Mass General Brigham

Institutional Review Board (IRB) Guidance

Human Research Affairs
Version Date: September 6, 2024

1 Contents

1. Submitting to the IRB

1.1 Modifying an Existing Study vs Submitting a New Study

All changes in approved research must be reviewed and approved by the IRB prior to implementation. When proposing changes to an existing study, investigators and the IRB should consider whether the changes warrant submission of a new study rather than an amendment. It is necessary to assess submissions on a case-by-case basis. It is ultimately up to the IRB to determine when a new study will be required. This guidance applies to all research studies overseen by the Mass General Brigham IRB including those under Single IRB Review.

We also encourage you to discuss your proposed changes with the IRB prior to submitting an amendment.

Some examples of when a new study must be submitted:

- For Single IRB studies, addition of new aims, hypotheses, populations, or shift in study design or research question for any site must be submitted as a new study. Of note, if there are new aims, hypotheses, or a change at a non-MGB site, this could potentially require a new submission at that site's respective IRB.
- Developing a medical device typically includes multiple stages. The first stage is to develop a prototype and test usability. The next stage is to test the safety and effectiveness of the prototype with a small group of patients. The final stage is to conduct a randomized trial. In this scenario, even though the overarching aim is consistent (i.e., to develop a medical device), it is best to submit three separate studies, rather than submitting amendments to the original study. This permits appropriate regulatory determinations to be made for each portion of the research.
- Adding new investigational drugs, medical devices, or procedures that are FDA-regulated to a study that has not previously been FDA-regulated requires a new study. The devices or drugs may impact the overall study design and research focus as well as study procedures and the overall consent form. The IRB will need to make determinations about the use of the investigational device or investigational drug in the study, which may now be subject to FDA regulations.
- Multiple sub-studies embedded within one study can be difficult to review and track for compliance over time. If the hypotheses, aims, populations, procedures, and/or funding source of sub-studies differ from the main study, the sub-study should be submitted as a new study.
- Requests to utilize data or samples from repository and registry studies to conduct human research projects (e.g., new analyses on identifiable samples or data) requires a new study submission to the IRB. Although investigators may wish to modify existing repository and registry studies to include new investigators who may have their own funding and seek to use the data or samples from these studies to conduct a secondary analysis study, this is not permitted since it increases the recordkeeping and compliance burden of the repository/registry owners and alters the original repository/registry protocol intent and structure. Rather, standalone secondary use studies which are limited in scope to the use of samples and/or data obtained during a previous research study should be established. These new studies using existing data or specimens must be submitted for IRB review and approval.
- Significant modifications to older studies may require reconsideration of risks and benefits of the study (e.g., new standards of care may have been established since the time the study was initially approved) and may need to be submitted as a new study. In addition, studies that have been open for an extended period may include

irrelevant or outdated information as portions of the research may be complete and this can create confusion about what activities are ongoing.

- If the proposed changes result in a "menu" of procedures that may be used, for instance, if there is a separate set of inclusion/exclusion criteria for different procedures and different risk profiles need to be considered in the consent form, the IRB finds it difficult to assess the risks of the research to individual participants. The IRB will need to consider all possible combinations of procedures for all possible participants, and an amendment could lead to multiple rounds of revisions and a longer time to review than a new study. In addition, studies with "menus" are difficult for study staff to execute compliantly, present challenges to proper recordkeeping, and lead to complexities in data analysis and results reporting. In this case, a new application would be advisable.
- Note: New studies must be registered separately on clinicaltrials.gov if they meet the requirements for registration rather than being added to existing clinicaltrials.gov record.

Some examples of when changes can be submitted via an amendment:

- Changes to recruitment materials or methods (e.g., using flyers to advertise to participants), or other documents used with participants (e.g., interview guides, substituting one questionnaire with another).
- Adding payment or modifying the amount participants are paid.
- Changes in inclusion or exclusion criteria without changing the overall study aims or design.
- A study is federally funded, and an investigator obtains an NIH-supplement to add a specific element to that study. The original funding is still necessary to complete the study and although the supplement adds a new hypothesis, procedure, and funding, the study population and overall design remains the same.
- Modifications to current study procedures (e.g., increase in radiation exposure, adding audio recording) when the modifications do not result in significant changes to the study design.
- Adding or removing study personnel.
- If changes do not significantly impact aims, hypothesis, procedures, or study populations, then an amendment may be submitted.

Consider the questions below when deciding whether to submit an amendment or a new study.

Question	Submit New Application	Submit Amendment
Do the proposed changes alter the research aims/purpose, hypotheses, study design, or population? Considerations: • The IRB must assess the risks and benefits of the research. If the research question, design, or population has significantly changed then this is likely to impact the risks and benefits of the study. • Consider the impact of proposed changes on the ability to accurately report study progress/results. If the proposed changes will make progress reporting at Continuing Review, on ClinicalTrials.gov, or to the FDA unworkable, then a new application for a separate study may be required.	• Changes that significantly alter the study aims/purpose, data analysis plans, procedures, or overall study design. • Changes that modify <u>more than one</u> of the following: study aims/purpose, study procedures, and study population. Keep in mind that submitting multiple amendments over time that change more than one of these aspects should be submitted as a new study. • New research questions that emerge from knowledge gained in an existing study should be submitted as a new study.	• Minor changes that do not significantly alter the overall study objectives/aims/purpose, data analysis plans, procedures, or overall study design

Question	Submit New Application	Submit Amendment
What changes will be made to the study procedures or methods? Considerations: • If the changes to the procedures or methods are significantly different from the ones already approved in the existing study, assess why it is necessary to make the proposed changes to the procedures/methods. Significant changes in the procedures/methods may mean you are trying to address changes/shifts in the study aims and may require a new study. • In addition, the original study can morph into a new study over time (e.g., changes/shift in the original aims, procedures, populations) consequently impacting the clarity and quality of research data. This can also cause confusion and errors among research team members, leading to non-compliance and/or impacting risks to participants.	• If the proposed procedures or methods deviate significantly from those approved in the existing research study, then a new application should be submitted.	• If the procedures or methods remain the same, or do not significantly alter the study design, then an amendment is permitted.

Question	Submit New Application	Submit Amendment
How long has the study been open? Considerations: • If the research has been active for several years, the information contained within the study can become outdated as clinical procedures, research regulations, and IRB and institutional policies change.	• Significant modifications to old studies may require reconsideration of risks and benefits of the study. • In addition, studies that have been open for an extended period may include irrelevant information as portions of the research may be complete and this can create confusion about what activities are ongoing. • As new risk information becomes available, studies that have been ongoing may not reflect the most current information. A new application would allow the protocol to be refined to meet the aims of the current research objectives, to include current standard of care, risks, regulatory considerations, and institutional approaches and policies, and to ensure it will reach completion.	• If the study is operating within the planned research timeline and if changes are otherwise not significant, then submitting an amendment is appropriate.
Will the study utilize new funding and/or require a new contract?	• If new funding changes the aims and research design of the project, adds new population, or procedures that significantly differ from the current study, a new application must be submitted. • In addition, whether the funding changes or not, the execution of a new contract with updated terms could result in the need for submission of a new application.	• If new funding is awarded to support the research as currently approved, then an amendment is appropriate.

1.2 Case Reports

1.2.1 Background and Rationale

Clinical experiences are often the genesis of research questions and the design and development of clinical research protocols. In an academic medical center, it is not unusual for unique and interesting clinical cases to be written up as case reports for publication in medical journals or presentation at medical or scientific meetings. This section provides guidance on when publication/presentation of case report(s) constitutes human-subjects research and requires prospective IRB approval.

1.2.2 Medical Case Reporting

The Federal Policy for the Protection of Human Subjects (45 CFR 46.102(l) defines "research" as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. In general, a case report of typically three or fewer patients is not considered human-subject research and does not typically require IRB review and approval because case reporting on a small series of patients does not involve the formulation of a research hypothesis that is subsequently investigated prospectively and systematically for publication or presentation. Reporting or publication is not typically envisioned when one interacts clinically with the participant. Comparing the three case reports to existing reports in the literature is not research and does not require IRB approval.

When larger series of patients are being reported, investigators usually begin to ask specific research questions and formal systematic collection of data occurs, moving these activities closer to prospectively designed research. Researchers are advised to consult with the IRB or submit larger case series reports for IRB review when uncertainty exists about whether formal and systematic collection of human subjects research is occurring.

It should also be noted that teaching and soliciting colleagues' advice on clinical care of a specific patient or groups of patients during presentation of a case at departmental conferences does not require IRB review. Generalized commentary by a clinician on the outcome of their clinical care of patients in accepted venues for discussion of clinical management is also not considered research requiring IRB review, if there isno prospective research plan and no formal, systematic, and prospective collection of information. This type of communication may occur at hospital or practice meetings, in continuing education venues, or in editorials, where the comments are explicitly identified as personal experience and not formal clinical research.

In certain cases, journals may require a formal determination from the IRB that a case report does not constitute research. Researchers seeking an official IRB determination that a case report is not research should submit a Not Human Subjects Research (NHSR) application.

1.2.3 HIPAA REQUIREMENTS

HIPAA requirements apply to the access, use, and disclosure of protected health information (PHI) in case reports. If the case report includes PHI, the patient may need to provide HIPAA Authorization. For any questions regarding HIPAA and its applicability to case reports, contact the Mass General Brigham Privacy Office at massgeneralbrighamprivacyoffice@mgb.org.

2 Informed Consent

2.1 Consent Discussion

The consent discussion should begin sufficiently in advance of the initiation of study-related procedures to allow potential participants time to reflect on the potential benefits and risks and possible discomforts of participation. The following method is preferred by the IRB, though it may need to be tailored to the circumstances of individual studies and may not be appropriate or feasible in all situations. First, potential participants are given general information about the research (e.g., through recruitment materials, information sheets, or discussion with their treating physicians), and if they are interested in learning more about the study, they contact or agree to be contacted by study staff. The research team then meets with the potential participant to review and to discuss the details of the research study using the informed consent document as a guide. This discussion should include all the required elements of informed consent, e.g., the purpose of the research, the procedures to be followed, the risks and discomforts as well as potential benefits associated with participation, and alternative procedures or treatments, if any, to the study procedures or treatments.

Comprehension and teaching aids such as videos, graphics, online resources may be used, but require prospective IRB review and approval. Investigators are advised to draft "standard operating procedures" to describe and document the consent procedures, and to ensure study staff are trained on the procedures and methods used to obtain informed consent.

Preferably, potential participants are then given a copy of the informed consent document to take home so they can carefully read the document and discuss the research with their family, friends and/or physician and develop questions to ask at their next meeting with the research staff. Please note that participants must always be given the opportunity to ask questions and have them answered by the investigator and, whenever possible, to consult with friends/family and/or their physicians. Once they have read the consent document and their questions are answered, if they agree to participate in the research, they sign and date the informed consent document. (Note also that under HIPAA Privacy Rule, participants must be asked for written authorization for the use and disclosure of their protected health information for research. The HIPAA authorization is included in the privacy section of the consent form.)

2.2 Individuals Who Cannot Read the Consent Form

When a person cannot read the consent form, the entire consent form may be read aloud to the person, provided as an audio recording that the person can listen to, provided in an electronic format that the computer can read to the person or, for persons who are visually impaired and able to read Braille, in Braille. These formats afford people who cannot read the consent form with equivalent consent procedures and an accessible version of the consent document for their records. When the consent form is provided in a recording, electronic format, or in Braille, the investigator or person obtaining informed consent should confirm that the participant listened to the audio version or electronic consent form or read the Braille consent form when they begin the consent discussion and provide an opportunity to review the information and ask questions. When enrollment of participants who cannot read the consent form is anticipated, the protocol submission should include a description of the process for obtaining and documenting informed consent of participants who cannot read the consent form.

, If a participant or their legally authorized representative is unable to read, an impartial witness should be present

during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to the participant is read and explained to the participant or their legally authorized representative, and after the participant or their legally authorized representative has verbally consented to the participant's participation in the study, and if capable of doing so, has signed and personally dated the consent document, the witness should sign and personally date the consent form. The witness must, at a minimum, have sufficient proficiency in the language of the oral presentation to be able to attest to the information that was presented orally to the participant, and the participant was given the opportunity to ask questions.

2.3 Electronic Consent (eConsent)

With prior IRB approval, electronic consent or eConsent platforms may be used by Mass General Brigham investigators to document informed consent. It is important to remember that informed consent policies, regulations, and details of the process as approved by the IRB apply equally to an electronic medium as to a paper medium. For example, if the IRB required a licensed physician investigator to obtain informed consent in a particular research study, that holds true whether a paper consent is signed or an eConsent. If the IRB did not permit LARs to provide informed consent on behalf of participants, that would be true regardless of the platform.

eConsent platforms can be used when investigators and participants are together in-person, or in a remote setting as described in the next section. If an investigator proposes to use an eConsent platform in a new protocol, they should name the platform and describe in detail the informed consent process in their protocol or Site Addendum. If an investigator wishes to add eConsent to an existing protocol, they will need to submit an Amendment with updated study documents referencing and describing the eConsent platform and process.

eConsent cannot be used unless and until it has been approved by the IRB, as it may not be appropriate for all research settings and studies.

eConsent Platforms available to MGB investigators:

- The MGB REDCap eConsent module has been developed and is supported by the MGB Digital Team and is available at no cost. If a team chooses to use the MGB REDCap eConsent module, it is critical for the study team to set up the project in accordance with instructions from the Digital Team, and to thoroughly test the project prior to implementation.
- Adobe Sign is available to MGB researchers at no cost and can be used to execute signatures on IRB-approved consent forms. Adobe Sign typically depends on exchanging emails among the signatories, so the study team is advised to carefully consider and test the process prior to implementation.
- Sponsors, Coordinating Centers, and Collaborative Groups sometimes propose to use an eConsent platform which has not been approved at the MGB-enterprise level. Such platforms and accompanying informed consent process information must be named/described in the Insight application and study documents so that they are reviewed and approved by the IRB and RISO prior to implementation.

The eConsent must match the IRB approved consent document. For instance, if a study is approved to use a Fact/Information Sheet under a waiver of documentation of consent (i.e., signature requirement waived), investigators cannot add a signature line to the eFact/Information Sheet. Instead, the eFact/Information Sheet should include an option to indicate agreement (e.g., I agree/ I do not agree check boxes) and capture participants' full name and date of consent.

Since using eConsent platforms may involve more steps and complexity than simply signing a paper consent form, study teams are advised to compose an eConsent SOP which describes their process for obtaining and documenting informed consent in compliance with all applicable policies and regulations.

Even if using electronic consent, it may be advisable to retain the option of paper consent in case there are technology

limitations or difficulties, or a participant prefers to use paper. If both eConsent and paper consent will be options for the research study, both should be listed and described in the study protocol or Site Addendum.

2.4 Remote (Phone or video) Consent

Consent discussions may take place by phone or video. When investigators plan to obtain informed consent remotely, they should describe how the remote consent process will be operationalized and documented. The remote consent process must be described in detail in the study protocol and prospectively approved by the IRB.

An example of a study for which remote consent by phone may be appropriate is a time sensitive therapeutic intervention in acute stroke patients where the patient is not able to give consent and an appropriate surrogate is not physically available. In thissituation, the investigator would call the surrogate and send them the consent form electronically. The surrogate would review the consent form, discuss participation in the study with the physician investigator, sign (handwritten or digital) and date (including time) the consent form agreeing to the patient's participation in the research and return the signed and dated consent form electronically. The investigator should sign and date (including time) the consent form once it’s been returned.

2.5 Mailed Consent

Mailed consent (including electronic mailing) may also be considered for certain minimal or low risk studies where some or all of the potential participants are unable to meet with the investigator due to logistical or other reasons. When investigators anticipate the need to obtain informed consent by mail, they should describe how the mail consent process will be operationalized and documented. The mailed consent process must be described in detail in the study protocol and prospectively approved by the IRB.

When documentation of informed consent is required in writing, the consent form is sent to the prospective participant by mail or electronically. If the consent form is sent and returned by mail, include two copies - one for the participant to keep for their records. The person reads the consent form and contacts the investigator if they wish to discuss participation in the study or have any questions about the study. If the person agrees to be in the study, they sign and date the consent form and return it by mail, or electronically to the investigator. The investigator should then sign and date the consent form once it’s been returned.

An example of a study for which consent by mail may be considered is a genetic study where only medical and family history and a mailed blood sample are needed.
Another example is a study of a vitamin supplement provided by mail, where participants take the vitamin, answer medical questionnaires and request their physicians send their medical records to researchers. The opportunity to discuss the study and ask questions must be offered, but some participants may find no discussion is necessary. The offer to discuss the study and consent discussions, if they occur, should be documented in the research records.

2.6 Timing of Informed Consent

Special consideration must be given to the timing of the consent process when the participant population includes patients who will, for example, be same-day admissions for surgical procedures or who present for diagnostic or other tests, such as cardiac catheterizations or radiological examinations. The time frame for the consent process will be more limited in these situations. Generally, the investigator should allow potential participants enough time to consider participation and ask questions. Whenever possible, patients should be providedwith information about the study well in advance, for example, when the surgery, test, or examination is scheduled.

With few exceptions, the informed consent of participants, whether patients or healthy volunteers, must be obtained and documented before the start of any study-related procedures, including screening tests and exams done solely to determine their eligibility for the study (see also Pre-Screening of Research Participants During Recruitment). For example, participants might be asked to fast before a morning blood draw or to bring in a stool sample to a screening visit. The participant's agreement must be documented in the research records.

2.7 Exculpatory Language

Any informed consent, whether written or oral, must not include exculpatory language such that the participant is made to waive, or appear to waive, any of their legal rights or to release the institutions or its agents, the investigators, from liability or negligence.

Examples of exculpatory language:

- By agreeing to this use, you will give up all claim to personal benefit from commercial or other use of these substances.
- I voluntarily and freely donate any and all blood, urine, and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items.
- By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.
- I waive any possibility of compensation for injuries that I may receive as a result of participation in this research.
- I agree to indemnify the sponsor, should there be any misuses of the mobile health application provided to me as part of this research.

2.8 Optional Questions

If the informed consent form contains any optional questions, the investigator should ensure that they have been appropriately completed and initialed by the participant when informed consent is obtained. It is the responsibility of the investigator to keep track of responses and ensure that participant preferences are followed. If a participant did not complete an optional question, it should be assumed that the participant did not opt-in or answer affirmatively the question that was being asked. The participant could be reconsented at a later date to obtain their responses to the optional question, if desired. If a participant is reconsented during the course of research, the study team should confirm that the answers to optional questions remain consistent, or, if they change, it is the true intent of the participant to change their answers. Answers to optional questions cannot be collected if a “short form” is used to consent a non-English speaking participant.

Due to the recordkeeping burden, limitations in using the "short form," and frequent mistakes and omissions in completing optional questions, study teams should consider carefully whether the optional item should be integrated into the research study as a standard component (not an option) or should perhaps be a separate study with its own consent form.

2.9 Individuals Who Can Obtain Informed Consent

Individuals qualified through their education, training, and experience can obtain informed consent from participants. Investigators should describe who will obtain consent and which research staff will participate in the consent process, and document the delegation on a Delegation of Responsibility/Authority Log. In considering who can obtain consent, the IRB considers the nature and details of each study.

In general, any Principal Investigator (PI), licensed physician investigator listed on the study staff, or licensed doctoral-level nursing investigator (e.g., Doctor of Nursing Practice or PhD in Nursing) listed on the study staff can independently obtain informed consent for studies involving more than minimal risk and/or investigational drugs/devices including those under IND/IDE, except as outlined below (see tables below).

If the Principal Investigator (PI) is a licensed clinical pharmacist, licensed psychologist, other licensed clinical faculty member outside the above noted categories or has any training other than the above noted categories but is the IND/IDE holder, the PI can obtain consent for studies involving more than minimal risk and/or investigational drugs/devices including those under IND/IDE with backup provided by a licensed physician investigator listed on the study staff. In this instance and the scenarios described below, the process for offering licensed physician backup should be described, including formally adding the licensed physician co-investigator to study staff and delegation of responsibility logs and ensuring the licensed physician be available to participants for consultation prior to completion of the consent process.

If the PI is a non-licensed or non-clinical faculty member (e.g., non-licensed physician, other doctoral-level scientist, etc. – and is not the IND/IDE holder), the PI can obtain consent for studies involving more than minimal risk only if the study is determined to be a non-significant risk, IDE-exempt, or IND-exempt investigational drugs/devices with backup provided by a licensed physician investigator listed on the study staff.

Licensed nurse practitioners and licensed physician assistants listed as co-investigators on study staff can obtain consent for studies involving more than minimal risk and/or investigational drugs/devices including those under IND/IDE with backup provided by a licensed physician investigator listed on the study staff.

Consent by licensed nurses or other appropriately trained and credentialed research investigators and research staff may be considered by the IRB for greater than minimal risk and investigational drug/device studies on a case-by-case basis, based on individual training and credentials. In these instances, the rationale and justification for this approach and the qualifications and training of the relevant study staff must be submitted.

In all circumstances, other study staff may assist in the consent process, and their involvement should be described in the IRB-approved protocol.

Based on the nature and details of the study, the IRB retains the authority to approve more limited consent procedures,

e.g., to require only licensed physician investigators be permitted to obtain consent for a specific study. Examples of when the IRB may limit studies to consent by licensed physician investigators include: first-in-human studies, when surrogate consent is to be obtained for research involving more than minimal risk with no potential for direct benefit to the participant, or when exceptionally challenging or risky research is performed, among other potential scenarios.

It is the PI's responsibility to provide training and oversight of research staff involved in the consent process and to ensure that proper informed consent is obtained from every participant according to the IRB-approved protocol and institutional policies.

Consent for most minimal risk studies involving investigational drugs or devices should be obtained by clinically licensed staff, including study nurses, co-investigators, and PIs. In general, the IRB allows consent to be obtained by an individual commensurate with their clinical role, e.g., a research coordinator, licensed nurse, or non-licensed physician investigator can obtain informed consent if that individual would be permitted, in a clinical setting, to perform the procedures for which consent is required. For minimal risk studies, other study staff including study nurses and research coordinators can obtain informed consent in most circumstances, with backup provided by the PI and/or other co-investigators listed on the study staff. The process for offering PI and/or other co-investigator backup should be described, including formally adding co-investigators to study staff and delegation of responsibility logs and ensuring the PI and/or co-investigators are available to participants for consultation prior to completion of the consent process.

If participants are to be enrolled from among the investigator's own patients, consent procedures must be put in place to ensure that participants do not feel obligated to participate because the investigator is their treating physician. There is concern about the possibility of patients feeling obligated to participate because it is their physician who is asking. While the IRB does not prohibit physicians obtaining consent from their own patients, researchers are asked to think about this issue and address it. There are many possible ways to do this. One can contact the patient in writing initially and allow them to pursue the research further, if interested. One can offer patient the opportunity to take home the consent form and call back if they wish to participate. One can ask a colleague to initially present the study to a patient. One can have colleague re-contact the patient after theinvestigator has presented the study or had the consent discussion and offer them an opportunity to ask additional questions, raise concerns, or opt out, with someone who is not their physician. One can recommend the patient discuss participation with other health care providers.

Who Can Obtain Informed Consent by Role:

Role on Study Staff	Can Consent for Which Types of Research Study?	Backup Needed?
➢ Licensed Physician Principal Investigators and co-Investigators ➢ Licensed Doctoral-level Nursing Principal Investigators and co-investigators	➢ More than minimal risk ➢ IND/IDE ➢ Minimal risk	➢ None
➢ Principal Investigators who are: ▪ Licensed Clinical Pharmacists ▪ Licensed Psychologists ▪ Other clinically licensed faculty members ▪ Other IND/IDE holders	➢ More than minimal risk ➢ IND/IDE ➢ Minimal risk	➢ Licensed physician investigator listed on study staff
➢ Principal Investigators who are non-licensed or non-clinical faculty including: ▪ Non-licensed Physicians ▪ Other doctoral-level scientists	➢ More than minimal risk ➢ Limited Investigational Device studies: Only Non-significant risk or IDE exempt ➢ Limited Investigational Drug studies: IND exempt ➢ Minimal risk	➢ Licensed physician investigator listed on study staff
➢ Other licensed advanced practice provider co-investigators including: ▪ Licensed Nurse Practitioners ▪ Licensed Physician Assistants	➢ More than minimal risk ➢ IND/IDE studies ➢ Minimal risk	➢ Licensed physician investigator listed on study staff
➢ Other study staff including: ▪ Study Nurses ▪ Research Coordinators	➢ Minimal risk* *Consent for minimal risk studies involving drugs or investigational devices should be obtained by clinically licensed staff, including study nurses, co-investigators, and PIs.	➢ Principal Investigator/Co-Investigators listed on study staff

Who Can Obtain Informed Consent by Type of Study:

Type of Study	Who Can Obtain Consent?	Backup Needed?
➢ Investigational drugs and devices, including under IND/IDE ➢ More than minimal risk	➢ Licensed Physician Investigators (PI and co-Investigators) ➢ Licensed Doctoral-level Nursing Investigators (PI and co-investigators)	➢ None
➢ Investigational drugs and devices, including under IND/IDE ➢ More than minimal risk	➢ Principal Investigators who are: ▪ Licensed Clinical Pharmacists ▪ Licensed Psychologists ▪ Other clinically licensed faculty members ▪ Other IND/IDE holders ➢ Other licensed advanced practice provider co-investigators including: ▪ Licensed Nurse Practitioners ▪ Licensed Physician Assistants	➢ Licensed physician investigator listed on study staff
➢ Limited Investigational Device studies: Only Non-significant risk or IDE exempt ➢ Limited Investigational Drug studies: IND exempt ➢ More than minimal risk	➢ Principal Investigators who are non-licensed or non-clinical faculty including: ▪ Non-licensed Physicians ▪ Statisticians ▪ Physicists ▪ Epidemiologist ▪ Other doctoral-level scientists	➢ Licensed physician investigator listed on study staff
➢ Minimal risk studies involving drugs or investigational devices	➢ Clinically licensed study staff including study nurses, co-investigators, and PIs.	➢ Principal Investigator/Co-Investigators listed on study staff
➢ Other minimal risk studies, including those involving non-invasive approved medical devices (e.g., standard MRI, EEG, EKG, etc)	➢ Study staff including research coordinators/assistants	➢ Principal Investigator/Co-Investigators listed on study staff

2.10 Use of a Participant Advocate

In certain situations, the IRB will require the use of a participant advocate in the consent process. The participant advocate is an individual who has no vested interest in the research and who agrees to act as an impartial third party in the consent process. When a participant advocate is appointed, the participant advocate is expected to act in the best interests of the participant by sharing in discussions with the investigator and with those responsible for giving consent. Individuals who might fulfill this role include a health care professional knowledgeable about, but not involved in, the research. Psychiatrists, social workers, or nurses, all typically with specialized expertise in a given field of medicine, have been chosen as advocates in studies supervised by the IRB. Advocates should be formally identified and may be paid for their time. The participant advocate is responsible for ensuring that the participant understands the research procedures and the risks and potential benefits of participation and that their consent is free and voluntary. When a participant advocate is used, the participant advocate must sign and date the consent form.

