators;
- oversee the conduct of research;
- suspend or terminate approval of a study;
- place restrictions on a study; and
- conduct reviews and inquiries regarding research activities as needed to obtain information necessary for the fulfillment of its responsibilities under the MIT Assurance.
- Monitor and audit all research conducted under the auspices of MIT

COUHES, as well as appropriate ancillary committees, must approve the research protocol and, when applicable, the consent form(s) to be used to obtain informed consent of subjects prior to the initiation of the research and enrollment of subjects. The decision of COUHES to disapprove a research protocol cannot be overruled by any other institutional body or individual(s). For exempt research as outlined in 45 CFR 46.104, investigators will be notified when they must complete and submit an exempt evaluation questionnaire to COUHES before the research can be initiated. Until such notice is given, they should continue to fill out an exempt research application to COUHES.

Membership

COUHES is composed of at least 5 members. Members are appointed by the President of MIT, upon nomination by the MIT community and/or by self-nomination. The membership includes:

- physicians;
- scientists;
- nurses;
- at least one member unaffiliated with MIT and who is not part of the immediate family of a person who is affiliated with the institution; and at least one member whose primary concerns are in nonscientific areas, such as lawyers, ethicists, and clergy.

Members include both men and women and members of minority groups. Designated alternates may be used. The membership list is updated when membership changes and is submitted to the Office for Human Research Protections (OHRP) as required by MIT's Assurance.

Management of Human Research Activities

COUHES is an autonomous committee of MIT. The administrative activities of COUHES are overseen by the Vice President for Research.

COUHES is supported by administrative staff consisting of a project manager, project coordinators, compliance specialists, and administrative assistants.

The Chairperson is appointed by the President of MIT. There are no term limits placed on length of service. The Chairperson is generally selected from among experienced members of COUHES or the MIT community, and is very familiar with regulatory requirements and ethical considerations. The Chairperson is required to attend at least one IRB-related workshop or meeting every year.

The Chairperson is responsible for:

- presiding at COUHES meetings during which initial and continuing review of all research protocols involving human subjects are conducted;
- conducting initial and continuing review of research protocols involving human subjects that may be approved using expedited review procedures;
- reviewing audit reports and approve corrective actions if applicable; and
- reviewing adverse events, amendments to protocols, and other activities as required to fulfill institutional responsibilities as set forth in the Assurances.

COUHES members are appointed by the President of MIT. Members are selected based on reputations for fairness, objectivity, and commitment to exercise faithfully their responsibilities for protection of human subjects in research according to the Belmont Report, and relevant federal regulations. There are no term limits placed on length of service.

New members are provided with IRB-related information, including, but not limited to, COUHES forms, COUHES Policies and Procedures Manual, and access to the COUHES web site, which links to applicable Federal regulations and the Belmont Report. New members are also required to take and pass the Collaborative Institutional Training Initiative (CITI Program) on IRB members and read the Institutional Review Board Member Handbook.

All members receive copies of various IRB-related publications, e.g., IRB, Human Research Report and IRB policy related communications from OHRP, FDA, or other governing agencies.

Members are responsible for initial and continuing review of all research protocols involving human subjects that require review at a convened meeting. Members are expected to attend at least two-thirds of the scheduled COUHES meetings. Attendance records are reviewed annually. Members who have not attended one-half of the scheduled meetings during the past year will be removed from the voting membership, unless the member has a designated alternate.

COUHES members are responsible for the review of research protocols scheduled for the meeting and for considering:

- the appropriateness of the study population;
- the risks and anticipated benefits to subjects, as well as the importance of the knowledge that may reasonably be expected to result from the protocol;
- the appropriateness of the methods of recruitment and the process for informed consent of subjects;
- the accuracy and completeness of information in the consent form as well as the language used and the presentation of the information;
- the adequacy of provisions for monitoring the data collected and ensuring the safety of subjects;
- the adequacy of provisions to protect the privacy of subjects and to maintain the confidentiality of data;

- the inclusion of additional safeguards in the study to protect the rights and welfare of subjects likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally or physically disabled persons, or economically or educationally disadvantaged persons

Although rarely needed because of the depth and breadth of the membership on COUHES, consultants may be used to supplement or provide expertise not available on the Committee. When used, consultants are asked to attend the meeting and/or provide a written summary of their findings relative to the scientific merits of the study and risks and benefits to subjects. Consultants are not voting members.

A member may not participate in COUHES initial or continuing review of any project, if he/ she is listed as an investigator/study staff on the protocol, or by virtue of otherwise having a conflict of interest. COUHES members should review the list of projects and disclose a conflict of interest as soon as possible to the COUHES Chair. At the outset of each meeting COUHES members are reminded of the conflict of interest policy. If a member has a conflict of interest the member must inform the Chair and leave the room during the discussion and vote of the project. COUHES minutes will reflect a recusal based on a conflict of interest. The COUHES member will not be counted as part of the quorum for the project.

Functions of COUHES

COUHES is responsible for the following:

- conducting initial and continuing review of all research protocols under their purview;
- reporting to the investigator (in writing) the findings and actions of COUHES;
- determining which studies require review more often than annually;
- determining which studies need verification from sources, other than the investigators, that no material changes have occurred since previous COUHES review;
- ensuring prompt reporting to COUHES of changes in research activities;
- ensuring that changes in approved research are not initiated without COUHES review and approval, except where necessary to eliminate apparent immediate hazards;
- ensuring prompt reporting to COUHES, appropriate MIT officials, OHRP and the FDA of (1) unanticipated problems involving risks to subjects or others, (2) serious or continuing noncompliance with regulations governing research involving human subjects or the requirements of COUHES; and (3) suspension or termination of COUHES approval; and
- determining which device studies pose significant vs. non-significant risk, according to guidance provided by the United States Food and Drug Administration (21 CFR 812).

