

Title:	Exempt Human Subject Research
Department:	Human Research Affairs
Policy Type:	Mass General Brigham System-wide
Applies to:	Employees, Professional Staff or Other Agents of Mass General Brigham
Approved by:	Chief Academic Officer
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Contact Person:	Director, Human Research Office

KEYWORDS:

IRB, Institutional Review Board

PURPOSE:

The purpose of this policy is to define the applicability of the exemptions from the requirements of 45 CFR 46 and/or 21 CFR 56 and the procedures the Mass General Brigham Institutional Review Boards follows when conducting review of exempt human subject research and clinical investigations.

DEFINITIONS:

See Definitions in Human Subject Research

POLICY STATEMENT:

The Mass General Brigham IRB is responsible for determining whether a research activity is exempt from 45 CFR 46 and 21 CFR 56. Investigators or others within the organization may not make exemption determinations. The Mass General Brigham IRB Chairpersons and designated reviewers are subject to the Mass General Brigham IRB policy on *IRB Member Conflicts of Interest* when reviewing and making exemption determinations.

PROCEDURES:

Investigators relying on the Mass General Brigham IRB for IRB review of human subject research are required to complete Insight application forms and provide all required information and documents to the Mass General Brigham IRB for review.

All the required forms and documents submitted by the investigator for review are reviewed by the Human Research Office staff for completeness and accuracy, and when complete and accurate, are assigned to a Mass General Brigham IRB Chairperson or designated reviewer for review.

The reviewing Mass General Brigham IRB Chairperson or designated reviewers (hereafter referred to as reviewer) is responsible for making determinations of exemption from the requirements of federal regulations. The Mass General Brigham IRB makes exempt determinations via the expedited review mechanism. Exemption determinations may not be made by researchers.

DHHS Regulated Research - Pre 2018 Requirements

Criteria for Exemption 45 CFR 46.101(b)(1)-(6) (pre-2018 Common Rule Requirements, applicable to IRB determinations prior to January 21, 2019). Under 45 CFR 46.101(b), the IRB may determine a research activity to be exempt where the only involvement of human subjects will be in one or more of the following six categories:

- (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- (2) Research involving the use of education tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless: (i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- (3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- (4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- (5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

Note: OHRP has determined that the following criteria must be satisfied to invoke the exemption for research and demonstration projects examining "public benefit or service programs": (1) The program under study must deliver a public benefit (e.g., financial or medical

benefits as provided under the Social Security Act) or service (e.g., social supportive, or nutrition services as provided under the Older Americans Act; (2) The research or demonstration project must be conducted pursuant to specific federal statutory authority; (3) There must be no statutory requirement that the project be reviewed by an Institutional Review Board (IRB); and (4) The project must not involve significant physical invasions or intrusions upon the privacy of participants.

- (6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Applicability to Vulnerable Subjects

Exemptions (1)-(6) do not apply to research involving prisoners, Subpart C.

Exemption (2), for research involving survey or interview procedures or observation of public behavior, does not apply to research involving children, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

Exemptions (1)-(5) do not apply to *clinical investigations* regulated by the Food and Drug Administration (FDA).

DHHS Regulated Research - 2018 Requirements

Criteria for Exemption (2018 Common Rule Requirements, applicable to IRB determinations made on or after January 21, 2019). Under 45 CFR 46.104(d), the IRB may determine a research activity to be exempt where the only involvement of human subjects will be in one or more of the following eight categories:

- (1) Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- (2) Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met (i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects; (ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or (iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

- (3) (i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met: (A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects; (B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or (C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).
- (ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.
- (iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.
- (4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met: (i) The identifiable private information or identifiable biospecimens are publicly available; (ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects; (iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or (iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.
- (5) Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those

programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended. (i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

- (6) Taste and food quality evaluation and consumer acceptance studies: (i) If wholesome foods without additives are consumed, or (ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.
- (7) Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).
- (8) Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met: (i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d); (ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117; (iii) An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and (iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

[Mass General Brigham is not implementing broad consent for use of identifiable private information or identifiable biospecimens at this time. As a result, exempt categories (7) and (8) are not applicable.]

Applicability to Vulnerable Subjects

Research involving prisoners does not qualify as exempt research except for research aimed at involving a broader subject population that only incidentally includes prisoners.

Exemption 2 [surveys, interviews, public observations] may involve children when the research is related to educational tests or observations in which the investigators don't participate in the activities being observed. Additionally, children are not eligible for this exemption if the project requires limited IRB review.

Exemption 3 [benign behavioral interventions] may not involve children.