Situations in which the use of a participant advocate may be required include:

- when the risks to participants are significant and the participant is the patient of the investigator and, as such, may feel obligated to participate;
- when consent is to be obtained in the emergency room or in an emergency situation when the time frame to obtain consent prior to start of study-related procedures is limited;
- when surrogate consent is to be obtained for research involving more than minimal risk with little or no potential for direct benefit to the participant;
- when exceptionally challenging or risky research is performed; or
- when many potential participants are expected to overestimate the likelihood of health benefits.

2.11 Documentation of the Consent Process

When the research will begin on the same day that informed consent is obtained, the IRB recommends recording time of consent in addition to date of consent to document that informed consent was obtained prior to any study-related procedures.

Every page of the informed consent form must be labeled with the participant's name and medical record number or date of birth. This allows proper identification of the consent form for auditors, inspectors, and other regulatory authorities, ensures consent form pages can be identified if they become separated, and facilitates proper document labeling for upload into Epic. Labeling of consent forms is not a violation of research regulations or HIPAA.

To demonstrate compliance with the consent process outlined in the protocol and research regulations related to obtaining consent, the investigator should document all elements and aspects of the informed consent process in a clinic chart/progress note, research note, or documentation of consent process checklist/other source document. Documentation should include:

- Who obtained consent and from whom;
- whether the consent discussion was conducted in person or remotely;
- details about timing;
- systems used such as phone, computer, or mail;

- other persons involved such as interpreter, surrogate, backup licensed physician investigator;
- affirmation that all questions were answered and that consent was obtained prior to the start of any study procedures;
- method for obtaining signatures (electronic or wet) or, if applicable, indication that verbal consent was given; and
- that a copy of the signed and dated consent form, info sheet, or other approved documents were given to the participant.
- Documentation of special circumstances such as a description of the relationship of the surrogate providing consent or notation of how a participant indicated consent if they were physically unable to sign the consent form is especially pertinent and should be added as appropriate.

Informed consent process documentation should be signed and dated by the person obtaining consent. See Mass General Brigham Compliance and Education Office template Documentation of the Informed Consent Process.

If consent is provided verbally or is implied (via completion of a survey, for example), investigators need to document those elements of the IRB-approved informed consent process which apply to their specific circumstance. For example, if an interpreter was used during a verbal consent process, it would be expected that this is documented in the research record.

2.12 Consent Form Storage

Usually, two copies of the signed and dated research consent form are needed. The original signed and dated research consent form should be retained in the research records. A copy of the signed and dated research consent form must be given to the participant. Lastly, the consent should be scanned/uploaded in the participant's medical record if relevant to the participant's ongoing medical care, or the participant is hospitalized when the research is initiated or hospitalization is expected (for example, an investigational device will be implanted during an upcoming procedure requiring hospitalization).

If the study involves sensitive research (e.g., alcohol or drug use, studies of illegal behaviors, and some genetic studies) a copy of the research consent form ordinarily should not be placed in the participant's medical record. Studies involving psychiatric illness, genetics and HIV infection should not automatically be presumed to be sensitive studies and excluded from the medical record. In the interests of participant safety, the IRB encourages sharing of information about research participation with treating clinicians and has a high bar for excluding research documentation from the medical record. If a study has no medical interventions (for example, longitudinal exams and surveys of outpatients or research involving non-patient healthy volunteers) investigators are not required to include consent forms in medical records.

2.13 Converting Paper Consent Forms to Electronic Documents

Study consent forms may be retained in electronic form when they were originally collected using paper consent forms. The IRB has developed guidance on Electronic Storage of Study Documents, including paper consent documents. See also Mass General Brigham HealthCare Policy *PHS-1055 Guidelines on Retention of Research Data, Materials, and Records.*

2.14 Participant Re-consent Requirements

The informed consent process is an ongoing exchange of information throughout a participant's involvement in research. During the course of conducting research, new information about the study or changes to the study may arise that affect the rights or welfare of participants. This may include newly identified risks or change in risk severity or frequency, new alternative treatments, decreased potential for benefit, and new study procedures. This is paramount if knowledge of the new information might affect participants' willingness to continue participation. New information can and should be added to a full study consent form, especially if new participants are still enrolling. Consent form changes and any accompanying revisions to the protocol, consent form/assent form/information sheet ("consent documents"), or other study documents must be submitted to the IRB for review and approval. In some instances, a consent form addendum, which focuses solely upon the new information can also be used.

Participants should be asked for new consent i.e., through the investigator's explanation and request to sign a revised, IRB-approved consent form when they are actively engaged in the research and there have been major changes to any component of the consent form, e.g., drug dose(s), device, study procedures, risks and discomforts, benefits, and alternatives.

Examples of when a participant should be asked for new consent in writing:

- the Procedures section of the consent form has been revised to include a new procedure that the participant will be asked to undergo, e.g., genetic testing, cardiac catheterization, biopsy, colonoscopy, mammogram, ultrasound, etc. An investigator may not perform a procedure on a participant without new consent if the procedure was not mentioned in the original consent process and form.
- the Risks and Discomforts section of the consent form has been revised to include a newly identified serious adverse event.
- the Risks and Discomforts section of the consent form has been revised to include a change in the severity or frequency of a serious expected event.
- the Alternatives section has been revised to include newly identified alternative therapies or diagnostic tests.
- the Procedures and Alternatives section have been revised to include a change in FDA approval status of the drug or device being studied.

When new information is added to the consent documents that might affect the willingness of already enrolled and active participants to continue in the research, investigators must inform the IRB of the following:

- **Who will be re-consented**: Depending on the change, all participants or only those currently active may need to be re-consented.
    - In some cases, investigators may find that it may not be necessary to re-consent participants who have completed participation in the study to be informed of new information unless the new information relates to risks that may manifest after such participation.
    - It may also not be necessary to inform participants who are still actively participating of new information when the change will not likely affect their decision to continue in the study (e.g., an increase in the number of study participants).
- **When re-consent will occur**: This could be immediate once the change is approved by the IRB, or at the next scheduled study visit.
    - But in **ALL** cases re-consent must be obtained prior to initiating any newly added procedures or study activities.

- **How re-consent will be obtained**: Investigators can obtain re-consent using the updated consent documents, a letter, written notification to participants, or phone calls.

For who can obtain re-consent, investigators should follow the IRB approved plan for who is approved to obtain consent originally. If re-consent is to be obtained by someone other than who has been approved to obtain consent originally, investigators must request approval from the IRB. Refer to the Individuals Who Can Obtain Consent in Human Subject Research section above.

Participants should also be notified of a change of principal investigator or contact information; however, in most cases this type of change can be adequately communicated by other means (e.g., verbal or email notification and documentation in the research record). Please note that a change in co-investigators and/or study staff is not considered a major change requiring new consent or notification.

Examples of when the IRB may approve a letter or email being sent or verbal communication to notify the participant of changes include:

- the principal investigator has been changed
- the study contacts have been changed and/or the contact telephone numbers have been changed
- the participant has completed the study interventions and is in the follow-up phase of the study or in some cases has completed the study, and the information is such that learning it would not materially affect the participant's decision to continue participation in follow-up

In the event that the IRB disagrees with the investigator's re-consent plan described in the Amendment form, the IRB will determine who needs to be re-consented, the timing and method of re-consent, and they will require modifications to the Amendment form to document this determination.

2.14.1 Documentation of Re-consent

When a revised consent form is used to inform enrolled participants of new information and to document their willingness to continue in the study, the participant must sign and date the revised consent document if they are willing to continue participating in the research.
For studies approved to obtain consent from legally authorized representatives (LARs) or parents/guardians, the LARs or parents/guardians must provide re-consent. Re-consent should be documented in participant files and documentation should include what information was provided, by whom, the date this occurred, and that the participant/LAR received a copy of the re-consent document. The Documentation of Consent Process Checklist template is available on the Human Research Affairs Compliance and Education Office website for this purpose.

Participants should be given the information above in a timely manner so that they can make a fully informed decision about whether they wish to continue their participation. The greater the import of the new information, the more quickly participants should be made aware of it.

For studies approved for verbal consent (e.g., use of information sheets), investigators should consider how new information will be relayed to participants. Investigators may update information sheets with new information or send information via letters or emails as described in this section. The re-consent should be appropriately documented in the participant's research records.

Industry sponsors have varying policies and requirements, and investigators are advised to discuss with them when and if formal written "re-consent" is desired when information that is new, but not of major importance, is added to a

consent form. The IRB does not recommend annual "re-consent" or new consent simply because the study consent form has been "re-approved" at the time of continuing review. Rarely, the Committee may advise annual "re-consent" - for example, if a participant is enrolled in a transplantation study where a significant waiting period is anticipated. Investigators are also encouraged to consult with the IRB as needed on these topics.

2.15 Obtaining and Documenting Informed Consent of Non-English Speakers

The Department of Health and Human Services (DHHS) regulations (45 CFR 46.116 and 45 CFR 46.117)and Food and Drug Administration (FDA) regulations (21 CFR 50.25 and 21 CFR 50.27) require that informed consent information be presented in language understandable to the participant or their legally authorized representatives (LARs), and in most situations, that informed consent be documented in writing using signed consent forms. Understandable means that the information presented to prospective participants, or their LARs is in a language and at a level they can comprehend, including an explanation of scientific and medical terms.

Given the diversity of individuals in our community, investigators may encounter a non-English speaking person who is interested in participating in a research study. When presented with this situation, investigators should carefully consider the ethical and legal ramifications of enrolling a participant when there is a language barrier. It is not ethically justifiable to exclude potential participants in a research study solely on the basis of language spoken nor to obtain consent from participants who do not have a clear understanding of the consent document or who do not have the opportunity to ask and receive answers to their questions freely. Without this understanding and opportunity, consent may not be truly informed and may not be legally effective.

In order to address these considerations, when enrolling participants who do not speak English in research, the participant must be provided with **BOTH**:

- a written consent document in a language understandable to them, AND
- a-qualified interpreter fluent in both English and the participant's spoken language

Depending upon the research, the *written* consent document can be either:

- a **full translation of the Informed Consent(s)**, in the participant's language, of the entire English version of the consent form approved by the Mass General Brigham IRB Office
    - A translated consent form should be used when enrollment of non-English speaking participants is anticipated or planned.

  OR

- a **Short Form**, which is a document that states that the elements of informed consent have been presented orally to the participant or their LAR and that contains a description of the required elements of informed consent and notes that these elements, as they pertain to the study, will be presented orally to the participant and/or their legally authorized representative.
    - While a short form written consent document may be used for incidental and unexpectedly encountered non-English speaking potential participants, the possibility of its use must be prospectively approved by the IRB.
    - The 'short form' should generally only be used when the research involves no more than minimal risk to participants or, if more than minimal risk, presents the prospect of direct benefit to individual participants. In most cases for studies that involve more than minimal risk with no direct benefit to individual participants the 'short form' consent process is not

permitted.

- The short form process can be used once for a particular language in a study.
    - A translation of the full informed consent form **must** be provided to the participant/LAR as soon as possible after the fact.

When obtaining parental permission, in the event the parents of a child do not understand English, the parental permission must be obtained and documented in a language that is understandable to the parents. The child who will be participating in the research should not be used as an interpreter for the parent, even if the child is fluent in English and may be able to assent. Similarly, if child assent is required, the information given to the child must be in a language that is understandable to the child. Investigators must follow the assent requirements approved for the study. For instance, if the child is 14 – 17 years of age and the IRB has determined that assent for this age group can be documented in the consent form, the child can provide their assent via the consent form.

2.15.1 Use of a Written Translation of the Entire English Version of the Mass General Brigham IRB-Approved Consent Document (Translated Consent)

When investigators can reasonably expect that more than an incidental number of participants speaking the same non-English language will be enrolled, the use of a written translation of the *entire* English version of the consent form is required.

The Mass General Brigham IRB must approve all written translated versions of the consent form and recommends that the written translation be done by Mass General Brigham-approved translation vendors or other qualified persons or services recommended by Interpreter Services. Investigators must also arrange for a medical interpreter from hospital Interpreter Services who is fluent in both English and the participant's spoken language to be present or available by phone or videoconference during the consent process.

The IRB may approve exceptions as described in the Use of Interpreters section below.

2.15.2 Use of a Written Translation of the 'Short Form' Consent Document

The '**short form**' attests that the required elements of consent have been presented orally. When the 'short form' is used to document informed consent, the consent process must include the text of the English version of the consent form presented orally in a language understandable to the potential participant. A medical interpreter must be present either physically, by phone or videoconference, to interpret the investigator's oral presentation of the English version of the consent form in the participant's language.

The use of short forms to enroll non-English speaking participants, including minors, must be reviewed, and approved by the IRB prior to their administration to participants. Although it is always preferable, and in some cases required by the Mass General Brigham IRB, to use a written translation of the *entire* Mass General Brigham IRB-approved English version of the consent form (see above), a translated version of a 'short form' consent document can be used to document informed consent when a non-English speaking individual is unexpectedly encountered, and the full Mass General Brigham IRB-approved consent form has not yet been translated. If a short form is used to enroll a non-English speaking participant, the English consent form ***must*** be translated promptly and provided to the participant or their LAR.

When making a decision to allow enrollment of a participant who does not understand English into a research protocol without waiting for a written translation of the consent form, the investigator (and, whenever feasible, the IRB) should consider whether the consent process, under this circumstance, will provide the participant with

sufficient opportunity to understand the information being presented. If consent is sought and the investigator believes that the prospective participant has not understood the information presented, then the individual should not be enrolled in the research.

If the study involves obtaining, accessing, using or disclosing identifiable health information, a stand-alone HIPAA Authorization in the participant's/LAR's language must be used in addition to the short form.

The short form consent document and HIPAA Authorization have been pre-translated in multiple languages and made available to the research community by the IRB. These documents are located on Research Navigator. If the study team encounters a non-English speaker who speaks a language into which the short form/HIPAA Authorization have not been translated, contact the IRB (partnersirb@partners.org).

The guidance in this section also applies to Single IRB (sIRB) studies for which the Mass General Brigham IRB is serving as the sIRB for multiple sites. If Mass General Brigham serves as the sIRB, relying sites must use short forms provided by the Mass General Brigham IRB. Site-specific requests that differ from the sIRB's guidance must be submitted as a site-specific amendment with supporting documentation from the site's IRB office. Sites are responsible for translating their own required language and HIPAA Authorization forms that differ from that provided by the sIRB.

The consent process for enrolling participants using the 'short form' consent document is outlined below.
ALL of the following requirements must be completed:

1. The Principal Investigator (or other member of the study staff with PI-delegated and IRB approved responsibility for obtaining informed consent) must present the Mass General Brigham IRB-approved *English version of the consent form* orally to the participant through a medical interpreter who is fluent in English and the language understandable to the participant;
2. The participant must be given a written translation of the *'short form'* consent document in a language understandable to them to read and must have the opportunity to ask and receive answers to questions. If the study involves accessing identifiable health information, the translated HIPAA Authorization must also be given;
3. The entire consent process must be witnessed by an individual who is fluent in English. The witness must, at a minimum, have sufficient proficiency in the language of the oral presentation to be able to attest to the information that was presented orally to the participant, and the participant was given the opportunity to ask questions. The interpreter may serve as the witness to the consent process, if they are willing to do so.
4. The witness must be independent of the study team. In addition, if possible, the witness should not be a family member of the participant. If a family member is used as a witness, investigators must document why an independent witness could not be used.
5. The Mass General Brigham IRB-approved *English version of the consent form* must be signed by the investigator obtaining informed consent **and** the witness to the consent process (see 3 above);
6. The written translation of the *'short form'* must be signed and dated by the participant, including the minor if the IRB required written assent, **and** the witness to the consent process (see 3 above).
7. Following participant enrollment using a short form, investigators must obtain a translated copy of the IRB-approved English version of the consent form promptly and submit it to the IRB for review and approval. Once the translated consent form is approved by the IRB, the investigator must provide it to the participant or LAR as soon as possible. If the study includes optional procedures, investigators must obtain reconsent of participants. Translation of the consent form is critically important as a means of providing participants or their LARs an ongoing source of information understandable to them.

2.15.3 Documentation of Translated Consent and Short Form:

1. The consent process should be documented in the study records and the participant's medical record, if the information is relevant to their medical care. Information about who was present (in-person/remote), and whether participant had questions and time to consider participation should be included.
2. If informed consent takes place remotely, there must be a process in place to obtain signatures from the appropriate parties and the procedure documented in the protocol.
3. Translated Consent: The participant must be given a signed copy of the translated consent form. The original consent document should be placed in the participant's research record.
4. Short Form: The participant must be given signed copies of **both** the English version of the consent form **and** the short form consent document as well as the translated HIPAA Authorization form. The original signed English version of the consent form with the original signed written translation of the short form document attached should be placed in the participant's research record. Once the translation of the full informed consent form is completed, a copy must be given to the participant, and this should be documented in the participant's research file.
    a. If the consent form includes optional questions, participants should be re-consented and all appropriate signatures should be documented. If there are no optional questions, obtaining additional signatures is not necessary.
5. The consent documents should be placed in the participant's medical record, if the information is relevant to their medical care.
6. The research record should document the use of an interpreter.
7. The following signatures are required:

Translated Consent	
Involved Parties	**Signature Required**
Participant	Translated Consent Form
Person obtaining consent	Translated Consent Form

Short Form	
Involved Parties	**Signature Required**
Participant	Translated Short Form Translated HIPAA Authorization Form When the translation of the full ICF is provided to the participant post hoc, no signatures on the translation of the full ICF are required unless the participant now consents to optional questions. Documentation of providing the full translation must be in the participant's research file.
Person obtaining consent	English Consent Form
Witness	Translated Short Form English Consent Form
Interpreter	None (unless the Interpreter serves as witness. Note: Interpreter IDs cannot be used in lieu of a signature.)

2.15.4 Optional Procedures

A short form consent document cannot be used to obtain informed consent for optional research procedures. A fully translated consent form in the participant's native language must be submitted to the IRB for review if participant consent for optional procedures is needed. If there is insufficient time to translate the consent form, study teams cannot obtain consent for optional procedure using the short form. In this case, study teams should document in the study records that optional procedures were not presented to participants. Once the study team has had the opportunity to translate the consent form, they may go back and obtain consent for optional procedures from participants.

2.15.5 After Initial Consent

Because informed consent is an ongoing process, issues related to the participant's ability to understand and ask questions should continue to be considered throughout the study, and not just at the time of initial consent. Research teams are expected to include an appropriate interpreter for subsequent study visits to ensure that participants have an opportunity to ask questions and receive relevant study information. Translated informed consent documents and study materials should be made available throughout the course of a participant's involvement in the research.

2.15.6 Use of Interpreters

When consenting participants using the translated consent or short form, the IRB requires that the interpreter come from the pool of experienced medical interpreters available through Interpreter Services. The IRB will consider approving an exception to the requirement to use an interpreter from Interpreter Services on a case-by-case basis.

If the Principal Investigator or a member of the research team with a medical background is a native fluent speaker of the participant's language and their qualification to interpret is described in the protocol and approved by the IRB, they may serve as the interpreter.

For minimal risk studies, a study staff member or healthcare professional may serve as the interpreter with IRB approval. If you would like to use this option, provide a description (in the "Informed Consent" section of the Detailed Protocol or Site Addendum attachment) of the individual and their credentials which make them an appropriate person to provide this translation.

2.15.7 Use of Translator Services

Individuals who translate study documents must be qualified to perform the translation. A translator's attestation of accuracy should be submitted in Insight.

For more than minimal or minimal risk studies that are a) FDA regulated, b) industry-funded, or c) involve multiple sites, the written translation may be done by Mass General Brigham approved translation vendors or other qualified person or service. Documentation of certified translation, such as the certificate or similar indication of translation certification must be included with the translated documents when submitting to the IRB for review and approval. More than minimal risk studies involving a single site must follow the above process.

For single site minimal risk studies that are not FDA regulated or industry funded, written translations may be performed by an individual considered by the Principal Investigator to be qualified to perform the translation. The qualifications of the translator must be described and presented to the IRB (e.g., native speaker, certificate of translation, training and/or experience in medical translation). The IRB will assess whether the translator's background is appropriate based on the study risks and complexities of study procedures.

Minor changes to IRB approved translated consent form may be made by bilingual coinvestigators for minimal risk

studies with prospective IRB approval. These changes may include minor corrections to the consent form, advertisements, data collection forms, recruitment letters or other study documents. The IRB Chair or designee will determine whether the changes qualify as minor or major modifications. The qualifications of these individuals must be described to the IRB.

The IRB may use its discretion and allow other bilingual study staff to translate approved study documents.

2.15.8 Translated Study Documents

All documents that will be used with participants must be translated. These may include:

- Verbal consent scripts
- Written informed consent documents
- Assent forms
- Information sheets
- Recruitment materials
- Surveys/questionnaires/interview guides
- Instructional materials
- Other documents as requested at the discretion of the IRB

In the interest of efficiency, it is recommended that the foreign language translations be submitted to the IRB by amendment after initial approval of the English versions.

2.15.9 Minimal Risk Studies with Verbal Consent

2.15.9.1 Expedited Research

If a study is approved to obtain verbal consent using an information sheet and investigators intend to enroll participants who do not speak English, investigators can translate the information sheet or use a short form in the potential participant's language. Short form templates without signature lines are available for use in expedited research and can be found on Navigator. The request to use short forms to enroll non-English speaking participants must be reviewed and approved by the IRB. When the short form is used, the consent process must include the text of the English version of the information sheet presented orally through an interpreter fluent in English and the language understandable to the participant. This consent process should be described in the protocol. Study teams should document all the relevant circumstances surrounding the consent process in the participant's study records. For additional information, refer to the Use of a *Written Translation of the Short Form Consent Document* and *Use of Interpreters and Use of Translator Services* sections above. If the study involves obtaining, accessing, using or disclosing identifiable health information, a stand-alone HIPAA Authorization in the participant's/LAR's language must be used in addition to the short form.

The English information sheet can also be translated if the study team expects to enroll individuals who do not speak English. If there are limitations to obtaining a translation, the reasons should be documented in the protocol. The Principal Investigator (or other member of the study staff with PI-delegated responsibility for obtaining informed consent) must present the Information Sheet orally to the participant through an interpreter fluent in English and the language understandable to the participant. This process should be described in the protocol. Study teams should document all the relevant circumstances surrounding the consent process in the participant's study records. Refer to the Use of Interpreters and Use of Translator Services above.

2.15.9.2 Exempt Research

If the study team expects to enroll individuals who do not speak English, the information sheet should be translated.

There is no short form available for exempt research.

2.15.9.3 Studies Conducted at Non-US Sites Where MGB is Engaged in the Research

Foreign language consent documents which are approved by the local ethics committee should be submitted to the MGB IRB along with an English translated copy.

2.15.9.4 Frequently Asked Questions (FAQ)

When a medical interpreter is used in conjunction with the translated version of the English version of the consent form, can the medical interpreter participate by phone or videoconference?

Yes. The medical interpreter may participate by phone or videoconference because they are not required to sign the consent form. However, participation of the medical interpreter by phone or videoconference should be documented in a documentation of informed consent process checklist/clinic chart/progress note/ or other source document. The investigator should be sure that the connection is clear and that technical problems do not interfere with the consent discussion.

When informed consent is obtained using the 'short form' written consent document, can the medical interpreter interpret by phone or videoconference?

Yes. A medical interpreter must be present either physically or by phone or videoconference to interpret, in the participant's language, the researcher's oral presentation of the English version of the consent form.

Can a family member serve as the interpreter when using the 'short form' written consent document or the translated version of the entire English consent form?

No. Family members may not be impartial and are not professionally trained medical interpreters. Family members may not have knowledge of medical terminology or the confidence to ask for clarification, and participants may not feel comfortable revealing certain sensitive personal or medical information through family members. Also, rather than interpret, family members often tend to speak for the participant, removing the participant from the decision-making process. Consequently, misunderstandings may inadvertently occur. Professional, trained medical interpreters should perform this important task.