Operations of COUHES

COUHES meets monthly, generally on the third Thursday of every month. The meeting dates and deadlines are posted on the COUHES website.

Initial and continuing review of research protocols is conducted either at a convened meeting of a quorum of the membership of COUHES, or using expedited review procedures as authorized in 45 CFR 46.

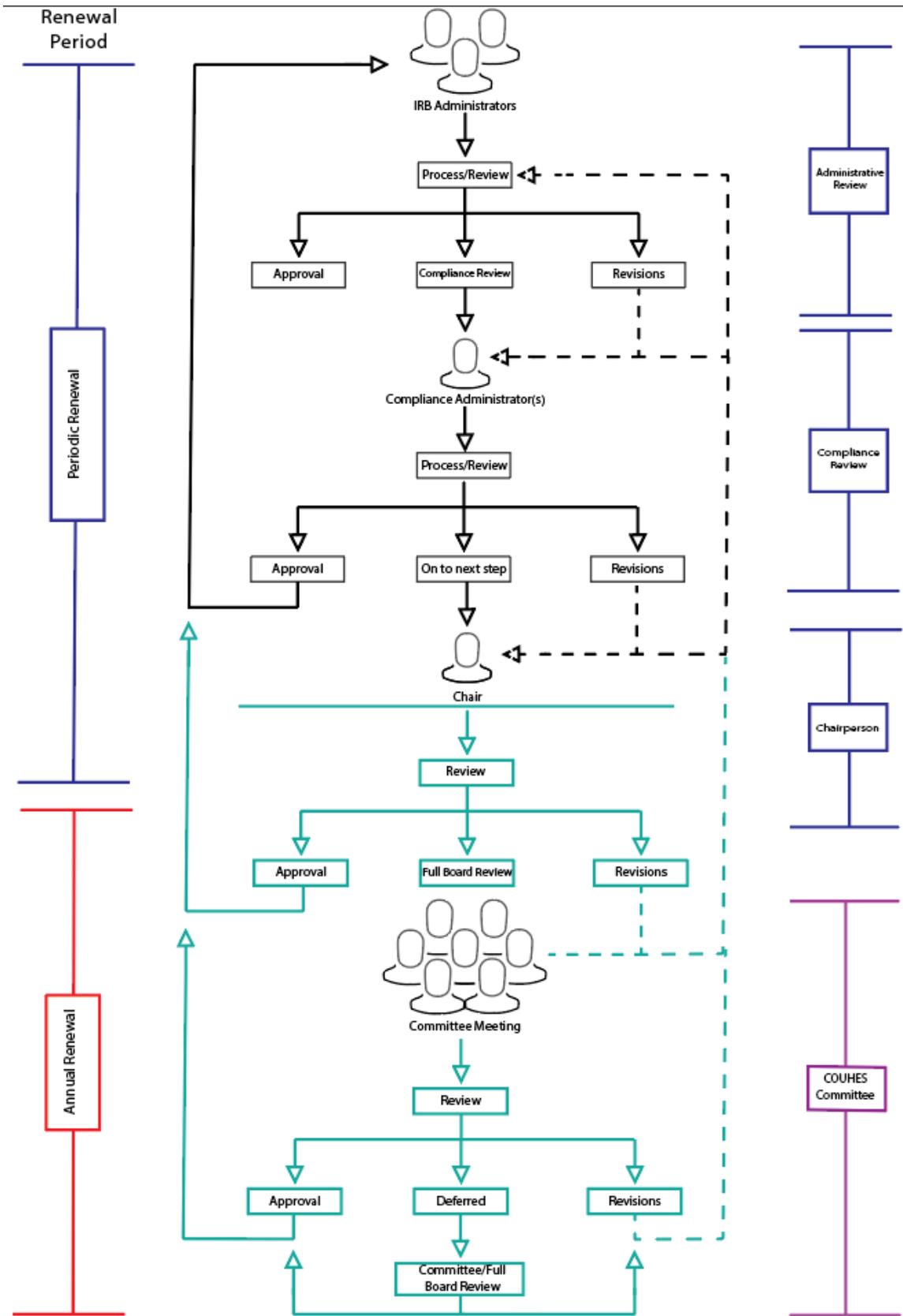
COUHES Workflow

When a new protocol is submitted, IRB administrators conduct administrative review to ensure that all essential information and documents are in place. Protocols missing essential information will be returned to the PI for revision. Protocols in good condition or missing a few nonessential documents will move on to compliance review.

Actions	Conditions
Return to PI for revision	Incomplete application missing essential documents/sections: application/consent is not fill out to completion, wrong consent template is used, missing recruitment materials (if applicable), missing questionnaires (if applicable), missing screening questionnaire (if applicable), etc.
Move on to compliance review	Complete application, missing signatures, missing human subject trainings, missing collaborating institutions' approval or support letters, missing translations, etc.

During compliance review, protocols missing essential details or requiring major clarifications will be returned to the PI for revision. Protocols in good condition will move on to Chairman review. All review comments will be shared with the Chairman. The Chairman will suggest three actions: approval, send to committee, return to PI for revision.

