Mass General Brigham

HUMAN RESEARCH AFFAIRS

INSTITUTIONAL REVIEW BOARD (IRB) POLICIES

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Table of Contents

1 AUTHORITY 6
2 INDEPENDENCE OF THE IRB 7
3 ETHICAL PRINCIPLES 8
4 APPLICABLE LAWS AND REQUIREMENTS 8
4.1 Requirements for Clinical Trials 8
4.2 Requirements for Off-Site Research 8
5 EDUCATION AND TRAINING 10
5.1 Investigators and Research Teams 10
5.2 Sponsor-Investigators 10
5.3 IRB Members 11
5.4 IRB Staff 11
6 RESPONDING TO CONCERNS OF RESEARCH PARTICIPANTS 11
7 CONFLICTS OF INTEREST 12
7.1 Institutional Conflicts of Interest 12
7.2 Individual Conflicts of Interest 12
8 INSTITUTIONAL REVIEW BOARD 14
8.1 Governance and Leadership 14
Senior IRB Chair 14
IRB Chairs 14
IRB Vice Chairs 14
IRB Office 15
IRB Executive Committee 15
8.2 Specific Functions 15
8.3 Membership 16
8.4 Appointment and Responsibilities 17
8.5 Onboarding 18
8.6 Evaluation 19
8.7 Offboarding 19
8.8 Rosters 19
8.9 Member Conflicts of Interest 20
9 EXEMPT HUMAN RESEARCH 21
9.1 Exempt Determinations 22

9.2 Administrative Check-In 22
9.3 DHHS Regulated Research 23
9.4 Applicability to Vulnerable Populations 25
9.5 Limited IRB Review 26
9.6 FDA-Regulated Research 26
10 FULL BOARD REVIEW 26
10.1 Full Board Meetings 26
10.2 Chair Responsibilities 28
10.3 Determinations of the Full Board 28
10.4 Discussion and Vote 29
10.5 Quorum 30
10.6 Minutes and Meeting Attendance 30
10.7 Continuing Review 31
10.8 Amendments 33
10.9 Data and Safety Monitoring Plans 33
10.10 Determining Which Studies Need Verification from Sources Other Than the Investigator 34
10.11 Use of Consultants 34
10.12 Guests 35
11 EXPEDITED REVIEW 35
11.1 Expedited Reviewer Responsibilities 36
11.2 Expedited Categories 36
11.3 Determinations of the Expedited Reviewer 38
11.4 Expedited Review Process 38
11.5 Continuing Review and Administrative Review 39
11.6 Amendments 40
11.7 Determining Which Studies Need Verification from Sources Other Than the Investigator 40
11.8 Reports of Expedited Determinations 41
11.9 Use of Consultants 41
12 VULNERABLE POPULATIONS 41
12.1 Pregnant Women or Fetuses 41
Federal Regulations at 45 CFR 46.204 41
State Law M.G.L. ch. 112, s. 12J(a) 42
12.2 Neonates 43

Federal Regulations 45 CFR 46.205 43
State Law M.G.L. ch. 112, s. 12J 44
12.3 Research on Pregnant Women, Fetuses or Neonates Not Otherwise Approvable 44
12.4 Children 44
Subpart D Child Categories (45 CFR 46 and 21 CFR 50) 44
Requirements for permission by parents or guardians and for assent by children (45 CFR 46.408/21 CFR 50.55) 46
Wards (45 CFR 46.40) 46
12.5 Participants with Impaired Decision-Making Capacity 47
12.6 Prisoners 48
13 RECRUITMENT OF RESEARCH PARTICIPANTS 48
13.1 Clinical Trial Website Postings 49
14 INFORMED CONSENT 49
14.1 General Requirements 50
14.2 Key Information 50
14.3 Basic Elements of Informed Consent 50
14.4 Additional Elements of Informed Consent 51
14.5 Massachusetts State Law 52
14.6 Applicable Clinical Trials 52
14.7 Requirement for Posting of Informed Consent Forms 52
14.8 Individuals Who Can Give Informed Consent/Permission 52
Parental/Legal Guardian Consent for Children 53
Assent of Children 53
Children Who Turn 18 During Study Participation 54
Children Who Can Give Legally Effective Informed Consent 54
Surrogate Consent for Adults 55
Individuals with Impaired Decision-making Capacity 55
14.9 Documentation of Written Informed Consent 55
Digital Signatures 56
Individuals Who Cannot Write or Are Physically Unable to Sign the Consent Form 56
14.10 Waiver of Documentation of Informed Consent 56
14.11 Alteration or Waiver of Elements of Informed Consent 57
14.12 Withdrawal of Participants: Record Retention and Requirements for Informed Consent for Continued Limited Participation 58

15 REMUNERATION FOR RESEARCH PARTICIPANTS 58
16 BONUS PAYMENTS IN CLINICAL TRIAL AGREEMENTS 58
16.1 Generally Acceptable Payment Structures 59
16.2 Unacceptable Payment Structures 59
17 NONCOMPLIANCE IN HUMAN RESEARCH 60
17.1 Allegations of Noncompliance 61
17.2 Handling Reports of Noncompliance 62
17.3 Noncompliance Review by the Full Board IRB 63
17.4 Corrective and Preventative Actions 63
17.5 Allegations of IRB Noncompliance 64
18 UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS 64
18.1 Investigator Reporting of UPIRTSOs 65
18.2 Handling Reports of UPIRTSOs 66
18.3 UPIRTSO Review by the Full Board IRB 66
18.4 Corrective and Preventative Actions 67
19 SUSPENSION OR TERMINATION OF IRB APPROVAL 67
20 REPORTING TO AUTHORITIES 68
21 INVESTIGATIONAL DRUG REQUIREMENTS 70
21.1 Clinical Investigations and Requirements for INDs 70
Dietary Supplements 70
Radioactive Drugs 70
21.2 IND Documentation 71
21.3 Drug Products not Manufactured by a Licensed Pharmaceutical Company 71
Drug Products with INDs 71
Drug Products without INDs 71
22 INVESTIGATIONAL DEVICE REQUIREMENTS 71
22.1 Clinical Investigations of Devices 72
Investigations Exempt from IDE Requirements (21 CFR 812.2(c)) 72
Investigations Requiring an IDE (21 CFR 812) 73
Nonsignificant Risk Device Investigations (21 CFR 812.2(b)) 73
22.2 Humanitarian Use Devices 74
23 EMERGENCY USE 74
23.1 Investigational Drugs or Biological Products 75

23.2 Unapproved Medical Devices 76
24 EXCEPTION FROM INFORMED CONSENT REQUIREMENTS FOR EMERGENCY RESEARCH 76
24.1 Protocol Submission Requirements 77
24.2 IRB Findings and Determinations 77
24.3 Additional IRB Responsibilities 79
24.4 Requirement for IND or IDE 79
24.5 Notification of Disapproval 79
25 MULTI-SITE RESEARCH 80
25.1 Single IRB Review 80
25.2 Reliance on an External IRB for Mass General Brigham Research 80
25.3 Mass General Brigham Serving as the Reviewing IRB 83
25.4 Establishing Reliance Agreements 84
25.5 Review of Operation Centers or Coordinating Centers 85
26 IRB RECORDS 85
27 APPENDICES 88
27.1 APPENDIX I: APPLICABLE LAWS 88
27.2 APPENDIX II: MASS GENERAL BRIGHAM INCORPORATED ENTITIES 90
27.3 APPENDIX III: IRB MEMBER RESPONSIBILITIES 91
27.4 APPENDIX IV: DEFINITIONS 93

1 AUTHORITY

The Mass General Brigham Institutional Review Board (IRB) has jurisdiction over all human research conducted by Mass General Brigham employees or its agents in connection with their system roles or responsibilities, under the auspices of Mass General Brigham, or in which our system is otherwise engaged, regardless of the location of the research or source of funding. References to "Mass General Brigham" in this Policy refers to Mass General Brigham Incorporated and its entities listed in Appendix II attached to this Policy. The IRB also has jurisdiction over human research conducted by entities that enter into Reliance Agreements documenting the IRB as the entity's IRB of record for specified research.

Mass General Brigham is engaged in human research whenever its employees or agents for the purposes of the research: (1) intervenes or interacts with living individuals to obtain data; (2) obtains or uses individually identifiable private information or biospecimens about living individuals; (3) obtains the informed consent of human participants;or (4) receives an award to conduct human research even when all activities involving human participants are carried out by a subcontractor or employees or agents of another institution. Mass General Brigham is also engaged when its employees or agents conduct clinical investigations subject to Food and Drug Administration (FDA) regulations. Mass General Brigham does not conduct classified research.

The IRB is authorized to review and oversee human research that is conducted by employees or agents of Mass General Brigham in connection with their system responsibilities, regardless of the location of the research or source of funding, in accordance with federal, state, and local laws and regulations.

Except for research exempted under 45 CFR 46.104 and 21 CFR 56.104 or waived in accordance with 45 CFR 46.101(i) or 21 CFR 56.105, all human research will be reviewed, approved, and is subject to continuing oversight and review as required under the Federal Policy for the Protection of Human Subjects codified by Health and Human Services (HHS) in 45 CFR part 46 and revised in 2018 (the 2018 Common Rule) requirements at 45 CFR 46.109 and FDA regulations at 21 CFR 56.109. The IRB has the authority, as recognized by the Institutional Officials (IOs) for Mass General Brigham, to:

1. approve, require modifications, or disapprove all research activities that fall within its jurisdiction;
2. suspend, place restrictions on, or terminate approval of research activities that fall within its jurisdiction that are not being conducted in accordance with IRB requirements or that have been associated with unanticipated problems;
3. observe or have a third party observe the consent process and/or the conduct of the research if the IRB determines it to be indicated;
4. request a directed audit by the Mass General Brigham Human Research Affairs (HRA) Compliance & Education Office (C&E Office);
5. otherwise investigate, address, remedy and, when required or appropriate, report on incidences of noncompliance with legal, regulatory, institutional, or IRB requirements or determinations;
6. conduct reviews and inquiries regarding human research as needed to obtain information necessary for the fulfillment of human research protection responsibilities and, for federally funded research, the institutional responsibilities outlined in the entities' Office for Human Research Protections (OHRP)-approved Federalwide Assurance (FWAs); and
7. act as the Health Insurance Portability and Accountability Act, and its implementing regulations (HIPAA) Privacy Board for research activities.

The IRB also has the authority for determining:

- whether a research activity is human subjects research as defined in 45 CFR 46 or a clinical investigation as defined in 21 CFR 50, 56, 312 and 812, or other applicable federal regulations;
- whether Mass General Brigham is engaged in human research within the meaning of DHHS regulations; and
- whether a research activity involving human participants is exempt from 45 CFR 46.104 and 21 CFR 56.104. Investigators or others within Mass General Brigham may not independently make exemption determinations.

Before employees or agents of Mass General Brigham undertake activities that might be considered human research, they are expected to consider whether the activity is research involving human subjects as defined in DHHS regulation 45 CFR 46 or a clinical investigation involving human subjects or subjects as defined in FDA regulations 21 CFR 50, 56, 312 and 812. If uncertain, an investigator should submit an application to the IRB for a determination. Determinations are based on whether the activity meets the definitions outlined in this Policy. The IRB determination will be documented in a determination letter sent to investigators.

When any research overseen by the IRB takes place in a foreign country, the procedures prescribed by the international organization, if any, must afford protections that are at least equivalent to those provided by the IRB and the research design will consider the local research context where research procedures will occur.

In exercising their authority, the IRB communicates its decisions regarding human research to investigators and to the organization through the IRB Office and/or the research application and data management system called Insight.

2 INDEPENDENCE OF THE IRB

The IRB acts as an independent authority in the review and oversight of human research for Mass General Brigham. Consistent with federal regulations at 45 CFR 46.112 and 21 CFR 56.112, no one may approve human research to be conducted at Mass General Brigham that has not been approved by the IRB or one of its designated external IRBs operating under a Reliance Agreement. However, research approved by the IRB may be subject to further institutional review and approval.

In the event of attempted undue influence on the IRB (e.g., someone outside of the IRB seeks to influence the outcome of IRB review of a research activity), the Mass General Brigham Vice President of Human Research Affairs (VP HRA) will work with system leadership and the IRB as necessary, to remedy any concern. If the allegation is found to have no basis in fact, the VP HRA will document the findings and take no further action. If it is determined that undue influence did occur, the VP HRA will preserve the IRB's review independence in all such instances. Measures may include, for example, discussion between the VP HRA and the person causing the undue influence and, when appropriate, discussion with the appropriate department or division chair or supervisor; reassignment of the protocol to another IRB reviewer; and/or recusal of the IRB member upon whom undue influence was exerted. Undue influence by the VP HRA will be reported to the Mass General Brigham Chief Academic Officer (CAO). The CAO will work with the individual(s) reporting concerns and others as appropriate to investigate allegations of undue influence. If the allegation is found to have no basis in fact, the CAO will document the findings and take no further action. If there is cause to believe that undue influence exists, the CAO will take the appropriate steps to eliminate the undue influence. These steps may include education and counseling, evaluation of processes and policies or other actions as appropriate.

3 ETHICAL PRINCIPLES

Mass General Brigham research is guided by the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, generally known as the "Belmont Report" in its review of exempt and non-exempt research and clinical investigations. Mass General Brigham, including, but not limited to, its organizational officials, institutional officials, department heads/chairs/chiefs, professional staff, investigators and study staff (including students), Human Research Protection Program, and all other employees of Mass General Brigham have the ethical obligation to protect the rights and welfare of research participants in accordance with legal requirements and ethical guidelines.

4 APPLICABLE LAWS AND REQUIREMENTS

Mass General Brigham and its IRB operates in full compliance with all applicable federal, state, and local laws and regulations, and with the FWAs and incorporated "Terms of the Federalwide Assurance for Institutions within the United States" held by the Mass General Brigham entities. Mass General Brigham follows DHHS, FDA federal regulations as well as state laws pertaining to research and human research protections. In research conducted or supported by federal entities, Mass General Brigham follows such federal entities' regulations, as applicable (*see Appendix I*). In research not conducted or supported by federal entities, Mass General Brigham may apply different requirements.

The IRB acts as the HIPAA Privacy Board for Mass General Brigham in compliance with HIPAA regulations and as such reviews exempt and non-exempt research with regard to the requirements of HIPAA.

4.1 Requirements for Clinical Trials

In addition to other applicable federal, state, and local laws and regulations, Mass General Brigham follows the International Council on Harmonization – Good Clinical Practice E6-R2 (ICH-GCP E6) for clinical trials to the extent it is consistent with FDA and DHHS regulations.

4.2 Requirements for Off-Site Research

When Mass General Brigham investigators conduct research at a location off-site in their Mass General Brigham capacity they must follow the Mass General Brigham policies and procedures for conduct of that research. Such research must also be conducted in compliance with applicable international, federal, state, and local laws and regulations of the location where the research occurs, as well as any requirements of the performance site's institution or entity, as applicable.

Research conducted by Mass General Brigham employees or agents wholly or partly in a space or a site leased by Mass General Brighamfrom another entity (the landlord) will be considered in the same way as research conducted in/at Mass General Brigham owned space/sites. However, the investigator is responsible for confirming with the landlord, the responsible Mass General Brigham office, or others as necessary that the specific proposed research activities are consistent with the activities permitted to be conducted in the space or at the site under the terms of the lease.

Investigators must specify in the Insight application the places where Mass General Brigham employees or agents will conduct the research, including any off-site locations. These sites may be institutions, facilities, or entities such as Mass General Brigham and non-Mass General Brigham healthcare institutions; private physician or group practices; rehabilitation, nursing, or assisted living facilities; private or public primary schools, colleges or universities; community or other activity-based centers; and patient or professional conferences. They may be located in Massachusetts, other U.S. locations, or outside the U.S.

The IRB will consider whether the performance sites listed in the application are engaged in human research and what, if any, additional IRB approvals are needed. The OHRP guidance document *Guidance on Engagement of Institutions in Human Subjects Research* will be used as the basis for determining engagement in human research. When the research will be conducted off-site at a performance site that is **not** engaged in human research, the IRB may require written documentation of permission to use the facilities for research signed by the performance site's legally authorized representative.

When the performance site is engaged in human research, the section on *Multi-Site Research* in this Policy applies. If the off-site research includes international performance sites, the following also apply:

- Research conducted outside the United States or its territories will generally be subject to approval of a local IRB or Ethics Committee (EC) and/or governmental officials, such as the Ministry of Health. When reviewing the research:
    - The IRB will ensure that the participants are afforded protections that are at least equivalent to those provided by IRB policies and the ethical standards outlined in the Belmont Report. This includes: (1) initial and continuing review; (2) review of changes in approved research; (3) reporting and handling of complaints, unanticipated problems involving risks to participants or others and noncompliance; and (4) post-approval monitoring.
    - The IRB will take into consideration the local IRB or EC review of the qualifications of the local investigators and study staff, the recruitment and consent procedures and language issues, as well as other culturally-based issues.
        - When the research is federally-funded, local IRB or EC approval must be obtained from an entity in that country that has a currently approved FWA and a registered IRB or EC.
        - When the research is also subject to review of the local IRB or EC, the IRB requires documentation of review and approval throughout the project.
        - When unanticipated problems or noncompliance are reported to the IRB, the IRB will require documentation of local IRB or EC review and, when appropriate, will communicate directly with the local IRB or EC.
        - Post-approval monitoring will be coordinated with the local IRB or EC when required and as needed.

- When the performance site is outside the United States or its territories and there is no local ethics review process at the international site, consultants at the international site or within the United States will be asked to provide information about the investigators, performance site and applicable laws. Consultants in this context are individuals with personal knowledge of the local research context, such knowledge having been obtained through extended, direct experience with the research institution, its participant populations and its surrounding communities. The IRB must confirm the qualifications of the investigators and study staff conducting research in that country and consider the cultural, economic and political conditions in the country where the research will take place when reviewing the study population and recruitment and consent procedures and when assessing the risks and potential benefits to participants.

5 EDUCATION AND TRAINING

Mass General Brigham has a legal and ethical responsibility to protect the rights and welfare of human participants in research it conducts or sponsors, or in which Mass General Brigham is otherwise engaged regardless of the location of the research or source of funding. Consistent with these responsibilities, Mass General Brigham requires every individual engaged in human research overseen by the IRB to have appropriate training in human research protections. The HRA also requires that IRB Staff have education and training appropriate to their roles.

5.1 Investigators and Research Teams

Mass General Brigham investigators and all members of their research teams must complete the HRA Good Clinical Practice (GCP) and Clinical Research Boot Camp live webinar or online courses in HealthStream prior to their involvement in the research. In addition, both courses must be completed every three years as continuing education.

For research conducted by sites for which Mass General Brigham is serving as the single IRB under a Reliance Agreement, the Reliance Agreement obligates the site to require appropriate human research training according to their local policies and procedures.

Notwithstanding this policy, the IRB may require an investigator and/or their research teams to fulfill additional education and training requirements based on the type of research they are conducting (e.g., IND/IDE sponsor-investigator research as described in this section) or as part of remedial education. It is strongly recommended, in addition to the training requirements listed above, that individuals take one or more of the human research education courses offered by the C&E Office.

Principal Investigators are responsible for ensuring that the study staff listed on their protocols complete their education requirements prior to addition to their research team and every three years for as long as the study staff are active on the research. New research involving human participants, continuing reviews, or amendments to add staff cannot be submitted to the IRB until all of the study staff listed on the protocol have completed the human research training requirements including, when applicable, continuing education requirements. Insight will not allow submission of a continuing review or amendment within 30 days of a staff member's certification lapsing.

Failure of the investigator or study staff to comply with the human research training requirements will be considered noncompliance with IRB policies and procedures.

5.2 Sponsor-Investigators

Before allowing a sponsor-investigator to conduct research as a first-time sponsor-investigator, the IRB requires the investigator complete the HRA Sponsor-Investigator Certification and undergo a review of FDA sponsor-investigator responsibilities with the C&E Office.

5.3 IRB Members

Potential IRB members must complete the Mass General Brigham required human research courses or the OHRP education (community members) and review training materials on IRB operations and federal regulations before becoming a member. During the course of their membership, continuing education is provided through presentations at meetings, distribution of educational materials, and opportunities to participate in webinars or online workshops. Additionally, members have access to additional HRA education courses offered by the C&E Office. The Senior IRB Chair or their designee(s) is responsible for educating members about new policies, procedures, or guidance from Mass General Brigham, the FDA, OHRP, or other governing or expert groups. Members are encouraged to attend local, regional, or national conferences each year. The cost of attending conferences is covered by Mass General Brigham HRA when funds are available in the budget.

5.4 IRB Staff

IRB Staff must complete initial and continuing education regarding human research protections via the required HRA education courses offered by the C&E Office. Additionally, IRB Staff receive ongoing training via various mechanisms, including participating in webinars, attending seminars/meetings and as provided by their supervisors or other Mass General Brigham HRPP leadership. IRB Staff who have responsibility for screening full board or expedited research or who are designated as expedited reviewers must be certified as a Certified IRB Professional (CIP) as a condition of employment. Staff are encouraged to attend local, regional, or national conferences each year. The cost of attending conferences is covered by Mass General Brigham HRA when funds are available in the budget.

6 RESPONDING TO CONCERNS OF RESEARCH PARTICIPANTS

Mass General Brigham designates the IRB to respond to research participants who wish to discuss problems, wish to express concerns, have questions, or wish to provide input to someone who is not affiliated with a specific research protocol (collectively, participant concerns). The IRB provides a safe, confidential and reliable point of contact for prospective, current, or past research participants.

All informed consent forms provide contact phone and email for the IRB Office. Research participants may also contact the Mass General Brigham Compliance Hotline by phone or email, submit a request via the Mass General Brigham public website, or be referred by research team members. HRA under which the IRB operates also oversees the Research Navigator Office (RNO) which provides a helpline for research participants during normal business hours. The RNO provides help with contacting research study personnel, finding research opportunities for individuals, and answering research questions. All participant concerns received via any of these other methods are referred to the IRB Office.

The IRB Office Director or designee is responsible for responding to research participants. The IRB Office Director documents the participant concern and resolution if any in the confidential IRB Office records. The IRB Office Director may engage others in the system as appropriate to help in resolving participant concerns.

7 CONFLICTS OF INTEREST

7.1 Institutional Conflicts of Interest

Review of human research by the IRB must take into consideration institutional financial interests that may be relevant to the conduct of the research. Collaborations between Mass General Brigham and industry provide opportunities for productive collaborations and advances in patient care. However, financial interests of Mass General Brigham or Mass General Brigham institutional officials cannot be allowed to compromise, or appear to compromise, the safety or integrity of human research.

An institutional conflict of interest (ICOI) may exist when any of the following might affect the design, conduct or reporting of the research:

1. Investments of the institution;
2. Payments from licenses, including royalties;
3. Major gifts to the institution; or
4. Interests of Mass General Brigham institutional officials.

The Mass General Brigham Office for Interactions with Industry (OII) is responsible for maintaining a list of financial holdings and financial interests or fiduciary duties of institutional officials that may create an ICOI (the "entity list"). OII will periodically, but no less frequently than annually, provide the IRB Office with a copy of the entity list. IRB Staff utilize the entity list when conducting triage and screening of applications submitted via Insight to identify studies for which there may be a related ICOI. The following situations may create an institutional conflict of interest:

1. Mass General Brigham human research is sponsored by an entity on the entity list;
2. Mass General Brigham human research is evaluating an investigational drug or device manufactured by an entity on the entity list.