How do I get research consent forms and other study-related documents translated into other languages?

Interpreter Services has provided a list of resources which can be found on Research Navigator: https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Translation-Resources.pdf (Mass General Brigham internal only link).
Interpreter Services can also serve as a liaison with approved outside vendors who have agreed to be contacted for translation services. Prices vary. Funds to pay for translation of research consent forms and other study documents should be built into research proposal budgets.

Can a bilingual investigator* obtain informed consent using the 'short form' written consent document or a translated version of the entire English consent form?

Yes, with prior IRB approval. When the investigator is fluent in the language understood by the participant AND English, they may obtain informed consent with prior IRB approval. Consideration should be given to how the

investigator acquired their language skills; for example, did they receive medical training in that language. When a bilingual investigator obtains informed consent using the 'short form' written consent document, there must be an independent witness to the presentation who is fluent in English. In addition, the witness must, at a minimum, have sufficient proficiency in the language of the oral presentation to be able to attest to the information that was presented orally to the prospective participant. Whenever the investigator obtains informed consent in another language, this should be appropriately documented in the study records.

*Note: Investigator refers to a member of the study staff approved by the Mass General Brigham IRB to obtain informed consent for a particular study.

Why does the Mass General Brigham IRB require that investigators use a medical interpreter from the hospitals' Interpreter Services?

The medical interpreters available through Interpreter Services are qualified by training and experience to interpret oral presentations of medical information to patients in clinical settings. Medical interpreters are tested and trained on the following:

- Oral and written fluency in English and at least one other language
- Interpreting skills and cultural competencies
- Medical terminology
- National Standards of Practice for Medical Interpreters
- National Interpreters' Code of Ethics
- Department and Hospital Policies and Procedures
- HIPAA

Researchers could also use medical interpreter services coordinated by the hospitals' Interpreter Services (e.g., use of Interpreter Phone on a Pole or IPOP).

Does the Mass General Brigham IRB ever grant an exception to the requirement to use a medical interpreter from Interpreter Services?

Yes. The Mass General Brigham IRB will consider exceptions on a case-by-case basis. Investigators desiring an exception must submit a formal request for approval of a protocol exception.

How do I request a medical interpreter?

Please contact Interpreter Services at your hospital to request a medical interpreter.

Will the hospital or the IRB cover the cost of using medical interpreter services or obtaining written translations of study documents?

No. Your study fund will be billed for this service. The IRB cannot pay for this. Build these funds into your research proposal budgets in future. Consider asking your sponsor for additional funds to cover this important service, which is necessary to enroll participants from among the diverse populations we see at our hospitals.

In the 'short form' consent process, will the medical interpreter perform a sight translation of the English version of the consent form?

No. The investigator is responsible for presenting the information in the English version of the consent form

orally to the participant. The interpreter will interpret the investigator's presentation. The investigator should direct their presentation to the participant, not to the interpreter.

In the 'short form' consent process, must the investigator present the entire English version of the consent form to the participant?

Yes. The investigator must present all of the information in the English version of the consent form. Investigators should present the information in simple lay terms (not "medicalese") and should encourage questions from participants and family members.

If using the 'short form' consent process, must the full informed consent form be translated and provided to the participant/LAR?

Yes. Following participant enrollment using a short form, investigators must obtain a translated copy of the IRB-approved English version of the consent form promptly and submit it to the IRB for review and approval. Once the translated consent form is approved by the IRB, the investigator must provide it to the participant or LAR as soon as possible.

Should the use of a medical interpreter/bilingual investigator during the 'short form' consent process be documented?

Yes. To further document and facilitate clarification of any future questions regarding the consenting process, the investigator should include the following information in a clinic chart/progress note/other source document:

- that **XX** study was presented orally to the participant in **specify language** through a medical interpreter OR by me because I am fluent in **specify language** and English;
- the participant's questions were answered (if any);
- participant agreed to participate and signed the 'short form' written consent document;
- a copy of the English version of the consent form signed by the investigator and witness was given to the participant; AND
- a copy of the 'short form' written consent document signed by the participant and the witness was given to participant.

This note should be signed and dated by the person obtaining consent.

When the 'short form' written consent document is used to obtain informed consent, which of the original signed consent documents are retained in the participant's research records?

The original signed English version of the consent form WITH the original signed written translation of the 'short form' document attached should be placed in the participant's research record.

When informed consent is obtained by a bilingual investigator using the 'short form' consent document, should the bilingual investigator sign the 'short form' written consent document?

No. The investigator should sign the English version of the consent form and the witness should sign the 'short form' written consent document AND the English version of the consent form.

When the entire English version of the consent form is translated into the language understood by the participant and used to initially consent the participant, do both the participant and investigator sign the translated consent form?

Yes. The translated consent form must be signed by both the participant AND investigator obtaining informed consent. A witness signature is not required; however, a medical interpreter must be available to interpret the consent discussion / questions and answers about the research. Participation by the medical interpreter in the consent process should be

documented in the participant records or clinic chart/progress note/other source document as applicable.

Can informed consent be obtained from a non-English speaking participant if there is a medical interpreter present BUT there is no 'short form' written consent document translated into the language understood by the participant on the Mass General Brigham IRB website?

No. In order to obtain and document informed consent of participants who do not speak English, you must have a 'short form' written consent document in the participant's language. The 'short form' explains that informed consent is being obtained for research and that, when applicable, addition elements of informed consent will be described to them orally and that their participation is voluntary. The Mass General Brigham IRB will have the 'short form' written consent document translated in additional languages upon request. Timeframe for completion of the translation will vary depending upon available resources. Available 'short form' written consent documents can be found on Research Navigator: https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb/Pages/Non-English- Consent.aspx#Short Forms

Can a family member who speaks English provide informed consent for a non-English speaking participant who is legally competent to give informed consent to participate in research?

No. When a participant is legally competent to give informed consent to participate in research, they must give their own consent.

What is the consent process when a participant speaks English but lacks the capacity to consent and a legally authorized representative (LAR) does not speak English?

If the LAR does not speak English, the same process for obtaining consent from non-English speaking participants would apply as described in the guidance above.

Can the Medical Interpreter Waiver Form (for informed consent discussions) ever be used for research?

No. The Medical Interpreter Waiver form can only be used for informed consent discussions for clinical care, not for research.

Must a medical interpreter be used for study visits or follow-up phone calls?

Yes. You will need to enlist the services of medical interpreters throughout the course of the research. When you think about enrolling someone who does not speak English, consider carefully whether you can accomplish this throughout the study. On occasion, safety issues may preclude enrolling non- English speakers.

Must study questionnaires/instruments, information sheets, and other study documents be translated into the participant's language?

Yes. Investigators are expected to provide participants with a written translation of all study documents that are given to participants to ensure that they can follow study directions and participate safely in the study. Submit translator's attestation of accuracy as an "Other" attachment in Insight.

3 Recruitment

3.1 Recruitment of Participants Identified Through Private Medical Information

Recruitment efforts frequently target individuals known to have a specific medical condition. Medical records, patient registries, clinical databases and referrals from treating physicians can be useful resources to identify potential participants; however, it is essential to take special precautions to ensure that patient privacy is protected and that the individual patient is appropriate to participate in the research.

3.2 Inpatient Recruitment

Through the review of medical records, study teams may identify potential participants who are receiving inpatient care. The study team cannot directly approach the potential participant. Two steps need to occur prior to approaching the patient about research recruitment. Research staff should first discuss this with the primary clinical team to ensure it is clinically appropriate to approach the participant about research participation. If so, a staff member known to the patient from clinical care (i.e., any staff member known to the participant from clinical care, it does not have to be the treating clinician) or administrative staff should ask the patient if they are interested in speaking to research staff prior to research staff direct approach.

3.3 Outpatient Recruitment

Study teams should obtain appropriate leadership approval if the study proposes to recruit from outpatient clinics. This documentation should be submitted with the IRB submission, along with a description of the workflow for how recruitment will occur in the outpatient setting. Study teams can directly approach potential participants in outpatient clinics if the clinic has provided approval. Flyers can be distributed or placed in waiting rooms with appropriate permissions. To protect patient privacy and confidentiality of data, recruitment should always occur in private settings and not in waiting rooms.

When recruiting within one's department, researchers should follow department policies and obtain approval as needed. For instance, study staff "cold-calling" patients in the waiting room of the clinic or directly approaching people without consent from clinical team or administrative staff in the waiting room may not be permitted by the department.

3.4 Guidelines for Use of Recruitment Letters and Research Notifications

3.4.1 Research Invitations

Research Invitations is an opt-out model for recruitment of Mass General Brigham patients to research. Research Invitations allows research recruitment of all Mass General Brigham patients unless they opt-out. Research Invitations method is required along with the use of Research Invitations templates when researchers recruit MGB patients via Patient Gateway or when sending mailed letters to patients. In-person recruitment in outpatient or inpatient areas do not require the use of Research Invitations if the in-person contact is the initial contact.

The IRB provides templates that may be customized with study-specific information which can be sent to patients through Patient Gateway or via US mail or Targeted Research Announcements. A targeted research announcement is a

message that appears on the Patient Gateway Research page for patients who meet specific research eligibility criteria. Each announcement is accompanied by a clickable button that allows the recipient to indicate "I'm interested" (or "No thank you"). Once a research announcement is sent, the Patient Gateway user receives an email notification that includes a link that will take the patient directly to the message after logging in. The announcement is also accessible by clicking on the Main Menu in Patient Gateway and selecting "Research Opportunities." Study staff must ensure that patients have not opted out of receiving Research Invitations.

The use of the Research Invitations letter should be limited to a maximum of three times and this should be specified in the IRB submission (e.g., a second letter will be sent to participants if we do not receive a response after one week). The use of Research Invitations must be described in the "Recruitment Procedures" section of the Site Addendum or Detailed Protocol. State in the Site Addendum or Detailed Protocol that Research Invitations will be used for direct recruitment of any eligible participants who have not opted out of receiving Research Invitations. Specify that patients who opted out will be filtered out of the recruitment list (e.g., from RPDR, Epic) and they will not be sent the Research Invitation. Also specify that the PI will conduct ongoing monitoring of patient responses to ensure that your selection criteria are identifying the right patients and that complaints about this method of recruitment will be submitted to the IRB as an Other Event. The Research Invitations templates can be found at this link: Pages - IRB Forms and Templates (sharepoint.com). The templates cannot be modified except in the designated areas. If mailing recruitment letters (e.g., for a single survey study), a copy of the survey and information sheet can be mailed along with the Research Invitation. Consent or information sheet language cannot be included in the letter template itself.

Research Invitations can be sent via email only if researchers have obtained prior consent from participants to use their email to be contacted for future research opportunities. How this permission was obtained should be described in the study protocol. Researchers cannot obtain email addresses from Epic or Patient Gateway for recruitment purposes. They must have prior permission from patients to use their emails, for example, from interaction as part of previous research participation. Study teams should provide the protocol number(s) where this option for future contact was approved so that IRB staff can verify that the use of email was approved. When email Research Invitations have been approved as described above, follow-up of participants via email is permitted and should be limited to 3 times with a 1-week interval between sending emails.

Phone follow-up can be permitted only if the optional opt-out language in the Research Invitations letter template (i.e., " If we do not hear back from you within one week, we may call you.") has been included in the initially sent Research Invitation. The IRB does not allow "cold-calling" patients on the phone to recruit them.

A QR code can be used for Research Invitations. The code can link to a flyer or survey.

Text messaging for Research Invitations is not permitted at this time.

Patients may opt out of receiving Research Invitations directly in Patient Gateway, through the Rally recruitment website, or by contacting the Mass General Brigham Research Navigator Office. Patients who opt out of receiving Research Invitations may not be contacted by mail or through Patient Gateway to be recruited for research studies and their clinical provider cannot override this decision. Researchers may continue to recruit in-person or through public advertisements regardless of a patient's opt-out decision.

Care should be taken to ensure that letters are properly addressed to avoid delivery to an incorrect party and return postcards must not contain information regarding the patient's medical condition, medication or diagnosis.

Recruitment letters and research notifications must be submitted for review and approval by the IRB.

Research Invitations should not be used for in person recruitment or to recruit non-MGB patients. Research Invitations cannot be used to contact MGB patients who have opted out. If patients opt-out of receiving Research Invitations, a patient's provider cannot "override" the patient's decision. The opt-out process will only apply to Research Invitations

sent to adults. The IRB would not normally approve invitations being sent directly to children or minors. Typically, a letter to recruit minors would be sent to the parent. If the parent has opted out of receiving Research Invitations, then they should not be sent Invitations for themselves or their children.

The use of co-signed (e.g., co-signed by primary care provider) personalized recruitment letter is not permitted. Investigators must use the Research Invitations templates.

3.5 Recruitment of Participants from Among the Investigator's Own Patients

When recruiting potential participants from among their own patients, investigators must consider the possibility that their patients may feel obligated to participate because they are being asked by their treating physician. Investigators should reinforce with their patients that participation is voluntary, that they do not have to participate, and that the decision not to participate will not affect their care, now or in the future. Further, the IRB asks researchers to describe any plans that are in place to minimize the possibility that patients will feel obligated to participate, e.g., initially contacting patients about the research in writing and allowing patients to make further inquiries if they are interested Please refer to the section on Informed Consent of Research Participants for additional information.

3.6 Clinical Referrals

Physicians or treatment providers can notify their patients about research studies and refer them to study teams to obtain information about a study. This can be done in person or in the course of routine medical care or by providing a flyer or other IRB-approved written recruitment materials to patients.

If information, including contact information, about the patient needs to be shared by a Mass General Brigham provider with a Mass General Brigham research team for recruitment purposes, investigators have the option to use the Authorization to Release Contact Information for Recruitment or request a preparatory to research determination from the IRB. The Authorization must be obtained from the patient prior to sharing patient information with the study team to initiate contact. This Authorization is not needed if the potential participant is provided with information about the study and they are asked to initiate contact with the study team. This Authorization does not need to be submitted to the IRB, but the recruitment section of the protocol must describe how this Authorization will be used to recruit potential participants. The signed Authorization should be maintained in the study records to document compliance with recruitment procedures. It is the research team's responsibility to obtain the completed Authorization from the Referring Provider, not the participants. If investigators would like to obtain a preparatory to research determination, the recruitment form in Insight should be revised to request this determination. Under the preparatory to research pathway, referring providers must, during the course of their clinical encounter: a) discuss with the patient that there is a study for which they may qualify or be interested, b) identify the name of the study and the PI, c) obtain verbal permission to provide their contact information to the PI/research team and minimal information necessary so that the research team can provide details about the study and answer questions, and d) communicate the contact information to the research team in a secure manner.

When seeking assistance of colleagues in referring patients to you, include additional information about study design, placebo, risks, and benefits. Provide enough information for colleagues to reasonably present a study to their patients.

When external institutions contact MGB investigators to approach MGB patients for research and share their contact information, MGB investigators are recommended to consult with their department/clinical unit where the recruitment takes place and if applicable, the local institutional research compliance officer. MGB researchers or providers can refer MGB patients to research being conducted at another institution, if approved by their department. Patients could be informed about studies and directed to contact external study teams. If flyers or other external study materials are shared, these documents must be approved by the

external institution's IRB. Posting of flyers is at the discretion of department/clinical unit or local research compliance approval, as applicable. MGB personnel cannot share any information about patients with another institution for recruitment purposes.
For MGB investigators recruiting at external sites, investigators are recommended to follow the procedures at the recruitment site for any site-specific approval that may be needed. The study's recruitment plan must be described in the detailed protocol or site addendum.

3.7 Mass HIway and Care Everywhere

Mass HIway and Care Everywhere cannot be used for research purposes. Researchers should not attempt to obtain patient consent for using either of these methods as the patient consent would not be valid and cannot override institutional agreements in place that restrict use for research. If external medical records are required, the study team must obtain informed consent and HIPAA Authorization from the participant to request medical records from another provider and obtain them through methods other than Mass HIWay or Care Everywhere. Care Everywhere cannot be used by the researcher to request records for a chart review or any other purpose. However, if there is data in MGB Epic that was already brought into the record for clinical purposes, then it can be used.

3.8 Recruitment of Potential Participants through Advertising

Under Federal regulations, the Mass General Brigham IRB must review and approve methods used to recruit participants, one of which is the use of advertisements in various media. The Mass General Brigham IRB has prepared the following guidelines to assist investigators in the preparation of advertisements. The text of all direct advertising for research participants, i.e., advertising that is intended to be seen or heard by prospective participants, must be reviewed and approved by the IRB prior to distribution, posting, publication, or broadcasting.

Unlike potential participants identified through private medical information, those responding to advertisements have initiated the first contact and therefore, have implicitly given their permission to be contacted by study staff.

3.8.1 Guidelines for Advertisements

Direct advertising for research participants, i.e., advertising that is intended to be seen or heard by prospective participants, must be reviewed, and approved by the Mass General Brigham IRB prior to distribution, posting, publication, or broadcasting. Direct advertising includes, but is not limited to, notices aimed at recruiting research participants that investigators intend to place in newspaper, radio, TV, bulletin boards and the internet. Advertisements developed by coordinating centers for multicenter study recruitment, study sponsors or Contract Research Organization (CRO), also require Mass General Brigham IRB approval if the Mass General Brigham sites intend to enroll from among the pool of prospective participants responding to these ads. In addition, notices directed to clinical colleagues seeking study referrals require Mass General Brigham IRB approval. These include, but are not limited to, letters, electronic and other postings, or notices in professional publications.

Requests for approval of advertisements should specify the mode of advertisement and where the advertisement is going to be placed/posted, e.g., newspapers, internet, public transportation. The Mass General Brigham IRB must review and approve the final copy of advertisements as the ad will appear in the newspaper or other print/multimedia form so the reviewer can assess the visual impact, emphasis, and graphic message. Similarly, the Mass General Brigham IRB must review and approve the final copy of the script of the audio/video tape that will be broadcast on radio, television, or the internet. **Note: Audio/video taped ads (for radio/television broadcast) cannot be uploaded in Insight. Contact the IRB office for assistance.**

Advertisements should include:

- Name of research facility and/or location;
- Purpose of the research
- Eligibility criteria (briefly stated);
- Benefits of participation; e.g., no-cost health examination (briefly stated)
- Duration of study and number of visits;
- Payment, if any, for participation;
- Contact person for more information;
- The word "research" somewhere prominent in the advertisement.

When a study includes minors, the advertisement must indicate that parental or guardian permission is required to recruit and/or enroll this population unless the IRB has granted a waiver of parental or guardian permission for screening and/or enrollment.

Advertisements should not:

- Claim, explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation or that the test article (drug, biologic, device) is known to be equivalent or superior to any other drug, biologic or device;
- Include references to "new treatment", "new medication" or "new drug" without explaining that the drug, biologic or device is investigational;
- Emphasize no cost treatment if a placebo is involved (you don't need to explicitly state that placebos are used in ads) and/or the protocol involves drugs, biologics, or devices not FDA approved for the condition under study;
- Feature monetary compensation as a lead in before the description of study purpose and procedures;
- Emphasize monetary compensation by using bolded italicized, underlined, or enlarged fonts;
- Include offers of compensation from a sponsor that would involve a coupon good for a discount on the purchase price of the product once it had been approved for marketing. All advertisements should be tastefully composed and not inappropriately emphasize monetary remuneration.

The use of logos (e.g., Mass General Brigham, Harvard Medical School) must comply with institutional policies. Posting advertisements in hospital facilities may require additional approval from the specific department, clinic or facility.

For Single IRB studies where the Mass General Brigham IRB is the reviewing IRB for multiple sites, advertisements intended for use at multiple sites should be submitted in a template format with generic placeholders for the site name and study contact information. This allows for submission and IRB approval of the advertisement once rather than per site.

3.9 Social Media

Social media can be used to recruit participants if approved by the IRB. Researchers should carefully consider whether social media is an appropriate and effective means of reaching their target study population, and design recruitment methods that adhere to ethical guidelines. Investigators need to provide the IRB with the names of the platforms they intend to use as well as all the advertisements they plan to use on these sites. It is the researcher’s responsibility to make sure that the advertisements adhere to the rules and policies of the

platform.

IRB-approved advertisements may be posted on Facebook or other sites. Screening of participants cannot be conducted on the social media platform to protect the privacy of potential participants. In addition, study teams cannot communicate with potential or enrolled participants via social media. Study teams are advised to turn off post commenting and direct messaging, whenever possible, and/or to develop standard language (to be submitted to and approved by the IRB) to notify participants that the research team cannot communicate via social media and how to contact the research team outside the platform.

Investigators are responsible for ensuring compliance with Mass General Brigham's Social Media policy available on Archer.

3.10 Recruitment of Employees or Students in Investigator's Department

Studies of volunteers who are directly supervised by the investigator(s) or who are the investigator's students should be avoided and will usually be disapproved by the IRB. In this setting, there are confidentiality problems and issues of coercion or obligation (either real or perceived) which are best avoided entirely. It is acceptable to advertise for volunteers in approved areas in the investigator's department or within the hospital (following hospital guidelines) and allow individuals in the department who are not directly supervised by the investigator(s) to participate in research studies.

3.11 Other Recruitment Considerations

The guidelines listed above may not be applicable to every situation that arises in the research process. Carefully justified alternative approaches will be considered on a case-by-case basis. The IRB staff will offer guidance to investigators upon request.

3.12 Recruitment of Harvard Medical School Students

For the mutual protection of the student, investigator, and the Medical School, any protocol in which Harvard Medical School (HMS) students are intended to be recruited must be submitted to the Program in Medical Education (PME) within the Office of Education Scholarship at HMS for review and approval before activation. Investigators must comply with the requirements of the student's home institution with regard to human research requirements.

3.13 Incentives and Rewards for Recruitment of Patients and Referral to Clinical Investigators

Timely enrollment of patients into approved trials is desirable, but care must be taken to ensure that the interests of patients are not jeopardized during the recruitment process. Cash payments or other financial or non-monetary incentives to physicians for referral of patients, otherwise known as "finder's fees", pose a conflict of interest and are not permissible. Financial incentives to physician-investigators to accelerate enrollment of their own patients in their own clinical trials pose a similar conflict of interest and are not acceptable. The IRB requires full disclosure of any financial arrangements that may encourage physicians to recruit patients for research participation that may not be in the patient's best interests. In some special circumstances, physicians who are not formally listed on the protocol may be performing

specific research-related activities (such as conducting screening examinations or tests) but solely in the role of service providers. These physicians may be reasonably compensated for their time and effort. Such arrangements should be clearly detailed and justified in the research protocol.

3.14 Snowball Sampling

Snowball sampling involves asking research participants to assist investigators in identifying and recruiting other potential participants. Snowball sampling may be used to recruit hard to reach participant populations. This method may involve asking study participants to provide names and contact information of another individual without their permission. The IRB will consider use of this method on a study-by-study basis. Investigators must provide adequate justification for the use of snowball sampling in the context of the study and participant population. Investigators must describe the steps taken to minimize the risk of violating an individual's privacy and to minimize potential pressure on an individual to participate. In addition, the study participants should be informed that they will be asked to assist with recruitment and be given the option to decline participating in the recruitment process. Incentives or compensation for referrals may be acceptable for studies that involve a hard-to-recruit population. Investigators should provide sufficient justification to support this request. The IRB will consider these requests on a case-by-case basis.

The IRB will consider the investigator's justification along with the risk level of the study, and why it may be challenging to recruit the participant population. The IRB must carefully consider the privacy interest of participants.

Snowball sampling may be acceptable to use for studies enrolling clinicians as participants.

3.15 Alternatives to Snowball Sampling

The IRB recommends providing information to participants such as flyers, letters, or other informational documents so they can share information about the study with other prospective participants. These potential participants can contact researchers on their own accord if they are interested in participating in the study.

3.16 Pre-Screening of Research Participants During Recruitment

Identifying potential participants to recruit for research often involves pre-screening and screening activities. Pre-screening of potential participants over the telephone, in person, or via completion of an online survey to determine their initial eligibility for and interest in a study is a common strategy in the recruitment process and occurs at the outset of a study before informed consent is obtained. Screening activities, on the other hand, take place after informed consent is obtained. Source documentation of both pre-screening and screening activities must be maintained, although for pre-screening there are restrictions on retaining identifiers since pre-screened individuals have not yet provided informed consent and HIPAA authorization for study participation. In contrast, since screening activities occur after participants have provided informed consent and HIPAA authorization, retention of identifying information is permitted even if post-consent screening activities determine that the participant is not eligible for the research study.

When pre-screening, investigators must adhere to the following guidelines to protect the privacy of the potential participant and the confidentiality of information collected about the participant. Only information pertaining to the participant's eligibility should be collected during pre-screening, as noted in Section II, below. Information that is not directly related to assessing eligibility should not be collected.

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule applies if protected health information (PHI) about patients will be accessed, collected, used, or disclosed during pre-screening. The HIPAA Privacy Rule requires a signed Authorization from prospective participants for the investigator to use and/or disclose their PHI for research purposes. In some cases, the IRB may grant a complete waiver, partial waiver or alteration of HIPAA Authorization as noted below:

- A complete waiver of HIPAA Authorization occurs when the IRB determines that obtaining a signed Authorization from participants will not be required for the investigator to use and/or disclose PHI for a particular research project (e.g., secondary use research of medical records).
- A partial waiver of HIPAA Authorization occurs when the IRB determines that the investigator does not need to obtain a signed Authorization to access PHI to pre-screen and recruit prospective participants for research.
- An alteration of HIPAA Authorization occurs when the IRB determines that some of the required elements of an Authorization do not need to be included. This may apply to studies using a Fact/Information Sheet. In these studies, the IRB may approve an alteration to remove the requirement for participants to sign and date the Authorization form or receive a signed and dated copy of the Authorization.