There are three outcomes after committee review: approval, deferred, and revisions required. For protocols that are deferred, they must be reviewed again by the committee. Protocols requiring revisions will be review by the Chairman and approval will be granted if the Chairman is satisfied with the response. An IRB administrator will perform the actions suggested by the Chairman and the committee.



Review at a Convened Meeting of a Quorum of the Membership

Initial and continuing review of research protocols that cannot be reviewed using expedited review procedures are reviewed at a convened meeting of COUHES at which a quorum of the membership is present, including at least one physician/scientist, at least one member whose primary concerns are in nonscientific areas, and at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. A *quorum* is defined as one more than one-half the voting membership. Approval of research is by a majority vote of the quorum.

As protocols, amendments, and continuing review questionnaires are received in the COUHES office, the Chairperson, or any other COUHES members designated by the Chairperson, will conduct a primary review and correspond with the investigator as needed. Approximately one week prior to the meeting, copies of all forms and research protocols, amendments, continuing review progress reports, reports of adverse events and other correspondence or documents relevant to the protocols listed on the agenda for the meeting are distributed to all members of COUHES.

The discussion of each new research protocol, continuing review questionnaire, amendment or adverse event listed on the meeting agenda is led by the Chairperson. At the end of the discussion, the Chairperson makes a motion to approve, require modifications in the protocol and/or consent form to secure approval (approve with modifications), or defer action on the protocol.

When the motion is to approve (or approve with modifications), the motion includes the period for which COUHES approval is to be granted, i.e. one year or less. The duration for which COUHES approval is granted is based upon the level of risk to subjects, and the analysis of this risk as it relates to usual standards of care, if applicable. COUHES performs this risk assessment as part of the review of each protocol at the convened meeting. When the risk is great in relation to the risk associated with alternative procedures, if any, COUHES will consider requiring continuing review be conducted in less than one year, or for one year with case-by-case reporting. A vote on the motion is taken (for, against, abstain) and recorded in the minutes.

All COUHES determinations on the Significant Risk or Non-Significant Risk status of an investigational medical device study shall be recorded in the minutes of the meeting at which these determinations are made. Any member with a conflict of interest recuses him/herself from review of the protocol and leaves the room before the discussion of and vote on the research protocol takes place. The names of those members who were recused from voting due to a conflict of interest are recorded in the minutes. Recused members are not counted towards the quorum requirement; therefore if a

quorum of the membership is not present for the review of any protocol, action on the protocol is deferred automatically.

Review Using Expedited Review Procedures

Research protocols involving no more than minimal risk, and in which the only involvement of human subjects will be in one or more of the categories of research procedures that may be reviewed through an expedited review procedure as authorized by 45 CFR 46.110, are reviewed by the Chairperson or by a COUHES members designated by the Chairperson. The reviewer(s) may approve or require modifications in the protocol and/or consent form to secure approval or defer action pending additional information; however the reviewer(s) may not disapprove a study. A list of all research protocols involving human subjects that have been approved using expedited review procedures is provided to COUHES at the next convened meeting.

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.

Exempt Research

Investigators conducting exempt research will go through an exempt evaluation questionnaire. If their research is deemed exempt at the end of the questionnaire, they will need to certify that they will conduct the research according to the Investigator Responsibilities, an institutional Code of Ethics to assist them with navigating best research policies and requirements. Their research is subject to routine audit.

According to the New Common rule, certain categories of exempt research may be eligible for Limited IRB Review. COUHES will not exempt any research eligible for Limited IRB review. The researcher needs to submit a comprehensive review application for such studies. They may be granted expedited approval and thus, under the New Common Rule, may not require annual renewal.

If an investigator has an exempt protocol that is approved before 1/21/2019 and wants to amend it, a new exempt evaluation will need to be submitted through COUHES Connect. The investigator should also send COUHES an email to close their existing study.

Criteria for Approval

COUHES will approve a research protocol only if the following criteria for approval are satisfied:

- that risks to subjects are minimized;
- that risks to subjects are reasonable in relation to anticipated benefits;
- the selection of subjects is equitable;
- informed consent is adequate and appropriately documented;
- where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and
- appropriate safeguards have been included to protect vulnerable subjects (i.e., children, prisoners, and pregnant women in accordance with 45 CFR 46 Subparts B, C, and D.

Notification of Investigators

Principal investigators are notified in writing of the results of COUHES review. COUHES findings fall into the following categories:

- approval;
- approval pending ancillary committee review and approval;
- approval subject to modifications to the protocol and/or consent form required by the Committee in order to secure approval;
- deferral subject to provision of additional information and response to questions and/or concerns raised by the Committee during the review; or
- disapproval, as not meeting ethical standards for conduct of human-subject research.

When the research protocol is approved, the investigator is notified of the following requirements:

- to use only COUHES approved copies of the consent form(s), questionnaire(s), letter(s), advertisement(s);
- to obtain COUHES approval of any modifications or changes to the protocol and consent form prior to initiation of the proposed changes, except when necessary to eliminate apparent immediate hazards to the subject;
- to report any serious and unexpected adverse events;
- to keep a research file containing all protocol related forms and correspondence for 3 years after completion of the research; and
- the expiration date of COUHES approval.

Responses to COUHES Review

Whenever modifications are required to a protocol and/or consent form to secure COUHES approval, or whenever a research protocol is deferred for additional information, investigators are asked to provide a point-by-point response to the Committee's requests for modifications or response to questions and concerns, as well as a revised protocol and/or consent form, if indicated.