When IRB Staff identify a study with which there is a potential ICOI, they will notify the IRB Director, or designee, who will in turn notify OII. OII will conduct an assessment to determine whether there is an ICOI that must be managed pursuant to the Mass General Brigham *Policy for Interactions with Industry and Other Entities* and applicable OII standard operating procedures.

In the event that OII determines there is an ICOI related to human research submitted to the IRB for review, OII will provide to the IRB documented controls for managing the ICOI, which may include that the research will not be reviewed by the IRB, or confirmation that management is not required. The IRB application will not be assigned to a Chair or designee for IRB review or to an agenda for review by the full board prior to the IRB receiving the documented management strategies or confirmation that management is not required. The Chair, designee or full board will ratify the documented management controls and may add additional management controls to ensure the protection of participants. The Chair, designee or full board may not remove any management controls required by OII.

7.2 Individual Conflicts of Interest

Review of human research by the IRB must take into consideration financial interests that may be relevant to the conduct of the research. In cases when the IRB determines that there is a financial conflict of interest that could affect or otherwise be relevant to the research, the IRB must determine that the conflict is either eliminated or appropriately managed to ensure that the rights and welfare of human participants are protected. The IRB, in its discretion, may consult or coordinate with other committees within the institutions in making such determinations. The IRB may choose to delegate portions of the collection, review, analysis,

and proposed resolution of any particular situation to other institutional officials. The IRB has final authority to make decisions regarding resolution of the conflict in the context of the conduct of the research. Note: Investigators are also subject to the disclosure and other requirements of the Faculty of Medicine Harvard University Policy on Conflicts of Interest and Commitment ("Harvard Medical School Conflicts of Interest Policy") and/or the Mass General Brigham Conflicts of Interest Policy.

Principal investigators, site responsible investigators, co-investigators and any other member of the study staff identified by the Principal Investigator as being responsible for the design, conduct, or reporting of human research or clinical investigations in such categories as determined by the IRB must disclose their Financial Interests through Insight by completing the Investigator Financial Disclosure Form on a study-by-study basis. For each study, investigators are required to disclose, whether they, or to their knowledge, any family member have a financial interest in a company that could reasonably appear to be related to the study, specifically whether a company in which they have a financial interest:

a. Is the sponsor of the study;
b. Owns, manufactures, or develops any drug, device, or technology that is used in a significant way in the study;
c. Is developing products or technology similar to any drug, device, or technology that is being investigated by the study;
d. Owns, manufactures or develops any drug, device, or technology, the value of which could be influenced by the results of the study;
e. Could reasonably be interested in any new IP resulting from the study; or
f. Could otherwise reasonably appear to be affected by the study.

Completion of the Investigator Financial Disclosure Form does not take the place of the obligation of staff to fill out other periodic conflict of interest disclosure forms that are required by Harvard or Mass General Brigham. Investigator Financial Disclosure Forms that disclose financial interests that could reasonably be related to the study are referred to the Office for Interactions with Industry (OII) for review.

The OII reviews any disclosed financial interests of individuals that are not prohibited by the Harvard Medical School Conflicts of Interest Policy, the Mass General Brigham Conflicts of Interest Policy, or other applicable policies and makes recommendations to the IRB relating to the disclosed financial interest. The recommendations may include (but are not limited to) that the disclosed financial interest is:

- not acceptable (in which case the financial interest must be divested or other action taken);
- acceptable with some form of management (such as disclosure, restrictions on the activities of the investigator, or such other form as determined appropriate); or
- acceptable without any need for management.

Investigators must report to the OII and to the IRB any changes to the information provided in the Investigator Financial Disclosure Form, as soon as possible, but in no event later than thirty (30) days after the change.

The Senior IRB Chair or designee or the IRB may request information on and review any other financial interests that could affect or otherwise be relevant to a specific research protocol.

The Senior IRB Chair or designee or the IRB reviews the recommendations of the OII and determines whether the recommendations are acceptable. If not, the IRB may determine that other action needs to be taken. The IRB has final authority to make decisions regarding management of the conflict and the conduct of the research.

The investigator with disclosed financial interests, and other pertinent institutional officials as appropriate, shall be notified of the determinations of the IRB with respect to disclosed financial interests as part of the IRB review notification process.

8 INSTITUTIONAL REVIEW BOARD

8.1 Governance and Leadership

The IRB operates under the VP HRA who reports directly to the Mass General Brigham Chief Academic Officer/Institutional Official (CAO) .

The VP HRA appoints a Senior IRB Chair, IRB Chairs and Vice Chairs. The Senior IRB Chair and IRB Chairs report to the VP HRA with respect to their IRB responsibilities. The Vice Chairs report to the Senior IRB Chair with respect to their IRB responsibilities. Chairs are selected based on their commitment to the mission and values of Mass General Brigham and to the field of human participant protections, their knowledge of research and regulatory affairs, personal integrity and collaborative approach, and ability to conduct an effective and efficient meeting. All chairs are expected to embody the highest standards of ethical and professional conduct and to comply with applicable federal regulations, state laws, and Mass General Brigham policies and procedures.

8.1.1 Senior IRB Chair

The Senior IRB Chair is responsible for the overall conduct of the IRB and for reviews conducted by the designated expedited reviewers to ensure compliance with federal, state, and local laws and regulations, Mass General Brigham policies and procedures, and the ethical principles described in the Belmont Report. This position acts as the primary liaison to HRA leadership and federal regulatory authorities on behalf of the IRB and involves regular interaction with Principal Investigators and research team members. The VP HRA evaluates and provides feedback to the Senior IRB Chair annually.

8.1.2 IRB Chairs

The IRB Chairs act as primary liaisons with investigators at their respective hospitals and assume the responsibilities of the Senior IRB Chair when that person is temporarily unavailable. The IRB Chairs are responsible for chairing full board IRB meetings on a regular basis and conducting expedited reviews as needed in compliance with federal, state, and local laws and regulations, Mass General Brigham Policies and Procedures, and the ethical principles described in the Belmont Report. The IRB Chair leads meetings in an organized and collaborative manner engaging and respecting the perspectives of both the scientists and community board members. IRB Chairs regularly interact with Principal Investigators and research team members to discuss their IRB applications and facilitate a collaborative review process. The VP HRA evaluates and provides feedback to the IRB Chairs annually.

8.1.3 IRB Vice Chairs

The Vice Chairs are responsible for chairing full board IRB meetings on a regular basis and conducting expedited reviews as needed in compliance with federal, state, and local laws and regulations, Mass General Brigham Policies and Procedures, and the ethical principles described in the Belmont Report. The Vice Chair leads meetings in an organized and collaborative manner engaging and respecting the perspectives of both the scientists and community board members. Depending on their contributed effort, this position may also regularly conduct expedited reviews as designated by the IRB Chair. This position involves regular interaction with Principal Investigators and research team members to discuss their IRB applications and facilitate a

collaborative review process as well as meetings with the IRB and HRA leadership to contribute to the development of policies and ethical approaches to the protection of human research. The Senior IRB Chair evaluates and provides feedback to the Vice Chairs annually.

8.1.4 IRB Office

The IRB Office provides professional and administrative infrastructure to support the mission and operations of the IRB. The IRB Office coordinates its activities with other Mass General Brigham committees, offices, and leadership that comprise the Mass General Brigham HRPP. The IRB Office oversees and enforces compliance system-wide with federal regulations governing the conduct of human research, with state and local laws and with system policies and procedures. Designated staff are responsible for conducting IRB expedited reviews and approvals on behalf of the full board IRB. The IRB Office develops system-wide policies and procedures for the conduct of research in compliance with federal regulations, state and local laws, and other Mass General Brigham policies and procedures. The IRB Office provides support and consultation to the research community through virtual office hours, an email helpline, and individual consultations. The VP HRA appoints the Director of the IRB Office. The Director oversees the day-to-day operations of the IRB office and delegates responsibilities to IRB Staff as appropriate to ensure completion of tasks. The IRB Office retains equipment and the resources required for the functioning of the IRB and the IRB Office.

8.1.5 IRB Executive Committee

The VP HRA establishes the IRB Executive Committee consisting of the Senior IRB Chair and the IRB Chairs. The IRB Executive Committee acts as an advisory committee to the VP HRA and contributes to the development of policies and ethical approaches to the protection of human research. The Senior IRB Chair acts as chair of the IRB Executive Committee and the IRB Office Director and Assistant Director, Full Board are ex officio members.

Policies implementing the authorities of the IRB or concerning IRB operations are developed by the IRB Office and IRB Executive Committee and approved by the VP HRA. Policies intersecting with or affecting other system offices or processes may be developed in consultation and coordination with those offices or entity research leadership and are generally approved by the CAO. All IRB policies and procedures comply with Mass General Brigham Policy Management Process.

The IRB policies and procedures, including IRB guidance documents and significant policy-related communications to the research community, are made available on the Research Navigator website and/or Research Hub and are maintained by the IRB Office for at least seven (7) years from the date of their adoption/distribution and are made available upon request to authorized representatives of the sponsor and, when applicable, authorized representatives of DHHS, FDA and other federal agencies for inspection within a reasonable time frame and copying onsite during normal business hours. IRB policies and procedures applicable to external entities for which the IRB serves as a reviewing IRB are available on the Mass General Brigham public facing website.

8.2 Specific Functions

The IRB conducts initial and continuing ethical and scientific review of non-exempt human research at intervals appropriate to the degree of risk and, when required by regulations, not less than once per year and reviews proposed changes in approved research during the period of IRB approval either at a full board meeting of the IRB or, when applicable, by use of the expedited review procedure authorized in 45 CFR 46.110 and, when applicable, 21 CFR 56.110. The IRB relies on the scientific review conducted as part of review by a federal funding agency, by the FDA, by a cancer center Scientific Review Committee or other organizational scientific review process. When a prior scientific review has not occurred or when the research

is regulated by the Department of Defense, the IRB conducts a scientific review in conjunction with its ethical and regulatory review. When conducting initial and continuing review or review of proposed changes in approved research, the IRB determines that all of the requirements for approval of human research in 45 CFR 46.111 and, when applicable, 21 CFR 56.111, are satisfied.

The IRB follows written policies and procedures for:

1. Determining whether a research activity submitted for IRB review is human research or a clinical investigation within the meaning of DHHS, FDA or other applicable federal regulations;
2. Determining exemptions from 45 CFR 46 and 21 CFR 56;
3. Conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and to the institution;
4. Determining which projects require review more often than annually;
5. Determining which projects need verification from sources other than the investigators that no material changes have occurred since the last review;
6. Ensuring prompt reporting of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the participant;
7. Ensuring prompt reporting to the IRB, appropriate institutional officials and, when required or appropriate, to the department or agency head (regulatory agencies) of any unanticipated problems involving risks to participants or others;
8. Ensuring prompt reporting to the IRB, appropriate institutional officials and, when required or appropriate, to the department or agency head (regulatory agencies) of any serious or continuing noncompliance with federal regulations or the requirements or determinations of the IRB;
9. Ensuring prompt reporting to the IRB, appropriate institutional officials and, when required or appropriate, to the department or agency head (regulatory agencies) of any suspension or termination of IRB approval; and
10. Except when an expedited review procedure is used, reviewing proposed research at full board meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present and eligible to vote when the research activity is reviewed at a full board meeting.

8.3 Membership

The IRB is composed of at least five (5) members with varying backgrounds to promote complete and adequate review of human research commonly conducted at the institutions. The membership includes individuals with the necessary experience and scientific or scholarly expertise and knowledge of the local research context to review the scope of biomedical and behavioral research conducted at Mass General Brigham. The membership does not include individuals who have responsibilities for negotiating grants or contracts with sponsors, or for business development of the research enterprise through research ventures and licensing.

The IRB is committed to supporting diversity, equity and inclusion across its membership and includes individuals who represent the perspective of the community from which individuals are recruited to

participate in research. No qualified individual will be rejected from the membership on the basis of race, gender, creed, religion, color, national origin, age, disability, or sexual orientation.

Each member has one vote and may have designated alternates with similar scientific or scholarly expertise. Should both the primary voting member and alternate voting member attend the same meeting and be present for review of the same research activity, only one member may vote on the specific research activity under review. The other is recorded in the minutes as attending, but not voting on the research activity.

The membership of each IRB panel includes:

- physicians;
- scientists;
- at least one member who is unaffiliated with Mass General Brigham or who is not part of the immediate family of a person who is affiliated with Mass General Brigham;
- at least one member whose primary concerns are in nonscientific areas, such as community members, ethicists, and clergy; and
- at least one member who represents the perspective of research participants.

8.4 Appointment and Responsibilities

IRB members are recruited on an ongoing basis as needed to ensure that the membership of the IRB continues to include individuals with varying backgrounds and the necessary experience and scientific or scholarly expertise to review the scope of biomedical and behavioral research conducted at Mass General Brigham and to represent the community from which participants are recruited. In addition, new members are recruited on an as needed basis to replace members who resign, whose term is ending, and, when needed, to provide additional scientific or scholarly expertise to review new research programs.

The IRB Executive Committee reviews the membership of the IRB at least annually to determine if the membership continues to include individuals with varying backgrounds and the experience and scientific or scholarly expertise needed to review the scope of biomedical and behavioral research conducted at Mass General Brigham. The IRB Office compiles information about member areas of expertise and representative capacity as well as the scientific areas covered by protocols reviewed at full board meetings. The IRB Executive Committee conducts a review of these data and provides a report to the VP HRA with recommendations for changes in IRB membership.

Affiliated members are recruited through the Chairs/Chiefs/Heads of the hospital departments, divisions or units, through direct outreach, or through current IRB members. Unaffiliated members may be recruited through current IRB members, direct outreach, or various community agencies or groups. Additionally, individuals who are affiliated or unaffiliated may self-refer.

The VP HRA appoints members to the IRB. The IRB Office prepares and distributes letters of appointment to the individual and when applicable, copies the relevant Department Chair, Chief or supervisor. If an individual's application for membership is not accepted, the VP HRA will provide notice in writing and include the basis for the decision.

Members are appointed for two-year renewable terms. The VP HRA has authority to make an exception to the appointment term for an individual member.

All members are expected to fulfill the responsibilities described in *IRB Member Responsibilities* (*see Appendix III*)

The VP HRA designates members at time of appointment as:

1. Physician Scientists, Other Scientists, or Nonscientists

    a. Physician Scientists are members who have a medical degree.
    b. Other Scientists are members whose training, background and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline or who have training or experience in scientific methods (e.g. PhD, MS, BSN, MSN).
    c. Nonscientists are members whose training, background and occupation would not incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline or does not have training or experience in scientific methods.

2. Affiliated or Unaffiliated

    a. Affiliated members include members or whose immediate family members have an affiliated role with Mass General Brigham. *"Immediate family member"* is defined as spouse, domestic partner, child, parent, or sibling. *"Affiliated"* includes, but is not limited to, employees including part-time employees; current students; members of any governing panel or board of the system; paid or unpaid consultants; healthcare providers holding credentials to practice at Mass General Brigham; retirees from Mass General Brigham receiving retirement benefits; and volunteers working at Mass General Brigham on business unrelated to the IRB.
    b. Unaffiliated members are those members who do not meet the definition of an Affiliated member.

3. Primary Member or Alternate Member

    a. Primary Members have responsibility to vote, abstain from voting, or recuse themselves from voting as applicable on each research activity considered by the IRB when they are present for the discussion and vote unless the primary member's alternate is present and is voting on the research activity.
    b. Alternate members have responsibility to vote, abstain from voting, or recuse themselves from voting as applicable on each research activity considered by the IRB panel when they are present for the discussion and vote and the primary member for whom they are a designated alternate member is not present or is not voting.

8.5 Onboarding

Prospective members provide information about themselves pertinent to their role on the IRB and participate in education prior to appointment including, but not limited to:

1. Providing a copy of their current curriculum vitae, resume, or personal statement summarizing their applicable background.
2. Completing the *IRB Member Information Sheet*.
3. Providing a signed Confidentiality/Non-Disclosure and Conflict of Interest Agreement.
4. Attending at least one meeting of the IRB.
5. Physicians and Other Scientist members complete the HRA Good Clinical Practice (GCP) and Clinical Research Boot Camp live webinar or online courses.
6. Nonscientist members complete the OHRP human subjects training.

7. Completing the IRB Member Orientation Program consisting of specific training in regulations and review of protocols.

8.6 Evaluation

Members are evaluated and provided feedback on a continual basis by the IRB Chairs and IRB sSaff based on fulfillment of their responsibilities designated in *IRB Member Responsibilities*. Concerns are provided to the Senior IRB Chair and/or IRB Executive Committee for consideration and remedy. Members are also surveyed every 2 years to provide a self-assessment of their knowledge of regulations and ethical principles, their participation at meetings, and to provide feedback on the IRB Chairs and IRB Staff. Members receive feedback from these surveys and are also provided with records of attendance and primary/secondary reviews.

8.7 Offboarding

A member may resign from the IRB prior to the end of their term by a written resignation submitted to the VP HRA. For members designated by their departments, the resignation must be with agreement from their Chair, Chief or supervisor.

The Chair, Chief or supervisor of members they have designated who resign from the IRB or whose term is ending, is responsible for identifying an appropriate replacement with similar scientific or scholarly expertise. The VP HRA or designee will notify the departments, divisions and supervisors of members whose terms are expiring at least 3 months prior to expiration to allow time for identification and onboarding of new members.

Members will receive a notification from the VP HRA if their membership is not renewed at the end of their term.

The VP HRA may suspend or remove any IRB member on recommendation from the IRB Executive Committee who fails to fulfill any of the responsibilities as defined in the *IRB Member Responsibilities.* The IRB Executive Committee or its designee is responsible for providing reasonable notice of the grounds for the suspension or removal and an opportunity to be heard.

8.8 Rosters

The IRB Office maintains a roster of members that includes the following:

1. Name;
2. Earned degrees;
3. Scientific status (physician scientist, other scientist, or nonscientist);
4. Experience and expertise, such as board certifications, licenses;
5. Representative capacity (e.g., children, pregnant women, economically disadvantaged, educationally disadvantaged, cognitively impaired adults); and
6. Affiliation, if any, with Mass General Brigham.

The IRB Office is responsible for updating the membership roster and IRB registration information when membership changes and submitting the updated information to OHRP as applicable on behalf of Mass General Brigham. IRB rosters are retained for at least seven (7) years and are made available upon request, to authorized representatives of DHHS, FDA and other federal agencies when applicable, for inspection and

copying onsite during normal business hours. Individual membership records are retained by the IRB Office for at least seven (7) years from date of last service.

8.9 Member Conflicts of Interest

All IRB Members (inclusive of all chairs), consultants and guests are required to disclose financial and non-financial conflicts of interest and recuse themselves from participating in the discussion and vote, as applicable, on human research with which they have a conflict of interest to ensure the objectivity of human research and clinical investigations, and to avoid actual or perceived conflicts of interest in the review of such research.

IRB Members, consultants or guests are considered to have a conflict of interest for the purposes of IRB review under the following circumstances:

Financial Conflicts: The individual, or their spouse, domestic partner, or dependent child:

1. Has received in the year preceding the protocol review, or has a relationship that is reasonably likely to cause them to receive in any year during the research or within the two years following completion of the research, ***any*** (more than $0) income from the entity that makes the product that is the subject of the research or that is sponsoring/funding the research;
2. Has any equity interest in the entity that makes the product that is the subject of the research or that is sponsoring/funding the research;
3. Is an employee, director, officer, executive, consultant, or trainee of the entity that makes the product that is the subject of the research or that is sponsoring/funding the research; or
4. Otherwise has a financial interest in or from the product or intervention under review, had such a financial interest in the year preceding the protocol review, or has the potential to receive such a financial interest within the two years following the completion of the research.

Professional Conflicts: The individual, or their spouse, domestic partner, child (dependent or independent), or other close relative *(if in doubt as to whether a relative is "close," the Senior IRB Chair and/or the VP HRA will make a final determination)*:

1. Is an investigator or study team member;
2. Is identified as key personnel on the funding mechanism of the protocol;
3. Is listed on the FDA 1572 form (does not include providing a service as part of their employment duties such as dispensing drug or drawing blood);
4. Expects or is reasonably likely to have authorship on publications resulting from the research;
5. Otherwise has a professional connection to an investigator or study team member that could be perceived as creating a conflict; or
6. Has any other situation such that when disclosed the Senior IRB Chair and/or VP HRA determine a conflict exists.

Personal Conflicts: The individual:

1. Otherwise has a personal connection to an investigator or study team member that could be perceived as creating a conflict; or
2. Has any other situation such that when disclosed the Senior IRB Chair and/or VP HRA determine a conflict exists.

IRB review includes acting as:

1. A primary or secondary reviewer;
2. A voting member at a full board meeting;
3. An expedited reviewer;
4. A consultant for a protocol under expedited review; or
5. Acting as a consultant for a full board review where they will not be a voting member.

When IRB members receive materials before a meeting, they will be asked to review the list of protocols on the agenda and identify any of their financial or nonfinancial interests to the Senior IRB Chair or designee. Members will also be reminded at the beginning of each meeting of the conflicts policy and must disclose any previously unreported interests at that time. Expedited reviewers are responsible for disclosing any conflicts with studies under their review.

The Senior IRB Chair or designee will review all disclosures, determine whether a conflict of interest exists, and determine appropriate management of the disclosed interest(s) with respect to protocol review. If the Senior IRB Chair or designee determines that the disclosed interest(s) would reasonably appear to affect the ability of the IRB member to objectively review the project, and therefore constitute a "conflict of interest," the IRB member will not be allowed to review the protocol (including full board review activities or expedited review.)

Any member with a conflict of interest is asked to recuse themself and leave the room while the protocol is being reviewed at full board, except to provide information to the IRB, after which the member must leave the room for the discussion and vote on the protocol. An IRB member with a conflict of interest will not be allowed to perform expedited review(s) or make determinations of exemption for that protocol. An IRB member may not consult, with or without compensation, for a business to assist it in shepherding a project through the IRB process when the project will be performed within Mass General Brigham. Consultants who are determined to have a conflict of interest regarding a specific protocol will not be allowed to act as a consultant for the research.

In preparation for each meeting, the IRB Office staff remind members that they must recuse themselves from the discussion and vote on protocols if they meet any of the conflict criteria. The Insight system identifies members who serve as members of the research team for protocols under review.

The names of those voting members who are recused from voting due to a conflict are documented in the minutes of the meeting as not present for the discussion and vote with the reason for the recusal. Recusals do not count towards the quorum requirement for the review.

9 EXEMPT HUMAN RESEARCH

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

The IRB Chair or designated expedited reviewer is responsible for making determinations of exemption from the requirements of the federal regulations. Limited reviews may be conducted by the IRB Chair or designated

expedited reviewers as part of an expedited review process. Limited IRB review applies only to research that is not regulated by the FDA.

The IRB Chair or designated expedited 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. The reviewer also ensures the research meets the institution's ethical principles for human participant protection, specifically the the Belmont Report and the requirements of HIPAA. When exempt research involves an interaction with participants, the IRB Chair or designated reviewer will review the research plan to ensure that participants (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. When the reviewer requires additional information or modifications in the research to secure the exemption determination, the expedited reviewer notifies the PI via Insight. 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).

