Mass General Brigham

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IRB, Institutional Review Board, Definitions

PURPOSE:

The purpose of this policy is to provide a listing of terms and their definitions used in regulations, policies and procedures that apply to human subject research.

DEFINITIONS:

Adverse event: 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 (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

External adverse events are those *adverse events* experienced by subjects enrolled at sites that are not relying on the Mass General IRB for IRB review of the research. In the case of an external adverse event, the principal investigator typically becomes aware of the adverse event upon receipt of a report from the sponsor, coordinating center or other monitoring group, such as a Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC), or collaborating investigator at another site.

Internal adverse events are those *adverse events* experienced by subjects at sites that are relying on the Mass General IRB for IRB review of the research. In the case of an internal adverse event the principal investigator typically becomes aware of the adverse event directly from the subject, co-investigator or other member of the study staff, or the subject's healthcare provider.

Applicable Clinical Trial: Interventional studies (with one or more arms) of FDA-regulated drugs, biological products, or devices that meet one of the following conditions:

1. The trial has one or more sites in the United States;
2. The trial is conducted under a FDA investigational new drug application (IND) or investigational device exemption (IDE); or
3. The trial involves a drug, biologic or device that is manufactured in the United States or its territories and is exported for research.

Applicable Clinical Drug Trial: A controlled clinical investigation, other than a Phase I clinical investigation, of a drug or biological product subject to FDA regulation.

Applicable Clinical Device Trial: A controlled trial with health outcomes of devices subject to FDA regulation, other than small feasibility studies or pediatric post-market surveillance required by FDA.

Authorization Agreement: Also called a Reliance Agreement, is the agreement that documents respective authorities, roles, responsibilities and communication between an institution/organization providing the ethical review and a participating institution relying on the ethical review.

Children: Persons who have not attained the legal age for consent to treatments or procedures involved in the research or clinical investigation, under the applicable law of jurisdiction in which the research will be conducted.

Clinical hold: An order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety. A clinical hold may be complete or partial. Delay or suspension of all clinical work under an IND is considered a complete clinical hold. Delay or suspension of only part of the clinical work under an IND is considered a partial clinical hold. A partial clinical hold could, for example, be imposed to delay or suspend one of several protocols in an IND, a part of a protocol, or a specific study site in a multi-site investigation.

Clinical investigation (FDA):	An experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58, regarding nonclinical studies. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous. (21 CFR 50.3(c) and 21 CFR 56.102(c))
Clinical trial:	(NIH and DHHS) 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. (ICMJE) A research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome.
ClinicalTrials.gov:	A registry and results database of publicly and privately supported clinical studies of human participants conducted nationally and/or internationally that serves as the mechanism for fulfilling registration and results reporting requirements of FDAAA and the NIH.
Collaborating individual investigator:	An investigator who is (a) not otherwise an employee or agent of the applicable Mass General Brigham-affiliated entities; (b) conducting collaborative research activities whether on or off-site from applicable Mass General Brigham-affiliated entities; and (c) not acting as an employee of any institution with respect to his/her involvement in the research being conducted by the applicable Mass General Brigham-affiliated entities (independent investigator) OR acting as an employee or agent of an institution that does not hold an OHRP-approved FWA and does not routinely conduct human subject research (institutional investigator).
Continuing noncompliance:	Any noncompliance that occurs repeatedly after appropriate remedial education or corrective action has been instituted taking into consideration all relevant factors, including, for example: (1) whether the continuing noncompliance was intentional, or (2) whether the investigator collaborated in remedial activity and the continuing noncompliance was not intentional.
Deviation:	Any alteration/modification to the PHRC-approved protocol without prospective PHRC approval. The term *protocol* encompasses all PHRC-approved materials and documents including the detailed protocol,

protocol summary, consent form, recruitment materials, questionnaires, and any other information relating to the research study.

Device:

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component part, or accessory, which is (1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes

Investigational device: A device, including a transitional device, that is the object of an investigation. [21 CFR 812.3(g)]

Transitional device: A device subject to section 520(l) of the act, that is, a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976. [21 CFR 812.3(r)]

Custom device: A device that: (1) Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist; (2) Is not generally available to, or generally used by, other physicians or dentists; (3) Is not generally available in finished form for purchase or for dispensing upon prescription; (4) Is not offered for commercial distribution through labeling or advertising; and (5) Is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice. [21 CFR 812.3(b)]

Directly identifiable tissue:

Tissue that is labeled or released to researchers with *personal identifiers*; for example, name, medical record number, social security number, laboratory accession number, etc. *Personal identifiers* include any of the 18 personal identifiers specified under HIPAA. While HIPAA regulations do not apply to tissue samples, they do apply to health information linked to the tissue. Of note, use of any part of an identifier, e.g., patient initials, in combination with code numbers, is also considered an identifier under HIPAA.