The HIPAA Privacy Rule requirements are covered in more detail in section IV below.

3.16.1 Identifying Potential Participants

Investigators use various methods to identify potential participants for pre-screening such as the use of medical records, advertisements and flyers, participants who have provided consent to be contacted for future research and Research Invitations if patients have not opted-out from being contacted. These recruitment procedures must be selected in Insight, described in the appropriate section of the Detailed Protocol, and be approved by the IRB prior to implementation. Those participants who respond to advertisements or recruitment letters have implicitly given their permission to be contacted. Refer to the IRB's guidance on Recruitment for other acceptable methods of obtaining an individual's permission to be contacted, particularly those who have been identified through their private medical information such as medical records or patient databases.

3.16.2 Acceptable Information to Gather During Pre-screening

Questions appropriate for pre-screening address the specific inclusion/exclusion criteria for the study and other issues of suitability, for example, an individual's ability to come to the research site multipletimes. It is not appropriate at this point in the process to gather information that is not directly related to assessing eligibility and suitability (e.g. complete medical histories). Also refer to Conducting Pre- screening in Person (III.C.) below for guidance on performing very limited routine clinical proceduresas part of pre-screening.

3.16.3 Methods for Conducting Pre-screening

3.16.3.1 Conducting Pre-screening over the Telephone

At the beginning of a phone pre-screening conversation, potential participants should be informed ofthe nature and sensitivity of the questions, asked whether this is an appropriate time for them to answer these questions, and told how long the phone call is expected to take. A phone pre-screening template is available on Navigator.

If the study includes remuneration, potential participants should be informed at the outset about any remuneration they may receive for their time and effort. Refer to the Remuneration and Reimbursement for Research Participants policy for more information about payment.

The telephone pre-screening script and pre-screening questionnaires or screening tools that will beused must be submitted to the Mass General Brigham IRB Office for review. Participants should be offered the option of completing the pre-screening in person, if they wish and if it is feasible.

3.16.3.2 Conducting Pre-screening Using an Electronic Platform such as REDCap

Study teams may wish to pre-screen participants using an electronic platform such as REDCap. As with other recruitment methods, all details of the pre-screening process must be described in the protocol and/or Insight and be approved in advance by the IRB. Study teams should specify: the electronic platform that will be used, how the participants will be provided a link to the pre-screening questionnaire, the content of the pre-screening questionnaire, when and where (in-person or remotely) the participant will complete the pre-screening questionnaire, and any other relevant details.

Participant Self-directed Pre-screening, Study Enrollment and Study Participation

There are certain studies, for example survey studies with limited inclusion/exclusion criteria, where study pre-screening, enrollment, and participation are self-directed by participants using an electronic platform without any study staff interaction. For instance, eligibility criteria may be self-reported by participants during the pre-screening process and subsequently participants may be routed to provide consent and HIPAA authorization, and then complete study procedures/surveys. For such studies, there must be:

- A robust process to ensure that only those individuals who meet all eligibility criteria are permitted through to provide informed consent
- A robust process to ensure only those individuals who provide informed consent are permitted to complete study procedures
- Documentation on file of participants meeting all eligibility criteria outlined in the study protocol and providing informed consent for study participation.

Note: prior to implementing a participant self-directed process, PIs should consider carefully whether any eligibility criteria require study staff or licensed physician review and verification. If it's identified that certain eligibility criteria must be verified by qualified study staff, then study procedures/questionnaires may not be initiated until the verification process is complete and all eligibility criteria have been confirmed and documented.

3.16.3.3 Conducting Pre-screening in Person

Investigators may choose to conduct pre-screening in person, for example, if potential participants are finding out about research during routine clinical care or while visiting the hospital. All of the questionnaires and checklists that would be used during phone pre-screens are appropriate in this setting as well. Complete medical histories and screening physical exams are not considered acceptable pre-screening activities but rather part of actual research procedures and should be conducted only after an individual has provided informed consent. That said, it is acceptable to perform very limited routine clinical procedures as part of a pre-screen if (1) IRB has provided prior approval for doing so, (2) the procedures directly relate to eligibility determinations, and (3) an individual verbally consents to have them performed before signing a consent form for a study. For example, it would be acceptable to weigh an individual in order to ascertain whether they qualify for a dietary study or briefly view a pigmented lesion or a participant's skin type to see whether they qualify for a dermatology study. Such exceptions are made in the interest of the convenience of the research participant, if they agree. All pre-screening activities, including verbal consent for limited procedures and outcome of the limited evaluations must be documented in the study files. Complete physical exams, full body skin exams and any sample collection or laboratory testing must not be undertaken until a participant has given

informed consent and has signed the consent form. If a researcher plans to conduct pre-screening in person, the researcher needs to include that in the protocol and obtain a partial waiver of HIPAA authorization (see Section IV, below).

3.16.3.4 Conducting Pre-screening using Third Party Platforms

Use of third-party platforms for research recruitment must be described in the protocol and approved by the IRB. The use of these platforms may require a business associate agreement (HIPAA Central (sharepoint.com)). A service agreement may also be needed. Please contact MGB Supply Chain Management.

3.16.4 Collection and Retention of PHI During Pre-Screening

Study teams may want to retain identifiable health information collected during pre-screening for various reasons such as to avoid recontacting a person who has declined participation or did not meet pre-screening criteria (i.e., "failure log"), or to document that prescreening was conducted according to the study protocol. The amount of data retained should be limited to the minimum necessary to prevent risks associated with the loss of confidentiality of data.

Please note: If the intent of storing prescreening data is to contact people for future research, a new recruitment registry protocol must be submitted to the IRB, as well as a separate consent and HIPAA Authorization. Refer to the IRB's guidance on Repository Protocols.

Retention of PHI with a Partial Waiver of HIPAA Authorization
If an investigator plans to collect identifying information during the pre-screening prior to obtaining informed consent and HIPAA authorization, the investigator needs to include that in the protocol and obtain a partial waiver of HIPAA authorization from the IRB prior to accessing, collecting, using, or disclosing PHI for pre-screening and recruitment purposes. The requirement for a partial waiver of HIPAA authorization applies to pre-screening activities conducted over the phone, via REDCap, or in person. If researchers intend to retain identifying information for participants who do not pursue the study or enroll, researchers should describe why this is necessary.

Retention of Non-PHI

- Alternatively, it is acceptable to retain non-identifying information about individuals who are pre-screened for a study, but do not actually pursue the study or enroll. In fact, this is often desirable or even requested by industry or academic sponsors to obtain information about the entire pool of individuals interested or potentially eligible for the study. Pre-screening case report forms or electronic case report forms (CRFs/eCRFs) which did not capture identifying information should be retained with no further action.

Removal of PHI

- Pre-screening CRFs/eCRFs with identifying information which was collected without either (1) a partial waiver of HIPAA authorization from the IRB or (2) the participant signing the informed consent form and HIPAA authorization, should also be retained in research files, but must have identifiable information elements deleted, blacked out, or cut off as soon as it is clear that the individual will not be enrolled. Since permanent deletion in electronic recordkeeping systems is usually not possible, study teams should avoid collecting identifiable data elements in electronic systems without informed consent and HIPAA authorization, since it may be impossible to permanently delete them later.

3.16.5 Alternative Pre-screening Approaches

The guidelines listed above may not be applicable to every situation that arises in the research process. Carefully justified alternative approaches will be considered on a case-by-case basis. The Mass General Brigham IRB Office staff will offer guidance to investigators upon request.

3.17 Communicating with Research Participants

All communication methods used with research participants must be approved by the IRB.

3.17.1 Use of Email with Research Participants

Send Secure is the preferred option when communicating with participants by email. For Send Secure: The participant may need to register in the Send Secure system, create a password, and login to access their messages, depending on their email address/server. Non-secure email may be used to communicate with research participants, but only if they have been informed of and agree to accept the associated risks. Refer to the MGB IS policy *Requests to Receive Unencrypted Email* on Archer for information about institutional requirements that govern the use of Send Secure and how research participants can indicate their agreement to non-secure emails (Partners HealthCare GRC).

Mass General Brigham business must be conducted using institutional email addresses only. Non-institutional domains (e.g., Gmail) must not be used for research communications.

Confirmatory information about research appointments can be sent by email without formal IRB approval of that communication and process**.** A short email lacking medical information, or diagnoses may be sent without formal IRB approval, as exemplified below:

> Thank you for your interest in our research study. I'm writing to confirm your appointment with Dr. Smith on January 2, 20xx on the 6th Floor of the COX building at 2 pm. Please call me if you have questions or cannot make it.
>
> Jim Jones, Study Coordinator
> Cardiology Division, Massachusetts General Hospital. Phone number, email.

Please include the minimum necessary information in such communications. If research consent forms or other study information which imply or state diagnoses will be attached in emails, the approved IRB protocol must describe this.

Specific information such as Social Security numbers (SSN's), financial account numbers (credit card numbers or account numbers) cannot be sent by unsecured email even if it is requested by a participant.

Email sent through REDCap is not secure unless you insert "Send Secure" in the subject line or use REDCap's Survey Login Feature as described below. Survey links sent though REDCap to a participant are secured once accessed, but the email itself is not.

For the Survey Login Feature: Remove all medical content, diagnoses, study descriptors, medical questions, or any other PHI from the REDCap email survey invite. Move all this information into the REDCap survey itself. The participant will need to authenticate (Log in) to the survey before they can view and complete the survey. The respondent will log in to the survey by entering one or more known values for fields in the project (up to three) – e.g., last name, date of birth.

These values must already be saved in the respondent's record in the project. Those values may have been entered or uploaded by a project user/admin or may have been entered on a previous survey by the respondents themselves.

3.17.2 Use of Texts with Research Participants

Texting with research participants is permitted but must be prospectively approved by the IRB and RISO and participants must agree to the risks of texting.

The following language must be added to the research study informed consent. When the IRB waives informed consent documentation, the following language must be added to the Information/Fact Sheet.

Text messages by mobile/cell phones are a common form of communication. The _____ (*insert study name*) research study involves sending you text messages that are relevant to the research study. Texting over mobile/cell phones carries security risks because text messages to mobile/cell phones are not encrypted. This means that information you send or receive by text message could be intercepted or viewed by an unintended recipient, or by your mobile/cell phone provider or carrier. Below are some important points about texting in this research study.

- Text messages are not encrypted, and therefore carry security risks. This research study and Mass General Brigham are not responsible for any interception of messages sent through unencrypted text message communications.
- You will be responsible for all fees charged by your carrier's service plan for text messaging. This research study and Mass General Brigham are not responsible for any increased charges, data usage against plan limits or changes to data fees from the research texts *(Include language if participants are paid/given stipends to cover potential charges).*

- Text messages will only be read [*Insert information specific to the research study, e.g. text messages will only be read during regular business hours. Texts sent on nights or weekends will not be read until _____].*

- Text messaging should not be used in case of an emergency. If you experience a medical emergency, call 911 or go to the nearest hospital emergency department.

- You may decide to not send or receive text messages with staff associated with this research study at any time. You can do this in person or by sending the research number a text message that says "Stop Research Text."

- Your agreement applies to this research study only. Agreeing to other texts from Mass General Brigham, for example appointment reminders, is a separate process. Opting out of other texts from Mass General Brigham is a separate process as well.

- It is your responsibility to update your mobile/cell phone number with this research study in the event of a change.

I have had the chance to ask questions about texting with staff associated with this research study. I have been informed of the risks and other information covered above and consent to the use of unencrypted text communications associated with this research study.

Obtain participant's signature and date if a written Informed Consent Form is being used. If an Information/Fact Sheet is used, record the participant's response, name, and date in the study files.

3.17.3 Patient Gateway

Use of Patient Gateway for research must be limited to sending Research Invitations or Targeted Research Announcements to recruit potential participants. It should not be used to communicate with research participants or send other study-related documents. Patient Gateway is primarily used for clinical purposes.

3.17.4 Rally Secure Messaging

Investigators can communicate securely with potential participants ages 18 and older using Rally secure messaging. Only an investigator can initiate messaging with a potential participant. Rally secure messaging is not 21 CFR Part 11 compliant. It may be used for things like scheduling screening visits or answering questions prior to enrollment.

If Rally advertisement and use of email was approved by the IRB, investigators may begin using Rally secure messaging without additional IRB approval. At next Continuing Review or Amendment, investigators should update their protocol to describe using Rally secure messaging.

If studies do not currently have IRB approval to use email communications, investigators will need to submit an amendment to use Rally secure messaging.

Studies approved by an external IRB should seek approval from the external reviewing IRB.

3.17.5 Other Communication Methods

Social Media

Study team members cannot communicate with participants via social media platforms as this is not secure. IRB-approved advertisements may be posted on social media platforms if the use of social media is approved by the IRB. The advertisements should include contact information for the study team so that potential participants can contact the study team directly rather than via social media. Commenting and messaging functionalities on these websites must be turned off wherever possible. Social media posts must also comply with MGB Social Media policy (search Social Media in Archer).

Other Electronic Communication

To inquire about the use of other forms of electronic communication, contact the Research Information Security Office at riso@partners.org.

Virtual Visits

There are also several resources available for virtual visits.

4 International Research

4.1 Considerations for International Research

All human research that involves Mass General Brigham Investigators or members of the research team traveling internationally to recruit, consent, conduct research activities and / or collect data must be submitted to the Mass General Brigham IRB for review. Additionally, research funded by the Mass General Brigham investigator or the investigator's grant, designed by Mass General Brigham investigators, or research occurring in another country under the direction of the Investigator must be submitted for IRB review.

Conducting human research outside of the United States (U.S.) poses complex regulatory and ethical challenges. To protect participant's rights and welfare, the research must follow the ethical standards, legal requirements, and cultural norms of the country where the research will be conducted. If research will be conducted in an embargoed country or involve an export control issue, investigators should contact Research Compliance.

Preparing for submission to the IRB should start at the initial planning stages of the research to allow time to obtain the necessary approvals from the country in which the research will take place. These approvals can take several months depending on the requirements of the country. Depending on the type of study and the country's legal requirements and cultural norms, the IRB may require additional information to complete their review.

4.1.1 Local Context

When developing materials related to recruitment, consent, data collection and the overall research, investigators should consider the local customs, cultural and religious norms. If culturally appropriate, the IRB will consider alternative consent formats. In some instances, it may be appropriate for the IRB to waive some or all requirements for written consent in favor of a verbal consent for cultural, religious or literacy reasons (e.g., cultures where signing consent is not the norm). Investigators must describe the cultural norms or conditions requiring such a waiver and explain how consent will be documented in the study records.

If the study provides compensation, investigators must take care to avoid unduly influencing participants. Investigators should consider local context when determining the amount, type, and/or method of payment. The remuneration should be described in the IRB application and protocol.

4.1.2 Ethics Committee (EC)/Institutional Review Board (IRB)

The U.S. Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) International Program works to ensure that research participants outside of the U.S. who participate in research projects conducted or funded by HHS receive an equal level of protection as research participants in the U.S.

If a country has a local EC/IRB qualified to review and oversee the research, approval from this committee is required. The approval documentation must be provided to the Mass General Brigham IRB. The approval documentation must be in English. Both the translated and original version should be submitted to the IRB along with the translator's certification

If there are no known local or national regulations or requirements, investigators are expected to consult with local experts, Regulatory Officials, or community leaders about the project and to secure their support for the conduct of the

research. Investigators should get documentation of this support. Documentation may include reference to a country's laws or policies online or an email/letter or statement from the appropriate authority in the country. Investigators should review OHRP's International Compilation standards to understand local and/or national regulatory requirements.

There are differences across and within Countries. Each place where the research is conducted should be treated as a separate entity and may be subject to different regulatory requirements. Local collaborators should be able to advise on the necessary regulatory requirements to conduct a study in that country. There are often country or national-level approvals that are needed in addition to the institutional IRB approval (i.e., in Uganda, you also need approval from the Uganda National Council for Science and Technology). There may also be other approvals needed to conduct the study. For instance, in Kenya, if you are submitting a proposal that involves study drugs or participant samples, you will need approval from the Pharmacy and Poisons Board (PPB).

The Mass General Brigham IRB does not serve as the Single IRB for international sites. It is often helpful to submit to the local IRB prior to submitting to the Mass General Brigham IRB to account for any changes the local IRB may request.

4.1.3 Federally Funded Research

All institutions (U.S. and international) engaged in the conduct of research funded by a U.S. federal agency must obtain a federal-wide assurance (FWA) with HHS. FWA is an assurance of compliance with the U.S. Federal Policy for the Protection of Human Subjects ("Common Rule"). Common Rule and the applicable subparts apply to international sites engaged in non-exempt research supported by HHS. See the *Resources* section below for additional information about obtaining FWAs.

A study funded by the FDA or subject to FDA regulations must comply with FDA regulations pertaining to human research or clinical investigations.

4.1.4 Mass General Brigham IRB Review

The IRB will review the research, taking into consideration the local context review, if required, and other legal requirements. The application should include a description of Mass General Brigham's role in the research, as well as information about the procedures that will be conducted at the international site and the name of the EC/IRB that will provide oversight. The IRB will obtain and consider information about the performance site and study population appropriate to the procedures involved in the research and the degree of risk to participants. The review may include some or all the following information:

- The anticipated scope of the research activities that will take place at the site;
- The size and complexity of the institution/facility/entity;
- Standards of professional conduct and practice;
- Policies and procedures of site at which off-site research will occur;
- Applicable laws and regulations;
- The types of participant populations likely to be involved;
- Language(s) understood by prospective participants;
- Method for equitable selection of participants;
- Method for minimizing the possibility of coercion or undue influence in seeking consent;
- Method for protection of privacy of participants;
- Method for maintenance of confidentiality of data; and
- Safeguards to protect the rights and welfare of vulnerable participants;

All modifications and reportable events (even if they occur at an international site) must be submitted to the Mass General Brigham IRB according to the IRB policy. The EC/IRB's approval or acknowledgment for amendments and

reportable events should also be submitted. Submissions should be submitted to the EC/IRB at the international site before being submitted to the Mass General Brigham IRB. If the EC requires documentation of Mass General Brigham IRB approval, Mass General Brigham IRB may provide an approval contingent upon receipt of the EC approval letter.

Reportable events that occur at international sites (e.g., unanticipated problems, major deviations) must be submitted to the Mass General Brigham IRB in accordance with IRB policies. Even if limited or preliminary information is available and the study team is still collecting information, the IRB must be informed within the specified reporting window (i.e., within 5 business days) by submitting an Other Event in Insight.

Consent Form:

- The consent form approved by the local EC/IRB should be translated into English and submitted for review. The consent documents should be uploaded as 'Other' attachments and a blank document may need to be uploaded in the 'Consent' attachment section. The consent form will not be stamped by the Mass General Brigham IRB.
- When the study is federally funded, the consent form must include the key information section, and language about certificate of confidentiality.
- If a study is subject to FDA regulations, the consent form must include all elements of consent as required by the FDA.

4.1.5 Other Considerations

Data privacy laws and regulations are quickly evolving and may impact research conducted in international settings. Requirements for data privacy and security may vary between countries. One example includes the General Data Protection Regulation (GDPR), a European data privacy law that protects the personal data of people located in the European Economic Area. GDPR is a European law that went into effect on May 25, 2018 and establishes protections for privacy and security of "personal data" about individuals in European Economic Area ("EEA")-based operations and certain non-EEA organizations that process personal data of individuals in the EEA. GDPR has strict requirements for transfer of data collected from citizens of the EEA (most countries in Europe including the United Kingdom) and transferred outside of Europe. The IRB has developed language to include in the informed consent form that complies with the GDPR. For more information on GDPR, see United States Health and Human Services OHRP's website: https://www.hhs.gov/ohrp/international/gdpr/index.html or https://gdpr.eu/ or the Mass General Brigham Research Compliance page on GDPR: Pages - EU General Data Protection Regulation (GDPR) (sharepoint.com)

Investigators must ensure that data is collected, managed, and shared in compliance with the law where the data was collected. For guidance on foreign laws impacting data security and privacy, refer to OHRP's International Compilation of Human Research Standards. If this guidance does not address the foreign site, then consult with an informed local partner.

MGB will need to execute an agreement with an international entity to share or transfer individual level human subjects data for use in research. Please contact the applicable Contracting Office in the Contracting Guidelines regarding agreement procedures.

4.1.6 Additional Resources for Investigators

- International Compilation of Human Research Standards: OHRP provides a listing of over 1,000 laws, regulations, and guidelines on human subject protections in over 100 countries and from several international organizations. This document should be consulted to determine country level guidelines on human subject research.
- Federalwide Assurance (FWA) Requirement: Review applicability for international sites.
- Obtaining FWAs

5 Investigator and Study Staff Responsibilities

5.1 Principal Investigators and Delegation of Study-Related Tasks

The Principal Investigator (PI) is responsible for personally conducting or supervising the conduct of the study. However, PIs are allowed to delegate certain study-related tasks to co- investigators and study staff. When tasks are delegated, the PI is responsible for providing adequate supervision of those to whom tasks are delegated and is accountable for regulatory violations (e.g., noncompliance) resulting from failure to adequately supervise the conduct of the study.

When delegating study-related tasks to co-investigators and study staff, the PI must ensure that:

5.1.1 Designated individuals are qualified to perform such tasks

The PI must ensure that any individual to whom a task is delegated is qualified byeducation, training, and experience to perform the delegated task.

When delegating tasks that are clinical or medical in nature, such as evaluating study participants to assess clinical response to an investigational therapy (e.g., global assessment scales, vital signs) or providing study-related medical care to participants, thePI must ensure that the individual has the relevant formal medical training and, when appropriate, licensing and/or certification.

Examples of inappropriate delegation include:

- Screening evaluations, including obtaining medical histories and assessmentof inclusion/exclusion criteria, conducted by individuals with inadequate medical training;
- Physical examinations performed by unqualified personnel;
- Evaluation of adverse events by individuals lacking appropriate medicaltraining, knowledge of the clinical protocol, and knowledge of the investigational product;
- Assessments of primary study endpoints (e.g., tumor response, global assessment scales) by individuals lacking appropriate medical training andknowledge of the protocol; or
- Informed consent obtained by individuals who lack the medical training, knowledge of the clinical protocol, or familiarity with the investigational product needed to be able to discuss the risks and benefits of a clinical trialwith prospective participants.
    - Note: Please reference “Individuals Who Can Obtain Informed Consent in Human Subject Research” for general guidelines of study staff roles/qualifications which are required for obtaining informed consent for different types of studies. Study staff roles that will be permitted to obtain informed consent must be approved prospectively by the IRB for each protocol.

Investigators need to maintain records of staff qualifications for performing tasks which have been delegated to them.

Investigators are required to maintain a list of the appropriately qualified persons to whom significant study-related tasks have been delegated, which tasks have been delegated to them, and the dates of their involvement in the study.

- Note: The Mass General Brigham Compliance & Education Office has developed a Study Site Signature/Delegation of Responsibility Log template which may be used for this purpose.

Co-investigators and study staff receive adequate training on how to conduct the delegated tasks and are provided with an adequate understanding of the study

The PI must ensure that there is adequate training for all staff participating in the conduct of the study. The investigator should specifically anticipate the possibility of staff turnover during the conduct of the study (particularly if the study is of long duration) and plan to ensure that there is adequate training of any replacement staff.

The PI must ensure that co-investigators and study staff:

- Have a specific understanding of the details of the protocol relevant to the tasks they will be performing and, when applicable, the investigational product;
- Are aware of regulatory requirements and acceptable standards for the conduct of human subjects research, both with respect to conduct of the study and human subject protection;
- Are competent to perform the delegated tasks; and
- Are informed of any pertinent changes to the protocol during the conduct of the study and are educated or given additional training as appropriate.

If the sponsor provides training materials for investigators in the conduct of the study, the PI must ensure that staff receives and reviews these materials and/or participates as necessary in any training sessions pertinent to their role in the study.

Documentation of training – whether provided by the PI, sponsor, or another entity – must be maintained in the study files.

There is adequate supervision and involvement in the ongoing conduct of the study

The PI must have a detailed plan for the supervision and oversight of a study. Supervision and oversight should be provided even for individuals who are highly qualified and experienced. An oversight plan might include the following elements, to the extent they apply to a particular study:

- Routine meetings with co-investigators and study staff to review progress ofthe study and update them on any changes to the study or other procedures;
- Routine meetings with the sponsor's monitors;
- A procedure for correcting problems identified by co-investigators or study staff, outside monitors or auditors, or other parties involved in the conduct ofa study;
- A procedure for documenting the performance of delegated tasks in a satisfactory manner and, where appropriate, verifying findings (e.g., observation of the performance of selected assessments or independentverification by repeating selected assessments);
- A procedure for ensuring that the consent process is being conducted in accordance with federal regulations 45 CFR 46 and 21 CFR 50 and the Mass General Brigham IRB Informed Consent of Research Subjects Policy;
- A procedure for ensuring that information in source documents is accuratelycaptured on the Data Collection Forms, Case Report Forms, or elsewhere asappropriate to the study;
- A procedure for dealing with data queries and discrepancies identified by thestudy monitor or other individuals responsible for oversight of the study; and/or
- Procedures for ensuring co-investigators and study staff comply with the IRB-approved protocol and reporting requirements of the IRB and sponsor.

There should be documentation in the study records for all oversight activities such as Meeting Minutes or an internal QA monitoring log.