9.1 Exempt Determinations

The reviewer makes one of the following determinations:

1. The research does not qualify for exempt status. Notification is provided in writing to the PI and includes the rationale for the determination and directs 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 determination is provided in writing to the PI through the Insight system.
3. Determination that the activity does not meet the definition of human subject research or a clinical investigation. Notification of exempt determination is provided in writing to the PI through the Insight system or by email.

9.2 Administrative Check-In

Unless the IRB determines and documents otherwise, continuing review of exempt research is not required including research reviewed by the IRB in accordance with the limited IRB review for exempt studies. To ensure that exempt research is appropriately closed when activity is completed or abandoned by the investigator, all exempt protocols are assigned a three (3) year expiration date from date of exempt determination.

1. The Exempt Check-In is a brief 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.
2. 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.

3. 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.
4. If the PI does not complete the Exempt Check-In, the exempt approval will automatically close 30 days after the expiration date. Insight will generate a letter documenting the automatic closure at 30 days.

9.3 DHHS Regulated Research

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. 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).

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.

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.

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

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.

9.4 Applicability to Vulnerable Populations

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

Children: 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. However, children are not eligible for this exemption if the project requires limited IRB review.

Exemption 3 (benign behavioral interventions) may not involve children.

FDA: Exemptions (1)-(5) do not apply to *clinical investigations* regulated by the FDA.

9.5 Limited IRB Review

Under the 2018 Common Rule 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, instead on the criterion at §46.111(a)(7) is determined by the IRB. This criterion requires that the IRB determine that there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of their data.

9.6 FDA-Regulated Research

The IRB reviewer or designated expedited reviewer is responsible for making determinations of exemption from IRB requirements in accordance with 21 CFR 56.104(b),(c), and (d) as described below:

1. Research that 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 section *Emergency Use* in this Policy. 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.

10 FULL BOARD REVIEW

10.1 Full Board Meetings

IRB meetings are held with sufficient frequency to accommodate the volume of submissions that require full board review. IRB members are asked to sign up to attend meetings in advance of meeting dates in the Insight system. Members are expected to attend meetings for which they sign up unless there is an emergency preventing them from attending, in which case they must notify the IRB Staff as soon as possible in advance of the meeting.

IRB Staff are responsible for screening protocols and working with the investigator to ensure the protocol application is complete and the investigator has provided sufficient information for the IRB to assess the criteria for approval and Mass General Brigham requirements. IRB Staff then route screened protocols to scheduling.

IRB Staff then schedule the submissions to specific IRB meetings where members with expertise are available to appropriately review the protocol.

Generally, protocols are scheduled for review based on when the investigator has completed the screening process with the IRB Staff; however, the IRB reserves the right to schedule or reschedule protocols for review based on other factors, such as the experience and expertise of the members planning to attend the IRB meeting or the expiration date of IRB approval.

Agendas are structured to allow sufficient time to review each item. The total number of protocols to be reviewed at a given IRB meeting may vary based on the nature or complexity of protocols in order to allow sufficient time for discussion of each protocol at the meeting or based on the availability of members for review.

The IRB Staff is responsible for making reviewer assignments and finalizing the agenda. When making reviewer assignments, the IRB Staff takes into consideration, the study population, the study procedures described in the protocol, and the experience and scientific or scholarly expertise of the members attending the meeting, and when applicable, knowledge of and experience in working with individuals with impaired decision-making capacity, children, pregnant women and fetuses, or neonates, or other vulnerable participants required to review the research. The qualifications, experience, and expertise, as well as the representative capacity of each member, are documented in the IRB roster. The Insight system matches key words describing the research and indication of any vulnerable populations from the Insight application with comparable information about each IRB member in Insight and upcoming meetings they are attending. This information is available to the IRB Staff as a tool to identify meetings with appropriate expertise. The IRB Staff also have access to the IRB roster and IRB member CVs when making reviewer assignments.

A Primary Reviewer is assigned and is typically a physician-scientist or other scientist with experience in working with the population being studied and/or expertise in the type of research under consideration, although this is not an absolute requirement, depending upon the type of study. The Primary Reviewer performs an in-depth review of all materials provided in the research application(s) relevant to the research they are assigned to review including, when applicable, any investigational drug brochure or investigational device information. A Secondary Reviewer is added to provide another perspective for Initial Reviews or for other submissions as determined by the Chair when needed to provide additional expertise (e.g. deferrals, complex amendments.) The Secondary Reviewer conducts a review of the IRB application and materials consistent with the reviewer's representative capacity. IRB Members who are not assigned as the primary or secondary reviewer perform review of materials in sufficient depth to vote on the research activity at the full board meeting.

Reviewers are required to notify the IRB Chair and IRB Staff prior to the meeting if they have questions about the study, particularly if they have significant concerns about the study or believe additional information is needed for the IRB to be able to assess the regulatory Criteria for Approval.

The meeting agenda and application, forms and documents submitted for IRB review for each item on the agenda are made available in Insight to all members planning to attend the meeting at least 5 business days prior to the meeting to allow sufficient time for review. In emergent situations where it is necessary to review research in an accelerated timeframe, materials may be provided less than 5 business days prior to the meeting when IRB Staff confirm in consultation with the meeting Chair that members will have sufficient time to review prior to the meeting. All IRB Members have access to guidance documents that include the regulatory criteria for approval and requirements for informed consent.

For initial review, all members attending the meeting receive the required Insight application forms and documents submitted by the investigator for IRB review, which include, but are not limited to, recruitment

materials including advertisements, detailed protocol, instruments and questionnaires, consent forms, and drug/device brochure.

For continuing review, amendments and other events all IRB Members attending the meeting receive the required Insight application forms and documents submitted by the investigator for IRB continuing review. The entire protocol file and minutes of prior meeting(s) at which the protocol was reviewed are available to all members.

10.2 Chair Responsibilities

When acting as the IRB Chair of a full board meeting, the chair or vice chair has the following responsibilities:

1. Serve as a voting member of the IRB;
2. Serve as a Primary or Secondary Reviewer as appropriate;
3. Preside at full board meetings during which the IRB conducts: (i) initial and continuing review of research activities involving human participants; (ii) review of proposed changes in approved research during the period of approval that are not minor; (iii) review of unanticipated problems involving risks to participants or others, including adverse events that are serious, unexpected and related to the research; and (iv) review of reports of possible serious or continuing noncompliance.
4. Review modifications in research required by the IRB at full board meetings to secure approval and confirm that modifications have been made as required by the IRB.

10.3 Determinations of the Full Board

Approve:	**When all regulatory Criteria for Approval are met with no additional information or modifications needed, the IRB may approve the research.**
Require modifications (in research to secure approval):	When the IRB votes to require modifications in the research (to secure approval), the investigator is notified in writing of the action voted on by the IRB and the required modifications to the research. The PI is asked to submit a point-by-point response and revised documents to the IRB. Required modifications must be: • Changes or documentation that require simple concurrence of the investigator; or • Confirmation of the understanding of the IRB based on protocol information (may include submission of additional documentation). When the investigator response is received, the IRB Chair, designated IRB Member, or Full Board Specialist reviews the response, including any revised forms or attachments, and documents through the Insight commenting function whether the modifications required by the IRB have been made and whether the protocol can now be approved. If the investigator is not willing to make the modifications as required, the response is scheduled for review at the next full board meeting of the reviewing IRB.

	Additional proposed changes submitted with the response are reviewed in accordance with the policies and procedures for review of proposed changes, i.e., either at a full board meeting or, if minor, using the expedited review procedure.
Defer (research for more information):	If the IRB determines that any of the regulatory Criteria for Approval are not met and the changes required are beyond those requiring simple concurrence by the investigator, the IRB defers the research for more information. The investigator is notified in writing of the action voted on by the IRB and any questions and concerns that need to be addressed as well as modifications required to the research. The PI is asked to submit a point-by- point response and revised documents to the IRB. When received, the PI's response, including revised documents, is scheduled for review at a full board meeting of the IRB.
Disapprove:	When the IRB determines that as designed, the study does not satisfy the applicable regulatory Criteria for Approval and IRB requirements for human research, the IRB disapproves the research. The PI is notified in writing of the action voted on by the IRB and the basis for the disapproval. The decision of the IRB to disapprove the research cannot be overruled by any other entity or individual(s); however, an investigator may appeal the decision of the IRB in writing directly to the Senior IRB Chair who is responsible for reviewing the appeal with the IRB Chair. Any appeal must be submitted in writing within 15 business days from the date the investigator is notified of the IRB disapproval. The appeal is then scheduled for review at a full board meeting of the IRB that includes the IRB Chair and/or Primary Reviewer from the meeting that disapproved the research. The investigator may attend the full board meeting at which the appeal is considered to provide information and answer questions. The investigator must leave the meeting prior to discussion and vote.

10.4 Discussion and Vote

The IRB Staff takes attendance at the virtual meetings and records voting members present and absent for each review. Votes of members are recorded through a clear visual or verbal process. Late arrivals, early departures, and individuals recused or out of the room for one reason or another during the discussion and vote on each protocol are recorded in the minutes.

The IRB Chair initiates the discussion of each item listed on the meeting agenda. The primary reviewer presents a brief synopsis of the research protocol, with the expectation that the other members have reviewed the protocol materials. The primary reviewer is responsible for presenting information about the criteria for IRB approval and, when applicable, additional protections for pregnant women, human fetuses, and neonates; children; prisoners; and individuals with impaired decision-making capacity. Secondary reviewers are asked to present any additional clarifications or commentary, and any questions or concerns, or modifications they would require for approval. All reviewers are encouraged to provide

written comments to ensure that the IRB convey the modifications required and/or questions and concerns raised by the IRB completely, accurately and precisely.

After the primary and secondary reviewers have presented the study and their review comments, the IRB Chair opens the protocol up for discussion by the membership. The meeting Chair and members may direct specific questions to the assigned reviewers or to other members with specific expertise or viewpoints (e.g., a layperson, nurse or other member who may bring a different perspective to the discussion).

At the end of the discussion, the IRB Chair makes a motion to approve, require modifications in the research (to secure approval), defer (pending receipt of additional information), or disapprove the protocol. A vote on the motion is taken (for, against, or abstain) by show of hands, voice vote, or electronic polling and recorded for the minutes. All motions are decided by majority vote of the members present for the review. A quorum of the members of the IRB must be present in order for the IRB to take a vote.

10.5 Quorum

Human research and clinical investigations that cannot be reviewed using the expedited review procedure are reviewed at a full board meeting of the IRB where a quorum is present. A quorum is the minimum number and type of IRB members that must be present at a full board meeting. In order to review research at a full board meeting, a majority of the members of the IRB must be present, including at least one physician-scientist and one member whose primary concerns are in nonscientific areas. In addition, reasonable efforts will be made to ensure that at least one unaffiliated member and at least one member representing the general perspective of participants are present at each meeting. The unaffiliated member, the member representing the general perspective of participants, and the non-scientific member may be the same person, or may be represented by two or three different persons.

The IRB Chair or designee is responsible for ensuring that quorum is achieved before the meeting begins and is maintained throughout the meeting. Quorum is maintained for the discussion and vote on each research activity on the agenda. Members not present for or recused due to a conflict of interest from the discussion and vote on a research activity do not count towards the quorum. When the primary member and alternate member are both present for the discussion and vote on a research activity, only one member is counted towards quorum for the specific research activity under review. The IRB Staff are responsible for recording attendance and vote on each research activity.

10.6 Minutes and Meeting Attendance

Full Board Analysts are responsible for documenting attendance at each meeting. Documentation of IRB Member attendance shall include:

- Each member's full name;
- Each member's representative capacity (scientist, non-scientist, member who represents the general perspective of research participants, unaffiliated);
- The names of members who participated in the convened meeting via an alternative mechanism, such as telephone or video conferencing;
- If a consultant is present at the full board meeting, the name of the consultant, and a brief description of the consultant's expertise, and documentation that the consultant did not vote with the IRB on the study;
- The names of non-members and guests, such as IRB support staff, investigators and study coordinators;

- When an alternate member replaces a primary member, including the name of the alternate member; and
- The names of IRB members who leave the meeting because of a conflict of interest, along with the fact that a conflict of interest is the reason for the absence.

Meeting minutes include actions taken by the IRB, with sufficient information to identify the research activities reviewed and voted on by the IRB at the meeting, including initial review, review of required modifications and continuing review. Minutes shall include the following information:

- Separate deliberations for each action;
- Number of votes on each research activity as number for, against, or abstaining from voting (documentation of quorum);
- Members attending the meeting but not present for the discussion and vote;
- Recusals of voting members with indication of those recused due to conflicts of interest;
- When applicable, summary of information provided by consultant(s);
- The basis for requiring changes in research;
- The basis for disapproving research, when applicable;
- For initial and continuing review, the approval period;
- Required determinations and protocol-specific findings justifying those determinations for:
    - Waivers or alterations of the consent process.
    - Research involving pregnant women, fetuses and neonates.
    - Research involving prisoners.
    - Research involving children.
    - Research involving participants with impaired decision-making capacity to consent.
    - For FDA-regulated research, the rationale for significant and non-significant risk device determinations.
    - Rationale for conducting continuing review on research that would otherwise not require continuing review.
- Summary of the discussion of controverted issues and their resolution, if any; and
- When applicable, justification of deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.

Minutes are drafted and made available to the IRB chairs, if needed, for review. Minutes are not to be altered once finalized.

10.7 Continuing Review

When the motion is to approve or require modifications in the research (to secure approval), the motion includes the duration of IRB approval (one year or less). When determining the duration of approval, the IRB considers the following factors:

- The nature of risks to participants;
- The degree of uncertainty regarding the risks involved;
- The vulnerability of participants;
- The experience of the clinical investigator in conducting clinical research;
- The IRB's experience with the investigator or sponsor;
- The projected rate of enrollment; and

- Whether the study involves novel therapies.

When the risks to participants related to participation in the research are greater than the risk associated with alternative treatments or procedures, if any, the IRB will consider requiring that continuing review be conducted more frequently than annually. Examples of research that may be considered for review more frequently than annually include:

- phase I studies of a challenging or novel new drug or biologic;
- research involving Category A significant risk devices;
- research in which healthy volunteers may undergo anesthesia or medical procedures involving sedation with no direct health benefits;
- research for which there is little external oversight or data safety monitoring;
- research involving gene transfer or xenotransplantation; or
- research involving infectious agents.

For initial review or continuing review, the approval date is the date the IRB voted to fully approve the protocol at the full board meeting or, if voted to require modifications to secure approval, the date the protocol is fully approved by the Full Board staff when they or an IRB-designated reviewer, reviews the Principal nIvestigator's response and determines that all of the required modifications have been made. The expiration date is based on the date of the full board meeting where the IRB approved or required modifications to secure approval of the research and the duration of approval voted on by the IRB. The continuing review must occur within one (1) year from the date of the full board meeting at which the IRB reviewed and approved the research study. The expiration date is the first date the protocol is no longer approved by the IRB.

Continuing review is required until the research is completed, or the investigator closes the research prior to completion. The investigator must submit the continuing review form to document that the study has been completed or is being closed prior to completion. For multi-site research, the research may be considered completed or may be closed prior to completion when the investigator at the site under Mass General Brigham IRB review is no longer intervening or interacting with participants or collecting, receiving, or analyzing identifiable data for research purposes.

Continuing review of research previously approved by the full board IRB may be conducted using the expedited review procedure as follows:

a) where (i) the research is permanently closed to the enrollment of new participants; (ii) all participants have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of participants; or
b) where no participants have been enrolled and no additional risks have been identified; or
c) where the remaining research activities are limited to data analysis; or
d) when research is not conducted under an investigational new drug application or investigational device exemption where Expedited Categories two (2) through eight (8) do not apply but the IRB has determined and documented at a full board meeting that the research involves no greater than minimal risk and no additional risks have been identified.

As a courtesy, the IRB Office via Insight sends a written notice to the Principal Investigator ninety (90) days, sixty (60) days, and forty-five (45) days prior to expiration of IRB approval, reminding them that continuing

review of the research is coming due. It is ultimately the Principal Investigator's responsibility to be aware of the date of IRB expiration and allow sufficient time for review and re-approval of the research.

When approval expires, the IRB Office notifies the PI in writing that all research activities must stop. Research activities include, but are not limited to, recruitment and enrollment of participants, collection of specimens, research on previously collected specimens, review of medical records or other health information, data analysis, performance of research tests/procedures, and treatment or follow-up on previously enrolled participants.

If treatment or follow-up of participants is necessary for their safety and welfare, the investigator must request permission from an IRB Chair to continue to conduct these procedures for currently enrolled participants. The IRB Chair considers each request on a case-by-case basis and provides the investigator with written documentation of permission, when granted.

If an investigator does not submit a continuing review within thirty (30) days after the approval expiration date, the study will be administratively closed by the IRB. To reactivate the study, the investigator will need to submit and receive approval for a new study.

10.8 Amendments

Amendments are proposed changes or modifications to previously approved research including requests for single participant exceptions. Amendments that are not minor (as defined in the *Expedited Review* section) must be reviewed by the Full Board IRB.

10.9 Data and Safety Monitoring Plans

The IRB requires the inclusion of a data and safety monitoring plan (DSMP) in interventional clinical research protocols that involve more than minimal risk to subjects. Data and safety monitoring is the process for reviewing accumulated outcome data from an ongoing clinical trial to ensure the continuing safety of current participants and those yet to be enrolled, as well as the continuing validity and scientific merit of the trial.

The DSMP must be described in sufficient detail for the IRB to determine whether the plan is appropriate for the research. A DSMP should be tailored to the nature, size, and complexity of the research protocol, the expected risks of the research, and the type of participant population being studied. Appropriate DSMPs may fall anywhere along a continuum from monitoring by the Principal Investigator or group of investigators to the establishment of an independent DSMB or Data Monitoring Committee (DMC).

The IRB will require the following information to determine whether the DSMP has appropriate provisions for data and safety monitoring:

1. The type of safety information that will be captured under the monitoring plan including serious adverse events.
2. How the safety information will be collected (e.g. via case report forms, at study visits, and/or telephone calls with participants).
3. How the safety information will be reported to the monitoring entity, such as the research sponsor, coordinating or statistical center, independent medical monitor, or DSMB/DMC.
4. The frequency for reporting safety information including adverse events and unanticipated problems including when the collection of safety information begins.
5. The frequency or periodicity of review of cumulative safety information captured by the monitoring plan, such as points in time or after a specific number of participants are enrolled.

6. Who will be responsible for monitoring the safety information, including unanticipated problems and adverse events, and their respective roles (e.g., the investigators, the research sponsor, a coordinating or statistical center, an independent medical monitor, a DSMB, DMC, or other data monitoring entity). Medical monitors or members of the DSMB or DMC must be independent of the research team.
7. Definition of specific triggers or *stopping rules* that will dictate when some action is required. *Stopping rules* are predetermined guidelines that are used to determine that the study should be altered or stopped, based on review of study related events that occur during the conduct of the study. Stopping rules should be specific about the endpoints that will be used and the decisions that will be made. Studies may be stopped, for example, when there is a greater than expected rate of morbidity or mortality or when the experimental arm of a head-to-head comparison study is shown to be better or worse statistically than the standard care arm.
8. As appropriate, procedures for communicating to the IRB, the study sponsor, and other appropriate entities the outcome of the reviews by the monitoring entity.

10.10 Determining Which Studies Need Verification from Sources Other Than the Investigator

Investigators are required to provide the IRB with all relevant information regarding the conduct of the research and fulfill all requirements for prompt reporting to the IRB of any reportable events.

To ensure that the research is conducted in compliance with all applicable regulations for the protection of human participants, the IRB may require verification of information from sources other than the investigator. Such independent verification may be considered in the following situations:

- complex projects involving unusual levels or types of risk to participants;
- research being conducted by persons who have previously failed to comply with all regulations or requirements of the IRB;
- research conduct that comes into question because of information provided at continuing review; or
- research in which substantial segments of the project are conducted off site by Mass General Brigham investigators or non-Mass General Brigham collaborators.

Independent verification may include, but is not limited to:

- audits by the C&E Office;
- communications between the FDA and the sponsor (IND/IDE holder);
- communications with the sponsor, collaborating institutions, coordinating centers, or regulatory agencies;
- communications from any monitoring group, e.g., DSMB or DMC
- NIH/agency communications and reviews; and/or
- communications with IRBs at collaborating sites.

10.11 Use of Consultants

The IRB may use consultants to supplement or provide scientific or scholarly expertise not available on the IRB, or to provide additional community perspective. The IRB Chair(s) in collaboration with the Senior IRB Chair or IRB Staff are responsible for determining when a consultant is needed to ensure appropriate review expertise for research scheduled to be reviewed at a full board meeting. The IRB Chair or designee is responsible for identifying the consultant and for requesting the consultation. Additionally, the IRB may vote

to defer action on a protocol and may require an expert in the scientific area or discipline to review the research and provide consultation to the IRB. Potential consultants will be identified and agreed upon by the IRB, or as indicated above.

Consultants are subject to the IRB policy on *IRB Member Conflicts of Interest*, and must sign the Confidentiality/Non-Disclosure and Conflict of Interest Agreement. If the consultant agrees to review the research and the consultant has no conflict of interest, they are provided with all forms and documents submitted to the IRB for review.

Consultants are asked to attend the meeting to present their findings relative to any of the regulatory Criteria for Approval and to answer questions; however, if the consultant is unavailable to attend the meeting, they may provide written comments for distribution or communication to the IRB members. Consultants are not considered members and do not vote on human research reviewed by the full board. When IRB members serve as consultants, they are not considered voting members. Their attendance is recorded in the minutes as guests (consultant).

10.12 Guests

Guests are not allowed at IRB meetings with the exception of individuals invited by the IRB to provide information pertinent to the review of research activities under consideration (e.g. HRA Compliance & Education Office staff, consultants, study PI and/or study staff), are new IRB members who are in the process of onboarding, or students or trainees of IRB Chairs or Vice Chairs with approval from the Senior IRB Chair or VP HRA. Other exceptions may be considered by the Senior IRB Chair and VP HRA on a case-by-case basis. In such cases, guests are are subject to the IRB policy on *IRB Member Conflicts of Interest* and must sign the Confidentiality/Non-Disclosure and Conflict of Interest Agreement. Guests are not members of the IRB by virtue of their attendance, do not participate in discussion or deliberations, and are not eligible to vote.

11 EXPEDITED REVIEW

The IRB may use the expedited review procedure for review and approval of certain categories of human research that involve no more than minimal risk, for certain categories of exempt research, and for review and approval of minor changes in approved research during the period of IRB approval (45 CFR 46.104, 45 CFR 46.110 and 21 CFR 56.110. When reviewing human research using the expedited review procedure, the IRB Chairs and designees are subject to the section *IRB Member Conflicts of Interest.*

The expedited review procedure may not be used where identification of the participants and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that the risk related to invasion of privacy and breach of confidentiality is no greater than minimal.

If the proposed research is not eligible for review using the expedited review procedure, the expedited reviewer provides a rationale and refers the research for review by the full board IRB.

11.1 Expedited Reviewer Responsibilities

The Senior IRB Chair is responsible for designating IRB members to conduct expedited review. Only experienced IRB members may be designated to conduct expedited reviews. The Senior IRB Chair and IRB Office Director determine when an IRB member has sufficient training on the federal regulations and standard operating procedures as well as experience to be designated to conduct expedited reviews.