Responses to a Committee vote to require modifications in the protocol and/or consent form are reviewed by the Chairperson. The Chairperson may give final approval once all required changes have been made. COUHES approval is affirmed once all modifications are made to the protocol and/or the consent form consistent with the requirements of the Committee. When, in the opinion of the Chairperson, an investigator fails to meet the requirements of the Committee the investigator's response is placed on the Committee agenda for reconsideration at the next convened meeting.

Responses to a Committee vote to defer action on a research protocol are reviewed at the next convened meeting of COUHES.

Review and Approval by Ancillary Committees

COREHS

When a research protocol involves exposure to ionizing or non-ionizing radiation, prior approval of the Committee on Radiation Exposure to Human Subjects (COREHS) is required.

CAB/ESCRO

All biological materials and technologies that fall within the preview of the Committee on Assessment of Biohazards and Embryonic Stem Cell Research Oversight (CAB/ESCRO) must be registered, reviewed and approved on an annual basis at meetings of the CAB/ESCRO. These include:

- recombinant DNA technologies
- human, animal or plant pathogens including prions
- primary human cells tissues or materials
- established human cell lines
- human embryonic stem (hES) cells
- biological agents at BL1 or greater, including viral vectors
- nanoparticle-based gene or drug delivery systems

Review of Proposed Changes in the Research During Period of Approval

Investigators are required to submit proposed changes to protocols and/or consent forms to COUHES for approval prior to implementation. A form is provided for the submission of proposed changes. Proposed changes are reviewed by the Chair, who determines whether or not the change is minor, based upon the nature of the proposed change and whether the change alters the risks and benefits considered by the Committee at the time of initial review.

When the proposed change is minor, it is reviewed by the Chair using the expedited review procedure. When a proposed change is not minor, or the Chairperson determines full Committee review is otherwise necessary, it is reviewed by COUHES at a convened meeting. The Chair however, may review a proposed non-minor change if the change is necessary to eliminate apparent immediate hazards to the research subjects.

If ancillary committee review(s) is required, activation of the proposed change is subject to approval by the appropriate ancillary committee as well as COUHES.

The procedures COUHES uses to ensure prompt reporting of proposed changes in a research activity, and to ensure that such changes may not be initiated without COUHES review and approval, are:

- inclusion of a statement in the initial approval letter reminding investigators of the requirement to submit any changes to the protocol and/or consent form to COUHES for approval prior to initiation of the change;
- inclusion of material in the human subjects research education program COUHES mandates for all research personnel, of the requirement to obtain COUHES approval for changes to the protocol and/or consent form; and
- the performance of random audits of investigator's protocol-specific records and files by the COUHES staff and the MIT Audit Office.

Notification of Need for Continuing Review

Sixty days prior to expiration of COUHES approval, the investigator is notified that continuing review of their research protocol is coming due. A form is provided to obtain the required information and documents. When COUHES Connect is launched, investigators will be notified that they can submit a questionnaire instead of the form to renew their study. Until such notice is received, investigators should continue to submit the form for continuing review. Once the completed form and required documents are received, the protocol is reviewed either at a convened meeting of COUHES or using expedited review procedures as described previously.

If a continuing review progress report has not been submitted by the date COUHES approval expires the investigator is notified in writing: that the study has been automatically terminated; that subjects may no longer be enrolled in the study until the protocol and consent form have been re-approved by COUHES; and that research grants

related to the study will be suspended. Enrolled subjects actively on study may continue on study while continuing review is in process. If the study has been completed or if the study is not active currently and there is no plans to activate or re-activate the study, the investigator is requested to submit a Final Report Closure Form.

For new protocols approved on or after 1/21/2019: Protocols granted expedited approval, closed to enrollment, or remained open only for data analysis may not require annual renewals. Expedited protocols require a yearly progress report and a full continuing review form every three years. If the committee imposes a different renewal frequency, they will document reasons for such decision. Principles Investigators will be notified of the due date of the progress report 60 and 30 days before. Progress report should be submitted no later than one year plus one month. Failure to return a yearly progress report or a 3 year continuing review will result in immediate closure of the study. If the investigator wishes to close the study, he/she needs to submit a final report closure form.

Independent Verification of No Material Changes since Prior IRB Review

COUHES may determine that a protocol requires verification from sources other than the investigators that no material changes have occurred since previous IRB review. The need for independent verification will be initiated in the case of:

- Complex projects involving unusual levels or types of risk to subjects;
- Projects conducted by investigators who have previously failed to comply with federal regulations or the determinations of COUHES;
- Projects where, based upon information provided in continuing review reports or from other sources, there is a concern that possible material changes have occurred;
- Projects where evidences suggest possible noncompliance or research misconduct;
- Projects where complaints about protocol or subject's rights, safety and welfare violations have been filed.
- Studies associated with unexpected harm to participants.
- Other situations where COUHES determines that independent verification may be necessary.

A COUHES staff member will notify the investigator in writing if a project needs independent verification that no material changes have occurred since previous COUHES review. The investigator will provide access to relevant documents, facilities, and other information required by the COUHES staff or their designee. Results of the independent verification will be reported to the COUHES Chair. The COUHES Chair and the full COUHES committee (if necessary), will review the findings, after which the PI will be notified in writing of the final results and any corrective actions that may be required.