5.2 Study Staff: Engagement and Responsibilities

5.2.1 Study Staff Engaged in Research

Federal research regulations require oversight of all individuals engaged in human subject research. Mass General Brigham is considered engaged in human subject research when its employees or agents receive an award directly from a federal agency or when employees or agents obtain:

- data about the participants of the research through intervention or interaction with them;
- identifiable private information or identifiable specimens about the participants of the research; or
- the informed consent of human participants.

Employees or agents refers to individuals who: (1) act on behalf of Mass General Brigham; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities. Employees and agents can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

Mass General Brigham employees engaged in the above research activities must be listed as study staff in the IRB Application in Insight. Please see Person of Interest section below for information about non-employees.

5.2.2 Study Staff Responsibilities

The study staff is made up of the Principal Investigator (PI) and individuals to whom the PI has assigned study-specific roles and responsibilities and includes, among others, co-investigators, research nurses, research coordinators, and research assistants.

The Department Chair/Chief

The Department Chair/Chief is responsible for ensuring that the principal investigator, site-responsible investigators, and other members of the professional staff conducting human research with participants are qualified by training and experience and have the necessary hospital credentials and privileges to conduct the research. The Department Chair/Chief may delegate signatory authority to another faculty member with delegated responsibility for oversight of research conducted by members of the department.

The Department Chair/Chief signs off on the proposed general concept of the research, confirming the department's support for the study and that it can be conducted as described.

Principal Investigator

The PI must be qualified by training and experience and must have the necessary hospital credentials and privileges to conduct the research. The PI must be a member of the professional staff at Mass General Brigham and have a clinical or non-clinical staff appointment above the level of resident, fellow or student. Exceptions to this requirement will be made by the Mass General Brigham IRB Office, the PI's Department Chair/Chief, and the Institutional Official on a case-by-case basis and may require a licensed physician co-investigator. Exceptions may be made when trainees are required to serve as PIs as a condition of training grants. An approval letter from the Department Chair/Chief should be submitted, along with the name of the mentor PI.

The PI is responsible for personally conducting or supervising the research and is allowed to delegate certain study-related tasks to appropriately qualified co-investigators and study staff. The PI is responsible for ensuring that co-

investigators and other study staff are appropriately qualified by training and experience to conduct the study-related tasks delegated to them including. The PI must have a plan for supervision and oversight of the research. The type of the supervision should take into consideration the study personnel conducting the research, the nature of the research, and the participant population. For more information refer to the above section on *Principal Investigators and Delegation of Study-related Tasks* .

The PI or other identified qualified individual(s) must be available to provide study participants with reasonable medical care for any medical problems that arise during participation in the research that are, or could be, related to the research. Additionally, when participation in the research might impact the participant's health and/or medical care, the PI should inform the participant's physician about the participant's participation in the research if the participant agrees to the physician being informed.

When protecting the rights, safety, and welfare of research participants, the PI must ensure that:

- They or another specific qualified individual are available to study participants to answer questions or provide care during the conduct of the research; and
- They and all research staff conducting the study adhere closely to the research plan, such as inclusion/exclusion criteria, safety assessments, safety monitoring and reporting of unanticipated problems, and procedures to protect privacy of participants and confidentiality of identifiable data, in order to minimize risks to participants.

The PI should not commence the research without adequate resources to protect participants enrolled in the research and should stop the research if the resources necessary to protect participants become unavailable. These resources might include research personnel, space, equipment, time, and availability of medical or psychological care for problems that arise during participation in the research.

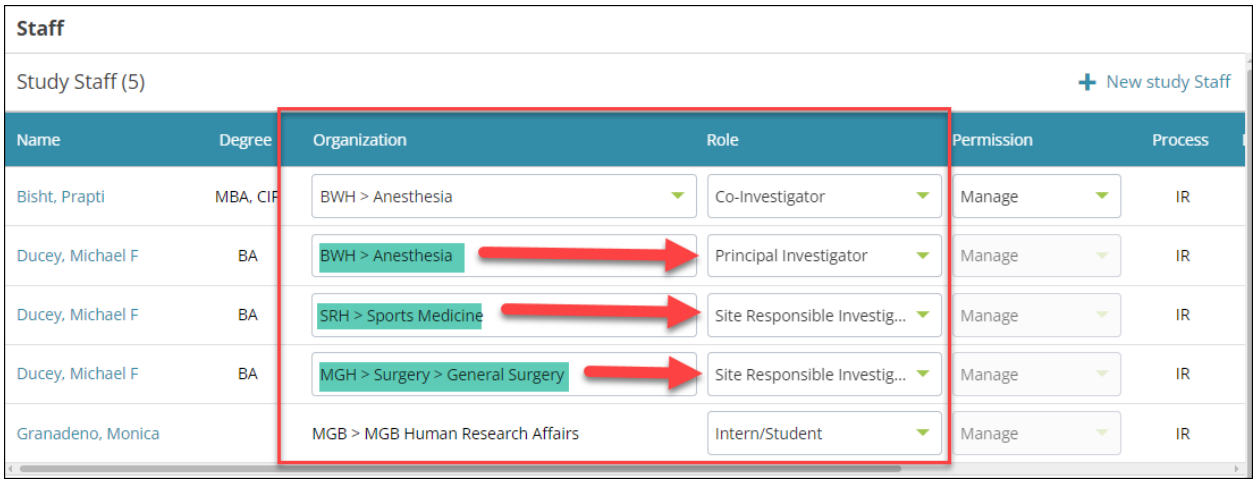
The PI is also responsible for maintaining adequate and accurate source documents and study records that include all pertinent observations and information for each participant in the study. The PI must ensure the accuracy, completeness, legibility, and timeliness of the study data. The PI must maintain the essential study documents in accordance with relevant research regulations and institutional policies. The PI is responsible for documenting and explaining any deviations from the approved protocol. If the study involves investigational drugs or devices (including non-significant risk devices), the PI is responsible for ensuring product accountability is documented and maintained and that the product is stored in accordance with the protocol and product information. (ICG GCP E6(R2) Sections 4 and 8)

For FDA regulated research, the PI is the responsible leader of the team as defined by the term *investigator* in FDA regulations 21 CFR 312.3(b) and 21 CFR 812.3(i).

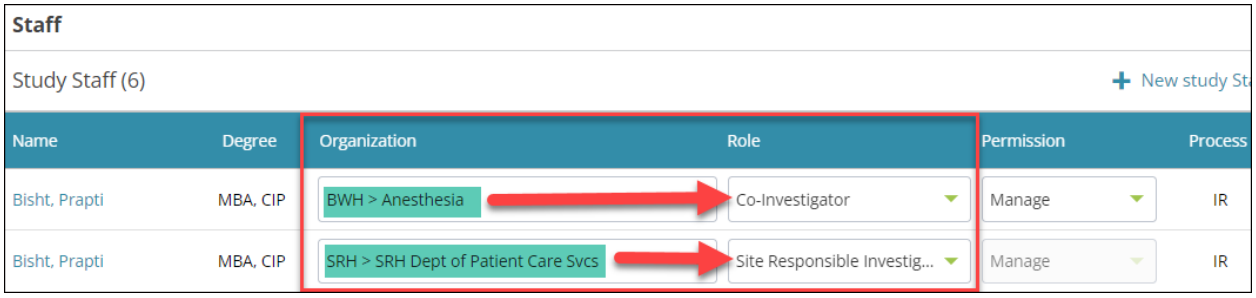
Site Responsible Investigator

When a study will be conducted at multiple Mass General Brigham sites under one IRB-approved study (one study #), there must be a Site Responsible Investigator for each Mass General Brigham institution. When working at more than one Mass General Brigham institution, an investigator can be both PI and Site Responsible Investigator. The same investigator may also serve as the Site Responsible Investigator at more than one Mass General Brigham site. The responsibilities and requirements for hospital credentialing and privileges for Site Responsible Investigators are the same as the requirements for the PI.

When an investigator is the PI and/or will serve as the Site Responsible Investigator at one or more MGB sites, they will need to be added to the Staff page multiple times. There needs to be one entry for each site the investigator will act as the Site Responsible Investigator and each entry needs to reflect the appropriate affiliation(s). The investigator/PI's Insight profile needs to be up to date reflecting all affiliated institutions to be able to act as the PI and or Site Responsible Investigator at multiple sites; for example, PI at BWH, affiliated and serving as the Site Responsible Investigator at Spaulding and MGH will need to be added with each affiliation and with the Site Responsible Investigator Role. See the example below.



Other staff members properly credentialed can also have multiple roles with different institutions; for example, co-investigator at BWH serving as the Site Responsible Investigator at SRH. See the example below.



A Site Responsible Investigator is required when a study involves interventions, interactions with participants and/or uses clinical resources (e.g., access to clinical unit or personnel). Examples include, but are not limited to, when a study involves blood draws (clinically indicated or research-specific), the pharmacy preparing the study drug, and/or interviews/surveys with participants. For surveys/interviews/focus groups, a Site Responsible Investigator is required only if there is an in-person interaction to complete these activities at an MGB site. If procedures are limited to online surveys or virtual visits, a Site Responsible Investigator is not required. A Site Responsible Investigator is also not required if in-person interactions are limited to a non-MGB off site location (e.g., a foodbank, a community center, etc.) and no in-person interactions take place at an MGB site. A Site Responsible Investigator is not necessary when a study does not involve interventions or interactions with participants (e.g., a medical records study involving records from multiple sites). Site Responsible Investigators are responsible for the conduct of the study at their institution and for providing site-specific information to the PI for continuing review and for fulfilling Mass General Brigham IRB Office reporting requirements (e.g., unanticipated problems involving risks to participants or others).

Co-Investigators

Co-investigators are typically individuals with doctoral or other professional degrees who contribute to the scientific development or execution of a study in a substantive, measurable way. Co-investigators must be qualified by training and experience and, when applicable, have the necessary hospital credentials and privileges to conduct the study-related tasks delegated to them by the PI.

Other Study Staff

Members of the study staff may include research nurse/manager, research coordinator/manager, research assistant, regulatory coordinator/manager, data coordinator/manager, laboratory technician/technologist, intern/student, among others. Study staff must be qualified by training and experience and, when applicable, have the necessary hospital

credentials and privileges to conduct the study-related tasks delegated to them by the PI.

5.2.3 Persons of Interest (POIs)

Non-employees are onboarded as "Persons of Interest," or POIs, through hospital-required processes. Investigators should consult their Department's Administrative Director or equivalent to obtain details of POI onboarding.

If POIs or non-employees are from another institution (e.g., Harvard Medical School, Boston Children's Hospital), their activities may also engage the home institution in research. Aside from the exceptions noted below, individuals who are affiliated with another institution cannot be listed as study staff in Insight.

- The POIs should consult with the IRB office at their home institution regarding their role in the research and request oversight from them.
- Engagement in federally funded non-exempt research would require oversight by a Single IRB. POIs must obtain an IRB reliance agreement, as determined by the IRB, in order to ensure appropriate regulatory oversight of their respective research activities.
- The Mass General Brigham IRB will not serve as a Single IRB or rely on another IRB for exempt studies. Therefore, for exempt research, the POI will need to secure a determination from their home institution. Information about Single IRB and Reliance Agreements is available on Research Navigator: Pages - sIRB Overview (sharepoint.com).

If POIs are not affiliated with another institution, an Individual Investigator Agreement (IIA) will be required for the Mass General Brigham IRB to provide oversight of the POI. The need for an IIA will be determined by the IRB Office. A reliance agreement is not needed for Mass General Brigham visiting or post-doc fellows, research trainees, or Fulbright scholars.

For U.S. students with a POI designation added to the study staff list as "Student/Intern," the PI and the student must sign the Individual Student Investigator Agreement (ISIA). A copy of the ISIA can be accessed on Research Navigator here: Pages - IRB Forms and Templates (sharepoint.com).

- During the review of the study staff amendment, the IRB reviewer will request a copy of the ISIA.
- All student researchers must reach out to their home institution's IRB to determine whether there are local submission requirements. This is a term of the ISIA.
- The ISIA is not applicable for students located outside the U.S as they will need to obtain a determination from their home institution.
    - These individuals do not need to be added to study-staff since the Mass General Brigham IRB will not have oversight of their research activities.
    - Any exceptions are considered on a case-by-case basis as part of the review process.

POIs cannot serve as a Principal Investigator on a research study overseen by the Mass General Brigham IRB.

5.2.4 Minors as Study Staff

Investigators requesting to add students who are less than 18 years of age, i.e., minors, as study staff will be asked additional questions about students' role in the project via the Individual Student Investigator Agreement (ISIA).

Minors that will be added as study staff will be limited in terms of the research activities that they can conduct. Typically, students work on research projects for a short period of time, without adequate experience to perform many research tasks. In contrast, study-related tasks must be completed by staff members who are appropriately qualified by training and experience to conduct the activities. As such, minors will be permitted to conduct only limited research activities as described in the ISIA form. Minors should not retain any data or research materials for their own use outside of the approved learning/training activity.

5.2.5 Other Personnel

Members of the hospital workforce, who provide standard clinical services or perform routine clinical procedures or tests as part of their institutionally designated non-research responsibilities are not considered study staff and should not be listed in the IRB Application. These could include:

- laboratory technologists/technicians, radiological technologists/technicians, phlebotomists, patient care services staff, who provide standard clinical services or perform routine clinical procedures or tests in the course of carrying out their usual non-research related responsibilities.
- nurses, pharmacists, or anesthesiologists who perform services or duties as part of their usual care without otherwise contributing to the research endeavor.
- individuals whose role in the research is limited to providing consultation on the development of questionnaires or analyzing de-identified data.
- individuals whose sole responsibility is to perform administrative tasks such as entering data from source documents into a database when they are not engaged in research, or individuals who maintain research databases or provide technical support.

The IRB may need to assess certain roles on a case-by-case basis. If there are questions about engagement, contact the IRB office.

5.3 Use of MyCap for Research Studies

MyCap, a new feature now available in REDCap is a customizable participant-facing mobile application (app) that captures patient reported outcomes based on a REDCap project. MyCap collects data through surveys and the automated administration of active tasks (activities performed by participants using mobile device sensors under semi-controlled conditions) from any mobile device (iOS or Android).

Researchers can distribute a QR code or hyperlink in relation to the REDCap MyCap project using any of the currently available methods in REDCap (e.g., displayed to participants after they complete a survey, sent via email). Details on MyCap QR code/link distribution can be found here. If participants do not currently have the app installed on their devices, they will be brought to their respective app store to download the app. The MyCap App can also be used for offline participant data collection, and all data collected are automatically sent back to the REDCap server as soon as an internet connection is available. This app makes it simple and inexpensive (no-cost) for researchers to use a mobile app to capture participant reported outcomes on both iOS and Android devices. MyCap provides a quick two-way messaging system between REDCap and the participant's MyCap app (e.g., messaging and announcements).

If you would like to use MyCap in your research, be sure to include its use in your protocol for new studies or submit an amendment for ongoing studies to the IRB along with a revised consent form and protocol incorporating the language described below. Include information in the amendment form about how you will use MyCap in your study.

5.3.1 MyCap Consent or Information Sheet Language:

In this study, we will collect data using a mobile application called MyCap. This app will need to be downloaded to your mobile device (iOS or Android). All data collected in the MyCap app is automatically sent back to the system where the research team stores data. Data collected via MyCap will live on your device or in the research system, and it will not be sent to third parties. Data charges may apply when using MyCap as this app requires internet connection to send and

receive data. You can send messages to the research team via the MyCap app. Do not use MyCap to send messages for urgent contact. Contact the study team directly using the information provided to you in the consent form for emergencies. We will use this app to: *Add information about how you will use MyCap in this study* (e.g., send you push notifications and reminders to complete tasks related to participation in this study. The tasks that you will complete include: *provide a description*)

5.3.2 Instructions to Investigators:

In the consent, in addition to the above, describe how participants will use MyCap in your study (e.g., how you will send the QR code or hyperlink for participants to download the app, what activities will participants complete via the app, who will be responsible for the data charges).

5.3.3 MyCap Protocol Language:

This study will be using a mobile application called MyCap that will need to be downloaded to a participant's mobile device (iOS or Android). We will use this app to: *Add information about how you will use MyCap in this study, including:*

- Use of push notifications and reminders to complete tasks related to participation in this study.)
- Surveys/questionnaires used
- Names of specific active tasks that will be used

Instructions to Investigators: *The protocol should describe how MyCap will be used, the type of data that will be collected, the tasks that will be completed by participants.*

Digital Health Form:

The Digital Health form in the Insight application should be completed as follows:

Section	Question	Answer
Digital Health Technology	Will you be using mobile and wireless devices, wearable devices, smartphone apps, digital health tools, health-related IT, new healthcare software and related new technologies to generate, use and/or disseminate health information or physiological data? Note: Wearable devices can include activity trackers (i.e., FitBit), free-standing monitors or sensors worn on body which connect through wireless, Bluetooth or other method to passively collect data.	Yes
	Indicate type of digital health technology being used in the study (check all that apply):	Smartphone application
	List name and manufacturer of each "digital health" technology that will be used in the study. You will be asked to complete questions for each "digital health" technology listed.	MyCap, part of MGB REDCap implementation
Web-based Data	Will you be using web-based survey or data collection tools to administer a survey or questionnaire?	Yes: *Then Choose:*

Collection Tools		Survey / Data collection tool hosted inside Mass General Brigham firewall. *Then Choose:* REDCap or StudyTRAX through Mass General Brigham

The above information should be included in your IRB submission if you are requesting to use MyCap at the time of Initial Review or should be revised for ongoing studies via an Amendment.

For questions about creating a MyCap project, contact the REDCap team: redcap@mgb.org or visit the REDCap Resource Center at this link.

5.3.4 MyCap FAQ for Investigators

1. **What is MyCap?**

   MyCap, a feature of REDCap is a freely available participant-facing mobile application that can be installed on iOS and Android devices to capture patient-reported outcomes for any REDCap project.

2. **How does the data from the app get sent to REDCap?**

   All data completed on a participant's device are automatically and immediately synchronized to REDCap. If data are completed while participants are offline, data are synchronized when internet connect is restored and the App is opened. All MyCap data is sent directly via an API call to the MGB REDCap server. Sent data is associated with a specific project and record. Data is not sent to third parties.

3. **How do I modify my existing studies to request the use of MyCap?**

   If you would like to use MyCap in your research, submit an amendment to the IRB along with a revised consent form and protocol incorporating the language described below. Include information in the amendment form about how you will use MyCap in your study.

   MyCap Consent Language:

   In this study, we will collect data using a mobile application called MyCap. This app will need to be downloaded to your mobile device (iOS or Android). All data collected in the MyCap app is automatically sent back to the system where the research team stores data. Data collected via MyCap will live on your device or on in the research system, and it will not be sent to third parties. Data charges may apply when using MyCap as this app requires internet connection to send and receive data. You can send messages to the research team via the MyCap app. Do not use MyCap to send messages for urgent contact. Contact the study team directly using the information provided to you in the consent form for emergencies. We will use this app to: *Add information about how you will use MyCap in this study* (e.g., send you push notifications and reminders to complete tasks related to participation in this study. The tasks that you will complete include: *provide a description*)

Instructions to Investigators*: In the consent, in addition to the above describe how participants will use MyCap in your study (e.g., how you will send the QR code or hyperlink for participants to download the app, what activities will participants complete via the app, who will be responsible for the data charges):*

MyCap Protocol Language:

This study will be using a mobile application called MyCap that will need to be downloaded to a participant's mobile device (iOS or Android). We will use this app to: *Add information about how you will use MyCap in this study including*

- Use of push notifications and reminders to complete tasks related to participation in this study.)
- Surveys/questionnaires used,
- Names of specific active tasks that will be used

Instructions to Investigators: *The protocol should describe how MyCap will be used, the type of data that will be collected, the tasks that will be completed by participants.*

Digital Health Form:

The Digital Health form in the Insight application should be completed as follows:

Section	Question	Answer
Digital Health Technology	Will you be using mobile and wireless devices, wearable devices, smartphone apps, digital health tools, health-related IT, new healthcare software and related new technologies to generate, use and/or disseminate health information or physiological data? Note: Wearable devices can include activity trackers (i.e., FitBit), free-standing monitors or sensors worn on body which connect through wireless, Bluetooth or other method to passively collect data.	Yes
	Indicate type of digital health technology being used in the study (check all that apply):	Smartphone application
	List name and manufacturer of each "digital health" technology that will be used in the study. You will be asked to complete questions for each "digital health" technology listed.	MyCap, part of MGB REDCap implementation
Web-based Data Collection Tools	Will you be using web-based survey or data collection tools to administer a survey or questionnaire?	Yes: *Then Choose:* Survey / Data collection tool hosted inside Mass General Brigham firewall. *Then Choose:* REDCap or StudyTRAX through Mass General Brigham

The above information should be included in your IRB submission if you are requesting to use MyCap at the time of Initial Review or should be revised for ongoing studies via an Amendment.

For questions about creating a MyCap project, contact the REDCap team: redcap@mgb.org or visit the REDCap Resource Center at this link.

4. **I am working on a new study and would like to request the use of MyCap. What do I submit to the IRB?**

   Refer to the information in # 3 above.

5. **Who do I contact for technical questions about MyCap?**

   For questions about creating a MyCap project, contact the REDCap team: redcap@mgb.org or visit the REDCap Resource Center at this link.

6. **What time stamps are logged for activities when a participant completes a survey offline (completion date/time) versus when the survey is actually transmitted (transmission date/time)?**

   Every REDCap instrument that has been activated as a MyCap task has a number of required fields that are automatically added if not already present. Two of these are "task start" and "task end". These fields automatically capture the time/date a task was started and completed on the users' device. This is in addition to the logging REDCap already records for record creation/update/deletion. Additionally, MyCap captures a sync date to record when the data was uploaded to the REDCap server.

7. **What user IDs are associated with entries?**

   These IDs are a combination of researcher defined and REDCap/MyCap defined: A researcher adds a record into a REDCap project for each participant. That record has a unique record ID. All activity including data entry is recorded in the project log associated with this record ID. In addition, MyCap assigns a random, anonymous participant identifier (@MC-PARTICIPANT-CODE) to each participant, which is required to ensure responses get tied to the correct record. This value is stored on every record in a MyCap enabled project. Each database entry (task completed) is automatically given a 36-character universally unique Identifier (UUID). This value is stored as a field in each MyCap enabled instrument.

   In MyCap, the account name/ PIN number created by a participant is stored locally on their device and not shared with researchers or sent back to MGB REDCap. No user IDs made by MyCap participants are saved to the MGB REDCap project.

8. **If an entry is changed (by staff or by participant), how is that reflected in the audit trail?**

   If any data is changed or modified by a researcher in REDCap, the activity and user who made this modification is stored in the REDCap project logs and associated with MGB/REDCap username, the same as current REDCap projects. When a MyCap participant enters/syncs data, the REDCap logging displays: startdate, enddate, uuid, and device uuid captured in mandatory fields as well as the data field updates.

9. **When someone completes a survey, does the data go directly to the study team's project in REDCap?**

All MyCap data is sent directly via an API call (Vanderbilt supported integration) to the MGB REDCap server. Sent data is associated with a specific project and record. Data is not sent to third parties.

10. Are there any potential charges to the participant's phone plan for use of the app (data costs, messaging etc.)?

Data charges may apply. The MyCap app requires internet connection to send and receive data, so any use of the app would require the device owner to have a funded data plan or to use a wifi data connection.

11. What are the requirements with regard to space on the person's phone for downloading the app?

The app currently has a size of 248mb for Android devices and 279mb for iOS.

12. Is there a user agreement that the participant must sign?

No specific end-user agreement is required to use the app. A MyCap privacy policy is provided within the app. Participants do not need to attest or confirm receipt of privacy policy.

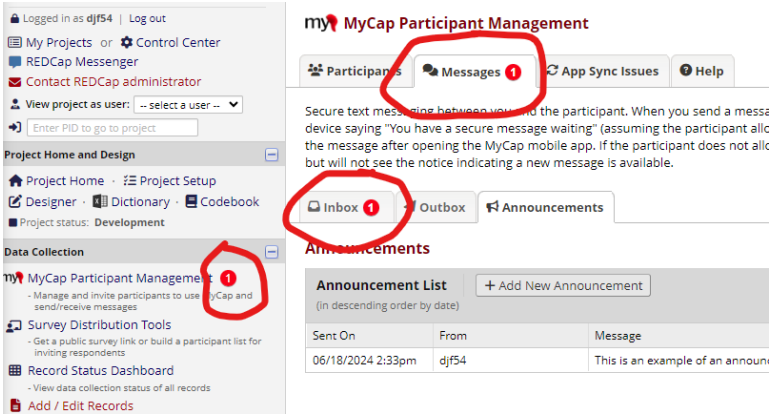
13. What are the full range of uses of the app for research?

The MyCap is best utilized for research projects that require routine or repeated data collection by a study participant. This may come in the form of fully remote trials, decentralized trials, or hybrid trials where MyCap augments in person visits. The MyCap Use Cases page on the website (https://projectmycap.org/mycap-use-cases/) outlines specific uses for medication adherence, program delivery/adherence, post op monitoring follow up, remote patient monitoring, surveillance studies, COVID studies, exercise tracking, etc.

14. How are messages sent by participants via the MyCap app received by the study team? Do they go to a central messaging location, a particular person?

Any message sent via the MyCap app is shown to the researcher in the REDCap project's "MyCap Participant Management" section of the tool. When a message is sent from the participant to the researcher, there's a visual indicator on the MyCap Participant Management screen, as well as the "Messages" tab.

Example:



For the researcher, messages can be sent to the entire cohort or to individual participants.