Emergency use of an investigational drug or biologic product:

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 IRB approval

Emergency use of an

unapproved device:	The use of an unapproved medical device with a human subject in a life-threatening situation in which no standard acceptable treatment is available
Employees or agents:	Members of the workforce of applicable Mass General Brigham-affiliated entities who: (1) act on behalf of the institution; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities. Employees and agents include professional staff, students/interns, contractors and volunteers, among others, regardless of whether the individual is being paid by the hospital.
Exception:	Any change in research or protocol requirements (e.g. eligibility criteria, laboratory tests, continuation on protocol) that is limited to a specific subject or situation and does not change the requirements for all subjects. Exceptions must be approved by the Mass General Brigham IRB prior to implementation.
Excess clinical/research tissue samples:	Tissue that was collected for clinical or research purposes and is no longer needed for the original purpose.
Financial interest:	An interest in a company consisting of: (1) any stock, stock option or similar ownership interest in the business, but excluding any interest arising solely by reason of investment in a company by a mutual, pension, or other institutional investment fund over which you do not exercise control; or (2) receipt of, or the right or expectation to receive, any income from such business (or from an agent or other representative of such business), whether in the form of a fee (e.g., consulting), salary, allowance, forbearance, forgiveness, interest in real or personal property, dividend, royalty derived from the licensing of technology, rent, capital gain, real or personal property, or any other form of compensation, or any combination thereof. For the purposes of Mass General Brigham IRB policies, the term financial interest includes, but is not limited to: (i) royalties presently being received; (ii) the right to receive royalties in the future; and (iii) licensing fees or milestone payments; including any of the foregoing (i)-(iii) which are paid or payable to the individual directly or through institutional revenue-sharing policies.
Generalizable knowledge:	Information produced for the purposes of dissemination to a scientific audience outside of the population served by the institution.
Human subject (DHHS):	A living individual about whom an investigator (whether professional or student) conducting research obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. (45 CFR 46.102)
Human subject (FDA):	An individual who is or becomes a participant in research, either as a recipient of a test article or as a control or an individual on whose specimen a medical device is used. A participant may be either a healthy human or a patient. (21 CFR 50.3(g), 21 CFR 56.102(e) and 21 CFR 812.3(p))
Human subject research:	Activities that meet the DHHS definition of *research* and involve a *human subject* as defined by DHHS or meet the FDA definition of *clinical investigation* and involve a *human subject* or *subject* as defined by FDA.

Per federal regulations, the following activities are deemed not to meet the definition of research (45 CFR 46.102):

- Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
- Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
- Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
- Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

Humanitarian Use Device: A medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8000 individuals in the United States annually.

Identifiable Private Information (DHHS): Private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. (45 CFR 46.102). Identifiable private information includes, but is not limited to, data that includes any of the 18 identifiers in the HIPAA Privacy Rule.

Identifiable Biospecimen (DHHS): A biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen. (45 CFR 46.102)

Indirectly identifiable (coded) tissue: Tissue that retains a link (or code) to information about the tissue donor that includes any of the 18 HIPAA *personal identifiers*.

Interaction (DHHS): Includes communication or interpersonal contact between investigator and subject. (45 CFR 46.102)

Intervention (DHHS): Includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (45 CFR 46.102)

Interventional clinical

research:	Any prospective study involving human subjects that is designed to answer specific questions about the effects or impact of a particular biomedical or behavioral intervention (i.e. drugs, devices, treatments or procedures, behavioral or nutrition strategies), or designed to answer specific questions about human physiology.
Investigator:	The principal investigator, site responsible investigator, co-investigators, and any other person who is responsible for the design, conduct or reporting of the research.
Investigational device exemption:	Documentation from the FDA that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 have been met.
Investigational new drug:	A new drug or biologic 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. [21 CFR 312.3(b)]
Life-threatening (FDA):	Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.
Minimal Risk:	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. (45 CFR 46.102 and 21 CFR 56.102)
Minor noncompliance:	Any noncompliance that is <u>not</u> serious or continuing noncompliance. For example, minor noncompliance might include the following deviations: (1) missing an original signed and dated research consent form; (2) missing pages of executed research consent forms; (3) inappropriate documentation of informed consent, e.g., missing one or more signatures or date; (4) obtaining informed consent using an invalid/outdated research consent form that contains all of the information required by the IRB; (5) failure to submit continuing review forms/documents prior to expiration of IRB approval;(6) unplanned deviation from the approved protocol where the deviation does not impact the rights and welfare of subjects or the integrity of the research.
Noncompliance:	Any failure to comply with any applicable federal, state, or local laws and regulations or the requirements or determinations of the IRB, which include PHRC and institutional policies related to human subject protection.