Review of Serious and Unexpected Adverse Events, unanticipated problems involving risks to subjects or others, and Sponsor Safety Reports

Investigators are required to report serious and unexpected adverse events and/or unanticipated problems involving risks to subjects or others to COUHES. The report should be filed within 48 hours by telephone, fax or e-mail, followed by a complete written report within 10 working days. All other adverse events must be reported to COUHES within 10 working days. A form is provided to facilitate on-site reporting and to obtain the required information. Adverse event and/or unanticipated problem reports are reviewed by the Chair to determine the relationship of the event to the study procedures, drug, and/or device, and whether any further action needs to be taken.

If the event is felt to be possibly, probably, or definitely related to the protocol, the reviewer will determine whether:

- changes to the protocol are needed to minimize risks to subjects;
- changes to the consent form are needed to accurately reflect the nature, frequency or severity of the event;
- subjects should be asked to re-consent to their participation in the study;
- the study should be placed on temporary hold to new enrollment, and/or the study procedures should be discontinued because, based on the information available, the risk benefit ratio appears to be unfavorable to the subjects.

Investigators are notified of the review and whether any modifications are required to the protocol and/or consent form. When the reviewer determines that the study must be placed on temporary hold pending further review by the Committee, the principal investigator and site responsible investigators are notified immediately by fax or e-mail. A copy of the notification is sent to the department head of the principal investigator.

When the reviewer determines that the adverse event(s) or unanticipated problem(s) must be reviewed by the Committee, all COUHES members are provided a copy of the Adverse Event report along with any supporting information provided by the investigator. After review, the IRB makes recommended actions. Possible actions COUHES may take include but are not limited to:

- modification of the protocol
- modification of the information disclosed during the consent process
- re-consent the study subjects
- observation of the informed consent process or other research activities
- alteration of the frequency of continuing review
- requiring additional training of the investigator and/or study staff
- notification of investigators at other sites
- termination or suspension of the research
- other actions appropriate for the local context

The results of the Committee review are recorded in the COUHES minutes, communicated to the investigator, and reported to the department head, institutional officials (Director of OSP/Institutional Official, Director of Research Administration and Compliance, and/or others), the supporting agency head (or designee), OHRP, and/or other regulatory agencies as appropriate. The COUHES administrator sends a letter to the appropriate parties (within 45 days of initial contact of the matter with the COUHES office) that contains the name of the investigator, nature of the event, title of the research, a detailed description of the problem including findings and reasons for COUHES' decision, actions COUHES is taking to address the problem, and other details as appropriate.

Investigators are required to submit copies of sponsor safety reports promptly to COUHES. They are reviewed by the Chair to determine the relationship of the event to the study procedure/drug/device, and, if possibly, probably or definitely related, whether changes to the protocol or the consent form are needed to minimize the risks to subjects and accurately reflect the nature, frequency or severity of the event. Investigators are notified when changes are required to the protocol and/or consent

An unanticipated problems involving risks to subjects or others include any incident, experience, or outcome that is:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, and (b) the characteristics of the subject population being studied; and
2. related or possibly related to participation in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An *adverse event* is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research

A *serious adverse event* is defined as any event that suggests a significant hazard, contraindication, side effect, or precaution. A serious adverse event includes any event that results in:

- death;
- a life threatening experience;
- hospitalization or prolongation of existing hospitalization; or
- a persistent or significant disability/incapacity;
- a congenital anomaly/birth defect.

In addition, events may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and require an intervention to prevent one of the outcomes listed above.

An *unexpected event* is defined as any event, the specificity or severity of which is not consistent with the risk information described in the general investigative plan or elsewhere in the current application, as amended.

Serious or Continuing Noncompliance with Human Subjects Regulations or COUHES Requirements

When COUHES becomes aware of possible serious or continuing noncompliance with the regulations governing research involving human subjects or the requirements of COUHES, the possible serious or continuing noncompliance will be investigated by the Chairperson, or a member(s) of COUHES designated by the Chairperson.

The Chairperson, or his designee(s), will prepare and forward a report to COUHES and other MIT Officials, as appropriate, who are responsible for the oversight of the protocol for review and action. If COUHES finds that there has been serious or continuing noncompliance on the part of an investigator(s), appropriate action will be taken and the COUHES administrator will file a report to the department head, the Vice President for Research, the Director of OSP/Institutional Official, the Director of Research Administration and Compliance, the supporting agency head (or designee), the Office for Human Research Protections, and the Food and Drug Administration as appropriate within 45 days of the IRB's awareness of the serious or continuing noncompliance. The report will contain the name of the investigator, the title of the research, a detailed description of the serious or continuing noncompliance including findings and reasons for COUHES' decision, the actions COUHES is taking to address the problem, and other details as appropriate.

COUHES may take the following actions:

- request a corrective action plan from the investigator
- intensify data and safety monitoring of the research activity
- request a directed audit of target areas of concern
- directly observe the informed consent process and/or other research activities
- request additional investigator and study staff education and training
- modify the protocol and study documents
- re-consent the study subjects
- alter the frequency of continuing review
- terminate or suspend the study
- terminate or suspend all human subjects research in which the investigator participates
- other appropriate actions

Suspension or Termination of Research

Whenever COUHES suspends or terminates a research protocol involving human subjects for any reason, the following individuals, in addition to the investigators listed on the protocol and departments/institutions involved in the research, may be notified by the COUHES administrator or designee within 45 days of the COUHES' decision, if applicable:

- MIT Officials (department head of the principal investigator, Director of OSP/Institutional Official, Director of Research Administration and Compliance, and/or others)
- The supporting agency head (or designee)
- Office for Human Research Protections (OHRP);
- Food and Drug Administration (FDA); and
- Commonwealth of Massachusetts Department of Public Health.