15. **How will the research team know if there is a message that needs to be acted upon immediately?**

    Researchers must check the notifications in the project every day and review. Study teams will need to set up internal processes/SOPs to ensure that notifications are reviewed at least daily when MyCap is used.

16. **How do the participants download the app? Does the study team have to send them a link, QR code, etc.?**

    Researchers can distribute a QR code or hyperlink in relation to the REDCap MyCap project using any of the currently available methods in REDCap (e.g., displayed to participants after they complete a survey, sent via email). Details on MyCap QR code/link distribution can be found here. If the participants do not currently have the app installed on their devices, they will be brought to their respective app store to download the app.

17. **Since data (including PHI) could be stored on the person's phone until they have a connection to transmit, what are the security requirements for the user's phone? Will participant phones require password protection?**

    MyCap does not modify the security settings on individual devices. When a participant installs the app, they are instructed to create a profile and are given the option of setting a PIN number associated with this profile.

Template Development Support:

MyCap example use cases: https://projectmycap.org/mycap-use-cases/

MyCap decision tree: https://projectmycap.org/wp-content/uploads/2021/06/MyCapDecisionTree.pdf

MyCap white paper: https://academic.oup.com/jamiaopen/article/5/2/ooac047/6601324?login=false

MyCap informative video: https://www.youtube.com/watch?v=unyWcEDip0Y

5.3.5 MyCap FAQ for Research Participants

1. **What is MyCap?**

   MyCap is a freely available participant-facing mobile application that can be installed on iOS and Android devices to capture data for research studies.

2. **How do I download MyCap?**

   Researchers will share a QR code or hyperlink with you. If you do not currently have the app installed on your device, you will be brought to "app store" on your phone to download the app.

3. **Can I send a message to the research team via MyCap?**

   Yes, you can send messages to the research team via the MyCap app. Do not use MyCap to send messages for urgent contact. Contact the study team directly using the information provided to you in the consent form for emergencies.

4. **Are there any potential charges to my phone plan for use of the app (data costs, messaging etc.)**

Data charges may apply. The MyCap app requires internet connection to send and receive data, so any use of the app would require the device owner to have a funded data plan or to use a wifi data connection.

5.4 Investigators Leaving Mass General Brigham

Research investigators who are part of the workforce at Mass General Brigham who leave their positions must complete the Mass General Brigham Transfer Out process in Insight which includes completion of certain tasks (e.g. data analysis, preparation for publication) associated with specific research projects that they initiated and conducted at Mass General Brigham.

Additional guidance on Investigator Transfer Out Processes can be found at: MGB Transfer Out Module Guidance Document.docx (sharepoint.com). Once an investigator leaves a Mass General Brigham entity, the Mass General Brigham IRB no longer provides oversight, unless the investigator's new institution is approved to cede IRB review to the Mass General Brigham IRB (see details in the Human Research section below).

When the research involves human participants, the investigator should notify the IRB to discuss their transition plan. Whether working on an active protocol or one that was deemed not human research (and therefore not under IRB review) there are issues to be considered regarding the transfer of human data or biospecimens to other institutions. In addition, if a study is federally funded, federal agencies have requirements regarding the transfer of grant awards or contracts. Additional information about this process is described in the Investigator Transfer Out Process guidance.

A variety of options may be considered regarding the management of human research projects in the event of an investigator's departure:

- Closure of project: If work on the project has been completed, the departing PI may choose to close the protocol. All regulatory files must be reviewed for completion. Study devices must either be returned to the sponsor or contract research organization (CRO) or disposed of in agreement with the sponsor.
- The investigator wishes to continue involvement in the project (not as PI) or if research (enrollment, follow-up or analysis) is ongoing at the Mass General Brigham institution: In advance of leaving Mass General Brigham, the investigator must request approval from their new institution to cede review to the Mass General Brigham IRB. If this is not anticipated to occur before the investigator's termination date, they must submit an amendment to transfer their active IRB protocols to a new Mass General Brigham PI. In some cases, it may be permissible for the departing investigator to remain a collaborator on the project. In these cases, the departing investigator will need to secure approval from the Mass General Brigham IRB and department chair and may need to sign agreements as appropriate.
- If the investigator does not wish to continue involvement in the project and the project is not to be closed, an Amendment must be submitted to the IRB to remove the current PI from the protocol and to name a new Mass General Brigham PI.
- Transition of project to new institution: If an investigator wishes to transition human research to a new institution, the investigator must terminate their protocol at Mass General Brigham and secure new approval at their new institution. In all situations, the investigator must contact the Mass General Brigham IRB to discuss the transition plan. Investigators must be sensitive to privacy and consent issues for future use of human data or biospecimens. Particular scrutiny should be given to transfer of identifiable data or specimens, secondary use of tissue specimens acquired for research, and data or specimens subject to material transfer agreements or sponsor restrictions. Transfer of identifiable data to outside institutions is typically not allowed.

Investigators who are a co-investigator on an open human research protocol, must notify the PI of the IRB protocols of their impending departure and work with the Mass General Brigham IRB to be removed from the protocol. Please note that the original research records from work done at Mass General Brigham are the property of Mass General Brigham and may not be taken to the new institution.

5.5 Recordkeeping and Record Retention Requirements

Investigators are required to maintain records of their human research activities. Good recordkeeping is essential for verifying the integrity of study data produced and for demonstrating investigator compliance with applicable regulations, and institutional policies andprocedures. The recordkeeping procedures outlined in this guidance document cover the following two types of files:

A. Regulatory document files
B. Individual research participant files

5.5.1 Regulatory Document Files

Regulatory documents, also called Regulatory Binder or Essential Documents, must be maintained for all research involving human participants, which includes obtaining data through:

- Intervention or interaction with participants;
- Access to identifiable private information in health/medical records; and/or
- Access to human materials/tissue collected for non-research purposes.

Regulatory document files serve as a central location for maintaining study management documents and when complete and appropriately maintained/updated, they demonstrate compliance with applicable regulations, and institutional policies and procedures. A separate regulatory document file should be maintained for each study.

Note: The Mass General Brigham Compliance & Education Office provides tools and resources for assembling and maintaining regulatory document files/Regulatory Binder. For more information, visit the C&E Office website or email CEoffice@mgb.org.

5.5.2 All studies involving human participants

Investigators must maintain the following study-specific documents for every research study that involves human participants:

1. A complete history of Mass General Brigham IRB submissions and correspondence from initial application through study close out, including, when applicable, but not limited to:
    - eIRB application forms
    - Protocol(s)
    - Protocol Amendments
    - Protocol Summary
    - Consent Form(s)
    - Recruitment materials
    - Any other documents approved by the Mass General Brigham IRB
    - Mass General Brigham IRB review notification letters
    - Investigator response to review notification letters
    - Any other correspondence between investigator and Mass General Brigham

    Note: Records of all Insight/eIRB submissions and related IRB review notification letters created and submitted after April 6, 2013 are maintained in Insight, with limited exceptions. Exceptions include, among others, records of IRB reviews ceded to another institution or entity, original review notification letters when new letters are reissued and replace the original in Insight, and documents or communications submitted outside Insight. The IRB maintains copies of originals of reissued letters and can provide copies upon request.
2. Sample case report forms (CRFs) and/or data collection forms
3. Completed study management logs or equivalent documentation of the following:
    - Delegation of responsibility / signature log

- Enrollment/health/medical records/excess human materials (for studies limited toaccessing individually private information or samples)
- Internal and if applicable, external monitoring activities
- Protocol deviations and unanticipated problems including adverse events

4. Correspondence and/or communications with study sponsor, funding agency, regulatoryagencies, research collaborators (e.g., data use agreements, materials transfer agreements, etc.)
5. Financial disclosure forms submitted by study staff responsible for the design, conduct or reporting of the research (of note, the eCOI forms are only available in Insight and only to the individual and the IRB, not to everyone on the study)

5.5.3 Studies that involve an intervention or interaction with participants

In addition to documents 1-5 above, investigators must maintain the following documents for studies that involve an intervention or interaction with participants:

6. Completed study management logs or equivalent documentation of the following, asapplicable:
   - Pre-screening
   - Adverse events
7. Study staff qualifications
   - CVs of all study staff, dated
   - Current licensure and board certifications of professional staff
   - Safety or other training (e.g., infection control, laser safety, Human Subject Protection, etc.)
   - Study specific training
8. Clinical laboratory certification (e.g., CLIA/CAP certificate) and normal reference ranges,and research laboratory director's CV, when applicable.
9. Correspondence and/or communications with collaborating sites (multi-site research)

Note: Study staff CVs, professional study staff licensure and board certifications, safety or other training and laboratory certification and normal reference ranges that support more than one study may be filed centrally for a research group/department.

5.5.4 Studies that involve FDA-regulated drugs/biologics or medical devices

In addition to documents 1-9 above, investigators should maintain the following documentsfor studies of FDA-approved or unapproved (investigational) drugs/biologics or FDA- approved/cleared or unapproved (investigational) medical devices:

10. Product information, to include, when applicable:

    10.1 FDA-approved drugs/biologics or approved/cleared medical devices
    - Drug package insert
    - Device manual / Instructions for Use

    10.2 IND drugs/biologics or IDE medical devices
    - Investigator's Brochure (IB)
    - Device information / Report of prior investigations

11. FDA Forms, Submissions and Correspondence

    11.1 IND/IDE Clinical Investigators (IND/IDE held by company, NIH or otherentity)
    - Form FDA 1572/Statement of Investigator (IND Investigator)
    - Investigator's Agreement (IDE Investigator)

11.2 Sponsor-Investigators (IND/IDE held by Investigator)

- IND/IDE submission
- IND protocol amendments / IDE supplements
- IND/IDE safety reports
- IND/IDE annual reports
- IDE updated list of investigators
- Form FDA 1571/IND Application
- Form FDA 3455/Disclosure: Financial Interests and Arrangementsof Clinical Investigators
- Form FDA 3674/Certification of Compliance, with Requirements ofClinicalTrials.gov

12. Drug/device accountability, to include, when applicable, records of:
    - Shipping and receipt
    - Dispensing to participants
    - Return of drug/medical device by participants
    - Return of drug/medical device to sponsor
    - Destruction of drug/medical device, when destroyed at the investigative site

    Note: The research pharmacy maintains these records for most drug studies. Investigators are expected to maintain investigational product accountability for each participant as well as for the study overall. Sponsor-Investigators have additional responsibilities related to the management and oversight of the investigational product as outlined in the Sponsor-Investigator Responsibilities Guidance. When the study does not utilize the research pharmacy, the above must be maintained by the investigator. Areas, such as the operating room or catheterization lab, may maintain records of medical device shipments, receipts and use. When someone other than the investigator maintains information about medical device accountability, document this ina signed and dated note-to-file.

5.5.5 Individual Participant Files

Investigators must maintain the following study-specific documents in a separate file for each participant who signs the consent form or provides oral consent (written documentation of informed consent is waived), as applicable:

- All original signed and dated consent forms
- Documentation of informed consent when written informed consent is waived
- Documentation of the informed consent process, whether consent was provided with a signature or orally
- Documentation of participant eligibility and study procedures
- All case report forms (CRF) and data forms, signed, dated and complete
- All instruments, questionnaires, diaries, or other documents completed by participants and/or study staff
- Correspondence, emails or phone calls to participants
- Adequate and accurate source documents and trial records. Source data should be attributable, legible, contemporaneous, original, accurate and complete.

For studies limited to health/medical records, excess human material, secondary use, or a data or tissue repository, participant files may be more limited in nature, depending on the protocol.

Note: Research participants cannot request that study data be “deleted” or “erased” once it has been collected. Contact the MGB IRB for guidance should a participant request that data collected about them be destroyed.

5.5.6 Record Storage and Retention

Study documentation may be collected, recorded and stored in physical (paper) or electronic form. Regardless of the form, investigators are responsible for storing study documentation securely to preserve the integrity of the records, protect identifiable health information and maintain the confidentiality of the data. Access to study documentation should be limited to study staff. Study documentation must be available for internal audits, external monitoring, or inspection by regulatory agencies.

Physical (paper) records should be stored in a secure area, such as in a locked file cabinet. Electronic records may be stored on Mass General Brigham and Institutionally compliant computers or mobile devices or other internally hosted services. Investigators should follow Research Information Services & Computing (RISC) recommendations to safeguard electronic protected health information (ePHI) when storing individual participant files electronically.

Research records should be retained for at least seven (7) years from the time the study was completed, or longer as required by the sponsor. For FDA regulated clinical investigations conducted under an IND/IDE, the sponsor of the IND/IDE is responsible for informing investigators when the study records can be destroyed. If the investigator leaves the institution,all such original permanent records must remain in the laboratory or unit, unless alternative arrangements are approved by the principal investigator's Department Chair/Chief or designee.

5.6 Electronic Storage of Research Documents

This guidance presents an acceptable process for creation of electronic copies of source documentation (including consent documents). This guidance is applicable to Investigator-initiated research, including NIH funded and FDA regulated research. Industry and other Sponsors generally have specific requirements for electronic records to comply with 21 CFR Part 11, when applicable. Investigators should seek the written permission of the Sponsor and follow the Sponsor's requirements for electronic storage of source documents prior to creation of electronic source document storage. Documentation of Sponsor permission should be filedwith study documents.

In order to convert existing paper source documentation to electronic source documentation, the site must create a ***certified copy***. A ***certified copy*** is "a copy of original information that has been verified, as indicatedby a dated signature, as an exact copy, having all of the same attributes and information as the original."

As with all research activities, the principal investigator (PI) is responsible for maintaining adequate records. The PI should, therefore, ensure that this guidance is followed when implementing electronic storage of source documents. It is recommended that Investigators create an SOP describing how source documents will be scanned, certified, and stored.

See also Mass General Brigham policy Guidelines on *Retention of Research Data, Materials and Records for guidance*.

5.6.1 Recommended Procedures

5.6.1.1 Creation of electronic files

Source documents/consent forms should be scanned individually and converted to an Adobe Acrobat PDF file.The PDF file name should be labeled with:

- The study's IRB-assigned protocol number
- The study's assigned participant ID
- The date the source document was obtained or completed
- A word identifying the specific source document (e.g. "consent", "HAM-D")
  (For example: 2015P000000_A12345_20150531_consent)

5.6.1.2 Certification of electronic files

The person who certifies the copy as an accurate and complete representation of the original, having all thesame attributes and information as the original, should be the same person who actually created the electronic copy from the original. The person certifying is verifying that they have done all of the following:

- Reviewed all pages of the scanned document and confirmed that they are EXACT copies of the originals.
- Confirmed that each scanned page is legible and facing in the appropriate direction.
- Confirmed that wet ink signatures and dates are legible on the scanned document.

Although the PI does not have to personally certify every document, the PI still bears the responsibility for ensuring that the certification process is being followed.

5.6.1.3 Methods and storage of electronic files

Different software and applications can be used to create certified copies. For FDA-regulated research documentation, systems and processes should be FDA-compliant (including 21 CFR Part 11). For non-FDA-regulated research documentation, systems must comply with Mass General Brigham policies.

In all cases, the person performing the certification should use their own personal account, identification, key, or unique credentials. Using a shared account or someone else's account, such as a PI's account, does not comply with regulatory requirements or Mass General Brigham policies.

Electronic files of scanned and certified source documents should be stored in a system approved by Mass General Brigham Research Computing for such purposes. More information about storage options is available from RISC: https://rc.partners.org/it-services/storage-backup .

5.6.2 Electronic Storage Frequently Asked Questions

- **Is IRB approval required when converting paper source documents to electronic storage?**
    - No, IRB approval is not required to convert study source documents to electronic documents. An internalSOP for document scanning and certifying should be maintained on-site. Additionally, records of documents scanned and documentation of certification should be maintained on site.

- **Once scanned, certified, and placed in an appropriate Mass General Brigham-approved system, can the paper documents be destroyed?**
    - Yes, once the document is scanned and certified, the paper copy can be destroyed.

- **At what point can source documents be scanned and stored?**
    - Anytime, as long as the site has a process/procedure for scanning, certifying, and storing electronic documents.

- **Can this be done for an ongoing (still enrolling) study?**
    - Yes.

- **How long should electronic source documents be maintained?**
    - Consistent with record retention requirements for paper source documents, electronic files of source documents should be kept for a minimum of 7 years following study closeout and in accordance with institutional policy. Sponsored studies may have additional requirements, which would need to be met inaddition to institutional policy.

- **How should Sponsor's permission for electronic storage of source documents be documented?**
    - Sponsors should agree to electronic storage of source documents in writing. This can be in the form of an email or letter. This email or letter should specify the person granting permission and their job title.
    - Documentation of sponsor agreement should be kept on file.

- **What Mass General Brigham-approved systems can be used to create certified copies of research documents?**
    - Veeva SiteVault Free can be used to create certified copies of research documents. It is 21 CFR Part 11 compliant and is available at no cost to Mass General Brigham researchers by contacting the Compliance & Education Office at CEoffice@mgb.org. Mass General Brigham REDCap is another system that can be used; it has a template for scanning, certifying, and storing research documents. More information is available in the REDCap Resource Center (https://confluence.partners.org/x/mgRVBQ).
    - To inquire about the use of other systems or vendors, contact the Research Information Security Office at riso@partners.org

- **Can documents be certified as a group/in bulk?**
    - Yes.
    - A group of documents can be scanned together and then the resulting file certified.
    - Keep in mind the overall size of the file so that it can be copied, moved, uploaded, etc., as well as how the file will be named so that the name reflects all the scanned components.
    - Alternatively, several documents can be scanned individually and then one certification attestation created listing all the individual files which have been certified.

- **Is REDCap 21 CFR Part 11 compliant?**
    - For information about REDCap, review the links below.
    - REDCap Resources:
    - REDCap Project: https://projectredcap.org/
    - REDCap at Mass General Brigham: https://confluence.partners.org/x/mgRVBQ
    - Mass General Brigham REDCap 21 CFR Part 11 compliance information: https://confluence.partners.org/x/kntVBQ

- **What other tools/technologies can we use to certify copies?**
    - In addition to REDCap and Veeva SiteVault Free, technologies that create a signature or certification on a PDF are acceptable as long as they comply with 21 CFR Part 11. Compliance includes, but is not limited to: systems validation, audit trail of the document to ensure no changes or only tracked changes have been made after certification, and access controls. Please contact riso@partners.org with any questions about technologies.

- **Do all pages of the informed consent form need to be scanned, or just the signature page(s)?**
    - All pages of the informed consent document should be scanned, verified and certified.

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6 Federally Funded Research

6.1 Federally Funded Research

6.1.1 Proposal Development and Submission

Writing an NIH Data Management and Sharing Plan (DMS Plan)

With the NIH Data Management & Sharing Policy effective Jan. 25th, 2023, PIs are required to submit Data Management & Sharing (DMS) Plans for most NIH-funded mechanisms. The policy requires the submission of a DMS Plan that outlines how Scientific Data and any accompanying metadata will be managed and shared, taking into account any potential restrictions or limitations in the six plan components (researchers should refer to the MGB policy on Limitations and Restrictions for Data Sharing).

The NIH does not require any particular tool to be used to write a DMS Plan, however, MGB has drafted a template with required language that is strongly recommended.

Additional information on writing a plan, NIH and MGB plan templates, and information on choosing a repository is available at the following link: 2023 NIH Data Management & Sharing Policy (sharepoint.com).

6.1.2 Just-in-Time (JIT)

Investigators submitting a funding proposal to the NIH may receive a notification from the funding agency that their grant proposal is likely to be funded and that more information is required to secure the funding – a JIT notice. If there are human subject activities included in the funding proposal, one of the JIT requirements will be to provide documentation of IRB approval. Investigators should follow the procedure below during the JIT process:

- **Real JITs - Submit the IRB protocol in Insight at this stage:** After the automatic notification, for proposals most likely to be funded, a more formal and detailed request is sent to the investigator by the grantor agency's Grants Management Specialist (the Real JIT).

See examples of Real JIT requests in Appendix A below.

PIs should not submit an Initial Review application or an Amendment with new funding to the IRB until they have received a notification from an NIH grants specialist (Real JIT), as this ensures the application will be funded. The application will be returned to the PI if the submission does not include a notification from a grants specialist (i.e., a Real JIT request).

6.1.2.1 What to Submit to the IRB for Approval

- The JIT documentation must be included in the IRB submission.
- The IRB will prioritize Real JIT submissions.
- For existing studies, the Real JIT documentation should be included with an amendment submission.

6.1.2.2 JIT and Clinicaltrials.gov Registration

For protocols which are required to be registered on ClinicalTrials.gov per NIH and/or FDA criteria, initial IRB approval is contingent upon completion of registration on ClinicalTrials.gov (receipt of National Clinical Trials number or NCT). The review of new Clinical Trials.gov registrations can take 2-4 weeks. It is not uncommon for the ClinicalTrials.gov reviewers to issue queries or comments that must be resolved before the registration is approved and the NCT number is assigned. If the timelines for completing registration on ClinicalTrials.gov, receiving IRB approval, and release of NIH funds are not compatible with each other, please email the HRA Compliance and Education Office at ClinicalTrials.gov@mgb.org to discuss your circumstances.

6.1.2.3 JIT and NIH Data Management and Sharing Policy

NIH Data Management and Sharing (DMS) plans are reviewed by NIH program officers who may request changes or modifications to the plan at JIT. When a JIT is received, Research Management initiates an email deliverable, sent to the PI from Insight to verify information regarding their research proposal. Based on that information, an additional ancillary review of the DMS plan by the Mass General Brigham Joint Committee may be triggered. When triggered, the Joint Committee will review the DMS plan and determine if the proposal is in compliance with MGB institutional policy. If it is not in compliance, the committee will work with the PI on revisions to the plan in accordance with MGB policy. Review and approval of DMS Plans by the Joint Committee will not hold up the submission of JIT materials. Revised DMS Plans may be submitted via JIT or NIH's Prior Approval mechanism through MGB Research Management.

6.1.3 When the Funding Proposal Does Not Describe a Specific Research Study, But Intends to Use Human Subjects (Research Protocol To Be Developed During the Project Period)

Under the Common Rule (45 CFR 46.118) certain types of applications for grants are submitted with the knowledge that participants may be involved, but definite plans may not be described in the funding application or proposal. These include:

- Institutional-type grants when the selection of specific projects is the institution's responsibility;
- research training grants in which the activities involving participants remain to be selected; and,
- projects in which human participants' involvement will depend upon the completion of instruments, prior animal studies, or purification of compounds.

In these cases, Federal agencies may still require investigators to obtain a determination from the IRB before an award is granted or before use of funding is allowed.

In order to meet federal agency requirements, the IRB will issue a "118 determination" letter for projects that meet the above definition, where the human research component is yet to be developed. To request a "118 determination," submit the following to the IRB via email (partnersirb@partners.org):

- Description of the study
- Description of the human research components that need to be developed
- Name of the federal agency and notification from the funder requesting IRB review
- A copy of the grant

After the human research components are developed, the investigators must submit an application to the IRB and obtain IRB approval prior to enrolling participants.

6.1.4 NIH Sponsored Research

The NIH has established a policy that requires each of its Institutes and Centers (IC) to have a system for the appropriate monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials. Investigators must comply with monitoring requirements of the relevant funding agency in addition to those of the IRB.

The establishment of DSMBs is required for multi-site clinical trials involving interventions that entail potential risk to the participants. This would include, in most cases, phase III clinical trials. A phase III trial frequently compares a new treatment to a standard treatment or to no treatment, and treatment allocation may be randomly assigned, and the data masked.

These studies usually involve a large number of participants followed for longer periods of treatment exposure. Even if the short-term risk to a participant is small, one must consider the long-term effects of a study agent and whether significant safety or efficacy differences emerge between the control and study groups for a masked study. An IC may require a DSMB to perform monitoring functions. This DSMB would be composed of experts relevant to the study and would regularly assess the trial and offer recommendations to the IC concerning its continuation.

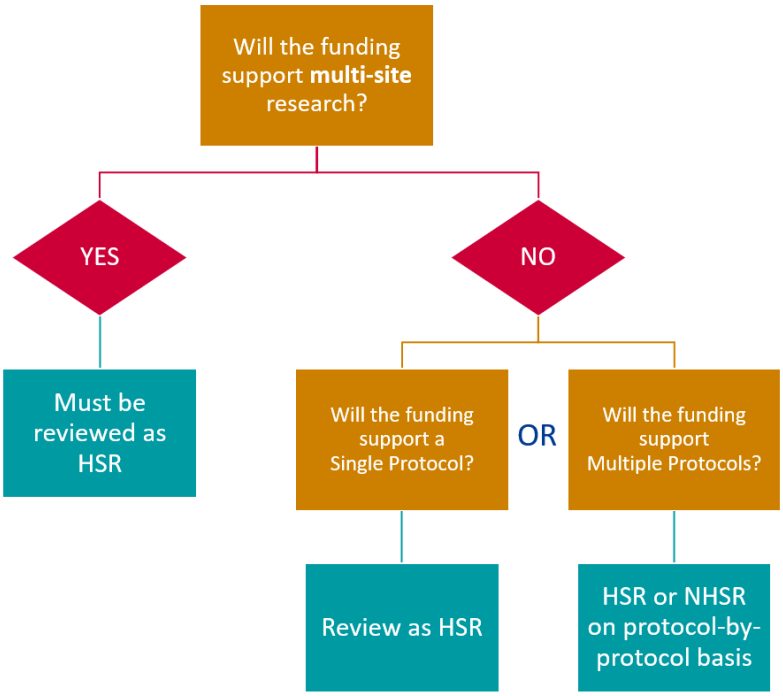
6.1.5 When Mass General Brigham Site is Prime Awardee of Federal Funding that Supports BOTH Human Subjects (HSR) and Not Human Subject Research (NHSR)

If Mass General Brigham is the primary awardee of federal funding, and if the funding supports both human subject research (HSR) and not human subject research (NHSR) aims or activities, the Mass General Brigham IRB ("IRB") will consider the funded research as follows:

- If the funding in its entirety is used to support a single protocol, the protocol will be reviewed as HSR.