Exemptions (1)-(5) do not apply to *clinical investigations* regulated by the Food and

Drug Administration (FDA).

Limited IRB Review

Under the 2018 Requirements, exempt category 2 (iii) and 3(i)(C), the reviewer must conduct a limited IRB review. The limited IRB review does not require consideration of all the approval criteria described in §46.111. In limited IRB review, the IRB must determine that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of subject data.

FDA-Regulated Research

The Mass General Brigham IRB reviewer or designated reviewer is responsible for making determinations of exemption from IRB requirements in accordance with 21 CFR 56.104(b)(c)(d) as quoted below:

1. Research which started before July 27, 1981, and either did not require FDA approval before that date, or, was subject to requirements for IRB review prior to that date, and remains subject to review by an IRB which meets FDA requirements
2. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.
3. Taste and food quality evaluation and consumer acceptance studies. If wholesome foods without additives are consumed or if the food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Services of the U.S. Department of Agriculture.

The exemption at 21 CFR 56.104(c), the emergency use of a test article, is covered in a separate policy *Emergency Use of an Investigational Drug or Biological Product, or Unapproved Medical Device*.

The exemption at 21 CFR 56.104(c) does not apply to human subject research regulated by the DHHS.

FDA-regulated research determined to be exempt from 21 CFR 56 IRB requirements is subject to 21 CFR 50 Informed Consent of Human Subjects.

Exempt Review

The reviewer is responsible for reviewing the application to determine that all the research procedures fit one or more of the exemption categories specified in the federal regulations (refer to the above categories). The reviewer may request additional information from the PI to aid in providing clarifications where necessary.

The reviewer ensures the research meets the institution's ethical principles for human subject protection, specifically the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (the "Belmont Report") and the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

When exempt research involves an interaction with participants, the Mass General Brigham IRB

Chairperson or designated reviewer will review the research plan to ensure that subjects (when appropriate) are (1) informed that the activity is research and that their participation is voluntary; and (2) given a description of the research activity and the name and contact information for the investigator conducting the research.

The reviewer may request additional information from the PI to make the determination or request changes in the research to meet the institution's ethical principles for human subject protection and the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

When the reviewer requires additional information or modifications in the research to secure the exemption determination, the Human Research Office notifies the PI in writing of the required modifications to secure the exemption determination or additional information required to make the determination.

When received, the reviewer considers the PI's response and, when applicable, makes the exemption determination. The reviewer may continue to request information or require modifications until a determination can be made. The reviewer uses the Exempt Checklist within Insight to document final determinations and exempt category(ies).

Review Outcome

The reviewer makes one of the following decisions:

- 1) Determination that the research does not qualify for exempt status. Notification is provided in writing to the PI and includes the rationale for the determination and recommendations for submission of non-exempt research application. If the reviewer determines the research does not qualify for exempt status, the reviewer shall direct the PI to submit an application for expedited or full Board review, as applicable.
- 2) Determination that the research qualifies for exemption. Notification of exempt determinations is provided in writing to the PI through the Insight system.

All exempt protocols are assigned a three (3) year expiration date from date of exempt determination.

- 1) Research designated exempt by the Mass General Brigham IRB does not require continuing review.
- 2) Research designated exempt by the Mass General Brigham IRB will be assigned an Exempt Check-In expiration date which will be scheduled 3 years from the date of the exempt determination.
- 3) The Exempt Check-In is a brief two question status update designed solely to track whether the research is active or closed. Closed protocols will be asked to provide total number enrolled, if applicable, and date of closure.
- 4) Thirty days prior to the Exempt Check-In expiration date, the PI will receive a notification instructing them to update the status of the project by creating an Exempt Check-In within Insight.
- 5) Once the Exempt Check-In is submitted and signed off by the PI, Insight will automatically process the submission and update the status to either Exempt, Active or Exempt, Closed.
- 6) Insight will generate a letter documenting completion of the Exempt Check-In submission, the status

of the protocol will be updated, and active protocols will be scheduled for another Exempt Check-In in 3 years.

- 7) If the PI does not complete the Exempt Check-In, the research will automatically terminate 30 days after the expiration date. Insight will generate a letter documenting the automatic closure at 30 days.

OTHER APPLICABLE MASS GENERAL BRIGHAM POLICIES:

IRB Member Conflicts of Interest

Emergency Use of an Investigational Drug or Biological Product, or Unapproved Medical Device

REFERENCE:

45 CFR 46

21 CFR 50, 56

21 CFR 56.104

DEVELOPMENT AND CONSULTATION:

Human Research Office