The IRB administrator or designee shall send a letter to the appropriate parties that contains the name of the investigator, the title of the research, a detailed description of the problem including findings and reasons for COUHES' decision, and any other relevant details.

Emergency Use of an Investigational Drug or Biologic

COUHES allows the emergency use of an investigational drug or biologic if the FDA requirements for emergency use, contained in 21 CFR 56.102(d) and 104(c), are met.

Emergency use of an investigational drug or biologic is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain approval from COUHES.

COUHES will allow a single emergency use of a test article without prospective review. This emergency use provision is an exemption from prior review and approval by COUHES. Any subsequent use of the investigational product at MIT must have prospective COUHES review and approval. However, in accordance with FDA guidelines, COUHES may consider it inappropriate to deny emergency treatment to a second individual if the only obstacle is that COUHES has not had sufficient time to convene a meeting to review the issue.

Investigators implementing these emergency use provisions shall do the following:

Determine if the proposed use meets the regulatory definition for emergency use of an investigational drug or biologic. Emergency uses must meet ALL of the following criteria:

- The subject has a disease or condition which is life-threatening (e.g., the likelihood of death is high) or severely debilitating (e.g., may cause irreversible morbidity, such as blindness, loss of limb, loss of hearing, paralysis or stroke);
- The subject's disease or condition requires intervention with the investigational drug or biologic before review at a convened meeting of COUHES is feasible; and
- No standard acceptable treatment is available.

Contact the manufacturer of drug/biologic to determine if it can be provided under an existing IND or, if not available through the manufacturer, contact the FDA for an Emergency IND.

Contact the COUHES office at MIT at 617-253 6787 to notify it of a planned emergency use of a drug or biologic.

Contact the MIT Pharmacy 617-253 1517 to inform them of the planned use and shipment of drug.

Obtain informed consent from subject or, if incompetent to give informed consent, the subject's next of kin or legally authorized representative. The requirement for informed consent may be waived if the investigator and a physician who is not otherwise participating in the clinical investigation certifies in writing to all of the following:

- The subject is confronted by a life-threatening (or severely debilitating) situation necessitating the use of the investigational drug or biologic;
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- Time is not sufficient to obtain consent from the subject's next of kin or legal representative; and
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

Submit to COUHES within 5 working days after the use of the investigational drug or biologic a comprehensive written report on the circumstances for the use of the test article.

Emergency Use of an Unapproved Device

COUHES will allow for the emergency use of an unapproved device if the FDA requirements for emergency use are met and, whenever possible, the COUHES Office is notified of intent to use an unapproved device.

Emergency use of an unapproved device is defined as the use of an unapproved device for a purpose or condition for which the device requires, but does not have, an approved application for premarket approval (FDA approval for marketing) with a human subject in a life-threatening situation where the unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE.

If a physician chooses to use an unapproved device in such an emergency, the physician must later justify to FDA that an emergency actually existed. Each of the following conditions must exist to justify emergency use:

- the patient is in a life-threatening condition that needs immediate treatment;
- no generally acceptable alternative for treating the patient is available; and
- because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

Even in an emergency situation, the investigator is required to obtain informed consent from the subject or the subject's legally authorized representative unless both the investigator and an independent physician certify in writing all of the following:

- the subject is confronted by a life-threatening situation necessitating the use of the investigational device;
- informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- time is not sufficient to obtain consent from the subject's legal representative; and
- no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

Although COUHES does not have to prospectively review the emergency use of an unapproved device in a life-threatening situation, whenever possible, investigators are required to contact the COUHES Office and document that an emergency exists.

Investigators are required to submit a report on the emergency use to COUHES within 5 working days. The report is reviewed by the Chairperson to ensure that the emergency use meets FDA regulations. The investigator is informed that if he/she anticipates the need to use the investigational device in additional subjects, prospective review by COUHES is required.

COUHES Recordkeeping Requirements

COUHES maintain records of its activities for at least 3 years after completion of the research. The records are available for inspection and copying by the Food and Drug Administration (FDA), federal or state government agencies, or hospital accrediting agencies in the course of carrying out their respective duties.

The following records are maintained:

- membership;
- written policies and procedures;
- minutes of meetings that include members present, summary of discussion where appropriate on protocol-related issues, actions taken by COUHES, and record of voting (for, against, abstain); and
- copies of research protocols reviewed, approved sample consent documents, continuing review progress reports, amendments to research protocols, adverse event reports as well as any other protocol-related correspondence between COUHES and the investigator.

Information Provided by Investigators for COUHES Review

Investigators are required to submit research protocols in accordance with COUHES submission instructions.

The submission requirements include the following:

Initial Review

- signed application form;
- recruitment materials (letters, advertisements, postings, e-mail announcements, etc.);
- questionnaires, interview outlines and standardized instruments;
- informed consent document;
- IRB approvals from collaborating institutions, if applicable;
- FDA approvals (IND, IDE), if applicable;
- investigator's brochure, if applicable and
- conflict of interest disclosure, if applicable.

Continuing Review

- signed Continuing Review Questionnaire;
- consent form; and

Unanticipated Problems/Adverse Events Experienced by Subjects

- signed adverse event/unanticipated problems form; and
- revised consent form and/or other documents (if applicable).