- When MGB is the only participating site, and the funding will support multiple protocols:
    - Protocols that meet HSR criteria may be reviewed as HSR.
    - Protocols that meet NHSR criteria may be reviewed as NHSR.

- Research involving multiple sites:



- Example: If the funding supports a multi-site protocol and the role of Mass General Brigham investigators is only to receive de-identified data or materials from other sub-award institutions or organizations that are conducting the HSR portions of the grant, Mass General Brigham's role then is considered NHSR.
    - However, since this grant supports HSR activities and NHSR activities, the grant is considered to be HSR overall.
        - Similarly, if the funding supports multisite research, the same principle applies.
        - The IRB, by regulation, cannot make a NHSR determination based only on Mass General Brigham's role since we are the prime awardee, therefore we consider the research to be HSR. We must make a determination based on all activities conducted at all sites.
        - This is the case regardless of whether Mass General Brigham serves as the single IRB or cedes review to another IRB.

Note: When Mass General Brigham is the primary awardee of federal funding that supports human subject research and animal research, investigators should consult with the Institutional Animal Care and Use Committee (IACUC) at their site to obtain a determination for animal research.

6.1.5.1 Sub-awards

If Mass General Brigham receives a sub-award and is engaged in NHSR activities, the IRB will review such applications as NHSR if it does not meet the regulatory definition of human subject research. Investigators can obtain a NHSR determination from the IRB by submitting an NHSR application via REDCap.

6.1.6 Completing the Insight Application

It is not necessary for the grant title to match the title of the IRB application as one grant may cover many different types of applications, which may need to be submitted separately to the IRB. The IRB is also not responsible for ensuring that grantees are listed as study staff.

6.1.7 Grants with Multiple Aims

If a grant supports several different aims, and if each aim builds on the results of previous aims, investigators should submit separate protocols for each aim. If all aims are submitted under one protocol, the IRB will likely not have all the information necessary for all aims in order to grant approval. Hence, the IRB will require that each aim be submitted as its own protocol application.

Having each aim as its own IRB protocol application will also facilitate registration and results reporting on ClinicalTrials.gov. For protocols which do not meet the regulatory criteria for ClinicalTrials.gov registration, it will be the responsibility of the PI to determine whether they wish to register them voluntarily for publication or other reasons.

6.1.8 Appendix A

Real JIT Example:

Re: Information Required for Finalizing Consideration of your Grant Application **GRANT APPLICATION NUMBER :** [redacted]

Dear Dr. [redacted]

Your application referenced above is being considered for possible funding by the National Institute of Mental Health (NIMH). At this time, we are requesting additional/updated Just-In-Time (JIT) information, which was not required as part of the original application. If you have already submitted materials in response to a letter from the NIH Office of Extramural Research, and there have been changes, resubmission of the JIT is required before finalizing funding decisions. **This request does not constitute a commitment of funding: funding decisions require Council concurrence, Program selection, and Institute approval.**

NIMH strongly urges submission of all JIT information using the NIH eRA Commons Just-In-Time feature accessible at: https://public.era.nih.gov/commonsplus/home.era. Instructions may be found at: https://era.nih.gov/erahelp/commons/default.htm#cshid=1033. Please note that applicants may submit multiple separate documents and revisions, including budget revisions, revised specific aims, IRB Approval dates, and any other required information not previously included in an initial JIT submission.

Please provide the following items and/or follow-up information **within 10 business days** of the date of this request. Delays in submitting this information will delay any eventual award. If it is not possible to provide any part of this information, please communicate what item(s) will be lacking and when we might expect the information.

Updated "Other Support" information is needed for all active and pending other support (Federal, non-Federal, commercial, or institutional) for the principal investigator and all key personnel, excluding consultants. If other support is part of a larger project, such as a center or program project, please provide information for both the parent grant and subproject(s). If other support is provided under a consortium or contractual arrangement, indicate the source and provide information only on the particular subproject tied to key personnel on this application. An illustration of the preferred format and instructions is provided at: http://grants.nih.gov/grants/funding/phs398/othersupport.doc

In addition, if you have another NIH application currently pending, please submit a brief statement outlining how the career development activities and research plans encompassed by your career development application will be impacted or modified should the other pending application be supported. Please identify how these applications relate to one another, highlighting any areas of scientific or budgetary overlap and your plans to rectify this.

Any salary being provided to the K-awardee on a current NIH grant freed as a result of this career award may not be routinely rebudgeted. Any proposed retention of such funds must receive prior written

approval from the NIH awarding component. The NIMH will consider each request for the use of released funds on a case-by-case basis.

Per Guide Notice NOT-OD-17-094, https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-094.html, for effort not directly committed to the "K" award, "K" award recipients may devote effort, with compensation, on awards from Federal or non-Federal sources as the Program Director/Principal Investigator (PD/PI) or in another role (e.g., co-Investigator), as long the specific aims of the other supporting grant(s) differ from those of the "K" award.

In the last two years of mentored Career award support, recipients are encouraged to obtain funding from NIH either as Principal Investigator on a competing research grant award or cooperative agreement, or as project leader on a competing multi-project award. Salary funds may be requested on these grants as appropriate per the criteria and guidelines described in the NIH GPS 12.3.6.2
https://grants.nih.gov/grants/policy/nihgps/HTML5/section_12/12.3_eligibility.htm#Level

Certification of IRB approval of the project's proposed use of human subjects, which must be active at the time of the expected project start date and must be submitted prior to award. Provide verification of IRB approval date (valid within 12 months) and any IRB-imposed changes. Since IRBs may not meet on a regular basis, please alert the Grants Management Specialist (GMS) identified below of the anticipated IRB review date and the anticipated date for submitting the IRB approval to our office.

Evidence of Compliance with the education in the protection of human research participants. The NIH requires certification that all key personnel have completed an educational program in the protection of human subjects. (See NIH GPS 4.1.15.5
https://grants.nih.gov/grants/policy/nihgps/HTML5/section_4/4.1_public_policy_requirements_and_objectives.htm#Human3). NOTE: Key personnel include all individuals responsible for the design and conduct of the study. This documentation must be in the form of a letter and signed by an institutional official. Training is available online at https://phrp.nihtraining.com/users/login.php. Additional information about this education requirement is available on the NIH Web site at: http://grants.nih.gov/grants/policy/hs_educ_faq.htm.

Tri-yearly Milestone Recruitment: This NIMH policy monitors the recruitment of participants in NIMH-sponsored clinical research studies proposing to enroll 150 or more subjects per study, and all clinical trials, regardless of size. Please refer to the automated Recruitment Milestone Reporting (RMR) system provided at: http://www.nimh.nih.gov/rmr. Contact your Program Officer if you have questions regarding this policy.

Authorizing Signatures: If JIT information is not submitted through the Commons JIT Feature, a cover letter containing the signature of the Authorized Organizational Representative (AOR) must be attached with the JIT document(s) submitted either by email or fax to (301) 480-1956 attention to the GMS indicated below.

Response to any scientific concerns raised in your application's Summary Statement will need to be addressed in writing and handled directly with your Program Officer with a copy to the GMS identified below. Depending on the nature of your application and its review, you may receive an additional request for scientific information. Thank you for your prompt attention to this request.

[redacted]
Grants Management Specialist
National Institute of Mental Health
6001 Executive Boulevard, Room 6126F, MSC 9605

6.2 Funding for Research Studies

Investigators may receive funding to conduct research. For studies that are funded, investigators must identify the source of funding in the Sponsor/Funding form in the Insight application (this includes linking and entering the Insight Agreement number) and ensure that the application submitted to the IRB is consistent with the funding.

It is not uncommon for a study to receive funding from multiple sources, and research activities as described in the IRB application must be consistent with those described across all of the grants or funding agreements. However, multiple sources of funding that support different types of research studies cannot be added under one application in Insight, as these must be submitted as separate applications to the IRB.

It is also possible that one funding award may include multiple studies which may have different specific aims, objectives, and populations. In addition, these studies may be conducted by different PIs and study teams or the same individuals could conduct the studies. These studies should be separately submitted for IRB review because differences in study scope, parameters, and risks may require different IRB review pathways (i.e., convened, expedited, exempt review) for different studies covered by the award.

6.2.1 New Funding Source for Existing Studies

If new funding changes the aims and research design or adds a new population or procedures that significantly differ from the current study, the IRB will require investigators to submit a new application. It is ultimately up to the IRB to determine when a new study will be required. If new funding is awarded to support the research as currently approved, then an amendment is appropriate.

The following information must be provided to the IRB when submitting an amendment for new funding:

- Description of the research activities supported by the funding source.
- If any of the research activities are new or different from what is approved in the study, include a description of those activities. If activities are not new or different, identify where the activities are described in the currently approved protocol (or where it was initially described e.g., either IR or other submission)
- Describe the changes being made to the study documents, if applicable.

If the funding does not relate to the existing study, a new study submission must be submitted to the IRB. For instance, existing health medical record studies may receive new funding that supports activities that differ from those approved by the IRB. Investigators may need to submit a new application in this instance, as the study may no longer be limited to reviewing health medical records.

If new federal funding involves domestic non-Mass General Brigham sites (e.g., federal funding awarded to Mass General Brigham with a sub-award to an external site or vice-versa), the Single IRB mandate may apply, and a new application may be required. Click here for additional information about Single IRB review.

If new federal funding is added to support the research, registration on ClinicalTrials.gov may become required per regulations if the protocol was not already registered. A ClinicalTrials.gov Ancillary Review will be triggered to confirm registration.

6.3 Research Supported by the Department of Defense

Research that is supported by the Department of Defense (DoD) or one of its components (e.g., Army, Air Force, Navy and Marine Corps) through a contract, grant, cooperative agreement, or other arrangement with Mass General Brigham must comply with DoD Regulations for "Protection of Human Subjects" at 32 CFR 219 and with DoD Instruction 3216.02. Other DoD component-specific requirements may also apply depending on the study.

This guidance is intended to highlight some of the primary issues for investigators when conducting DoD-supported research but is not a substitute for investigators to obtain project-specific information about DoD's requirements from the applicable DoD human research protection administrator as directed below. Investigators are expected to include information relevant to and address any applicable DoD requirements in their protocol submissions.

When Mass General Brigham receives DoD funding for human-subjects research, the recipient institution, at the request of DoD, will sign a DoD Addendum to its Federal wide Assurance (FWA) attesting that the institution will comply with applicable federal regulations and DoD requirements for the protection of human subjects in research.

6.3.1 DoD Instruction3216.02 Requirements

The DoD and its components have adopted the "Common Rule" Federal policy for the protection of human subjects in research. DoD's implementation of the Common Rule is found at 32 CFR Part 219. Additional DoD policies and requirements for the protection of human subjects are described in DoD Instruction 3216.02.

Most of the DoD requirements outlined in DoD Instruction 3216.02 are consistent with Mass General Brigham Human Research Office policies and procedures. However, the DoD has imposed certain restrictions on the use of surrogate consent and waiver of informed consent and additional protections for research participants involving greater than minimal risk.

Investigators should be aware of these and other additional requirements when developing proposals for DoD support. Some of the main additional requirements are described below.

Because components of DoD may have additional requirements for human subject protection, investigators should obtain DoD component-specific requirements from the applicable DoD human research protection administrator when applying for funding.

1. **Scientific Merit**
   The IRB must consider the scientific merit of non-exempt research.

2. **Education and Training**
   DoD may impose additional education and training requirements on investigators beyond those required by Mass General Brigham. Investigators should contact their DoD human research protection administrator for information about specific education requirements.

3. **Additional Protections for Human Subjects**
   DoD-supported research must meet the additional protections for pregnant women, human fetuses, neonates, prisoners and children in 45 CFR 46, Subparts B, C, and D unless modified by DoD as below:

   a. Pregnant Women, Human Fetuses, and Neonates as Subjects
   When applying Subpart B regarding pregnant women, human fetuses, and neonates, the phrase "biomedical knowledge" shall be replaced with "generalizable knowledge." The applicability of Subpart B is limited to research involving pregnant women as human subjects involved in research that is more than minimal risk and includes interventions or invasive procedures to the woman or the fetus or

involving a fetus or neonate as human subjects. Research involving human subjects using fetal tissue must comply with sections 289g-289g-2 of US Code Title 42 When applicable, investigators are required to provide an assessment of risks and potential benefits to pregnant women and fetuses, nonviable neonates and neonates of uncertain viability and children in the Mass General Brigham Insight Human Research Application.

b. Prisoners

When applying Subpart C regarding prisoners, Mass General Brigham relies on the Harvard School of Public Health (HSPH) IRB for review of research involving prisoners. Contact the Mass General Brigham IRB Office before submitting research involving prisoners.

When a previously enrolled participant becomes a prisoner, and the researcher asserts to the IRB that it is in the best interest of the prisoner-participant to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner- participant may continue to participate until the convened HSPH IRB can review this request to approve a change in the research protocol and until the DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB Chair shall require that all research interactions and interventions with the prisoner-participant (including obtaining identifiable private information) cease until the convened HSPH IRB can review this request to approve a change in the research protocol.

The convened HSPH IRB will promptly review the research protocol to ensure that the rights and wellbeing of the human participant, now a prisoner, are not in jeopardy. If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened HSPH IRB may approve a change in the study to allow this prisoner-participant to continue to participate in the research. This approval is limited to the individual prisoner-participant and does not allow recruitment of prisoners as participants.

c. Detainees or Prisoners of War

Research involving a detainee or a prisoner of war as a human participant is prohibited. This prohibition does not apply to activities covered by investigational new drug or investigational device provision when for the purposes of diagnosis or treatment of a medical condition in a patient. Such treatment may be offered to detainees or prisoners of war with their informed consent when the medical products are investigational and only when the same product may be available to DoD-affiliated personnel consistent with established medical practices.

d. Children as Participants

When applying Subpart D to children, the exemption 45 CFR 46 104(d)(2) of research involving survey or interview procedures or observation of public behavior does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

e. Military Personnel as Participants

Investigators should describe the procedures for recruitment of any military personnel in the protocol submission. The recruitment plan should adhere to the following DoD requirements for selection of participants:

If the human participant research involves DoD-affiliated personnel, the principal investigator must receive approval from the DoD-affiliated personnel's command or DoD Component to conduct the research. If the human participant research takes place on a DoD facility, the principal investigator must also receive approval from the command or DoD Component responsible for the facility.

Superiors (e.g., military, and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decision of their subordinates (e.g., junior enlisted personnel and equivalent civilians) regarding participation as participants in research.

Superiors of Service members (e.g., unit officers, senior NCOs and equivalent civilians) in the chain of command must not be present at any human participant recruitment sessions or during the consent process for DoD-affiliated personnel. When applicable, superiors excluded from these recruitment sessions will be given the opportunity to participate in the research in a separate recruitment session.

Service members and all Reserve Component and National Guard members in a federal duty status are considered to be adults. If a Service member, Reserve Component or National Guard member in federal duty status, student at a Service Academy, or trainee is under 18 years of age, the IRB must carefully consider the recruitment process and the necessity of including such member as a human participant.

For research that involves more than minimal risk to participants and when recruitment occurs in a group setting, the IRB will appoint an ombudsman. The ombudsman must not have a conflict of interest with the research or be part of the research team and must be present during the recruitment in order to monitor that the voluntary involvement or recruitment of the Service members is clearly and adequately stressed and that the information provided about the research is clear, adequate, and accurate. The ombudsman should be available to address DoD-affiliated personnel's concerns about participation.

f. DoD Civilians as Participants
DoD Civilians must follow their organization's policies regarding the requirement to obtain permission to participation in research involving human participants. As above, supervisors are prohibited from influencing the decisions of their subordinates regarding participation in research and may not be present at any human participant recruitment sessions or during the consent process. When applicable, supervisors will be afforded the opportunity to participation as human participants in a separate recruitment session.

4. Informed Consent

No DoD component may support research involving a human being as an experimental participant without requiring the prior informed consent of the participant with certain limited exceptions described below. Investigators should take these restrictions into consideration when describing the consent process in the protocol submission.

a. DoD-affiliated Personnel as Human Participants
In order to approve research involving DoD-affiliated personnel as human participants, the IRB must determine whether the consent document must include, if applicable, potential risks for the revocation of clearance, credentials or other privileged access or duty.

b. Legally Authorized Representatives
For research involving a human being as an experimental participant to which Section 980 of Title 10, U.S.C., applies, informed consent must be obtained in advance from the experimental participant or the participant's legal representative (consistent with Part 219 of Title 32, CFR, if the participant cannot

consent). If consent is obtained from the participant's legal representative, the intention of the principal investigator must be for the research to be beneficial to the participant.

c. Waiver of Informed Consent
The requirement for prior informed consent may be waived by DoD officials if all of the following conditions are met:

- The research is to advance the development of a medical product necessary to the DoD;
- The research may directly benefit the individual experimental participant; and
- The research is conducted in compliance with all other applicable laws and regulations.

Research subject to DoD requirements is prohibited from using an exception from consent in emergency medicine research unless a waiver is obtained from the Secretary of Defense.

5. Research-related Injury

All human participants research that is determined to be greater than minimal risk must meet the requirement of Section 219.116 of Title 32, CFR, to provide participants with an explanation as to whether any compensation and any medical treatments are available for research–related injuries.

a. Explanations must include a statement that participants may, for the duration of the study, be eligible for health care services for research-related injuries at a military treatment facility, in accordance with Part 108 of Title 32, CFR. This eligibility for health care services extends beyond participants' participation in the study to such time after the study has ended.

b. The Mass General Brigham HRPP must document how institutions will care for participants with research-related injuries, including injuries that are the direct result of activities performed by DoD-affiliated personnel in studies that are collaborative with a non-DoD institution.

c. Participants injured in DoD-conducted research may obtain care for such injuries at a DoD medical treatment facility on a space-available basis during the pendency of the research study.

6. Compensation of DoD-affiliated Personnel

- Compensation to DoD-affiliated personnel for participation in research while on duty is prohibited. U.S. military personnel may be compensated for research if they participate in the research when not on-duty.
- Federal employees while on-duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.
- Non-Federal persons may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

7. Multi Site Research and International Research

Single IRB is required for DOD supported multi-site research subject to the 2018 Common Rule. A reliance agreement must be executed between the reviewing IRB and the relying institution, outlining each party's roles with respect to the research under review.

DoD institutions collaborating in human subjects research with non-DoD institutions may rely on the collaborating non-DoD institution's IRB if all of the following conditions are met:

a. The DoD institution determines the non-DoD institution has an appropriate federal assurance or that a federal assurance is not required.

b. The non-DoD institution's IRB is registered in accordance with Subpart E of 45 CFR 46.

c. The DoD institution and the non-DoD institution enter into an agreement specifying that the non-DoD IRB will apply the DoD requirements specified in DoD Instruction 3216.02.

d. The DoD institution reviews the protocol to ensure all applicable local and DoD requirements are addressed in the protocol.

When the research is conducted outside the United States or its territories, and the research involves participants who are not U.S. citizens or DoD personnel, the investigator must obtain permission of the host country and follow Mass General Brigham Human Research Office policy and procedures for research conducted outside the United States or its territories. See Mass General Brigham IRB policy on Review of Human-Subjects Research Conducted Off-Site.

8. Surveys of DoD Personnel

Surveys of DoD personnel generally must be submitted to DoD for review and approval.

9. Reporting Noncompliance and Research Misconduct

a. Noncompliance
Allegations of noncompliance related to DoD-supported research must be investigated by the Mass General Brigham IRB in accordance with applicable support agreement, and furnished to the supporting DoD organization via the HRPO. Reports of noncompliance must be submitted in accordance with the Mass General Brigham IRB policy on Noncompliance in Human-Subjects Research and reporting requirements on Reporting to Institutional Officials and Regulatory Agencies.

b. Research Misconduct
DoD must be notified of any allegations of research misconduct and misconduct proceedings in DoD-supported research. The requirement to report is consistent with the Mass General Brigham Policy and Procedures for Handling Allegations of Research Misconduct to also follow any specific requirements of the funding agency. Reports of allegations of research misconduct and misconduct proceedings should be coordinated with the relevant institutional Research Integrity Officer.

10. Additional Reporting Requirements

The following findings in DoD-supported research must be promptly (within 30 days) reported to the DoD human research protection officer:

- Any unanticipated problems involving risks to participants or others
- Any serious or continuing noncompliance
- Any suspension or termination of IRB approval
- When the organization is notified by any Federal department, agency or national organization, official governing body of a Native American or Alaskan native tribe, other entity, or foreign government that Mass General Brigham's DoD-supported research is under investigation.

For DoD-supported research, the principal investigator must report the following within 30 days to the DoD human research protection officer:

- IRB approved changes to human participant research that involve changes to principal investigators or institutions; decreased benefit or increased risk to participants in greater than minimal risk research, addition of vulnerable populations, or DoD-affiliated personnel as participants
- Change in status when a previously enrolled human participant becomes pregnant, or when the researcher learns that a previously enrolled human participant is pregnant, and the protocol was not reviewed and approved by the IRB in accordance with Subpart B of 45 CFR 46
- Change in status when a previously enrolled human participant becomes a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with Subpart C of 45 CFR Part 46
- Results of IRB continuing review, if required
- Study closure
- Change of reviewing IRB

11. Records

Mass General Brigham IRB records, including records that document compliance or noncompliance with DoD Instruction 321602 must be accessible for inspection and copying by authorized DoD representatives.

6.4 Certificates of Confidentiality (CoCs)

Certificates of Confidentiality (CoCs)are issued by the National Institutes of Health (NIH) and other HHS agencies to protect identifiable, sensitive research information from forced disclosure in civil, criminal, administrative, legislative, or other proceedings, whether federal, state, or local. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for participants, such as damage to their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help to minimize risks to participants by adding an additional level of protection for maintaining confidentiality of private information.

Any investigator or institution conducting research protected by a Certificate of Confidentiality **shall not**, without the specific consent of the individual to whom the information pertains, disclose identifying information to any court or other person not connected with the research.

Disclosure of protected information is permitted only when:

1. Required by Federal, State, or local laws;
2. Made with the consent of the individual to whom the information, document, or biospecimen pertain, including disclosure necessary for an individual's medical treatment; or
3. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human participants in research.

The consent form must include information about the protections provided by the certificate and any restrictions.

6.4.1 Requests for Information Pursuant to Subpoena, or Federal, State or Local Civil, Criminal, Administrative, Legislative or Other Proceeding

- Whenever you receive requests for information related to the above, contact the Office of the General Counsel.

6.4.2 CoC Frequently Asked Questions (FAQs):

- **What is a Certificate of Confidentiality?**
  - A certificate of Confidentiality protects the privacy of research participants enrolled in biomedical, behavioral, clinical or other research. With limited exceptions, researchers may not disclose names or any information, documents or biospecimens containing identifiable, sensitive information. The Certificate prohibits disclosure in response to legal demands, such as a subpoena.

- **What information is protected by a Certificate?**
  - Certificates protect "covered information." Covered information includes names or any information, documents, or biospecimens containing identifiable, sensitive information related to a research participant. In addition, if there is at least a very small risk that information, documents, or biospecimens can be combined with other available data sources to determine the identity of an individual, then they are also protected by the Certificate.

- **Do the requirements of a Certificate apply to copies of information shared for other research?**
  - Yes. The protection covers all copies of information collected or used by the investigator in the research covered by the Certificate, even those copies that are shared for other research.

- **How long does a Certificate's protection last?**
  - The protection of the Certificate lasts in perpetuity. However, data collected after a Certificate expires or NIH funding ends may not be protected.
  - For NIH-funded research, a Certificate protects the information that you collect or use during the period in which your research is funded by NIH. If the study continues after your NIH funding ends and you want Certificate protection for new information that will be collected, you should request a Certificate following the process for non-NIH funded research.
    - You may want continued protection, for example, if you were collecting new information from participants or enrolling new participants after the period in which the research was funded by NIH.
  - If a research project was issued a Certificate and continues under a no-cost extension, the research is covered by the Certificate for the duration of the no-cost extension.

- **How long is a CoC Valid?**
  - NIH Funded Studies: CoCs automatically cover research activities and do not need to be extended or amended while the research remains funded by NIH. If there is a lapse in funding for any reason, the COC protections might not apply to information collected during that time period.
    - However, CoC protections continue for the duration of a no-cost extension.

- If the NIH funding ends, the study will no longer be deemed issued a CoC. While CoC protections remain in perpetuity for already collected or used information, a new CoC will need to be obtained in order to cover any new data collected from already enrolled participants or any new participants. See the CoCs for Research Not Funded by NIH page for additional information on requesting a non-NIH funded CoC through the online NIH CoC System. If NIH funding will or has ended and enrollment and data collection are complete, there is no need to request a new CoC.
- Other CoCs: Check with the issuing agency for information about expiration.