When human research is reviewed using the expedited review procedure, the expedited reviewer is responsible for determining:

1. That all Criteria for Approval are met (45 CFR 46.111 and/or 21 CFR 56.111);
2. Any applicable regulatory requirements for inclusion of vulnerable populations are met;
3. Whether the research is minimal risk; and
4. The applicability of the expedited review categories.

The designated expedited reviewers have the authority to approve or require modifications in the research to secure approval, however they may not disapprove the research. Research may be disapproved only after review by the full board IRB.

11.2 Expedited Categories

The categories in this list apply regardless of the age of participants, except as noted:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

   (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increase the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
   (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

   (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
   (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a

dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications). Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

8. Continuing review of research previously approved by the full board IRB as follows:

    (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
    (b) where no subjects have been enrolled and no additional risks have been identified; or
    (c) where the remaining research activities are limited to data analysis.

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a full board meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Research activities that are not FDA-regulated and meet the requirements for Limited Review under 45 CFR 46.104(d)(2)(iii) or 45 CFR 46.104(d)(3)(i)(C) as follows may be reviewed using the expedited procedure:

1. 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 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).
2. 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 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).

11.3 Determinations of the Expedited Reviewer

Approve:	**When all regulatory Criteria for Approval are met with no additional information or modifications needed, the Expedited Reviewer may approve the research.**
Require modifications (in research to secure approval):	When the Expedited Reviewer does not have sufficient information to determine whether all Criteria for Approval are met, they require modifications in the research (to secure approval). The investigator is notified in writing of the required modifications to the research. The investigator is asked to submit a point-by-point response and revised documents to the Expedited Reviewer. When the investigator response is received, the Expedited Reviewer reviews the response, including revised documents, and documents in Insight whether the modifications required by the IRB have been made. If the investigator is not willing to make the modifications as required, the response is scheduled for review at the next full board meeting of the reviewing IRB. Additional proposed changes submitted with the response are reviewed in accordance with the policies and procedures for review of proposed changes, i.e., either using the expedited review procedure or referred to full board as appropriate.
Refer to Full Board:	When the Expedited Reviewer determines that the research 1) does not meet the definition of minimal risk, 2) the proposed procedures are not included in Expedited Categories, or 3) the investigator is not willing to make required changes to meet the Criteria for Approval, the Expedited Reviewer refers the research for full board review.

11.4 Expedited Review Process

The protocol application submitted by the investigator for review is screened by the IRB Staff to ensure information is complete and provides sufficient information to assess the Criteria for Approval. When

accepted, applications are assigned to an expedited reviewer. The person who screens the research may be the same person who conducts the expedited review. The expedited reviewer has access to the entire protocol record maintained by the IRB Office.

When the expedited reviewer requires modifications in the research to secure approval the required modifications or additional information required for review is communicated via the Insight system. The PI is asked to submit a point-by-point response and revised documents as applicable to the IRB. When received, the expedited reviewer assesses the PI's response, including revised documents, and determines whether the modifications have been made as requested and the research can be approved. The expedited reviewer may continue to request additional modifications or information until the research meets all Criteria for Approval and can be approved or determines that referral for review at a full board meeting of the IRB is appropriate.

The expedited reviewers use an Insight reviewer checklist that includes the applicability of expedited review and the categories of research eligible for expedited review to document that:

- The research is applicable for expedited review;
- The research is minimal risk;
- The research activities fall within one or more of the research categories eligible for expedited review; and
- The consent form includes the basic elements of informed consent or a waiver or alterationof informed consent is approved, or no consent is required under Limited Review.

11.5 Continuing Review and Administrative Review

When human research is reviewed using the expedited review procedure, the date of expiration of IRB approval is set as follows:

1. For non-FDA regulated research, no continuing review, but administrative Expedited Check-In in 2 years (expedited research) or 3 years (research under Limited Review) from the date the Expedited Reviewer approves the research.
2. For FDA-regulated research or as determined and justified by the expedited reviewer, one year (or sooner as designated by the reviewer) from the date the Expedited Reviewer approves the research.

When continuing review is not required and an Expedited Check-In is required, the IRB Office is still responsible for tracking and overseeing ongoing human research. The expiration date of research determined to require either a continuing review or an Expedited Check-In is the first date the research is no longer approved by the IRB.

Continuing review or administrative review is required until the research is completed, or the investigator is ready to close the research. The investigator submits a Continuing Review or Expedited Check-In form in Insight to close research. For multi-site research, the research may be considered completed or may be closed prior to completion when the investigator at a site overseen by the Mass General Brigham IRB is no longer intervening or interacting with participants, or collecting, receiving, or analyzing identifiable data or research materials.

Continuing review may be conducted by the expedited review process for research previously reviewed by the full board IRB as described in the *Full Board Review* section.

As a courtesy, the IRB Office via Insight sends a written notice to the investigator ninety (90) days, sixty (60) days, and forty-five (45) days prior to expiration of IRB approval or need for administrative Check-In, reminding them that continuing review of the research is coming due. It is ultimately the investigator's responsibility to be aware of the date of IRB expiration and allow sufficient time for review and re-approval of the research.

When approval expires, the IRB Office notifies the PI in writing that all research activities must stop. Research activities include, but are not limited to, recruitment and enrollment of participants, collection of specimens, research on previously collected specimens, review of medical records or other health information, data analysis, performance of research tests/procedures, and treatment or follow-up on previously enrolled participants.

If treatment or follow-up of participants is necessary for their safety and welfare, the investigator must request permission from an IRB Chair to continue to conduct these procedures for currently enrolled participants. The IRB Chair considers each request on a case-by-case basis and provides the investigator with written documentation of permission, when granted.

If an investigator does not submit a continuing review within thirty (30) days after the approval expiration date, the study will be administratively closed by the IRB. To reactivate the study, the investigator will need to submit and receive approval for a new study.

11.6 Amendments

Amendments are proposed changes or modifications to previously approved research including requests for single participant exceptions. The IRB Chair or designated expedited reviewers are responsible for reviewing and determining whether the amendment is minor, and if minor, may review and approve the change using the expedited review process.

The proposed change is considered minor when the research meets <u>all</u> of the following criteria:

- the proposed change does **not** significantly alter the risk to benefit assessment the IRB relied upon to approve the research;
- the proposed change does **not** significantly affect the safety of subjects;
- the proposed change does **not** involve the addition of procedures, interactions orinterventions that add significant medical, social or psychological risks;
- the proposed change does **not** involve the addition of a vulnerable population in research not otherwise eligible for expedited review; and
- the proposed change does **not** significantly alter the scientific question or the scientific qualityof the research.

11.7 Determining Which Studies Need Verification from Sources Other Than the Investigator

Independent verification of information provided at initial review, continuing review, or for review of amendments may be requested by the expedited reviewer in the course of conducting the review. Such independent verification may be considered in the following situations:

- research being conducted by persons who have previously failed to comply with all regulations or requirements of the IRB;
- research conduct that comes into question as a result of information provided at continuing review; or

- research in which substantial segments of the project are conducted off-site by Mass General Brigham investigators or non-Mass General Brigham collaborators.

Independent verification may include, but is not limited to the following sources of information:

- audits by the Human Research Affairs C&E Office;
- communications with the sponsor, collaborating institutions, coordinating centers, or regulatory agencies
- communications from any monitoring group, e.g., DSMB or DMC
- NIH/agency communications and reviews; and/or
- communications with collaborating IRBs.

11.8 Reports of Expedited Determinations

The IRB Office is responsible for preparing and distributing a report of all human research approved using the expedited review procedure, including initial and continuing review, and amendments. Reports are made available on a monthly basis to the members of the IRB.

11.9 Use of Consultants

The expedited reviewer may consult another IRB member(s) or a non-IRB member consultant with special scientific or scholarly expertise in the scientific area or discipline or special population being studied; however, the reviewing expedited reviewer is responsible for the review and approval of research using the expedited review procedure. When a consultant is used, the expedited reviewer is responsible for communicating with the consultant and for verifying that the consultant does not have a conflict of interest as defined in the *IRB Member Conflicts of Interest Policy*.

12 VULNERABLE POPULATIONS

The IRB will approve human research and clinical investigations that involve the inclusion of pregnant women or human fetuses, nonviable neonates or neonates of uncertain viability, prisoners, or children only if the IRB finds and documents that the research satisfies the conditions of 45 CFR 46, Subpart B, C, or D, as applicable, and, when also applicable, 21 CFR 50 Subpart D, and applicable state law.

12.1 Pregnant Women or Fetuses

Pregnant women or fetuses may be involved in research if all criteria as set forth in federal regulations and state law below are met:

12.1.1 Federal Regulations at 45 CFR 46.204

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) Any risk is the least possible for achieving the objectives of the research;

(c) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal;

(d) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or if there is no such prospect of direct benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(e) and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of Subpart A of 45 CFR 46;

(f) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of Subpart A of 45 CFR 46, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;

(g) Each individual providing consent under paragraph (d) or (e) of 45 CFR 46.204 is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(h) For children as defined in 45 CFR 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of Subpart D of 45 CFR 46;

(i) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(j) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(k) Individuals engaged in the research will have no part in determining the viability of a neonate.

12.1.2 State Law M.G.L. ch. 112, s. 12J(a)

1. No person shall use any live human fetus whether before or after expulsion from its mother's womb, for scientific, laboratory, research or other experimentation. This section shall not prohibit procedures incident to the study of a human fetus while it is in its mother's womb or a neonate; provided that in the best medical judgment of the physician, made at the time of the study, the procedures do not substantially jeopardize the life or health of the fetus or neonate, and provided further that, in the case of a fetus, the fetus is not the subject of a planned abortion.
2. This section shall not prohibit or regulate diagnostic or remedial procedures the purpose of which is: (i) to determine the life or health of the fetus or neonate involved; (ii) to preserve the life or health of the fetus or neonate involved or the mother involved; (iii) to improve the chances of a viable birth for a fetus with a congenital or other fetal conditions that would otherwise substantially impair or jeopardize the fetus's health or viability; or (iv) research approved by an institutional review board applying federal regulations for the protection of fetuses and neonates, that are conducted for the purpose of developing, comparing or improving diagnostic or therapeutic fetal or neonatal interventions to improve the viability or quality of life of fetuses, neonates and children.
3. No experimentation shall knowingly be performed upon a dead fetus or dead neonate unless the consent of the parent or guardian has first been obtained, provided, however, that such consent shall not be required for a routine pathological study.
4. No person shall perform or offer to perform an abortion where part or all of the consideration for said performance is that the fetal remains may be used for experimentation or other kind of research or study.

5. No person shall knowingly sell, transfer, distribute or give away any fetus or neonate for a use which is in violation of this section.

12.2 Neonates

Neonates may be involved in research if all criteria as set forth in federal regulations and state law below are met:

12.2.1 Federal Regulations 45 CFR 46.205

1. Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

    a. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;
    b. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate; and
    c. Individuals engaged in the research will have no part in determining the viability of a neonate.

2. Until it has been ascertained whether or not a neonate is viable, a neonate may <u>not</u> be involved in research unless:

    a. The IRB determines that: (i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or (ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
    b. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained except that consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

3. Nonviable neonates may not be involved in research unless all of the following additional conditions are met:

    a. Vital functions of the neonates will not be artificially maintained;
    b. The research will not terminate the heartbeat or respiration of the neonate;
    c. There will be no added risk to the neonate resulting from the research;
    d. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
    e. The legally effective informed consent of both parents of the neonate is obtained in accord with 45 CRF 46 Subpart A, except that the waiver and alteration provisions of 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent

of a nonviable neonate will suffice. Consent of the father need not be obtained if the pregnancy resulted from rape or incest. Consent cannot be obtained from a legally authorized representative.

4. Viable neonates may be included in research only to the extent permitted by 45 CFR 46 Subpart D - Additional Protections for Children Involved as Subjects in Research.

12.2.2 State Law M.G.L. ch. 112, s. 12J

The IRB will also consider research involving neonates under M.G.L. ch. 112, s. 12J, as quoted in relevant part above.

12.3 Research on Pregnant Women, Fetuses or Neonates Not Otherwise Approvable

Pregnant women, fetuses, or neonates may be involved in research not otherwise approvable under 45 CFR 46.204 or 45 CFR 46.205 only if the IRB finds that the research presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates and, if HHS-funded, the research is submitted to the Secretary of HHS for consultation with a panel of experts in pertinent disciplines and opportunity for public review and comment. When the research is funded by a federal agency other than HHS, the IRB will consult with appropriate officials at the relevant federal agency or department funding the research.

When the research is supported by a non-federal sponsor, the IRB will consider convening a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and provide an opportunity for review and comment by the local community where the research is to be conducted before deciding whether to proceed with the research.

12.4 Children

Children may be involved in research if all criteria as set forth in federal regulations below are met and the state law defining age of majority apply *(see Children in definitions appendix)*:

12.4.1 Subpart D Child Categories (45 CFR 46 and 21 CFR 50)

46.404 / 50.51: Research not involving greater than minimal risk.
The IRB must find that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

46.405 / 50.52: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
The IRB must find that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

a) The risk is justified by the anticipated benefit to the subjects;
b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

46.406 / 50.53: Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

The IRB must find that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

a) The risk represents a minor increase over minimal risk;
b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

46.407 / 50.54: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Research in this category is **approvable** only if:

a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
    (1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or
    (2) the following:
        (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
        (ii) the research will be conducted in accordance with sound ethical principles;
        (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

Research in this category must be submitted to the Secretary of HHS, if funded by HHS, and/or the Commissioner of Food and Drugs, if the research is FDA-regulated, for consultation with a panel of experts in pertinent disciplines and opportunity for public review and comment. When the research is funded by a federal agency other than HHS, the IRB will consult with appropriate officials at the relevant federal agency or department funding the research.

When the research is supported by a non-federal sponsor, the IRB will consider convening a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and provide an opportunity for review and comment by the local community where the research is to be conducted before deciding whether to proceed with the research.

12.4.2 Requirements for permission by parents or guardians and for assent by children (45 CFR 46.408/21 CFR 50.55)

The IRB must determine whether permission of one or both parents must be obtained for participation of the children in the research. When the research is approved under 46.404 / 50.51 or 46.405 / 50.52, the IRB may determine that permission of one parent is sufficient. When the research is approved under 46.406 / 50.53 or 46.407 / 50.54, permission of both parents must be obtained unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child.

The IRB must also determine whether assent of the children participating in the research is required. When making determinations regarding assent, the IRB will consider the capacity of the children to assent, taking into consideration the age, maturity and psychological state of the children involved.

Determinations regarding assent may be made for all children participating in the research or for each child. When the IRB determines that assent is required, the IRB determines whether assent will be documented and if so, the process to document assent. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably by consulted or that the intervention or procedure involved holds out the prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not necessary for proceeding with the research. Even when the IRB determines that the children are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with 45 CFR 46.116, Subpart A.

12.4.3 Wards (45 CFR 46.40)

Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406 or 46.407 and 21 CFR 50.53 or 50.54 only if the research is:

1. related to their status as wards; or
2. conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research is approved based on the paragraph above regarding children who are wards, the IRB will require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate will be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization. In Massachusetts, parents of children in Department of Children and Families (DCF) care or custody generally retain the right to consent to participation of their child in any medical or psychological research. If the parents consent, DCF shall also consent. If the parents refuse to consent, the child shall not participate. When DCF has custody pursuant to surrender or termination of parental rights, or when parents cannot be located, DCF must seek judicial approval in order for the child to be enrolled.

12.5 Participants with Impaired Decision-Making Capacity

A person with impaired decision-making capacity who cannot give informed consent may participate in research only after the investigator obtains consent from a legally authorized representative (LAR) on that person's behalf . The determination of who is legally authorized to give consent for a specific research protocol will be made by the IRB.

Research studies that involve individuals with impaired decision-making capacity require additional safeguards to protect the rights and welfare of these participants. The IRB will require that the protocol include specific information justifying the enrollment of adults who are unable to consent, the plans for recruitment and enrollment, and who the investigator proposes to serve as a LAR.

For adults who are unable to consent, the IRB will review and determine whether the investigator's proposed plan is adequate and the proposed LAR is appropiate.

Persons who the investigator might propose to the IRB as appropriate LAR (in order of general preference):

<table>
<tr><td>1</td><td>Court-appointed guardians with authority to consent to participation in the proposed research or authority to make decisions for a class of health care decisions inclusive of the proposed research</td><td>May be required by the IRB in research such as some research involving greater than minimal risk and no prospect of direct medical benefit.

Required in research that is within the jurisdiction of the Massachusetts Department of Developmental Services.</td></tr>
<tr><td>2</td><td>Health care proxy with authority to make decisions for a class of health care decisions inclusive of the proposed research</td><td rowspan="3">Key factors that will be considered by the IRB for use of these LARs in both minimal risk and more than minimal risk research, include:
the research offers the prospect of potential for direct personal health benefit or if no potential for direct benefit, the research could not be carried out in any other population and achieve its scientific goals;
the risks and potential benefits of participation;
the possible alternative treatments and current standards of care for the condition;
the risks are commensurate with other accepted treatments that might be considered, or there are no other accepted, standard treatments;
the LARs know the subjects well and have been involved in their care;
the nature of the condition under study, and whether the condition responsible for lack of capacity is the focus of the study;
the presence or absence of a placebo arm, and whether risks undertaken by placebo recipients are otherwise commensurate with routine medical risks; and
the consent process, including among other details, how the LARs are included in and make decisions as part of the consent process.</td></tr>
<tr><td>3</td><td>Durable powers of attorney with authority to make health care decisions inclusive of the proposed research</td></tr>
<tr><td>4</td><td>A spouse, adult child, parent, adult sibling, or other close family member</td></tr>
</table>

12.6 Prisoners

Research involving prisoners can only be approved by an IRB that satisfies the following regulatory requirements in 45 CFR 46.304, as quoted in part below:

a. The majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
b. At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

The IRB will rely on the IRB of the Harvard School of Public Health (HSPH) for review of research involving prisoners until such time as the IRB includes a prisoner representative. The HSPH review conforms to the requirements of 45 CFR 46, including the additional protections for prisoners outlined in Subpart C.

If, during the course of previously approved research, an individual participant becomes a prisoner the investigator is required to notify the IRB promptly. At that point the investigator must discontinue all research activities with the participants unless the investigator asserts in writing and the reviewing IRB Chair agrees in writing that it is in the best interests of the participants to continue to participate in the research while the research is being re-reviewed by the HSPH IRB in accordance with the additional protections for research involving prisoners.

In making this determination, the reviewing IRB Chair will consider: (1) whether the research involves an intervention or procedure that holds out a prospect of direct benefit that is important to the health or well-being of the individual and is available only in the context of the research; and (2) whether the research can be performed safely while the individual is a prisoner.

13 RECRUITMENT OF RESEARCH PARTICIPANTS

In compliance with Federal regulations, the IRB will review and approve all methods used to recruit participants to ensure that selection of participants is equitable, that the methods do not create undue influence or coerce someone to participate, and that the confidentiality and privacy of potential participants are protected. Every protocol must include a recruitment section that clearly describes:

- A description of the study populations to be enrolled;
- How potential participants are identified, recruited and enrolled;
- How and by whom participants are approached about participation;
- When consent is obtained in relation to the start of the study procedures; and
- Whether third parties (calling centers/centralized screening centers or other digital platforms) will assist with recruitment of participants for sites.

Selecting appropriate recruitment methods depends upon how the potential participant was initially identified. Potential participants can be identified:

1. through private medical information about individuals who are NOT patients of the investigator(s) (e.g., medical records, clinical databases, patient registries or by referring physicians),
2. from among the patients of the investigator(s),

3. by advertisements in various media,
4. from among the employees/students of the investigator(s),
5. from employees/students at Mass General Brigham, or
6. from the general community and/or the public at large.

13.1 Clinical Trial Website Postings

As described in OHRP guidance *(Clinical Trial Websites: When is IRB Review Required and What Should IRBs Consider with Reviewing? (OHRP Guidance, 2005))* the IRB does not require review of information posted on a clinical trial website if it does not go beyond a directory listing with basic descriptive information and is limited to:

- Study title
- Purpose of the study
- Protocol summary
- Basic eligibility criteria
- Study site locations(s)
- How to contact the study site for further information

Listing risks and potential benefits or requesting identifiable private information is not allowed without IRB approval.

14 INFORMED CONSENT

Informed consent is a vital part of the research process, and as such entails more than obtaining a signature on a form. Investigators must educate potential participants to ensure that they can reach a truly informed decision about whether to participate in the research. Their informed consent must be given freely, without undue influence or coercion, and must be based on a clear understanding of what participation involves.

The process of educating participants about the study begins during initial contact and continues for the duration of their participation. Thus, information conveyed through advertisements, recruitment letters, pre-screening phone calls, study description sheets as well as written informed consent documents and discussions must be understandable to the participants and should contribute to their understanding of the research. Technical and medical terminology should be avoided or explained in "lay" language, and materials should be written at a level that is understandable to the patient population. Participants must have information presented in a language they understand.

The IRB must approve written and oral information (including recruitment materials) provided to participants before and during the informed consent process.

When employees or agents of Mass General Brigham conduct human research, or when the Mass General Brigham IRB serves as the reviewing IRB for external sites, informed consent will be obtained in compliance with all applicable federal and state regulations and the requirements of the IRB, unless the IRB has waived or altered the informed consent requirements.

In compliance with the DHHS regulations and FDA regulations the IRB requires that the following requirements for informed consent be followed for all research:

14.1 General Requirements
(45 CFR 46.116(a)(1-3, 6) and 21 CFR 50.20)

1. Before involving a human subject in research covered by this policy, an investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative.
2. An investigator shall seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.
3. The information that is given to the subject or the legally authorized representative shall be in language understandable to the subject or the legally authorized representative.

(4. & 5. – see below)

6. No informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

14.2 Key Information
(45 CFR 46.116(a)(4-5)

(For research funded or conducted by DHHS)

4. The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

5.(i) 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.

5.(ii) Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

14.3 Basic Elements of Informed Consent
(45 CFR 46.116(b)(1-9) and 21 CFR 50.25(a)(1-8))

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 subjects will be maintained, and when applicable, that notes the possibility that the FDA may inspect the records;
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;
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; and
9. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
    - 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
    - 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.

When appropriate, one or more of the following additional elements of information shall also be provided to each subject:

14.4 Additional Elements of Informed Consent (45 CFR 46.116(c)(1-9) and 21 CFR 50.25(b)(1-6))

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) that 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 that may relate to the subject's willingness to continue participation will be provided to the subject;
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).

14.5 Massachusetts State Law

Massachusetts has a patients' rights law, which provides that a person has the right to refuse to serve as a research participant and to refuse care or examination when the primary purpose is educational or informational rather than therapeutic [M.G.L. ch.111 70E(i)]. This law is generally consistent with federal requirements for informed consent or assent to research. Information about Patient Rights and Responsibilities is available through the Mass General Brigham's Admitting and Registration Services Department and public website.

14.6 Applicable Clinical Trials (42 U.S.C. 282(j)(1)(A))

When seeking informed consent for Applicable Clinical Trials, the following statement shall be provided to each clinical trial participant, "A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

14.7 Requirement for Posting of Informed Consent Forms

The 2018 Common Rule that went into effect January 21, 2019, included a requirement for federally funded clinical trials research approved on/after January 21, 2019, or existing research that is transitioned to the revised rule, to upload a copy of the Informed Consent Form (ICF) used to enroll participants to an approved Federal website (e.g.Clinical Trials.gov). The regulations (45 CFR 46.116(h)) require that:

1. For each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.
2. If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (e.g. confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.
3. The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

For research funded or conducted by NIH, an English language informed consent to enroll participants must be submitted/uploaded.