Proposed Changes to Protocol and/or Consent Form

- signed change form;
- detailed description of proposed changes;

- rationale for the changes; and
- revised consent form (if applicable).

If a protocol, continuing review, unanticipated problems/adverse event report, or a proposed change are to be reviewed at a convened meeting of COUHES, all members receive a copy of the relevant submitted documents.

If a protocol, continuing review, unanticipated problems/adverse event report, or a proposed change is to be approved by expedited review, the Chair or a COUHES member designated by the Chair receive a copy the relevant submitted documents. A list of all protocols, continuing reviews, unanticipated problems/adverse event reports, and proposed changes that have been approved using expedited review procedures is provided to COUHES at the next convened meeting. The complete documentation is available to all members for review.

Once COUHES has migrated to COUHES Connect, if an investigator has a current exempt protocol and wants to amend it, a new exempt evaluation will need to be submitted through COUHES Connect. The investigator should also send COUHES an email to close their existing study.

Required Elements of Informed Consent

Except for broad consent obtained in accordance with 45CFR46.116(d), informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

In seeking informed consent, the following information shall be provided to each subject:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject;
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and 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;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens: (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

(9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

Criteria for Waiving or Altering Consent

COUHES may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided that the research meets all applicable regulations (45 CFR46.116):

- (1) The research involves no more than minimal risk to the subjects;
- (2) The research could not practicably be carried out without the requested waiver or alteration;
- (3) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- (4) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- (5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

A waiver or alteration of consent does not apply to research under FDA regulations. The FDA does not allow a waiver or alteration of the requirements for obtaining informed consent except in special circumstances.

Criteria for Waiving Documentation of Consent

At the discretion of COUHES, the requirement for a signed informed consent may be waived. Situations where this may occur include the following:

- That the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject (or legally authorized representative) will be asked whether

the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

- That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context; or
- If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects or legally authorized representatives with a written statement regarding the research.

Health Insurance Portability and Accountability Act (HIPAA)

MIT is not considered a covered entity. Therefore, research conducted outside of MIT Medical or MIT Medical Billing is not subject to Health Insurance Portability and Accountability Act (HIPAA).

If a study involves health information about a research subject, then researchers may need to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH) and their implementing regulations. The application to COUHES will enable investigators to make a determination whether HIPAA applies to your study protocol.

If an investigator plans to share or disclose a subject's PHI in connection with a research study that is indeed subject to HIPAA, he/she must first obtain the written permission of the subject. This permission, called an Authorization for Release of Protected Health Information, must specify precisely what information will be released, why it is being released, and from and to whom it is being released. A template for this form is provided on COUHES website. This form must be appended to the informed consent form and completed by the subject at the same time the subject completes the informed consent form. A subject cannot participate in the research if he or she does not complete the Authorization. Additionally, the investigator must maintain a detailed record of each release of health information, and this record must be accessible under certain circumstances to the subject.

COUHES, however, may permit the disclosure of PHI subject to HIPAA without a subject's specific prior authorization, (1) if the research cannot be practically conducted without access to the PHI, and (2) the disclosure involves no more than minimal risk to the privacy of the subject. If investigators are requesting such a Waiver of Authorization, then they must complete the relevant portions of the COUHES standard application form.

HIPAA applies only to identifiable health information. If the health information is de-identified it is exempt from HIPAA's requirements. To be completely de-identified, the data set must meet strict criteria and be stripped of all direct and indirect subject identifiers. As an alternative method, a researcher may choose to use a limited data set, which is less restrictive and excludes mostly direct subject identifiers. For use of a limited data set, the researcher must complete a formal data use agreement that sets forth permitted uses and disclosures of the limited data set information with the data source.

If HIPAA applies to a research study, any failure to comply with HIPAA will result not only in termination of the study and suspension of related research grants, but also potentially in criminal and/or civil penalties to the researcher(s) and MIT (for an individual, penalties may be as severe as \$1,500,000 or 10 years imprisonment.).

A more detailed description of the HIPAA Privacy Rule requirements is contained in the COUHES HIPAA Guidance Document.

Training of Research Personnel

Federal regulations require that all personnel involved in any government sponsored research take and pass a training course on human subjects research before embarking on such research. MIT policy extends this requirement to all MIT personnel involved in any human subjects research. This requirement extends to all personnel who play a role in research involving human subjects including principal investigators, associate investigators, student investigators, study coordinators, visiting scientists, consultants, laboratory technicians and assistants. The requirements encompass all types of interactions with human subjects including, direct contact, indirect involvement, analysis of data and analysis of blood/tissue samples. To enable study personnel to meet this requirement, MIT has developed a web-based training course. It can be accessed via the Human Subjects Training link on the COUHES website. All personnel involved in studies utilizing humans as research subjects must undergo recertification in human subjects research training every three years from the date of original approval.

Additional training for NIH funded clinical trials

All NIH-funded investigators and staff who are involved in the conduct, oversight, or management of clinical trials should be training in Good Clinical Practice (GCP). A clinical trial is defined as 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. For more information regarding the GCP training policy and the definition of clinical trial, please click [here](#). The GCP training is an additional requirement; it does NOT replace the Protections of Human Participants training.

The CITI program offers two courses that are acceptable GCP training by the National Institute of health in fulfillment of their GCP training policy. You can select one of them that is most applicable to the type of research that you conduct. If in doubt, you should take GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA Focus).

- **GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA Focus)**

(Suitable for individuals proposing to conduct clinical trials of drugs and devices primarily in the U.S. and/or who would prefer a more U.S. FDA-centric curriculum.)