Non-identifiable tissue: Tissue that cannot be linked to a specific individual either because the existing link (such as a code key) to the identity of the individual was destroyed or because a link was never created or retained. Non-identifiable tissue lacks all of the 18 personal identifiers specified by HIPAA. Information that cannot be used to identify the individual, such as diagnosis, age, and gender, may be recorded with or linked to the tissue.

Prisoner: Any individual involuntarily confined or detained in a penal institution. OHRP Guidance extends the definition to individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Private Information (DHHS): Includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (*e.g.,* a medical record).*Research (DHHS):* A *systematic investigation*, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. (45 CFR 46.102).

Radioactive Drug: Any substance defined as a drug in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any non-radioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides.

Research: A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

Research Tissue Bank (or Repository): An entity involved in procuring, processing, storing and/or distributing tissue expressly for use in research.

Serious adverse event: any event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to

prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Serious noncompliance: Any noncompliance that negatively impacts the rights and welfare of subjects or compromises the integrity of the study data.

Scientific Misconduct: *A*ny fabrication, falsification, plagiarism, or other practice that seriously deviates from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research.

Severely debilitating (FDA): Diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Sponsor-investigator (FDA): An individual who both initiates and actually conducts, alone or with others, a test article is administered, dispensed, or used involving a subject. The term does not include any person other than an individual.

Subject (FDA): A human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease. (21 CFR 312)

Suspension: To cause some aspect of the research to be stopped temporarily or permanently while the research continues under review or an investigation takes place.

S*ystematic Investigation:* An activity that involves a prospective research plan which incorporates data collection, either quantitative or qualitative, and data analysis to answer a research question. Systematic investigations that are designed to develop or contribute to *generalizable knowledge* are those that allow the knowledge gained from the research to be applied to populations other than the study population, inform policy, or generalize findings.

Termination: To cause the research to be stopped permanently in its entirety. Of note, expiration of Mass General Brigham IRB approval is not considered termination of research

Test Article (FDA): Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n). (21 CFR 50.3(j) and 21 CFR 56.102(l))

Tissue: Any biological specimen obtained from patients or human research subjects. This includes, for example, fixed, frozen or fresh pathology or

autopsy specimens, blood, urine, saliva, CSF, semen, breast milk or other biological material, and any purified DNA, RNA, or cell lines. Distant derivatives, for example, recombinant proteins, are not necessarily considered human tissue. The terms *tissue*, *specimens*, and *samples* are used interchangeably in this policy.

Unanticipated adverse device effect:

Any serious adverse effect on health or safety or any life- threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated problem involving risks to subjects or others (UPIRTSO):

Any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given
   a. the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
   b. the characteristics of the subject population being studied;
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.

Unexpected:
The incident, experience, or outcome in terms of nature, severity or frequency is **not** consistent with either:

1. The known or foreseeable risk of events associated with the procedures involved in the research that are described in
   a. The protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and
   b. Other relevant sources of information, such as product labeling and package inserts; or
2. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing an adverse event and the subject's predisposing risk factor profile for the adverse event..

Related or Possibly Related:
Events that are determined to be at least partially caused by the procedures involved in the research. Events that are caused soley by an underlying disease, disorder, or condition or events caused solely by other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject are <u>not</u> considered related or possibly related.

Greater Risk of Harm Than was Previously Known or Recognized:
Any event that is serious as defined below or an event that is not serious, but that warrants consideration of substantive changes in the research protocol

or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

Serious:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. requires inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unexpected: The incident, experience, or outcome is unexpected (in terms of nature, severity or frequency) given the (a) research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document and (b) the characteristics of the study population being studied.

REFERENCES:

45 CFR 46
21 CFR 50, 56, 312, 812

DEVELOPMENT AND CONSULTATION:

Human Research Office