Investigators are responsible for complying with the posting requirement or for confirming that the federal department or agency funding or supporting the research will comply with the posting requirement.

14.8 Individuals Who Can Give Informed Consent/Permission

Informed consent is to be obtained directly from participants, with the exception of children and adults with impaired decision-making capacity.

14.8.1 Parental/Legal Guardian Consent for Children

Federal regulations require that consent to participate in research on behalf of a child be provided by a parent or an individual authorized under applicable state or local law to provide consent on the child's behalf to general medical care. Under Massachusetts law, a parent is generally authorized to consent to general medical care on behalf of their child. However, in some circumstances (such as when both parents are deceased), it may be necessary to identify another individual with this authority (for example, a court-appointed guardian). Before an investigator allows an individual other than a parent to consent on behalf of a child, the investigator should document the basis for the individual's authority to consent on behalf of the child to general medical care and place any relevant documentation in the research record. In situations when it is unclear under state law who has the authority to provide consent to general medical care on behalf of a child, and thus who can consent to the child's participation in research, the IRB will consult with the Mass General Brigham Office of General Counsel as needed or an investigator may consult directly with the Mass General Brigham Office of General Counsel.

Under the federal regulations, where consent to the research is to be provided by a child's parent and the research involves no greater than minimal risk or greater than minimal risk, but with the prospect of direct benefit to the participants, the IRB may decide that consent of one parent is sufficient. However, when the research involves greater than minimal risk and no prospect of direct benefit to the participants, permission must be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when one parent has legal responsibility for the care and custody of the child. In such instance, the investigator or designee must document in the study record the reason for only one parent providing permission. Investigators should consider carefully what is "not reasonably available". For example, if a parent is unable to attend a research visit because they have to work, but are otherwise involved in the child's life, that would not be considered "not reasonably available". Alternatively, if one parent was deployed and that was the reason they could not provide consent for their child to participate, that would be considered "not reasonably available".

In certain circumstances, it may be appropriate for the investigator to provide justification regarding why it is not appropriate to require parental permission for a particular study. The IRB may grant a waiver of parental permission for non-FDA regulated research pursuant to the criteria set forth in 45 CFR 46.116(f)(3) if it finds that the criteria set forth in that provision and the additional criteria outlined below, set forth in 45 CFR 46.408(c), are met:

1. The research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects;
2. An appropriate mechanism for protecting the children who will participate as subjects in the research is substituted; and
3. The waiver is not inconsistent with Federal, state or local law.

For Single IRB studies where the Mass General Brigham IRB is the reviewing IRB for multiple sites, the sites should follow their local policies related to consenting.

14.8.2 Assent of Children

In addition to permission of the parent(s) or guardian, assent to participate in the study should be obtained from each child age 7 years or older who, in the opinion of the investigator, is able to provide assent based on their age, maturity or psychological state. When the IRB determines that the intervention or procedure

involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children involved in the research and the intervention or procedure is only available in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even when the children are capable of assenting, the IRB may waive the assent requirement as described elsewhere in section *Alteration or Waiver of Elements of Informed Consent*. When assent is not obtained, the investigator must document the rationale in the study records.

When assent is obtained, it is generally advised that it be documented in writing using the IRB-approved consent/assent form. Written assent is not always mandated, and investigators may request verbal assent. When assent of children is planned, the protocol submission should include a description of and justification for the method chosen for obtaining and documenting assent of children.

14.8.3 Children Who Turn 18 During Study Participation

Children who turn 18 years of age while they are participating in a study are now adults and must give consent to continue their participation if any of the remaining study procedures require informed consent for participation, including consent to future uses of individually identifiable specimens or data. When a child is enrolled in a repository research study, the PI is responsible for identifying any child who reaches the age of majority and either ceasing the use of the data or research materials in the repository or reaching out to the now adult to obtain consent for continued participation in the repository.

14.8.4 Children Who Can Give Legally Effective Informed Consent

Under Massachusetts State law and applicable Mass General Brigham clinical policies, some children (less than 18 years of age) can provide legally effective consent for their own medical care, in certain circumstances, without parental consent or knowledge and therefore may not meet the definition of "children" and the relevant regulatory requirements may not apply. "Emancipated" children, i.e., those who are married, widowed or divorced, or have a child or are pregnant (or believe themselves to be), are in the armed forces, or living apart from their parents and managing their own affairs, can provide informed consent for their own medical care.

Children in Massachusetts may also give consent to research procedures that involve:

- psychiatry treatment, if the child is 16 or over;
- treatment of drug dependency, if the child is 12 or over; and
- treatment of certain diseases dangerous to public health (e.g., sexually transmitted infections and others).

When the IRB approves the obtaining of informed consent from "emancipated" children or children for the treatments specified above, informed consent generally follows the same procedures that are being followed for adults. The investigator must also document the specific circumstances that justify designating a particular participant less than 18 years of age as capable of providing consent to the treatments and procedures involved in the particular research. This documentation would usually be in a note in the research records.

14.8.5 Surrogate Consent for Adults

Federal regulations require informed consent for research to be obtained from the participants or the participants' legally authorized representative (surrogate). In general, research that involves more than minimal risk and no anticipated direct medical benefit to participants should be conducted in participants who personally give consent and who sign and date the written consent document. When investigators propose research that involves adults who are unable to give informed consent to participate in research, they must follow IRB guidance on Surrogate Consent.

14.8.6 Individuals with Impaired Decision-making Capacity

Research that is determined to be more than minimal risk by the IRB may be conducted in participants with the consent of a legally authorized representative, provided that the following conditions are fulfilled:

1. The objectives of the research cannot be met by means of a trial in participants who can give consent personally;
2. The foreseeable risks to the participants are low;
3. The negative impact on the participant's well-being is minimized and low;
4. The research is not prohibited by law; and
5. Such research, unless an exception is justified, should be conducted in participants having a disease or condition for which the investigational product or intervention is intended. Participants in this research should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

Research that is determined to be minimal risk by the IRB may be conducted in participants with the consent of a legally authorized representative, provided that the following conditions are fulfilled:

1. The research is not prohibited by law; and
2. Such research, unless an exception is justified, should be conducted in participants for which the research is intended to benefit or to gain new knowledge that could potentially benefit participants in the future. Participants in this research should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

14.9 Documentation of Written Informed Consent

For research that is determined to be more than minimal risk or when required by the IRB, investigators must document the informed consent process by use of a written consent document (research consent form) signed and dated by the participant or their legally authorized representative (or surrogate) and the investigator (or study staff if approved by the IRB) who obtained the participant's consent.

The entire text of all research consent forms must be approved by the IRB as part of the review process. For research approved by the Mass General Brigham IRB, the effective date of the IRB-approved consent form and expiration date of IRB approval (one year or less) are noted in the footer added to the research consent form by the IRB Office post approval. Participants must be given and sign the most recently approved version of the research consent form. Outdated and/or expired research consent forms must not be used. A copy of the fully executed informed consent must be provided to participants.

14.9.1 Digital Signatures

Digital signatures may be acceptable forms of documentation of written informed consent. Electronic, computer or tablet-based consent documents may facilitate record keeping even when an individual is present and could sign a paper form. Digital signatures may be considered for face-to-face and remote consent.

There are two forms of digital signatures: (1) actual signatures on tablets or computers (where an individual uses a stylus or finger to make a representation of their signature, as available in many retail stores) OR (2) validated electronic signatures on platforms with password entry (such as those used to sign medical notes or electronically write prescriptions). Validated electronic signatures typically require one to "set up" an identity and password within an electronic system. Both forms of digital signature may be used in research in certain research settings. When a stylus is used to collect a signature in person, the usual methods of identity validation should be used (typically patient is asked to provide a picture identification card when they check in at the clinic). Note: Scanned signatures that are copied and pasted to a document are not acceptable "digital" signatures. When validated password-protected signature platforms are proposed, investigators must use a Mass General Brigham-approved platform.

14.9.2 Individuals Who Cannot Write or Are Physically Unable to Sign the Consent Form

When a person cannot write or is physically unable to sign the consent form, they can make their mark on the signature line in the consent form. People who cannot make their mark on the consent form can indicate consent by other means, e.g., orally, nodding their head, etc. The means by which consent was given by the participant should be documented in the research record.

14.10 Waiver of Documentation of Informed Consent

The IRB may waive the requirement to document informed consent with a signed written informed consent document for some OR all participants if it finds any of the following:

1. the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject (or legally authorized representative) will be asked whether they want documentation linking them with the research, and their wishes will govern (does not apply to FDA regulated research);
2. 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 (Note: For FDA regulated studies, only this criterion applies). Examples of such activities include completing surveys, performing an abbreviated physical exam, using a mobile software application, or providing a blood or urine sample; or
3. 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 (does not apply to FDA regulated research).

When the IRB approves a waiver of the requirement to obtain a signed written consent based on considerations above, the full consenting process remains the same for these participants, which may include being given a written informed consent document embodying all the elements of informed consent.

In some instances a participant may be informed that completing a task, such as filling out a survey, suffices as indication of consent. If the survey is presented in an electronic environment, the participant may be asked to check a box to indicate whether they agree or decline to participate. The checkbox is not considered a signature and this method still requires a waiver of documentation of consent from the IRB.

If written consent is waived, the IRB may require the investigator to provide the participants with information regarding the research, which could be provided in person, by mail, or electronically. The IRB provides templates for this type of consenting process.

Even when written consent is waived by the IRB, the investigators are still required to document all elements and aspects of the informed consent process that continue to apply.

14.11 Alteration or Waiver of Elements of Informed Consent

The IRB can approve a consent process that does not include, or that alters, some or all of the elements of informed consent or even waives the requirement to obtain informed consent provided the IRB documents that all of the following requirements are met:

1. the research involves no more than minimal risk to the subjects;
2. the waiver or alteration will not adversely affect the rights and welfare ofthe subjects;
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 forma
4. the research could not practicably be carried out without the waiver or alteration, and
5. whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

For research regulated by the FDA, all of the following requirements must be met:

1. The clinical investigation involves no more than minimal risk to the subjects;
2. The clinical investigation could not practicably be carried out without the requested waiver or alteration;
3. If the clinical investigation involves using identifiable private information or identifiable biospecimens, the clinical investigation 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 or legally authorized representatives will be provided with additional pertinent information after participation.

14.12 Withdrawal of Participants: Record Retention and Requirements for Informed Consent for Continued Limited Participation

When a participant withdraws from the study before completion, there may be concerns about how to handle the incomplete set of data. When the study is regulated by FDA, the data that have already been collected cannot be removed from study databases and the consent document cannot give the participant the option of having these data removed.

An investigator may ask a participant who is withdrawing whether they wish to allow continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. The discussion with the participant about their limited continuation in the study should distinguish between study-related interventions and continued collection of associated clinical outcome information, such as medical course or laboratory results obtained through medical record review and address the maintenance of privacy and confidentiality of the participant's information. In some situations, participants may agree to surveys or observational follow-up, but not wish to receive study drug or other interventions or attend study visits. If the participant agrees to more limited observational follow-up, the investigator must obtain the participant's informed consent for this limited participation using a separate IRB-approved consent form, unless this limited participation after participant withdrawal was described in the original IRB-approved consent form. If the participant does not agree, the investigator must not access the participant's medical record or other confidential records for purposes related to the study. However, an investigator may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

15 REMUNERATION FOR RESEARCH PARTICIPANTS

The IRB is responsible for reviewing and approving participant compensation. The IRB reviews proposed participant compensation to ensure that:

1. The amount and proposed method of payment and the timing of disbursement do not unduly influence or coerce participants;
2. Credit for payment accrues as the study progresses and is not contingent upon a participant completing the entire study;
3. Any amount paid as a bonus for completing the study is reasonable and not so large as to unduly influence participants to stay in the study when they would otherwise have withdrawn; and
4. All information concerning payment, including the amount and schedule of payments, is set forth in the consent document.

16 BONUS PAYMENTS IN CLINICAL TRIAL AGREEMENTS

The responsible conduct of clinical trials requires that the trials be conducted in a manner that does not create inappropriate risk for study participants. Any financial arrangements that could influence, or reasonably be perceived as influencing, the way that study investigators recruit and otherwise interact with study participants are not acceptable. Of particular concern are payment structures that may provide an inappropriate incentive for the recruitment of patients.

Accordingly, the following applies to clinical trials conducted at Mass General Brigham:

1. Payments for a clinical trial should be directly based upon the cost of the study, including the total costs for the infrastructure, personnel, and equipment necessary to recruit, screen, and enroll subjects in the trial.
2. Any extra payment or increase in payment that is not attributable to an increase in actual costs to implement the study is considered to be a "bonus payment" and is not allowed.

While payment structures for clinical trials vary, typically, a sponsor pays the hospital or other entity on a per-subject basis in order to reimburse costs proportionally. The IRB may develop further guidelines and make decisions in individual cases that do not clearly fall into "acceptable" guidelines. Examples of acceptable and unacceptable structures include the following:

16.1 Generally Acceptable Payment Structures

Payment structures that provide for unvarying per-participant payments, or payments which are to be made at fixed times, with no contingencies, and that are based upon the actual cost of the study, including recruitment, screening, and enrollment, will be presumed acceptable under this policy, absent unusual circumstances (e.g. unusually high per patient payments).

Payment structures that provide for increasing per-participant payments over the course of a trial may be acceptable if both of the following conditions are met:

- The increased payments are based on increased costs associated with the additional participants, which costs do not accrue unless and until those additional participants are enrolled (for example, costs of additional staff that will not be needed unless a certain number of subjects are enrolled);
- Mass General Brigham Clinical Trials Office (CTO), in consultation with the IRB, reviews and approves the payment schedule.

In the foregoing examples, reasonable mark-ups from actual costs will generally be acceptable when tied to fair market value of the work performed.

Increased payments which are not provided for, or anticipated in, the initial budget may be acceptable during the course of a study if the increased payment is based on past expenses having been higher than anticipated, or on unanticipated increases in future costs.

16.2 Unacceptable Payment Structures

Payment structures which create an incentive to hasten or complete enrollment of participants are unacceptable. Examples of payment structures which will be presumed unacceptable include the following:

1. A per-subject payment schedule that increases after the enrollment of a specified number of participants (e.g. $100 per subject for the first 10 participants and $150 per participant for the next 10 participants, etc.), unless such increase is based on a clear increase in costs (see above).
2. Additional "bonus" payments upon the completion of a specified number of participants.

3. Payments that are made only if a specified number of participants are recruited, e.g. no payments for 48 participants, but full payment for 50, or payments made only if 50 participants are enrolled by a certain date. These payment schemes could influence, or reasonably be perceived as influencing, the way the last few participants may be recruited.

17 NONCOMPLIANCE IN HUMAN RESEARCH

Mass General Brigham provides and maintains a culture characterized by integrity, responsible behavior, and a commitment to the highest legal and ethical standards of human subject protection. Consistent with these principles, the IRB complies with the DHHS regulations at 45 CFR 46.108(a)(4)(i) and the FDA regulations at 21 CFR 56.108(b)(2) for ensuring prompt reporting to the IRB, appropriate institutional officials, OHRP, and/or the FDA, of any serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB. Even if the investigator is still in the process of collecting outcome or other information about the event, the investigator is responsible for meeting the reporting timeline based on when the event is recognized as a reportable event. Additional information can be submitted to the IRB when it becomes available

Any investigator or other individual employed by, on staff at, or otherwise affiliated with Mass General Brigham who observes or otherwise becomes aware of potential noncompliance with applicable federal, state, and local laws and regulations or the requirements or determinations of the IRB in connection with human research and clinical investigations has the duty and responsibility to report the noncompliance to the IRB.

Noncompliance is often referred to as a deviation from the IRB-approved research and may include deviations that are unplanned or unintentional. Noncompliance may occur during the conduct of a research study or may be discovered during routine data monitoring activities of the sponsor or investigator, or audits conducted by Mass General Brigham or a regulatory agency. Noncompliance may also be discovered as the result of a complaint from a research participant or a report from others not otherwise associated with the research. When an investigator discovers or is made aware of any noncompliance, they must report the deviation to the IRB as follows:

1. Noncompliance that involves a major deviation from the IRB-approved research must be reported to the IRB within five (5) working days/seven (7) calendar days of the date the investigator becomes aware of the noncompliance.
2. Noncompliance that involves a minor deviation from the IRB-approved research are to be recorded by the investigator in a protocol-specific Minor Deviation Log.

The investigator is responsible for reporting noncompliance consisting of either major or minor deviations to their study sponsor as outlined in the sponsor's protocol or research or investigative plan.

It is the responsibility of the investigator to review the noncompliance and decide if it constitutes a major or minor deviation and ensure proper reporting to the IRB. To make this determination, it should be considered whether the noncompliance negatively affected any of the following:

- The rights, safety, or welfare of the participant;
- Risk-benefit assessment; and
- The ability to draw conclusions from the data, the ability to confirm the validity of the research conduct or the credibility or accuracy of any reported research results.

When the HRA C&E Office conducts an audit or is notified of noncompliance, the C&E office staff have the authority to determine if a noncompliance report must be made to the IRB.

Examples of Noncompliance that involve a major deviation from the IRB-approved research include but are not limited to:

- Failure to follow IRB approved consent process
- Enrollment of a participant who did not meet all inclusion/exclusion criteria
- Study procedures completed without prior IRB approval or not conducted in accordance with the IRB-approved protocol, Mass General Brigham policy, and/or applicable research regulations having an impact on participant safety and/or data integrity.
- Failure to ensure the accuracy and completeness of the records of each participant's case history and records of all correspondence with another sponsor, a monitor, an investigator, an IRB, or the FDA.
- Complaint by/on behalf of a research participant that indicates that the rights, welfare, or safety of the participant have been adversely affected or that cannot be resolved by the investigator
- Violation of applicable regulations or requirements or determinations of the IRB identified by the research team or others (e.g., FDA Form 483 or Warning Letter) that indicates that the rights, welfare, or safety of participants have been adversely affected

Examples of Noncompliance that involve a minor deviation from the IRB-approved research include but are not limited to:

- Only photocopy is available of the original signed and dated consent form (original paper or certified scanned copy is not available)
- Inappropriate documentation of informed consent, including:
  - Missing investigator signature
  - Copy not given to the person signing the form
  - Someone other than the participant dated the consent form
  - Use of outdated/expired/unstamped consent form that is identical or consistent with currently approved consent or consent approved at that time
- Failure to follow the approved study procedure that, in the opinion of the PI, does not affect subject safety or data integrity:
  - Study procedure conducted out of sequence
  - Omitting an approved portion of the protocol
  - Failure to perform a required lab test
  - Missing lab results
- Study visit not involving safety assessments conducted out of visit window
- Failure of participant to return study medication

NOTE: Any noncompliance that involves repetitive minor deviations may represent a systemic issue and should be reported as noncompliance involving a major deviation

17.1 Allegations of Noncompliance

Allegations of noncompliance or suspected noncompliance in the conduct of research or the operation of the IRB may be submitted to the IRB Office by a PI, study team, IRB Staff, IRB members, the C&E Office, other groups tasked with auditing, a research participant or any other person who has a concern.

Mass General Brigham intends to protect, to the extent possible, the privacy of an individual who in good faith reports noncompliance on the part of another individual. Allegations of noncompliance made in good faith will not reflect negatively on the individual reporting such noncompliance and, when applicable, will not affect his/her employment, in accordance with the "Mass General Brigham No Retaliation Policy."

Allegations of noncompliance, whether written or oral, and whether made directly to the IRB through Insight or as part of another report to the IRB, should include a complete description of the noncompliance, of the observed circumstances and, the names of the individuals involved, if known. Whenever possible, the report should contain sufficient details to allow an assessment of noncompliance.

Allegations of noncompliance related to conduct of research are normally routed to the Senior IRB Chair or designee for screening and assessment of complete information, and to assess whether the allegation has a basis in fact. If unable to resolve whether the allegation has a basis in fact, the Senior IRB Chair (or designee) may engage other organizational leadership in the investigation or may refer the matter to the IRB for further investigation.

The Senior IRB Chair or designee screens events believed to have a basis in fact and then refers them for review by the Other Event Committee (OEC). The OEC is comprised of the Senior IRB Chair, the IRB Director, the C&E Office Director or designee, other IRB Chairs or Vice Chairs as applicable, and IRB Assistant Directors or IRB Staff, as appropriate. The OEC is not considered a full board IRB.

17.2 Handling Reports of Noncompliance

Investigation of research noncompliance may include contact with the PI, research team members, and other individuals involved in the initial report, as applicable. The OEC may also consult with the VP HRA, OGC, Office of Research Complianc (ORC), or other institutional officials.

The PI may voluntarily place the research on hold in whole or in part while the investigation into reports of noncompliance is being conducted. Such holds are not subject to the reporting requirements in 45 CFR 46.108(4)(i) and 21 CFR 56.108(b)(2). At any point during the initial fact gathering process or later, the Senior IRB Chair or IRB Chair may suspend in whole or in part the research or refer the research to the IRB for suspension or termination. Such suspensions or terminations will be reported in accordance with section *Suspension or Termination of Human Subjects Research* in this Policy.

Once the investigation has been completed, the Senior IRB Chair/designee or the OEC make one of the following determinations:

1. The facts do not support a finding of noncompliance. The report of noncompliance is dismissed and no further action is required.

2. The allegation has a basis in fact and meets the definition of noncompliance and determines whether:

    a. The noncompliance is not serious or continuing:
        1) If the proposed corrective action plan is appropriate,
        2) If the proposed corrective action plan is not appropriate, the Senior IRB Chair or designee may take one or more of the actions noted below.

b. The noncompliance is potentially serious or continuing, the report is referred to the full board IRB.

The Senior IRB Chair or designee will document review in the Insight expedited review checklist.

17.3 Noncompliance Review by the Full Board IRB

Research noncompliance may be reviewed by any IRB; however, reports are routinely reviewed by IRB 02 which meets on a monthly basis or as needed.

The Senior IRB Chair (or designee) assigns reviewer(s) with appropriate experience or expertise to review the noncompliance. IRB members are provided access in Insight and/or are provided a copy of the report, any correspondence related to the report, the protocol, approved consent form and any other documents or information submitted by the investigator for review of the problem, (e.g., monitoring reports.) Any revised materials in response to the report are provided to members as well as a proposed corrective and preventative action plan, as applicable.

The primary and secondary reviewers are responsible for an in-depth review of the noncompliance and associated materials. All other members are responsible for review of the report and any other materials sufficient for determining how to vote at the meeting. The IRB determines whether an event constitutes serious and/or continuing noncompliance.

The review by the IRB, and associated findings, determinations and recommendations are documented in the full board IRB meeting minutes. The IRB sends written notification of determinations and actions taken to the PI through the Insight system. Reports to other entities are made in accordance with the section *Reporting to Authorities* in this Policy.