- **GCP for Clinical Trials with Investigational Drugs and Biologics (ICH Focus)**

(Suitable for individuals involved in clinical trials of drugs and biologics when the research may be international or where the individuals would prefer a more ICH-focused curriculum.)

- **GCP – Social and Behavioral Research Best Practices for Clinical Research**

(Suitable for individuals involved in clinical trials using behavioral interventions and social science research).

Training of IRB Members and Staff

New members and staff are provided with IRB-related information, including, but not limited to, COUHES forms, COUHES Policies and Procedures Manual, and access to the COUHES web site, which links to applicable Federal regulations and the Belmont Report. New members are also required to take and pass the Collaborative Institutional Training Initiative (CITI Program) on IRB members and read the Institutional Review Board Member Handbook.

All members receive copies of various IRB-related publications, e.g., IRB, Human Research Report and IRB policy related communications from OHRP, FDA, or other governing agencies.

Clinical Trial

A *clinical trial* is 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 the interventions on biomedical or behavioral health-related outcomes.

MIT will allow the conduct of clinical trials provided:

- The research does not involve significantly greater than minimal risk, AND

- MIT has or has access to the appropriate resources necessary for the conduct of the research.

Requirements for NIH sponsored clinical trials:

- Data Safety Monitoring Plan
- Good Clinical Practice Training
- ClinicalTrial.Gov registration and reporting
- Single IRB Review
- Certificate of Confidentiality

Clinical trials not sponsored by the NIH require the following:

- Data Safety Monitoring Plan
- Good Clinical Practice Training

Single IRB

The new Common Rule requires that (with some exceptions) federally funded studies with more than one investigator must use a single IRB (sIRB). Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. This excludes when IRB review is required by law (tribal law, etc.) or Federal department or agency supporting or conducting the research determines the use of a single IRB is not appropriate.

Single IRB is also required for clinical research funded by the NIH.

Request Single IRB Review

The term “cede review” refers to a reliance in which two or more institutions agree that one will be designated as the Single Reviewing Institution/IRB for the study while the other serves as the Relying Institution/IRB.

Ceding a protocol allows streamlined IRB oversight for multi-site research where two or more institutions are engaged in human subject research, meaning only one IRB will have jurisdiction and oversight over the ethical review and safety of the research. Only non-exempt studies are eligible for cede reviews.

If the protocol is ceded to an external IRB, the MIT investigator(s) is required to obtain all regulatory information regarding the study, including but not limited to the approved protocol and consent documents. The investigator(s) will also be required to remain in compliance with the policies set by the reviewing institution. Any questions and required reporting must be done through the reviewing IRB.

Cede requests must be submitted through the SMART IRB platform.

Investigators are encouraged to discuss any possible cedes with COUHES staff (or COUHES Smart IRB contact) before creating a request.

Posting of Consent form

Research conducted or supported by a Federal department or agency that meets the definition of a clinical trial requires one IRB-approved informed consent form used to enroll subjects be posted on a publically available Federal website. The supporting Federal department or agency may determine that certain information should not be made publically available and may permit or require redactions of the information posted. The informed consent must be posted after the clinical trial is closed to recruitment, no later than 60 days after the last subject visit.

Investigational Drugs and Devices in Research

Use of investigational drugs must be conducted according to FDA IND regulations, [21 CFR Part 312], and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations [21 CFR Part 812], and other applicable FDA regulations.

GDPR

GDPR applies to projects that involve with the collection of "personal data" from subjects residing in the EEA. If GDPR applies to a study, the researchers are required to obtain consent using the GDPR statements in the COUHES consent template.

The following key elements are included in the COUHES consent template:

- The identity of the Principal Investigator;
- The purpose of data collection;
- The types of data collected, including listing of special categories: racial or ethnic origin; political opinions; religious or philosophical beliefs; trade union membership; processing of genetic data; biometric data; health data; and/or sex life or sexual orientation information;
- The right to withdraw from the research and the procedure for withdrawal;
- Who will have access to the data;
- Information regarding data security, including storage and transfer of data;
- How long data will be stored (this may be indefinite);
- Whether and under what conditions data may be used for future research, either related or unrelated to the purpose of the current study.

Affirmative evidence (signature, recording of the consent process, or another acceptable mechanism as determined by COUHES staff) is required to show that subject has consented to providing their personal information for research.

Commonwealth of Massachusetts

MIT complies with Massachusetts state regulations specific to human subject research.

New Common Rule

The New Common Rule becomes effective on January 21, 2019. All studies approved on or after Jan 21, 2019 need to follow the new common rule. Existing protocols approved before Jan 21, 2019 fall under the Old Common Rule. Investigator will be notified when

electronic submission and exempt research evaluation questionnaire becomes effective. Until such notice is given, they should continue to fill out the exempt or standard application. Investigators will be informed separately on when and how existing protocols will be transitioned to the New Common Rule. Until such notice is given, if an investigator wishes to transition a protocol approved before Jan 21, 2019 to the New Common Rule, he/she needs to close the protocol, submit a new application and go through the entire review process.

Changes and Modifications of Policies and Procedures

From time to time, as may be necessary or appropriate to ensure fulfillment of institutional responsibilities under existing Assurances, to improve operational efficiency, or to address other concerns that may arise, these *Policies and Procedures* may be revised. All revisions will be documented as an addendum until such time as a revised version of this document is prepared.

Adopted February 1, 2003

Last modified on January 14, 2019