17.4 Corrective and Preventative Actions

The IRB Chair/designee, OEC, or full board IRB may take corrective and preventative actions related to the review of noncompliance including (but are not limited to):

- Approve the research to continue with no further action required
- Defer action pending additional information
- Require modifications in the research and/or consent form
- Require that subjects who are still participating in the research be re-consented or notified in writing of the noncompliance
- Require observation of the consent process by a member of the IRB or the C&E Office.
- Require that subjects whose participation has ended be notified in writing of the noncompliance
- Modify the continuing review schedule
- Require periodic audits by the C&E Office
- Require remedial education
- Require oversight by a senior investigator
- Restrict the conduct of research
- Restrict research privileges.
- Suspend the research (Senior IRB Chair or full board IRB)
- Terminate the research (full board IRB only)

17.5 Allegations of IRB Noncompliance

Allegations of noncompliance of the IRB are routed to the VP HRA. The VP HRA investigates the potential noncompliance and may conduct discussions with IRB Staff, IRB members, and/or IRB leadership. The VP HRA makes a determination as to whether the allegation has a basis in fact and constitutes noncompliance, and if determined to be noncompliance, whether it constitutes continuing and/or serious noncompliance. The VP HRA reviews proposed corrective and preventive actions and may require additional corrective actions to prevent future occurrences including, but not limited to:

- Revision of standard operating procedures
- Retraining and education of IRB Staff, IRB leadership, IRB members
- Auditing by the C&E Office.

The Senior IRB Chair, OEC and IRB report serious or continuing noncompliance in accordance with the section *Reporting to Authorities* in this Policy.

18 UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS

Mass General Brigham complies with DHHS regulations 45 CFR 46.108(a)(4)(i) and the FDA regulations 21 CFR 56.108(b)(1) that require prompt reporting to the IRB, appropriate institutional officials, and the department or agency head / FDA of any unanticipated problems involving risks to participants or others (UPIRTSOs) and is consistent with OHRP and FDA guidance on reviewing and reporting UPIRTSOs.

Principal Investigators are required to report to the IRB any event that meets the definition of UPIRTSO as defined in this Policy *(see Definitions in Appendix IV)*:

Events meeting the UPIRTSO definition must be reported if they occur during the conduct of the study, after study completion, or after participant withdrawal or completion. Events meeting the definition of UPIRTSO include, but are not limited to:

- Unanticipated drug or unexpected device adverse reactions attributable to the intervention and that place participants at increased risk of harm
- Events that occur more frequently than expected or that represent a more severe instance of the event than has previously occurred
- Breach of confidentiality or violation of HIPAA (e.g., lost or stolen laptop)
- Medication, procedural or laboratory error (e.g., errors in drug administration or dosing, surgical or other procedure, or testing of samples or test results) regardless of whether participants experienced any harm
- Interim analysis, safety monitoring report, publication in a peer-reviewed journal, or other finding that indicates that there are new or increased risks to participants or others or that participants are less likely to receive any direct benefits from the research
- Change in FDA labeling (e.g., black box warning), withdrawal from market, manufacturer alert from the sponsor, or recall of an FDA-approved drug, device, or biologic used in the research

- Incarceration of a research participant during participation in research that is not approved for involvement of *prisoners* as participants
- Suspension or termination of the research by an entity other than the IRB, in whole or in part, based on information that indicates that the research places participants at an increased risk of harm than previously known or recognized (e.g., FDA clinical hold)
- Premature suspension, termination or hold of the research by the sponsor
- Suspension or disqualification of an investigator by FDA, sponsor, or others
- Scientific misconduct

18.1 Investigator Reporting of UPIRTSOs

Reports of UPIRTSOs are to be submitted through Insight via an Other Event form within 5 working days (7 calendar days) of the date the investigator *first* becomes aware of the problem. Even if the investigator is still in the process of collecting outcome or other information about the event, the investigator is responsible for meeting the reporting timeline based on when the event is recognized as a UPIRTSO. Additional information can be submitted to the IRB when it becomes available.

The investigator must provide the following information in the report:

1. a detailed description of the event (including how and when the PI/study team learned of the event);
2. the basis for determining that the event is unexpected in nature, severity, or frequency;
3. the basis for determining that the event is related or possibly related to the research procedures;
4. the basis for determining that the research places participants at an increased risk of harm; and
5. whether any changes to the research or other corrective actions are warranted.

The IRB does not accept, and investigators should not report, expected and/or unrelated adverse events or expected serious adverse events or expected adverse events. Only events the sponsor and/or investigator has determined and provided justification that the event meets the definition of a UPIRTSO should be reported. Sponsor IND/IDE safety reports that do not meet the UPIRTSO definition will not be accepted.

Events that are UPIRTSOs that occur at sites that are not under the oversight of the IRB should only be submitted when they impact the Mass General Brigham participant's safety, rights or welfare, or the conduct of the research at Mass General Brigham. Such reports would likely warrant changes to the conduct of the research, consent process, or require notification to participants.

When making reports, investigators should take into consideration whether substantive changes in the research protocol or informed consent document, or other corrective actions may be warranted to protect the safety, welfare, or rights of participants or others. Changes to the protocol and/or the informed consent document are to be submitted through Insight as an Amendment (in addition to the Other Event report).

Examples of substantive changes include:

- changes to the eligibility criteria
- changes to safety monitoring procedures
- changes to the informed consent document to describe newly identified risk or new information
- suspension of enrollment of new participants
- suspension or termination of the research

18.2 Handling Reports of UPIRTSOs

The Senior IRB Chair (or designee) and/or OEC will evaluate whether events meet the definition of a UPIRTSO and make the following determinations:

1. The event does not represent a UPIRTSO. The event is noted in Insight and no further action is required.
2. The event is a UPIRTSO.
a. The event is a serious UPIRTSO. The event is referred to the full board IRB for review.
b. The event is a UPIRTSO but not serious. The OEC and/or Senior IRB Chair/designee complete the review through the expedited review process.
3. If the event occurred at sites that are not under the oversight of the IRB, the IRB Chair/designee, OEC and/or the full board IRB will not make an Unanticipated Problem determination for the event. The IRB Chair/designee, OEC and/or the full board IRB may still take other actions, as noted below.
4. If the event suggests noncompliance, the procedures in *Noncompliance in Human Research* in this Policy are followed.

When the OEC and/or Senior IRB Chair or designee determines that changes are necessary to protect the rights and welfare of participants, the changes may be approved prior to additional review by the IRB at a full board meeting. The Senior IRB Chair may also, at their discretion, suspend the research to protect the safety of participants. The VP HRA may also suspend the research to protect the safety of participants. In the event that the Senior IRB Chair or VP HRA suspends the research, such suspension will be reported to and reviewed by the full board IRB.

The IRB Chair/designee and OEC are subject to the section on *IRB Member Conflicts of Interest* in this Policy when reviewing and making determinations about UPIRTSOs.

18.3 UPIRTSO Review by the Full Board IRB

UPIRTSOs may be reviewed by any IRB, however reports are routinely reviewed by IRB 02 which meets monthly or as needed.

The Senior IRB Chair (or designee) assigns reviewer(s) with appropriate experience or expertise to review the UPIRTSO. IRB members are provided the OE report, the approved consent form, and, when applicable, the revised consent form, and the detailed protocol as well as any other documents or information submitted by the investigator for review of the problem (e.g., monitoring group reports) via Insight. Any revised materials in response to the report are provided to members as well as a proposed corrective and preventative action plan as applicable. All members have access to the complete protocol file as well.

The primary and secondary reviewers are responsible for an in-depth review of the report of the problem and materials provided. All other members are responsible for review of the report of the problem and the consent forms in sufficient depth to vote at the meeting.

The review by the IRB and its determinations and recommendations are documented via the meeting minutes. The IRB sends written notification of determinations and actions taken to the PI through the Insight system. The Senior IRB Chair, OEC and IRB report UPIRTSOs in accordance with the section *Reporting to Authorities* in this Policy.

18.4 Corrective and Preventative Actions

The IRB Chair/designee, OEC, or full board IRB may take corrective and preventative actions related to the review of UPIRTSOs including (but are not limited to):

1. Accept the report and approve the proposed changes, if any, with no further action required;
2. Require additional information from the investigators and/or others (e.g., pharmacy, legal, privacy, or departmental chairpersons);
3. Require modifications in the protocol and/or consent form;
4. Require that participants currently on protocol be notified of the problem;
5. Require that participants whose participation has ended be notified of the problem;
6. Require that participants currently on protocol be re-consented;
7. Request a directed audit by the C&E Office;
8. Other actions as appropriate;
9. Suspend the study (IRB Chair/designee or full board IRB); and/or
10. Terminate the study (full board IRB only).

19 SUSPENSION OR TERMINATION OF IRB APPROVAL

Consistent with federal regulations at 45 CFR 46.108(a)(4)(ii), 45 CFR 46.113 and 21 CFR 56.108(b)(3), the IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with regulations, the requirements, or determinations of the IRB or that has been associated with unexpected serious harm to participants. The VP HRA, and the Senior IRB Chair have the authority to suspend research. Additionally, the IO may suspend or terminate research approved by the IRB for human participant protection, administrative, financial, or other reasons.

When the IO, VP HRA, or Senior IRB Chair suspends or terminates IRB-approved research, they are responsible for promptly notifying the Principal Investigator, Department Chair/Chief, and the IRB in writing of the suspension or termination and the reasons for doing so. Suspension or termination directives made by the Institutional Official, VP HRA, or Senior IRB Chair will be reported to the full board IRB for review by the Senior IRB Chair or designee.

When the IRB suspends or terminates approved research, the IRB sends written notification to the PI through the Insight system.

When the IO suspends or terminates research, or when the VP HRA suspends research, they will consult with the Senior IRB Chair when possible to ensure the rights and welfare of currently enrolled participants are not negatively impacted. Likewise, the Senior IRB Chair when suspending research and the IRB when suspending or terminating research will ensure the rights and welfare of currently enrolled participants are not negatively impacted.

When the suspension or termination involves withdrawal of participants from an interventional study, Senior IRB Chair, and/or IRB considers and determines what, if any, withdrawal procedures are required for the safety and welfare of those participants. Withdrawal procedures may include, but are not limited to the following:

- Requiring notification to the participants including the content and manner of notice. The notification may be to
    - all participants who have been or are enrolled;
    - participants currently on protocol; or
    - participants who participated in a certain aspect of the protocol.
- Tapering of the drug
- Making a final study visit at which a physical exam and/or laboratory or other tests willbe performed; and/or
- Making arrangement for participants to receive medical care by their primary care physician or specialist or through referrals to other healthcare providers.

When research is suspended, the investigator is subject to the requirement for continuing review (if required for the study) and all reporting requirements for the duration of the suspension.

The IRB reports suspensions or terminations in accordance with the section *Reporting to Authorities* in this Policy.

20 REPORTING TO AUTHORITIES

Consistent with federal regulations, the IRB is responsible for reporting on behalf of Mass General Brigham to the applicable institutional officials and, as required or appropriate, to the applicable regulatory agencies:

1. any unanticipated problems involving risks to subjects or others;
2. any serious or continuing noncompliance of federal regulations or determinations of the IRB; or
3. any suspension or termination of IRB approval.

If one of the events involves human research that is not federally conducted or supported, the IRB is not required to report the event to OHRP or other relevant federal department or agency head. However, reporting to the FDA may still be required, if the research is subject to FDA regulations. The IRB may voluntarily report any such event to OHRP or other agencies at its discretion. All other reporting requirements described below apply regardless of funding source.

The IRB Office is responsible for reporting any major event to the Association for the Accreditation of Human Research Protection Programs (AAHRPP) within 48 hours after Mass General Brigham becomes aware of any of the following:

- Catastrophic event that results in an interruption or discontinuance in a component of or the entire Human Research Protection Program;
- Sanctions taken by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports of the IRB with official action indicated, and FDA Restrictions Placed on IRBs or Investigators;
- Any litigation, arbitration or settlements initiated related to human research protection; or
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the Organization's HRPP.

The Director, IRB Office or designee is responsible for preparing reports, which include the following information or for reports to OHRP, the information required on the OHRP Incident Report Form:

- Name of the entity and the Principal Investigator conducting the research;
- Title of the research project and protocol number assigned by the IRB, the name of the research sponsor and the number of any applicable federal award(s)(grant, contract, or cooperative agreement);
- The nature of the event (unanticipated problem involving risks to subjects or others, serious or continuing noncompliance, suspension or termination of approval of research);
- Brief description of the research;
- A description of the problem including the findings of the IRB and the reasons for the decision;
- Actions the IRB and, if applicable, the entity is taking or plans to take to address the problem (e.g., revise the protocol, suspend enrollment, terminate the research, revise the informed consent document, inform enrolled participants, increase monitoring of participants, etc.); and
- Plans, if any, to send a follow-up or final report by the earlier of: (a) a specified date, or (b) when the investigation has been completed or a corrective action plan has been implemented.

In addition to the information above, the FWA number of the reporting entity and the entity conducting the research as well as names of the FWA Signatory Official, Human Protections Administrator, and the individual submitting the report must be provided on the OHRP Incident Report form.

The VP HRA is responsible for review and approval of the final incident report. The report is sent to the following under the VP HRA signature (as applicable):

1. Institutional officials

    a. Signatory of the FWA
    b. Director, IRB Office
    c. Chief Research Compliance Officer

2. Regulatory Agencies and Accrediting Organizations

    a. OHRP, if the study is federally supported or conducted
    b. FDA, if the study is subject to FDA regulations

3. Others

    a. Any Common Rule Federal Agency that is supporting the research, when applicable
    b. The Privacy Officer, if the report involves unauthorized use, loss, or disclosure of individually identifiable health information from the covered entity
    c. Others, such as the Chief Medical Officer, Corporate Sponsor or Entity supporting the research, deemed appropriate by the Institutional Officials named above

The IRB Office Director or designee will ensure that all steps of this policy are completed generally within 30 days of the date when:

- The IRB determines that an incident is an unanticipated problem involving risks to subjects or others;
- The IRB determines that an incident is serious or continuing noncompliance; or
- The IRB suspends or terminates approval.

21 INVESTIGATIONAL DRUG REQUIREMENTS

Non-exempt clinical investigations of drug products that are reviewed and approved by the IRB must comply with Food and Drug Administration (FDA) regulations 21 CFR 312 - Investigational New Drug Applications (INDs) as well as any other applicable federal requirements.

When the research involves drug products, the investigator is required to provide the IRB with sufficient information about the drug product, including FDA status, and its intended use to assess the risks and potential benefits to participants.

21.1 Clinical Investigations and Requirements for INDs

The clinical investigation of a drug product requires submission of an Investigational New Drug (IND) Application to the FDA, unless one of the exemptions at 21 CFR 312.2(b) applies to the investigation.

In accordance with FDA regulations, the potential sponsor or sponsor-investigator of a clinical investigation is responsible for initially determining whether the investigation meets the criteria for an exemption. The sponsor or sponsor-investigator should provide a point-by-point response to each exemption criterion and appropriate documentation in support of the criteria to the IRB for consideration.

An IRB Exemption subcommittee will determine whether the justification for exemption is met. If the subcommittee determines the exempt criteria are not met or if there is uncertainty about whether the exemption criteria are met, the subcommittee will require the study team to obtain a determination from the FDA and submit documentation to the IRB. It is ultimately up to the subcommittee to determine when the FDA must be contacted. In these cases, the review of a study cannot proceed until the sponsor or sponsor-investigator obtains a determination from the FDA.

21.1.1 Dietary Supplements

When a lawfully marketed dietary supplement is being studied for its effects on diseases (i.e., to cure, treat, mitigate, prevent, or diagnose disease including its associated symptoms) it is an investigational new drug and is subject to the 21 CFR 312 IND requirements. Investigators may request an exemption from 21 CFR 312 as described above for drugs either via submission for IRB Exemption subcommittee review or by making a submission directly to the FDA.

When a lawfully marketed dietary supplement is being studied for its dietary supplement use (i.e., structure and/or function claims), it is not an investigational new drug and is not subject to the 21 CFR 312 IND requirements. Structure and function claims are statements that describe the effect a dietary supplement may have on the structure or function of the human body.

21.1.2 Radioactive Drugs

When a radioactive drug is used in humans for research intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial), the radioactive drug is not an investigational new drug subject to the 21 CFR 312 IND requirements; however the research is subject to review and approval of the Radioactive Drug Research Committee (RDRC).

When the research is designed to conduct a clinical trial of a radioactive drug, the radioactive drug is an investigational new drug and is subject to the 21 CFR 312 IND requirements. Additionally, the research must be approved by the Radiation Safety Committee (RSC).

21.2 IND Documentation

The IRB requires the IND number be included in the application. As confirmation that the IND number is valid, the IRB will accept the IND number printed on the sponsored study protocol or for sponsor-investigator research the IRB will require documentation from the sponsor or the FDA of the IND number.

The IND goes into effect 30 days after the FDA receives the IND unless the sponsor receives earlier notice from the FDA that the IND may begin and must be in effect before submission to the IRB. The IRB can make an exception and allow submission for sponsor-investigator studies while the IND is under consideration, however the IND must be in effect before the IRB approves the study.

21.3 Drug Products not Manufactured by a Licensed Pharmaceutical Company

21.3.1 Drug Products with INDs

When an individual or entity other than a licensed pharmaceutical company manufactures the drug product being investigated, the IRB will rely upon FDA review of the chemistry, manufacturing, and control information contained in the IND Application.

21.3.2 Drug Products without INDs

When an individual or entity other than a licensed pharmaceutical company manufactures the drug being administered to participants and an IND is not required, the IRB will require a Certificate of Analysis.

22 INVESTIGATIONAL DEVICE REQUIREMENTS

Non-exempt human research and clinical investigations must comply with FDA regulations for devices intended for human use, pursuant to 21 CFR 812, Investigational Device Exemptions (IDE).

When the research involves a device, the investigator is required to provide the IRB with sufficient information about the device, including FDA status, to assess the risks and potential benefits to participants.

When an investigator is conducting a clinical investigation of a device, the IRB requires the investigator to have a standard operating procedure for control of the investigational device and device accountability to ensure that the device is used only by investigators listed on the protocol and in participants enrolled in the research study. The investigator is responsible for the control of the investigational device and device accountability in accordance with Mass General Brigham policy and FDA regulations.

Non-FDA approved devices or commercially available devices that are used according to their FDA-approved labeling are not subject to the IDE regulations if they:

- are used in investigations as tools to measure data or to study human physiology; and

- are safe for use in humans and do not place participants at undue risk of harm.

Such devices are subject to the requirements of the Mass General Brigham Medical Equipment Management Program when used within the Mass General Brigham system.

Studies designed to evaluate the sensitivity or specificity of a non-FDA approved device or FDA-approved device that intends to collect safety and effectiveness data or data to obtain FDA approval/change in labeling are subject to the IDE regulations.

22.1 Clinical Investigations of Devices

When a device is being evaluated for safety and effectiveness, the device is considered "investigational" and is subject to the requirements of the Investigational Device Exemption (IDE) regulations in 21 CFR part 812 (except as noted below).

22.1.1 Investigations Exempt from IDE Requirements (21 CFR 812.2(c))

Clinical investigations that fall into one the following categories are considered exempt from the requirement to obtain an IDE:

- A device, other than a transitional device, introduced into commercial distribution before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
- An FDA-approved device, which means a device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence.
- A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the test is: (i) noninvasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution if the testing is not for the purpose of determining safety or effectiveness, and does not put subjects at risk.
- A custom device as defined in 812.3(b) unless the device is being used to determine safety or effectiveness for commercial distribution.

The IRB generally makes the determination of exempted device investigation; however, the IRB may consult with the FDA or request the investigator seek a written determination from the FDA. Exempted device investigations must comply with the FDA requirements for IRB review (21 CFR 56) and Informed Consent (21 CFR 50).

22.1.2 Investigations Requiring an IDE (21 CFR 812)

Investigations that require an IDE are considered Significant Risk (SR) device investigations, meaning a device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents potential for serious risk to the health, safety, or welfare of a subject.

When the IRB, the sponsor, or the FDA determines that the research is a SR device investigation, the sponsor must submit an IDE application to the FDA, unless the investigation is exempt from the requirements of the IDE regulations as noted above. The sponsor generally makes the determination regarding the need for an IDE; however, the IRB is responsible for making the determination when the sponsor has not submitted an IDE application to the FDA. The IRB may require the investigator to submit to the FDA for the determination of need for an IDE application, in which case the FDA decision will govern. Device investigations under an IDE are scheduled for review at a full board meeting of the IRB.

The IRB requires the IDE number be included in the application. As confirmation that the IDE number is valid, the IRB will accept the IDE number printed on the sponsored study protocol or for sponsor-investigator research, the IRB will require documentation from the sponsor or the FDA of the IDE number. The IDE goes into effect 30 days after the FDA receives the IDE, unless the sponsor receives earlier notice from the FDA that the IDE is approvied or approved with conditions, and must be in effect before submission to the IRB. The IRB can make an exception for sponsor-investigator studies and allow submission while the IDE is under consideration, however the IDE must be in effect before the IRB approves the study.

22.1.3 Nonsignificant Risk Device Investigations (21 CFR 812.2(b))

Nonsignificant risk (NSR) device investigations include any investigation of a device other than those that meet the definition of a significant risk device or is exempt (as noted above), the device is not a *banned device,* and the sponsor labels the device in accordance with 21 CFR 812.5 and meets all other sponsor requirements in 812.2(1). A *banned device* means a device that has been banned by the Commissioner of the FDA. NSR studies are considered to have an approved IDE when the IRB concurs with the nonsignificant risk determination and approves the study. NSR studies must follow the abbreviated requirements of 21 CFR 812.2(b).

For devices that require an NSR risk determination, the research will be reviewed at a full board meeting of the IRB. The sponsor or sponsor-investigator is responsible for providing justification for why the proposed use of the device in the investigation should be considered NSR. The IRB bases its determination on the proposed use of the device in the investigation, and not on the device alone. If the proposed use of the device involves a procedure, e.g., a surgical procedure, the IRB considers the potential harm that could be caused by the procedure as well as the device in making its NSR determination.

When the IRB concurs with the sponsor or sponsor-investigator that the research is an NSR device investigation, the investigation may proceed when fully approved by the IRB and relevant ancillary committee(s).

When the IRB makes an NSR determination and all risks of the study are determined to be minimal risk in accordance with 21 CFR 56.102(i), the IRB may vote to allow continuing review to be conducted using the expedited review procedure.

22.2 Humanitarian Use Devices

(21 CFR 814)

Humanitarian use devices (HUDs) with approved Humanitarian Device Exemptions (HDEs) may be used for the FDA-approved indication only with approval of the IRB even though the FDA does not consider such uses to be research. The IRB may vote to allow continuing review to be conducted using the expedited review procedure, if the use of the HUD is within the scope of its approved labeling.

When HUDs are being evaluated for safety and effectiveness beyond the scope of the FDA-approved HDE indication, they are subject to the requirements of investigations of non-FDA approved devices as described in *Investigational Device Requirements* in this policy.

23 EMERGENCY USE

The FDA regulations allow for the emergency use of an investigational drug or biological product, or unapproved medical device with a human participant 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. Such emergency use does not meet the DHHS definition of *research* involving *human subjects;* however, the emergency use of a drug or biological product meets the FDA definition of *clinical investigation*. As such, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application.

When a member of the Mass General Brigham medical staff proposes to use an investigational drug or biological product, or unapproved medical device, they must comply with FDA regulations and Mass General Brigham policies and procedures.

- Whenever possible, investigators should submit a request via email to the IRB Office of a proposed emergency use prior to the emergency use (however, such notifications do not constitute IRB approval.)
    - Email correspondence is used to document in writing the emergency exemption from prospective IRB approval.
    - The Senior IRB Chair or designee is responsible for either concurring with the emergency exemption or for finding that the proposed use does not meet the criteria for an emergency exemption from prospective IRB approval.
    - The Senior IRB Chair or designee may request additional information or review by an independent physician when determining whether the criteria for an emergency exemption are met.
    - The Senior IRB Chair or designee is responsible for informing the investigator of their concurrence or disagreement with the emergency exemption.

- If the Senior IRB Chair or designee disagrees with the emergency exemption, the proposed use will be scheduled for review at the next available full board meeting of the IRB.
- The notification includes the requirement for prospective IRB review and approval of any subsequent use of the investigational drug or biological product, or unapproved medical device.

- When time is not sufficient for the investigator to notify the IRB before the emergency use the investigator must notify the IRB of such use within 5 working days.

Although the FDA regulations require prospective IRB review and approval prior to subsequent uses of the investigational drug or biological product, or unapproved medical device, the FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the protocol.

23.1 Investigational Drugs or Biological Products

FDA regulations permit a physician to treat a patient with an investigational drug or biological product in an emergency situation if they conclude that:

- 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 full board meeting of the IRB is feasible; and
- no standard acceptable treatment is available.

In such cases, the physician (also referred to as the "investigator") is responsible for contacting the manufacturer to determine whether the investigational drug or biological product can be provided under an existing IND. When the investigational drug or biological product is not available under an existing IND, the investigator is responsible for contacting the FDA to obtain an emergency IND.

Once an IND is in place, the investigator may administer the investigational drug or biological product with the informed consent of the participant or the participant's legally authorized representative. An exception to the requirement for informed consent may be made if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all 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 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.

If, in the investigator's opinion, immediate use of the investigational drug or biological product is required to preserve the participant's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the investigator should make the determination and, within 5 working

days after the use of the investigational drug or biological product, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The investigator is responsible for alerting the relevant pharmacy of the proposed emergency use and arrangements for drug shipment.

23.2 Unapproved Medical Devices

FDA regulations permit a physician to treat a patient with an unapproved medical device in an emergency situation if they conclude that:

- The patient has a life-threatening condition that needs immediate treatment;
- No generally acceptable alternative treatment for the condition exists; 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.

FDA expects investigators to follow as many of the patient protection procedures listed below as possible:

- Informed consent from the patient or a legal representative;
- Clearance from the institution;
- Concurrence of the IRB chairperson;
- An assessment from a physician who is not participating in the study; and
- Authorization from the IDE sponsor, if an IDE exists for the study.

In such cases, the physician (also referred to as the "investigator") is responsible for contacting the manufacturer to determine whether the unapproved device can be provided under an existing IDE. When the unapproved device is not available under an existing IDE, the investigator is responsible for reporting the emergency use to the FDA Center for Devices and Radiological Health (CDRH) or Center for Biologics Evaluation and Research (CBER) within 5 working days of the use. The report should contain a summary of the conditions constituting the emergency, patient outcome information, and the patient protection measures that were followed (e.g., informed consent from the patient or the patient's legal representative; clearance from the institution as specified by institutional policies; concurrence of the IRB chairperson; and an assessment from a physician who is not participating in the study.

When applicable, the investigator is responsible for alerting the operating room or other facility of the proposed emergency use and arrangements for device shipment.

24 EXCEPTION FROM INFORMED CONSENT REQUIREMENTS FOR EMERGENCY RESEARCH

The IRB will approve exceptions from informed consent requirements for planned emergency human research only if it finds and documents that the research satisfies all of the requirements of 21 CFR 50.24 for an exception from informed consent requirements for emergency research and/or 45 CFR 46.101(i) for emergency research consent waiver.

The emergency research consent waiver does not apply to research involving fetuses, pregnant women, and human in vitro fertilization (Subpart B of 45 CFR 46) and research involving prisoners (Subpart C of 45 CFR 46).

For the purposes of the emergency research consent waiver, "family member" means any one of the following legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the participant is the equivalent of a family relationship.

24.1 Protocol Submission Requirements

When submitting research requesting an exception from informed consent requirements for emergency research, the investigator must address each of the required IRB findings and determinations in their Insight submission, specifically:

- Justification for the research;
- Justification for waiver of informed consent, including that obtaining informed consent is not feasible for the reasons outlined in 21 CFR 50.24;
- Relation of risks to anticipated benefits;
- Informed consent procedures and an informed consent document consistent with 21 CFR 50.25;
- Impracticability of conducting the research without the waiver of informed consent;
- Therapeutic window and consent process;
- Plan for community consultation;
- Plan for public disclosure prior to and after completion of the clinical investigation;
- Establishment of an independent data monitoring committee to oversee the clinical investigation;
- Procedures to be followed when attempting to contact a family member who is not a legally authorized representative, within the therapeutic window and asking whether he or she objects to the participant's participation in the clinical investigation, when obtaining informed consent is not feasible and a legally authorized representative is not reasonably available;
- Procedures to inform, at the earliest feasible opportunity, each participant, or if the participant remains incapacitated, a legally authorized representative of the participant, or if such a representative is not reasonably available, a family member (as defined above), of the participant's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document, that they may discontinue the participant's participation at any time without penalty or loss of benefits to which the participant is otherwise entitled;
- Procedures to inform the participant should the participant's condition improve; and
- If feasible, procedures to provide the participant's legally authorized representative or family member with information about the clinical investigation should the participant die before a legally authorized representative or family member can be contacted.

24.2 IRB Findings and Determinations

The IRB must make and document the following findings and determinations:

1. Conducting the research is justified because:

    a. The human participants are in a life-threatening situation;
    b. Available treatments are unproven or unsatisfactory; and

c. The collection of valid scientific evidence, which may include evidence obtained through randomized, placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

2. Waiving informed consent is justified because:

   a. The participants will not be able to give informed consent as a result of their medical condition;
   b. The intervention under investigation must be administered before consent from the participant's legally authorized representative is feasible; and
   c. There is no way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

3. The risks are reasonable in relation to the anticipated benefits because:

   a. Participants are facing a life-threatening situation that necessitates intervention;
   b. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual participants; and
   c. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

4. The clinical investigation could not practicably be carried out without the waiver.

5. The investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for consent within the window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and the informed consent document are to be used with participants or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a participant’s participation in the clinical investigation consistent with 21 CFR 50.24(a)(7)(v).

7. The following additional protections of the rights and welfare of participants will be provided:

   a. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the participants will be drawn;
   b. Public disclosure to the community in which the clinical investigation will be conducted and from which the participants will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.

c. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and investigators of the study, including the demographic characteristics of the research population, and its results;
d. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
e. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the participant's family member who is not a legally authorized representative, and asking whether he or she objects to the participant's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

24.3 Additional IRB Responsibilities

The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity each participant, or if the participant remains incapacitated, a legally authorized representative of the participant, or if such a representative is not reasonably available, a family member, of the participant's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB must also ensure that there is a procedure to inform the subject, or if the participant remains incapacitated, a legally authorized representative of the participant, or if such a representative is not reasonably available, a family member, that he or she may discontinue the participant's participation at any time without penalty or loss of benefits to which the participant is otherwise entitled. If the legally authorized representative or family member is told about the clinical investigation and the participant's condition improves, the participant is also to be informed as soon as feasible. If a participant is entered into a clinical investigation with waived consent and the participant dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the participant's legally authorized representative or family member, if feasible.

24.4 Requirement for IND or IDE

Protocols involving an exception to the informed consent requirement under FDA regulations 50.24 must be performed under a separate IND or IDE that clearly identifies such protocols as protocols that may include participants who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists.

Applications for investigations involving an exception to the informed consent requirement may not be submitted as amendments to an existing IND/IDE.

24.5 Notification of Disapproval

If the IRB disapproves a clinical investigation because the investigation does not meet the exception criteria, the IRB will document its findings and provide these findings promptly in writing to the investigator and to the sponsor of the investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent clinical investigation by that sponsor.

25 MULTI-SITE RESEARCH

25.1 Single IRB Review

Mass General Brigham acknowledges that each institution that is engaged in multi-institutional collaborative research is responsible for safeguarding the rights and welfare of human participants and for complying with applicable federal and other regulations. With respect to such collaborative research, Mass General Brigham may enter into Reliance Agreements under which Mass General Brigham or Mass General Brigham research personnel use the services of and rely on an external IRB for review and oversight. Alternatively, the IRB may agree to provide IRB review and oversight for external, non-Mass General Brigham sites and non-Mass General Brigham affiliated personnel.

When Mass General Brigham relies on an external IRB for oversight, or when an external entity relies on the IRB for oversight, Mass General Brigham will be responsible for executing a Reliance Agreement that describes how the responsibilities for human research protections are divided between Mass General Brigham and the non-Mass General Brigham entity. When the research involves federally-funded research, an appropriate assurance must be held by the entities party to the agreement. In most cases employees or agents of Mass General Brigham must be collaborating with employees or agents of the non-Mass General Brigham entity on one or more research projects. When research is subject to the DHHS 2018 Common Rule, Mass General Brigham complies with the requirement to rely on the review of a single IRB (sIRB) for that portion of cooperative research conducted in the United States. The IRB Office is responsible for maintaining Reliance Agreements and associated documentation.

The 2018 Common Rule requires that any institution located in the United States that is engaged in cooperative research must rely on the review of a sIRB for that portion of the research conducted in the United States. "Cooperative research projects" are projects covered by this policy that involve more than one organization in the United States. The IRB will enter into a written Reliance Agreement with other organizations to (i) take on oversight of some or all participating sites in a multi-site study or (ii) rely on the review of another qualified IRB for research activities taking place at Mass General Brigham when engaged in cooperative research projects.

25.2 Reliance on an External IRB for Mass General Brigham Research

Mass General Brigham entities may rely on an external IRB for research conducted at Mass General Brigham entities. The VP HRA or designee(s) is responsible for determining whether relying on an external IRB is appropriate. Mass General Brigham relies on the following external IRBs when appropriate:

- The Dana-Farber Cancer Institute IRB for review of oncology research conducted under the auspices of the Dana-Farber/Harvard Cancer Center. An exception is Mass General Brigham IRB reviews industry- initiated and sponsored Phase I research conducted at the Mass General Cancer Center.
- The Harvard School of Public Health IRB for research involving prisoners, which occurs only occasionally.
- Commercial/Independent IRBs designated for review of Phase II-IV multi-site research. Phase 0-I and other research are approved for ceding on a case-by-case basis.
- IRBs designated to serve as the reviewing IRB when use of a sIRB is mandated by federal regulatory or sponsor requirements or as deemed appropriate by the VP HRA or designee.

The decision to rely is based on a number of factors, including but not limited to:

- Whether the use of a sIRB has been mandated by the study sponsor or funding agency;
- The number of proposed sites and/or studies involved in the collaboration;
- The anticipated level of risk associated with the proposed study;
- Whether the reviewing IRB's policies and procedures meet Mass General Brigham HRPP standards. If the reviewing IRB is part of an AAHRPP-accredited HRPP, then it will be presumed that the Mass General Brigham HRPP's standards are being met. However, AAHRPP accreditation in and of itself does not necessarily suffice as a basis for reliance;
- The location in which the majority of study procedures will take place, and by whom;
- Qualifications and experience of the investigators performing more than minimal risk interventions or procedures;
- For more than minimal risk research, whether the entity has acceptable liability insurance coverage and other safety-related issues;
- The Principal Investigator's standing with Mass General Brigham and their role in the overall research;
- Whether there are any conflicts with the reviewing IRB;
- The ability of the reviewing IRB to be sufficiently informed about local context issues, including local laws and regulations; and
- The terms and conditions of the proposed IRB Reliance Agreement.

When reliance on a non-AAHRPP accredited IRB is proposed, the evaluation of whether to cede review may involve additional considerations based on the nature of the research and the assessed experience and regulatory knowledge of the proposed reviewing IRB. The review may include, but is not limited to, review of the proposed reviewing IRB's policies and/or procedures, IRB rosters for identification of areas of expertise or potential conflicts, and Mass General Brigham's prior experience with the proposed reviewing IRB. *(AAHRPP Standard I-2).*

Reliance on an external IRB requires a Reliance Agreement with the proposed reviewing IRB, which outlines roles and responsibilities and documents the agreement of both parties. Additionally, Mass General Brigham investigators seeking to rely on an external IRB must submit a cede application in Insight, which is administratively reviewed by the IRB to ensure compliance with Mass General Brigham policies as well as IRB policies and procedures.

When Mass General Brigham cedes the IRB review of research to another organization, Mass General Brigham retains overall responsibility for oversight of the research and remains responsible for maintaining a human research protection plan, including but not limited to:

- Safeguarding the rights and welfare of human participants within the local context. The IRB retains the responsibility to maintain oversight for local unanticipated problems involving risks to participants or others and local non-compliance in collaboration with the reviewing IRB;
- Conducting audits to ensure compliance in collaboration with the reviewing IRB as appropriate;
- Conducting conflict of interest review for Mass General Brigham investigators;
- Conducting ancillary reviews (e.g. pharmacy, radiation safety, biomedical engineering) to ensure the research is conducted in compliance with Mass General Brigham policies and procedures;
- Educating members of the Mass General Brigham research community to establish and maintain compliance with federal regulations, state law and local policies relevant to human subjects research; and

- Implementing appropriate oversight mechanisms to ensure compliance with the determinations of the reviewing IRB.

IRBs reviewing research on behalf of Mass General Brigham have the authority to:

- Approve, require modifications to secure approval, and disapprove the human research overseen and conducted by Mass General Brigham. All Mass General Brigham human research must either be approved by the IRB or a reviewing IRB. Mass General Brigham institutional officials may not approve human research that has not been approved by the IRB or a reviewing IRB;
- Suspend or terminate approval of human research not being conducted in accordance with an IRB's requirements or that has been associated with unexpected serious harm to participants;
- Observe, or have a third party observe, the consent process and the conduct of the human research;
- Determine whether an activity is human research;
- Require investigators and study staff disclose conflicts of interest according to the process agreed up on between Mass General Brigham and the reviewing IRB and comply with any resulting conflict of interest management plans; and
- Serve as the Privacy Board, as applicable, to fulfill the requirements of the HIPAA Privacy Rule for use and disclosure of protected health information for research purposes.

When Mass General Brigham cedes its oversight for research activities to another qualified IRB:

- The IRB review process and oversight requirements will be governed by the terms outlined in the executed Reliance Agreement;
- Mass General Brigham and their investigators will comply with the reviewing requirements and determinations of the reviewing IRB;
- The IRB Office provides the reviewing IRB with requested information about local requirements or local research context issues relevant to the reviewing IRB's determinations prior to review;
- The IRB Office will notify the reviewing IRB when local requirements or research context impacting the reviewing IRB's oversight are updated;
- Investigators must cooperate with the reviewing IRB with regard to their responsibility for initial and continuing review, record keeping, reporting, and must provide information in a timely manner to the reviewing IRB;
- Investigators and study staff must disclose conflicts of interest according to the Reliance Agreement and comply with any conflict of interest management plans;
- Investigators must report promptly to the reviewing IRB any proposed changes to the research and cannot implement changes without prior review and approval by the reviewing IRB, except where necessary to eliminate apparent immediate hazards to the participants;
- Investigators will not initiate the research prior to approval of the cede application by HRA;
- Investigators will not initiate the research prior to review and approval by the reviewing IRB as well as meeting all other applicable requirements and approvals for the study;
- When required by the reviewing IRB, investigators will obtain, document, and maintain records of consent for each participant or their legally authorized representative;
- Investigators will comply with all reporting requirements of the reviewing IRB according to the Reliance Agreement and IRB reporting requirements when relying on an external IRB;
- Investigators will comply and cooperate with the monitoring requirements of both the reviewing IRB and Mass General Brigham;

- The IRB Office will provide contact information for investigators and staff to obtain answers to questions, express concerns, and convey suggestions regarding the use of the reviewing IRB;
- Mass General Brigham will ensure investigators and staff have appropriate qualifications and expertise to conduct the research, are knowledgeable about laws, regulations, codes, and guidance governing their research; and
- The investigator is responsible for being knowledgeable about both the Mass General Brigham and the reviewing IRB's policies and procedures.

Mass General Brigham officials will not approve research that has not been approved by the reviewing IRB.

25.3 Mass General Brigham Serving as the Reviewing IRB

The IRB may serve as the reviewing IRB for multi-site research. The IRB adheres to both the NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research and the 2018 Common Rule Single IRB requirement. The IRB may serve as the reviewing IRB for domestic sites of multi-site studies where each site will be working from the same protocol involving non-exempt human research or for domestic sites of 2018 Common Rule agency-funded cooperative research, or for other multi-site research as determined by the VP HRA.

When the IRB provides IRB review for other institutions, the IRB will follow established policies and procedures to ensure that the composition of the IRB is appropriate to review the research and will comply with applicable laws of the relying site. This includes ensuring that the IRB is appropriately constituted, members are appropriately qualified, members will not participate in the review of research with which they have a conflict of interest, and that the IRB separates business functions from ethical review. Additionally, when the IRB is serving as the sIRB, all reviews of the research, including initial review, continuing review and review of proposed changes to the research, are done in accordance with applicable regulations and IRB policies and procedures.

When the IRB serves as the sIRB, the overall protocol must be reviewed and approved by the IRB before any external sites can be reviewed. External, relying sites are added to the protocol and Insight application via an amendment, and are typically reviewed via expedited procedures unless otherwise directed by the IRB during initial review, the local site identifies additional risks to participants specific to its site, or the amendment includes other proposed major changes that require review and approval by the full board IRB. Relying site investigators are notified of IRB determinations via letters generated in Insight and transmitted to the relying site investigator by the Mass General Brigham lead study team.

Investigators must request that the IRB provide sIRB review for non-Mass General Brigham sites and/or non-Mass General Brigham affiliated personnel by submitting a Single IRB Request form via REDCap.

Whether the IRB will provide review for another institution is determined by the VP HRA (or designee(s)) based on a number of factors, including but not limited to:

- Whether Mass General Brigham is the prime awardee of the funds;
- Whether sIRB review is required by the sponsor or regulation;
- The time and resources required to accept review;
- The number of proposed sites involved in the collaboration;
- The anticipated level of risk associated with the proposed study;
- The location in which the majority of study procedures will take place; and
- The Principal Investigator's standing with Mass General Brigham and their role in the overall research.

When sites are relying on the IRB, a Reliance Agreement is required. When individual investigators (i.e., investigators not acting as agents of an external institution) are relying on the IRB, an Individual Investigator Agreement is required. When individual students are relying on the IRB, an Individual Student Investigator Agreement is required, with exception to this if the student's home institution requires its own IRB review or an IRB Reliance Agreement.

Mass General Brigham lead study teams are encouraged to identify an individual on their team who can serve as the sIRB liaison, facilitating communication between external sites and the IRB. Mass General Brigham lead study teams are responsible for submitting applications on behalf of sites (e.g. to obtain initial approval, amendments and continuing reviews) to the IRB and for communicating IRB determinations to sites.

25.4 Establishing Reliance Agreements

Reliance agreements established for the purposes of sIRB review are signed by Mass General Brigham Institutional Officials or their designees.

Reliance agreements generally address the following:

- Scope of covered research;
- FWA status of the parties;
- Responsibilities for HIPAA determinations in connection with the covered research;
- IRB independence and authority;
- IRB decisions;
- Compliance responsibilities of relying entity;
- Reporting of noncompliance, injuries and participant safety, unanticipated problems (including reporting to external oversight/funding authorities);
- Cooperation in investigations and corrective actions;
- Conflict of Interest
- HIPAA determinations
- Recordkeeping and access to minutes;
- Termination of the relationship and provision for continued oversight of ongoing research; and
- Communications.

Regardless of whether Mass General Brigham is ceding review to an external IRB or the IRB is to serve as the reviewing IRB, the Reliance Agreement will include sufficient information to ascertain which party is responsible for the following:

- Providing education to investigators and study staff;
- Conducting scientific review;
- Reviewing potential noncompliance, including complaints, protocol deviations, and results of audits;
- Identifying which organization is responsible for deciding whether each allegation of noncompliance has a basis in fact;
- Identifying which organization's process is used to decide whether each incident of noncompliance is serious or continuing;

- Obtaining management plans for investigator and study staff conflicts of interest. If the relying organization maintains responsibility for this issue, the management plan must be provided to the IRB of record in a timely manner prior to the IRB's determination;
- Managing institutional conflicts of interest related to the research; and
- Ensuring that, should the Reliance Agreement be terminated, one of the parties is clearly responsible for continued oversight of actives studies until closure or a mutually agreed upon transfer of the studies.

25.5 Review of Operation Centers or Coordinating Centers

When employees or agents of Mass General Brigham are responsible for the operations center or coordinating center for multi-site human research, the IRB will review the standard operating procedures of the center to ensure that there are appropriate mechanisms in place to protect the rights, safety and welfare of the participants participating in the research at the collaborating sites.

Investigators must specify in the Insight application what operations center or coordinating center activities they are engaged in and provide a copy of the center's standard operating procedures. Although the IRB does not need to approve the protocol as part of the operations center or coordinating center protocol, the investigator is asked to submit the protocol and model consent form and, when applicable, provide information about drugs, biologics, dietary supplements or devices being investigated so that the IRB can ensure that the operations center or coordinating center's standard operating procedures are appropriate for the study. Note that when participants will be enrolled in the study at Mass General Brigham, the enrolling site protocol must be submitted separately to the IRB for approval.

The IRB will review the center's standard operating procedures and determine whether the operations center or coordinating center has sufficient mechanisms in place to ensure that, where applicable:

- Management of information that is relevant to the protection of participants is adequate; and
- Appropriate communication and reporting procedures are in place between the operations/coordinating center and applicable sites including (but not limited to):

    - Unanticipated problem involving risks to subjects or others
    - Noncompliance with federal regulations or the determinations of the IRB
    - Interim results
    - Protocol modifications
    - Suspensions or terminations of research.

During the period of approval, investigators are required to report to the IRB any changes in the center's standard operating procedures and any reports from sites that meet the Mass General Brigham reporting requirements. If Mass General Brigham is a participating site, any protocol or consent changes as well as other applicable amendments do need to be submitted for IRB approval under the applicable site protocol.

26 IRB RECORDS

Research at Mass General Brigham is supported by a systemwide web-based application and data management system called Insight. The IRB and IRB office uses Insight and shared web-based electronic folders to maintain required documentation of IRB review activities.

Investigators who rely upon the IRB for review of human research and clinical investigations are required to complete Insight application forms and provide all required information and documents to the IRB Office for review by the IRB via Insight. When the research has received all required Mass General Brigham approvals, the IRB notifies the Principal Investigator and study contacts of approval and provides the IRB approval documentation, approved consent form(s), and any approved recruitment materials via Insight. The Insight application retains a complete record of protocol submissions and documentation of IRB and ancillary committee reviews and approvals.

The IRB Office is responsible for notifying the investigator in writing of all review determinations via Insight. Approval letters are provided via Insight and include the date of expiration of IRB approval or the date for expedited check-in or exempt check-in as applicable. Minutes for each protocol are also provided to the PI via Insight. The expiration date is the first date the research is no longer approved by the IRB.

Records of research activity reviewed by the IRB, whether at a full board meeting, using the expedited review procedure, or for exempt research include (but are not limited to):

- Insight application form(s)
- Protocol or research plan
- Drug/device investigator brochure or package inserts (as applicable)
- Scientific evaluations when provided by an entity other than the IRB
- Recruitment materials (including submitted and IRB approved)
- Consent form(s) (including submitted and IRB approved)
- Progress reports submitted by investigators
- Reports of injuries to participants and/or adverse events
- Records of continuing review activities
- Amendments (modifications) to previously approved research
- Unanticipated problems involving risk to participants or others
- Documentation of noncompliance
- Significant new findings
- A resume or CV for each IRB member
- Previous membership rosters
- Data and safety monitoring reports, if any
- Minutes of full board meetings
- Correspondence between the IRB and investigators
- Documentation for the justification for exempt determinations
- Any findings required by laws, regulations, codes, and guidance to be documented
- Administrative information on research for which the IRB relies on an external IRB for review
- For initial and continuing review of research by the expedited procedure:
    - Justification for using the expedited procedure for review
    - The rationale for conducting continuing review of research that otherwise would not require continuing review
    - The rationale for a determination that research appearing on the list of eligible expedited review categories is greater than minimal risk
    - Actions taken by the reviewer

Records of research activities are retained by the IRB Office for at least seven (7) years from completion of the research or closure of the file. Files are maintained in electronic format in the secure Insight system on the Mass General Brigham network or sent to an external vendor for long-term storage, as needed.

Access to records is provided to:

- The relevant IOs of Mass General Brigham and to IRB chairs, IRB members, and IRB Staff to carry out their human research protection responsibilities. Minutes of meetings are made available on request to the IOs of Mass General Brigham and to IOs of other institutions who, by appropriate IRB reliance agreement, rely on the IRB.
- Investigators have access to electronic records pertaining to their own research activities through the Insight system.
- Other access to records is limited to those with a legitimate need for access, such as other institutional offices or departments within the Mass General Brigham HRPP.
- Authorized representatives of DHHS, FDA and other federal agencies for inspection and copying onsite at request during normal business hours.
- Copies of records may be made available to authorized representatives of the sponsor when appropriate.

IRB review proceedings and records of review activities are considered confidential and protected from access except as provided in this Policy. IRB members or others with access to these proceedings or records will not use them for any purpose other than to carry out their review responsibilities and will not disclose them to others who are not authorized under these procedures to have access. Such protection is essential to encourage open discussion by the IRB in review of proposed research, maintain the integrity of the deliberative process, safeguard the privacy and confidentiality of participants in research and avoid disclosure of information that is proprietary to the research sponsor or other third party and which Mass General Brigham may be contractually obligated to keep confidential. Internal HRA, IRB Staff, or others with the permission of the VP HRA and Senior IRB Chair, may additionally utilize IRB review proceedings and records for quality improvement and research purposes.

Without limiting any of the above, HRA specifically prohibits distribution of documents and records containing confidential and proprietary information of Mass General Brigham or of a third party beyond the research team and others within Mass General Brigham with a need to know without prior written approval of Mass General Brigham or the third party involved, as applicable.

27 APPENDICES

27.1 APPENDIX I: APPLICABLE LAWS

Federal Statutes and Regulations	State Statutes and Codes:
20 U.S.C. 1232h (Consent in School-Based Surveys/Evaluations) 42 U.S.C. 241(d) (Certificates of Confidentiality) 42 U.S.C. 290dd-2 (Confidentiality of Substance Abuse Records) Pub. L. No. 104-191, 110 Stat. 1936 (HIPAA) Pub. L. No. 111-5, 123 Stat. 226 (HITECH) Pub. L. No. 113-240, 128 Stat. 2851, § 12 (Informed Consent for Newborn Screening Research) 21 CFR Part 11 (Electronic Records; Electronic Signatures) 21 CFR Part 50 (Protection of Human Subjects) 21 CFR Part 54 (Financial Disclosure by Clinical Investigators) 21 CFR Part 56 (Institutional Review Boards) 21 CFR Part 210 (Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs: General) 21 CFR Part 211 (Current Good Manufacturing Practice for Finished Pharmaceuticals) 21 CFR Part 312 (Investigational New Drug Application) 21 CFR Part 314 (Applications for FDA Approval to Market a New Drug) 21 CFR Part 320 (Bioavailability and Bioequivalence Requirements) 21 CFR Part 330 (Over-The-Counter (OTC) Human Drugs which are Generally Recognized as Safety and Effective and Not Misbranded) 21 CFR Part 361 (Radioactive Drugs) 21 CFR Part 601 (Biologics Licensing) 21 CFR Part 610 (Biological Products) 21 CFR Part 803 (Medical Device Reporting) 21 CFR Part 812 (Investigational Device Exemptions) 21 CFR Part 814 (Premarket Approval of Medical Devices) 21 CFR Part 820 (Quality System Regulation) 21 CFR Part 860 (Medical Device Classification Procedures) 34 CFR Part 98 (Consent in School-Based Examination/Treatment)	M.G.L. c. 19A, § 15 (Elder Abuse Reporting) M.G.L. c. 93H (Security Breaches) M.G.L. c. 94C § 8 (Controlled Substances in Research) M.G.L. c. 111, § 70E (Patients Rights/Informed Consent/Confidentiality) M.G.L. c. 111 § 70F (Consent to HIV/AIDS Testing / Disclosure of Results) M.G.L. c. 111 § 70G (Genetic Testing and Privacy) M.G.L. c. 111 § 119 (Venereal Disease Records) M.G.L. c. 111, § 202 (Disposition of Fetal Remains) M.G.L. c. 111B, § 11 (Alcohol Abuse Treatment Records) M.G.L. c. 111E, § 18 (Drug Dependency Treatment Records) M.G.L. c. 111L (Human Embryonic Stem Cell Research) M.G.L. c. 112, § 12E (Consent by Drug Dependent Minors) M.G.L. c. 112, § 12F (Consent by Minors) M.G.L. c. 112, § 12J (Experimentation on Fetuses) M.G.L. c. 112, § 129A (Psychologist – Patient Communications) M.G.L. c. 112, § 135A (Social Worker – Client Communications) M.G.L. c. 119, § 51A (Child Abuse/Neglect Reporting) M.G.L. c. 190B, Art. V. (Guardianships) M.G.L. c.201D (Health Care Proxies) M.G.L. c. 233, § 20B (Psychotherapist – Patient Communications) M.G.L. c. 233, § 20K (Communications with Domestic Violence Victims' Counselor) 103 C.M.R. 180.07 (Research with Prisoners) 104 C.M.R. 31.00 (Department of Mental Health Research) 105 C.M.R. 130.381-87 (Consent for Autopsy Tissue) 105 C.M.R. 130.395 (Disposition of Fetal Remains)

42 CFR Part 2 (Confidentiality of Alcohol/Drug Abuse Records) 42 CFR Part 50 (Research Integrity: Objectivity in Research – Financial Conflicts of Interest 45 CFR Part 46 (Protection of Human Subjects) 45 CFR Parts 160 and 164 (Security and Privacy; Breach Reporting)	105 C.M.R. 700.009 (Controlled Substances in Research) 105 C.M.R. 960.000 (Human Embryonic Stem Cell Research) 115 C.M.R. 10.00 (Department of Developmental Services Research) 201 C.M.R. 17.00 (Protection of Personal Information) 603 C.M.R. 23.00 (Access to Student Records/Information)

27.2 APPENDIX II: MASS GENERAL BRIGHAM INCORPORATED ENTITIES

The Brigham and Women's Hospital, Inc. (BWH)
Brigham and Women's Faulkner Hospital, Inc. (BWH/F)
The General Hospital Corporation doing business as Massachusetts General Hospital (MGH)
The MGH Institute of Health Professions, Inc. (MGH IHP)
The McLean Hospital Corporation (McLean)
North Shore Medical Center, Inc. (NSMC)
The Spaulding Rehabilitation Hospital Corporation (SRH)
Spaulding Hospital - Cambridge, Inc. doing business as Spaulding Hospital for Continuing Medical Care Cambridge (Spaulding Cambridge)
Rehabilitation Hospital of the Cape and Islands Corporation (Spaulding Cape Cod)
Spaulding Nursing and Therapy Center Brighton, Inc.
Mass General Brigham Home Care, Inc.
Newton-Wellesley Hospital (NWH)
Massachusetts Eye and Ear Infirmary (MEE)
The Schepens Eye Research Institute, Inc. (SERI)
Cooley Dickinson Hospital, Inc.
Nantucket College Hospital
Wentworth-Douglass Hospital
Mass General Brigham Community Physicians, Inc.

27.3 APPENDIX III: IRB MEMBER RESPONSIBILITIES

Participation as an IRB member provides invaluable service for our research participants, our researchers, and our broader community. Membership is a commitment to advancing medicine through medical discovery and innovation that embodies the highest ethical standards for participant protections, engagement with our community, and contribution to ongoing improvement of our human research system.

1. Understand and apply the basic ethical principles of the Belmont Report (Respect for Persons, Beneficence and Justice).
2. Execute responsibilities in compliance with federal regulatory requirements and MGB policies and procedures related to human subject protections.
3. Serve for a period of 2 years, which may be renewed upon approval of the Vice President, Human Research Affairs.
    a. Attend one MGB IRB meeting each month. Meetings will be 60-75 minutes in length and occur via Zoom.
    b. Sign up to attend meetings on a per quarter basis at least 3 months in advance. The member may sign up to attend any one of 16-20 meetings held during the month in which their role (Physician Scientist, Other Scientist, Non-Scientist) has an open seat.
    c. Notify IRB Staff at least 2 weeks in advance if a schedule change is needed.
    d. Arrive promptly to meetings and stay until all agenda items and education are completed.
4. Complete required human subjects and IRB member onboarding training and continuing education as provided.
5. Support and participate in IRB initiatives on diversity, equity and inclusion (DEI) with respect to the IRB membership, the approach to review of research, as well as the conduct of human subject research and translation into improved health care in our community.
6. Maintain the confidentiality of all meeting proceedings, meeting materials, and communications with PIs or their research staff as part of the review process. Information may not be used for any other purpose except the IRB review and may not be disclosed outside of the IRB unless permission is received in writing from the VP HRA.
7. Serve as a Primary reviewer when requested (Physician Scientist, Other Scientist)
    a. Conduct a complete a thorough evaluation of all materials submitted with an IRB application in compliance with the Belmont Report, the federal Criteria for Approval (45 CFR 46.111 and 21 CFR 56.111) and MGB policies. Typically, a member is assigned 1-2 protocols for primary review per meeting.
    b. Correspond with the IRB Chair/IRB Staff for assigned protocol(s) sufficiently in advance of a meeting to resolve any open questions regarding the study. The IRB Chair/IRB Staff will facilitate communications with the research team.
    c. Alert the IRB Chair and IRB Staff to any major issues of concern that would require a deferral sufficiently in advance of the meeting to allow resolution with the PI.
    d. Complete reviewer checklists prior to the meeting to document determinations.

    e. Present the key points of the protocol relative to the Criteria for Approval at the convened board and participate in discussion related to controverted issues.
8. Serve as a Secondary reviewer when requested (Physician Scientist, Other Scientist, Non Scientist/Community Representative.)
    a. Conduct a review of specific parts of the IRB application and selected materials consistent with the reviewer's representative capacity in compliance with the Belmont Report, the federal Criteria for Approval (45 CFR 46.111 and 21 CFR 56.111) and MGB policies. Typically, a member is assigned 1-2 protocols for secondary review per meeting.
    b. Correspond with the Primary Reviewer/IRB Chair/IRB Staff sufficiently in advance of a meeting to resolve any open questions.
    c. Alert the IRB Chair and IRB Staff to any major issues of concern that would require a deferral sufficiently in advance of the meeting to allow resolution with the PI.
    d. Complete reviewer checklists prior to the meeting to document determinations.
    e. Present the key points of the protocol relative to the Criteria for Approval at the convened board and participate in discussion related to controverted issues.
9. All members are expected to have read selected materials for all agenda items including but not limited to the IRB application, protocol, consent materials, recruitment materials such that they can address the principles of the Belmont Report and the Criteria for Approval from their representative capacity and perspective.
10. Vote to agree, disagree, or abstain from voting on each motion to approve, approve with modifications, defer, or disapprove a protocol.
11. Comply with MGB Conflict of Interest and IRB policies. Notify IRB Staff of any conflicts of interest with protocols prior to attending a meeting and voluntarily recuse themselves from the review, discussion and vote where a conflict exists.
12. Participate in periodic evaluations related to service on the IRB and evaluation of the IRB Chairs and IRB meeting staff.
13. If selected, participate in interviews with teams from AAHRPP during on-site accreditation reviews which occur every 5 years.

27.4 APPENDIX IV: DEFINITIONS

Term	**Definition**
Adverse event	Any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant'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).
Applicable Clinical Trial (ACT)	The Food and Drug Administration Amendment Act of 2007 (FDAAA) definition of clinical trials includes interventional studies (with one or more arms) of FDA-regulated drugs, biological products, or devices that meet one of the following conditions: The trial has one or more sites in the United States; • The trial is conducted under a FDA investigational new drug application (IND) or investigational device exemption (IDE); or • The trial involves a drug, biologic, or device that is manufactured in the United States or its territories and is exported for research. There are two types of FDAAA-defined Applicable Clinical Trials: • **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.
Reliance Agreement	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. Consistent with Massachusetts state law that allows persons who have attained the age of 18 to consent to treatment or procedures, the IRB defines children as persons under the age of 18. The IRB notes, however, that certain statutes and case law provide children with majority status for medical decision-making in some circumstances, for example: emancipated minor; mature minor; or minor seeking care for drug addiction, sexually transmitted diseases, emotional disorders, or abortion. Because Massachusetts law and the Mass General Brigham policies do not specifically address consent of children with majority status to research, the IRB will review issues of consent related to the enrollment of children with majority status on a case-by-case basis.

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) A research study in which one or more human participants 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. (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
Collaborating Individual Investigator	An investigator who is (a) not otherwise an employee or agent Mass General Brigham; (b) conducting collaborative research activities whether on or off-site from Mass General Brigham; and (c) not acting as an employee of any institution with respect to his/her involvement in the research being conducted by Mass General Brigham (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 research (institutional investigator).

Compassionate use of an Investigational device (for single patient)	Use of an investigational device to treat or diagnose an individual patient or small group of patients with a serious disease or condition when there are no available options (i.e. non-emergency use). Compassionate use can be for devices that are being studied in a clinical trial under an IDE for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating or diagnosing their disease or condition. It can also be used for devices that are not being studied in a clinical investigation (e.g., IDE for the device does not exist). This provision is typically approved for individual patients but may be approved to treat a small group, if the small group request is under an IDE.
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
Coordinating Center	A study site that may be responsible for overall data management, monitoring, communication among sites, overseeing all or certain aspects of a multi-site study, and general oversight of research activities at all sites.
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)
Data Use Agreement	An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected.

De-identified health Information	Health information that has had identifiers removed in accordance with one of the following acceptable methods of de-identification: **Expert determination method:** A method for creating de-identified health information or determining that health information has been de-identified that requires an "expert" (meaning a person who has appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable) to determine that the risk is very small that the anticipated recipient could identify any of the individuals. **Safe harbor method:** A method for creating de-identified health information that requires: • removal of the following specific identifiers of the individual as well as of any relatives, employers, or household members of the individual; and • after removing identifiers, the entity must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify an individual who is a subject of the information.
Deviation	Any alteration/modification to the IRB-approved protocol without prospective IRB approval. The term *protocol* encompasses all IRB-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 (Including Investigational Device and Transitional 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)]
Directly identifiable tissue	Tissue that is labeled or released to investigators 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, for example full dates of specimen collection are considered personal identifiers. 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.

Drug	A drug is defined as: • A substance recognized by an official pharmacopoeia or formulary. • A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. • A substance (other than food) intended to affect the structure or any function of the body. • A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. • Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)
Emergency use	The use of a test article (investigational drug, biologic or device) on a human participant 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 Investigational Device for a Single Patient	Use of an investigational device when an individual patient is in a life-threatening situation and needs immediate treatment (there are no alternative options and no time to use existing procedures to get FDA approval for the use). Emergency use may apply if the device is being studied in clinical trials under an investigational device exemption (IDE) such as when a physician is not part of the IDE clinical study wishes to use the device to treat a patient in an immediately life-threatening situation. An IDE allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data. Emergency use may also apply if there is no IDE or ongoing clinical studies for the device.
Employees or agents	Members of the Mass General Brigham workforce who: (1) act on behalf of the institution; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities. Employees and agents include medical and professional staff, students/interns, contractors and volunteers, among others, regardless of whether the individual is being paid by the hospital.
Enrolled	any individual that signs a consent or has completed a consent process to participate in research (including those who screen out).
Exception	Any change in research or protocol requirements (e.g. eligibility criteria, laboratory tests, continuation on protocol) that is limited to a specific participant or situation and does not change the requirements for all participants. Exceptions must be approved by the IRB prior to implementation.
Excess clinical/ reseach tissue samples	Tissue that was collected for clinical or research purposes and is no longer needed for the original purpose.
Exempt research	Research activities in which the only involvement of human subjects will be in one or more of the categories defined in 46.104(d) are considered exempt from the requirements of the federal policy for the protection of human subjects.
Expedited research	Certain categories of research involving no more than minimal risk that may be reviewed by the IRB through an expedited review procedure. A list of categories is published as a Notice in the Federal Register.

Food and Drug Administration Amendment Act if 2007 (FDAAA), Section 801	Federal Statute, enacted September 27, 2007 that requires registration of an "applicable clinical trial" (defined above) that is initiated after September 27, 2007 or ongoing as of December 26, 2007
Full Board	The convened Institutional Review Board
Generalizable Knowlege	Information that has relevance beyond the population or program from which it was collected and knowledge that may contribute to a theoretical/scientific framework of an established body of knowledge
Guardian	*Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of an individual to general medical care.
Health Information	Any information, including genetic information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.
Human Participant/ Participant	A living individual that meets the DHHS or FDA definition of Human Subject and Subject, respectively.
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 Research (DHHS)	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)) 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 (HUD)	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*

Individual 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 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.
Individually Identifiable Health Information	Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.
Institutional Conflict of Interest (ICOI)	An institutional conflict of interest may exist when any of the following may affect the design, conduct or reporting of research: (1) proprietary interests related to the research, including patents, trademarks, copyrights or licensing agreements and royalties resulting thereof; (2) investments of the institution; (3) major gifts to the institution; or (4) financial interests of Mass General Brigham institutional officials.
Interaction (DHHS)	Includes communication or interpersonal contact between investigator and subject. (45 CFR 46.102)
International Committee of Medical Journal Editors (ICMJE)	Group of general medical journal editors. They are the authors of The Uniform Requirements for Manuscripts Submitted to Biomedical Journals.
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 participants 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.
Investigator-Initiated Studies	Investigator-Initiated Studies are studies initiated and managed by a noncommercial company researcher/s who could be an individual investigator, an institution, or a group of institutions, and a collaborative study group or a cooperative group.
Investigational Device Exemption	Allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution.

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 full board meeting of the IRB is feasible.
Limited Data Set	Refers to PHI that excludes 16 categories of direct identifiers but may include city, state, zip code, elements of date, and other numbers, characteristics, or codes not listed as direct identifiers. A limited data set may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, with a data use agreement.
Majority	In the setting of a full board IRB meeting, majority is more than half of the voting members present at the time of any vote taken.
Minimal Risk & Minimal Risk for Research Involving Prisoners	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) **Prisoners:** is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.
Minor Deviation	Any deviation from the IRB-approved research that does not have the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data), or affect subject's willingness to participate in the study.
Major Deviation	Any alteration/modification to the IRB-approved research that has the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data) or affect the subject's willingness to participate in the study.
Noncompliance	Any failure to comply with any applicable federal, state, or local laws and regulations or the requirements or determinations of the IRB, or 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, including full dates of specimen collection. Information that cannot be used to identify the individual, such as diagnosis, age, and gender, may be recorded with or linked to the tissue.
Nonsignificant risk device (NSR)	An NSR device study is one that does not meet the definition for an SR device study.
Primary Completion Date	The date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

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).
Protected Health Information	Individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium.
Qualifying Clinical Trial (QCT)	A Center for Medicare and Medicaid Services (CMS) designation for clinical trials that qualify for coverage as specified in the "Medicare National Coverage Determination (NCD) Manual," Section 310.1. The purpose of the trial must be the evaluation of an item/service that falls within a Medicare benefit category (e.g., physicians' services, durable medical equipment, diagnostic test). The trial must have therapeutic intent and must enroll patients with diagnosed disease not only healthy volunteers.
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.
Record Owner	The person who creates the record becomes the Record Owner. All email messages about the record will be sent to this person.
Repository	A repository collects data and/or research materials (e.g., biospecimens, images, etc.) for future research use. Data/research materials can be collected from multiple sources and could be used by investigators for future research. No research questions or hypotheses are addressed under a repository protocol. Repositories may also called "registries," "banks," or "libraries.".
Research (DHHS)	A *systematic investigation*, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. (45 CFR 46.102).
Research Data or Data	Any and all data, images, and information created, collected, or used in the process of performing research.
Research Materials	Includes all types of materials generated and used in Research and including all media and forms in which Research Data are stored and any tangible embodiment of Research Data. These include, but are not limited to, materials such as unmodified and modified biological specimens; new or modified chemical entities; original or modified biological samples; gels; spectra; cell lines; reagents; protocols; algorithms; graphs, charts, numerical raw environmental results; instrumental outputs; other deliverables under sponsored agreements; statistics; findings; conclusions; computer programs, databases and documentation; laboratory notebooks and notes of any type; materials submitted to and approved by the IRB, IACUC, IBC, ESCRO or other research oversight committees (e.g., applications, outreach/advertising materials, sample consent forms, survey routines/questionnaires); signed consent forms; and any other records or source documentation in any form necessary for reconstruction, evaluation or replication of reported or otherwise published results.
Scientific Misconduct	Any 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

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, significantly compromises the integrity of the study data, or otherwise affects the integrity of the research or the human research protection program.
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.
Significant risk device (SR)	An SR device means an investigational device that: • Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; • Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; • Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or • Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
Single Patient IND	Emergency Use: Individual patient IND that provides expanded access to an investigational drug for treatment use by a single patient in an emergency situation. Treatment is initially requested by the licensed physician and authorized by telephone (or other rapid means of communication) and may start immediately upon FDA authorization. The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and FDA must determine that the patient cannot obtain the drug under another IND or protocol. Non-emergency Use: FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician. The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and the FDA must determine that the patient cannot obtain the drug under another IND or protocol. IRB and FDA approval must be obtained prior to treatment. Physicians may administer treatment 30 days after an application is received by the FDA (or earlier if notified by FDA).

Sponsor	Primary organization conducting study and associated data analysis (not necessarily a funding source). When a clinical study is conducted under an investigational new drug application (IND) or investigational device exemption (IDE), the IND or IDE holder or who is conducting an NSR device study is considered the sponsor. When a clinical study is not conducted under an IND or IDE and is not an NSR device study, the single person or entity who initiates the study, by preparing and/or planning the study, and who has authority and control over the study, is considered the sponsor.
Sponsor-investigator	An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by the subject. The term does not include any person other than an individual (e.g., it does not include a corporation or agency). The obligations of the Sponsor-Investigator includes both those of a sponsor and those of an investigator
Study Completion Date	The date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated.
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
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. Of note, expiration of IRB approval is not considered suspension of research requiring reporting to federal regulatory authorities
Systematic 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 IRB approval is not considered termination of research requiring reporting to federal regulatory authorities
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 (UADE)	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. ***NOTE: UPIRTSOs include events that would meet the definition of a UADE*** *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 solely 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).