- **Does the NIH CoC policy apply to training awards include F, K, and T awards?**
  - CoCs are issued for applicable NIH funded research. In F and K awards, NIH is funding the research by providing direct support to the Principal Investigator (PI) to conduct a specific research project and a CoC would be automatically issued. In general, most T awards are not providing funding for a research project but instead are providing funding to allow trainees to work for a short time period on a mentor's project that has a separate source of funding.
    - Thus, the T award would not provide CoC protection for the mentors' projects.
    - Note that the mentor projects may have CoC protection if they are funded by NIH under another mechanism (such as an R01 award). In a minority of T awards, the trainees conduct their own unique research project; in such cases where the award is supporting the conduct of the research, the CoC would be issued automatically through this award.
      - But most T awards simply provide a training opportunity by allowing trainees to work for a short time period on a mentor's project that has another separate source of funding (not through the T award).

- **What disclosures are allowed?**
  - The CoC allows the following disclosures:
    - If required by Federal, State or local laws (e.g., reporting child, elder abuse, communicable diseases) – but excluding civil, criminal, administrative, legislative proceedings
    - For medical treatment with the consent of the individual
    - With the consent of the individual
    - For other research that is in compliance with human subjects protection regulations

- **What disclosures are prohibited?**
  - Disclosing or providing, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name or any information, document or biospecimen that contains identifiable sensitive information that was compiled or generated for the purposes of the research; unless, that individual gives consent for the disclosure.
  - Disclosing or providing to any other person not connected with the research the name or any information, document or biospecimen that contains identifiable sensitive information that was compiled or generated for the purposes of the research; unless, that individual gives consent for the disclosure.

- **Which agencies issue a CoC?**

- The National Institutes of Health (NIH), the Centers for Disease Control (CDC), Food & Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA), Indian Health Service (HIS), and Health Resources & Services Administration (HRSA) issue CoCs.
- Investigators whose research is funded by CDC, HRSA, IHS, or SAMHSA should contact the Certificate Coordinators at their funding agency to determine how to obtain a CoC.
- Investigators whose research is operating under an IND or IDE and is under the authority of the FDA should contact the FDA Certificate Coordinators at the relevant Center.
- For more information about the agencies, review the table at the end of this guidance.

- **Which Federal agencies currently issue a CoC automatically upon award of funding?**
  - The NIH, CDC, and the FDA* issue CoCs automatically as part of the funding for any research using identifiable, sensitive information.

  - *This applies to studies funded by the FDA. Research under FDA oversight but not funded by the FDA do not receive automatic CoCs.

- **What is meant by identifiable, sensitive information?**
  - The statute that governs Certificates of Confidentiality broadened the meaning of sensitive, identifiable information and focuses more directly on identifiability. Identifiable, sensitive information is information about an individual, gathered or used during biomedical, behavioral, clinical, or other research, through which the individual is identified, or there is at least a very small risk that some combination of the information, a request for the information, and other available data sources could be used to determine the identity of an individual.
  - Identifiable, sensitive information includes but is not limited to name, address, social security, or other identifying number; and fingerprints, voiceprints, photographs, genetic information, tissue samples, or data fields that when used in combination with other information may lead to identification of an individual.

- **What are the recipient's responsibilities under a Certificate?**
  - Any investigator or institution issued a Certificate shall not:
  - Disclose or provide covered information, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding; or
  - Disclose or provide covered information to any other person not connected with the research.
  - Researchers with a CoC many ONLY disclose identifiable, sensitive information in the following circumstances:
  - If required by other Federal, State, or local laws, such as for public health reporting of communicable diseases or child or elder abuse reporting
  - If the participant consents; or
  - for the purposes of scientific research that is compliant with human participants' regulations
  - As a PI, what are my responsibilities if I have a CoC?
  - You are expected to:
  - Be aware of which disclosures are permitted and which are prohibited.

- Notify sub-awardees and any secondary users of the covered data/specimens that there is aCoC and what protections and disclosure restrictions must be in place
- Contact the Office of General Counsel in the event of a request for identifiable sensitive data/biospecimens for the purposes of a legal proceeding. Do not disclose the information.

- **How will research participants be informed?**
  - The only notification will be via the informed consent form (ICF) or an Information/Fact Sheet that includes language describing the protections with a CoC. The consent form must include information about the protections provided by the certificate and any restrictions.

- **Are summary results of research prohibited from disclosure by Certificates?**
  - NIH generally does not consider summary research results, such as genomic summary results or summary results of clinical trials, to be identifiable, sensitive information as summary results are not "about an individual," but rather, are about a group of individuals. Moreover, summary results generally pose less than a very small risk that individuals could be re-identified, even when used in conjunction with other available data sources.

- **Is it possible to share information protected by a Certificate with other researchers? Can such information be shared openly (e.g., on a public website without any requirements for download)?**
  - Information protected by a Certificate can be shared openly on a public website only where otherwise authorized to be disclosed by the statute, for example, if participants have consented to such sharing. The NIH Policy on Certificates of Confidentiality expects that the recipient of a Certificate will ensure that an investigator or institution who receives a copy of information protected by a Certificate understands that they are also subject to the requirements of subsection 301(d) of the Public Health Service Act.

- **CoCs are not new, what has changed?**
  - The 21st Century Cures Act introduced two changes:
  - CoCs are now *automatically issued* for research involving identifiable sensitive data or biospecimens funded by an HHS Agency (NIH, FDA, CDC, HRSA, SAMHSA). There is no longer a need to proactively apply for a CoC if funded by one of these agencies.
  - The old CoC protects an investigator from being forced to disclose research information pursuant to Federal, State or local civil, criminal, or legislative proceedings. The new policystates that investigators are <u>prohibited</u> from making any such disclosures of identifiable sensitive information.

- **Can the IRB require a CoC for my non-federally funded or unfunded research?**
  - The IRB may require the researcher to obtain a CoC as a condition for IRB approval if identifiable sensitive information is being collected.

- **Can I obtain a CoC for my non-federally funded or unfunded research?**

- Investigators conducting research that is not federally funded in which identifiable, sensitive information is collected or used, may request a Certificate of Confidentiality (CoC) from NIH. Click here for more information.

- **What studies would NOT be eligible for a Certificate?**
  - Examples of research that would be ineligible to receive a Certificate include:
    - not research based,
    - not collecting or using identifiable, sensitive information pertaining to research participants,
    - a research program, rather than an individual research study/project
    - establishing and maintaining a data and/or biospecimen repository where the main source of the data and/or biospecimens was originally obtained for clinical care or other purposes, rather than research purposes,
    - not involving a topic that is within a mission area of the National Institutes of Health or the Department of Health and Human Services.

- **What kind of non-NIH-funded research is eligible for a Certificate?**
  - Generally, any research project on a sensitive health-related topic that collects names or other identifiable, sensitive information pertaining to participants, that has been approved by an IRB, and that is in compliance with the F*ederal Policy for the Protection of Human Subjects* at 45 CFR 46 (the Common Rule) or follows relevant provisions of the Common Rule relating to consent, may be eligible for a Certificate. The study topic (e.g., purpose, objectives, aims) must fall within a mission area of the National Institutes of Health or the Department of Health and Human Services. NIH issuance of Certificates is discretionary.

- **Are there any costs or fees associated with requesting a Certificate of Confidentiality from NIH for a non-NIH funded research project?**
  - There are no costs or fees associated with requesting a discretionary Certificate of Confidentiality for a non-NIH funded research project. Detailed information on Certificates of Confidentiality is available at the Certificate of Confidentiality website.

- **Can NIH issue a Certificate to me for a non-research activity with a vulnerable population?**
  - No. NIH is unable to issue a Certificate to an investigator or institution for non-research activities since these activities are not eligible for a Certificate of Confidentiality.

- **Where can I find more information about CoCs?**
  - The table below provides agency-specific information about CoCs. For multi-site studies, a coordinating center or lead institution can apply for a CoC on behalf of all participating sites.

Agency	CoC Information
National Institutes of Health	Automatically issued as a term of the grant or contract for NIH-funded research that involves collection of *sensitive identifiable information*. Researchers without NIH funding may submit an application for a NIH CoC. Click here for NIH CoC FAQs
Food and Drug Administration	Automatically issued as a term of the grant or contract for FDA-funded research that involves collection of *sensitive identifiable information*. For non-federally funded research operating under an IDE or IND, the FDA will consider requests to issue a *discretionary CoC*.
Centers for Disease Control	Automatically issued as a term of the grant or contract for CDC-funded research that involves collection of *sensitive identifiable information*.
Health Resources & Services Administration (HRSA)	Automatically issued as a term of the grant or contract for HRSA-funded research that involves collection of sensitive identifiable information.
Indian Health Service	Contact the IHS CoC Coordinator to request a CoC.
Substance Abuse & Mental Health Services Administration (SAMHSA)	Can be requested for studies with a SAMHSA grant or contract and that involve collection of *sensitive identifiable information*.
Department of Defense	Contact the Directorate of Human Research Protections for more information
Other federal agencies and non-federally funded research	Contact the federal agency for more information. The Agency for Healthcare Research & Quality (AHRQ) has its own privacy regulations which may apply; NIH will not issue a CoC for projects covered by AHRQ's regulations. Contact AHRQ for further information about their privacy regulations. Issuance of a CoC for research that is not funded by NIH is at the discretion of NIH. Click here for more information.

7 Reportable Events

7.1 Deviations and Noncompliance

Unplanned or unintentional deviations in IRB-approved research may occur during the conduct of a research study or be discovered during routine data monitoring activities of the sponsor or investigator.When an investigator discovers or is made aware of an unapproved deviation, they must report the deviation to the IRB as follows:

1. Unapproved **major deviations** must be reported to the IRB within five (5) working days/seven (7) calendar days of the date the investigator becomes aware of the unapproved deviation.
2. Unapproved **minor deviations** are to be recorded by the investigator in a protocol-specific Minor Deviation Log.

Unapproved deviations should be reported to the sponsor as outlined in the sponsor's protocol or research or investigative plan.

Every deviation needs to be evaluated for whether it negatively affected the rights, safety, or welfare of the participant, the risk: benefit assessment for the participant, and/or the integrity of the data (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) in order to determine if it's a major or minor deviation.

Deviations that have a significant impact on any of these factors are major. The same type of deviation, depending on its extent and significance, could be major or minor. For example, over-enrolling participants can be minor or major depending on total approved enrollment number, study population, and the total number over-enrolled. An out-of-window study visit can also be minor or major depending on the procedures performed at that study visit and how far it is outside the permitted window. For this reason, each deviation requires a case-by-case assessment of its exact details in order to appropriately categorize it. This should be done by the PI and not delegated to study staff. Minor deviations must be recorded on the Minor Deviation Log with an appropriate corrective action to address the issue and/or additional steps planned or taken that will prevent the deviation from happening in the future.

Investigators are responsible for monitoring their studies throughout the year for adherence to the IRB approved protocol. The purpose of this monitoring is to identify major deviations and identify trends in minor deviations that may indicate a systemic issue in how the study is being conducted, which could potentially negatively impact participants' rights, safety, or welfare or the integrity of the data. Frequent minor deviations of a similar nature should be reported to the IRB as a major deviation.

Investigators must follow the written protocol as approved by the IRB. Implementing changes without IRB approval must be reported to the IRB per policy. This applies to deviations from the protocol which are done intentionally or unintentionally, deviations which are identified before they occur but cannot be prevented, and deviations which are discovered after they have occurred. If deviations occur during the conduct of a research study, the investigator must assess whether each deviation is minor or major.

Investigators should assess whether more flexibility can be built into the protocol via amendment to reduce the number of changes that need IRB review, the number of protocol deviations, and non-compliance by investigators. Areas of flexibility might include broadening eligibility criteria, adding more flexible study visit or sample collection windows, allowing remote or electronic study participation/procedures. Flexibility and optional study procedures should always be evaluated in the context of the study design to ensure that the options can be practically implemented, and that evaluable data will still be collected to address study hypotheses, aims, and outcomes/endpoints.

7.2 Exception Requests

Investigators conducting human subject research approved by the Mass General Brigham IRB are required to submit proposed changes in approved research, including single participant or other limited exceptions, for review and approval prior to initiation of the change, except where necessary to eliminate apparent immediate hazards to participants.

7.2.1 Changes to Eliminate Apparent Immediate Hazards to Participants

Changes to study conduct to eliminate apparent immediate hazards to participants are permissible without prior IRB approval to protect the safety and welfare of enrolled participants. Investigators must report to the IRB any unapproved changes to study conduct which were made in order to eliminate apparent immediate hazards to participants. Such changes must be reported in an expedited manner using an Other Events submission, subsequent to the change being made.

7.2.2 Single Participant or Other Limited Exceptions

For planned exceptions from the protocol, for a single or more participants, a formal protocol amendment must be submitted to obtain IRB approval for the modified study procedure. Planned exception requests such as non-time sensitive enrollment of a participant who does not meet all eligibility criteria or planned modifications to an upcoming part of the protocol for an enrolled participant must be submitted as protocol amendments. The IRB will not approve planned or anticipated deviations as exception requests, unless the change is time-sensitive and relevant to only one participant as described below. Planned or anticipated changes to the protocol , for a single or more participants, need to be formalized through an amendment process; if they occur without an amendment, they are incurred protocol deviations and should be recorded/reported in accordance with deviation policies.

If the investigator submits an amendment to propose a protocol change, the investigator should not also submit an exception request to implement the change while the amendment is pending IRB review. The change cannot be implemented until the amendment has been approved by the IRB.

For unplanned exceptions, or planned exceptions for which there is insufficient time to get an amendment approved (i.e., <X days), the IRB will consider single participant or limited exceptions on a case-by-case basis. These requests must be submitted to the IRB in a prospective manner (i.e., before the change is implemented) as an Other Event submission and cannot be implemented until the IRB has approved the exception request. If there is any indication or plan that the same or similar exception request will be needed for additional participants in the future, an amendment to the protocol should be submitted. Typically, the IRB will not approve the same type of exception for a second participant. In most circumstances, such exception requests will be returned to the research team with the requirement to submit an amendment instead.

An exception request will not be approved by the IRB if the protocol change has already occurred without prior IRB approval, even if approval was obtained from another entity (e.g., study sponsor). Such change is then an incurred protocol deviation and should be recorded/reported in accordance with deviation policies.

For studies ceded to an external IRB, amendment and exception requests should be submitted to the IRB providing oversight.

7.3 When and How to Report Events to the IRB

7.3.1 Guidance for Reporting Events:

Certain events and new information require prompt reporting to the reviewing and/or relying IRBs, sponsors, and/or funding entities. These events include, but are not limited to, noncompliance, unanticipated problems, major deviations, information that represents new risks, suspensions by other regulatory agencies, and certain types of audit and inspection

outcomes. This guidance summarizes what types of events require reporting to the IRB or other Research Offices, details on how to submit/report, and associated reporting timeframes.

For guidance on what to include in Other Event submissions (OEs) (events that are reportable to the Mass General Brigham IRB) and Corrective and Preventative Actions (CAPAs), please review the information provided at the end of this document.

7.3.2 When Relying on an External Reviewing IRB:

****Important Note:** When the Mass General Brigham site is relying on an external (non-Mass General Brigham) IRB for review of the research (i.e., Cede Review), you **must** report to the external reviewing IRB and follow their reporting requirements. In addition, you **must** notify the Mass General Brigham IRB within the specified timelines, as indicated in the tables below. Please note that if the study is ceded to an external reviewing IRB, include documentation of the external IRB's determination of the event with your other event submission to the Mass General Brigham IRB. However, do not wait to submit; include as much information as possible and then submit the external reviewing IRB's determination once received.

7.3.3 Reporting Events when using either Mass General Brigham or an External IRB

	Mass General Brigham Reporting Timeframes			
Event Type	5 Working Days (of becoming aware of the event)	Continuing Review	Other	**How to Report**
An event that meets the definition of an **unanticipated problem involving risk to participants or others (UPIRTSO):** Any incident, experience, or outcome that meets ALL of the following: • Unexpected • Related or possibly related AND • Places participants or others at a greater risk of harm. Note: This includes: • **unexpected and related adverse events (serious or non-serious)** that place participants or others at a greater risk of harm, as well as • **expected and related adverse events** where the nature, frequency, or severity of the events exceeded what was expected and place participants or others at a greater risk of harm.	X	X		**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight **At Continuing review when Mass General Brigham is the reviewing IRB:** • Provide a list of these events and when they were reported to the IRB. • Provide detailed descriptions of any UAPs that have not previously been reported to the IRB.
	Mass General Brigham Reporting Timeframes			
Event Type	5 Working Days (of becoming aware of the event)	Continuing Review	Other	**How to Report**

Any event that meets the definition of an **Unanticipated Adverse Device Effect (UADE):** • Any **serious adverse event/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 participants.	X	X		**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight **At Continuing review when Mass General Brigham is the reviewing IRB:** • Provide a list of these events and when they were reported to the IRB. • Provide detailed descriptions of any UADEs that have not previously been reported to the IRB.
Protocol exception - a <u>planned</u> change in the conduct of the research for <u>one</u> participant.			X	**IRB approval <u>must</u> be obtained prior to implementation.** **Submit an Other Event (OE) in Insight.** Please note that in certain circumstances (e.g., when more than one participant is or will be impacted), submission of an amendment instead of or in addition to an OE may be required.
Changes initiated without IRB approval to alleviate an immediate hazard.	X			**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight
	Mass General Brigham Reporting Timeframes			
Event Type	**5 Working Days** (of becoming aware of the event)	**Continuing Review**	**Other**	**How to Report**

A Major Deviation that has the potential to negatively impact the participant safety or integrity of study data or affect the participant's willingness to participate in the study	X	X		**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight **At Continuing review when Mass General Brigham is the reviewing IRB:** • Provide a list of these events and when they were reported to the IRB. In addition, provide detailed descriptions of any Major Deviations that have NOT previously been reported to the IRB.
Minor Deviations			X	Must be documented on a deviation log maintained in the research records.
Frequent Minor Deviations of a similar nature should be reported to the Mass General Brigham IRB as a major deviation.	X			**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight
Complaints Complaint by/on behalf of a research participant that indicates that the rights, welfare, or safety of the participant have been adversely affected.	X	X		**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight **At Continuing review when Mass General Brigham is the reviewing IRB:** • Summarize any complaints, their resolution, and previous reporting to the IRB.
Complaints that the Investigator cannot resolve.	X			**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight
Breach of confidentiality or Violation of HIPAA	X			**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight
	Mass General Brigham Reporting Timeframes			
Event Type	**5 Working Days** (of becoming aware of the event)	**Continuing Review**	**Other**	**How to Report**

Incarceration of a participant in a protocol not approved to enroll prisoners	X	X		**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight **At Continuing review when Mass General Brigham is the reviewing IRB:** Describe incarcerated participants in the enrollment description.
New Information: • That indicates the frequency or magnitude of harms/risks or benefits of the research may be different than initially presented to the IRB. • Data Safety Monitoring Board/ Data Monitoring Committee reports or Annual Reports that state changes are needed. • Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol-black box warning. Revised Investigator Brochure (IBs) or Development Safety Update Reports (DSURs)	X			**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight ○ Revised IBs or DSURs can only be submitted via an Other Event if there are no changes being made to the protocol, consent, or other study documents. • Submit an Amendment as appropriate. Revised IBs should be submitted via Amendment when they are accompanied by other updated study documents.
Data Safety Monitoring Board reports, Data Monitoring Committee reports, and/or Annual Reports that indicates No Changes are required.		X		**Submit the report(s) at Continuing Review when Mass General Brigham is the reviewing IRB.**
Regulatory Agency Inspection or Audit (for example, FDA, NIH etc.) from any agency			X	Immediately email the Compliance & Education Office upon notification CEoffice@mgb.org Pages - Audits & Inspections (sharepoint.com) Microsoft Word - FDA Inspection SOP_January 2022 FINAL (sharepoint.com)
	Mass General Brigham Reporting Timeframes			
Event Type	**5 Working Days** (of becoming aware of the event)	**Continuing Review**	**Other**	**How to Report**

Inspection Observations or Audit Findings from any regulatory agency documenting: • noncompliance and/or • reportable outcomes (e.g., FDA form 483, untitled letters, warning letters, suspensions, etc.) .	X		X	You must work with the Compliance & Education Office on responses to Regulatory Agency Inspections, Observations, or Audit findings. CEoffice@mgb.org **Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight
Reportable Event(s) or Finding(s) resulting from Routine Audits, Monitoring Visits, Inspections, or Inquiries (by either internal or external entities)—where there are reportable findings. This would include, but is not limited to: • Non-compliance • Major Deviations • Unanticipated Problem(s) Involving Risk to Participants or Others (UPIRTSO) • Unanticipated Adverse Device Effects (UADE)	X			**Within 5 working days of becoming aware of the event, regardless of who is the reviewing IRB.** • Submit an Other Event (OE) in Insight
Routine Audits, Inspections, or Inquiries—where there are no reportable findings.			X	Maintain these reports in your research records. **No submission to the IRB is needed.**

7.3.4 Submitting Other Events and Identifying the Root Cause

What to submit with your Other Event:

While conducting research, even the most experienced and diligent research teams deviate from the approved protocol or experience unexpected events. These deviations and unexpected events must be identified, evaluated, and responded to in order to protect the rights, safety, and welfare of participants and others and the integrity of the research data.

When events occur that require prompt reporting (i.e., within 5 business days), it is important to provide to the IRB as much information as is known at the time of initial reporting. Even if limited or preliminary information is available and you are still collecting information, it is required that the IRB is informed within the specified reporting window, i.e., by submitting an Other Event in Insight. Inform the IRB if additional information is still pending, **but do not wait for it to submit the initial report.**

For more information about Identifying the Root Cause and developing a robust Corrective and Preventative Action Plan (CAPA), see the sections below.

In addition to completing the Other Event form in Insight, utilize the worksheet below to help gather information needed for IRB review. A Word version of the worksheet can be downloaded here: **Other Event Reporting Worksheet**.

7.3.5 Other Event Reporting Worksheet

Other Event Reporting Worksheet Please note that if the study is ceded to an external reviewing IRB, include documentation of the external IRB's determination of the event with your other event submission to the Mass General Brigham IRB	
Event Description and Root Cause Analysis	
Provide a detailed description of the event (If only limited or preliminary information is available, provide as many details about the event as possible at the time of initial reporting.)**:**	
Where (what location) did the event occur? *For multisite studies, please include the enrolling site's PI and the name of the site where the event occurred.	
When did you first learn of the event? • If the event is not being reported within the time frame required by policy, provide an explanation for the delay in reporting the event and an appropriate corrective action plan	
How did you first learn of the event?	
How many total participants have consented to and enrolled in the study?	
How many participants were impacted?	
Have all study records been checked to identify all affected participants or data? • If not, what are the plans to do so?	
What is/was the source of the event/problem? • Why/how did the event/problem occur?	
Is the problem specific to this study, or is it systemic (e.g., research group or department-wide)**?**	
PI Assessment of Event	
In the opinion of the PI, did the event have any impact on participant safety or potential to have an impact on participant safety? Why or why not? *Please note, if this is a single IRB study where Mass General Brigham is the IRB of record, then please describe the assessment of the site PI who enrolled the participant.	
In the opinion of the PI, was data integrity negatively impacted by the event? Why or why not? *Please note, if this is a single IRB study where Mass General Brigham is the IRB of record, then please describe the assessment of the site PI who enrolled the participant.	
****Include the following for Adverse Events and Other Events that may be Unanticipated Problems****	
Was the event/problem unexpected (in terms of nature, severity, or frequency)?	☐Yes ☐No ☐N/A-Event was not an AE or UP
	Why or why not:
	How did the Investigator make that determination?
	☐Yes ☐No ☐N/A-Event was not an AE or UP

Was the event/problem more likely than not related to participation in the research, or in other words, is there a >50% likelihood of the event having been caused by the procedures involved in the research?	Why or why not:	
	How did the Investigator make that determination?	
Is the adverse event or unanticipated problem serious (Yes or No)?	☐Yes ☐No ☐N/A-Event was not an AE or UP	
	Why or why not:	
Does the event/problem indicate that the research places participants or others at an increased risk of harm than was previously known or recognized?	☐Yes ☐No ☐N/A-Event was not an AE or UP	
	Why or why not:	
	How did the Investigator make that determination?	
Corrective and Preventive Actions		
Describe the actions(s) already taken to address the event/problem. • Including who was responsible for implementing the corrective actions and • a timeline for when the actions occurred.		
Describe the future action(s) that will be taken to address the event/problem. Please describe: • what is being done to prevent the event/problem from recurring in the future, • including who will be responsible for implementing the corrective actions and • a timeline for when the actions will be implemented. Potential corrective actions could include, but are not limited to: • Careful review of all study records, including informed consent, to identify similar issues. • Re-education of study staff (must be documented) o Re-education could include completion of relevant courses in HealthStream available from the HRA Compliance and Education Office Pages - Education (Human Research) (sharepoint.com) o Develop an internal study team monitoring plan to periodically assess compliance with approved protocols, research regulations, institutional policies, and compliance with the corrective actions.		
Have participants been notified, or will they be notified of the event? • Why or why not? • If notifying, specify which participants, e.g., all active participants, all consented participants, etc., along with justification for this plan.		
When applicable, will participants need to be re-consented considering the event? • If they do, please describe the timeline for re-consent.		
Will a study amendment (e.g., revisions to the protocol and/or consent form(s)) be needed to address the event? • **Note:** An amendment may be required for patient-facing documents/notifications, such as emails, letters, phone scripts, etc. o Revised Investigator Brochures (IB) should be submitted via Amendment if there are changes being made to the protocol, consent, or other study documents. • If **yes**, include: o What is the timeline for the amendment?		

○ Whether an amendment has already been submitted to the IRB or when an amendment will be forthcoming (e.g., The sponsor is working on changes to the protocol and informed consent, and an amendment will be submitted once received.	
How will the effectiveness of the corrective and preventive actions (CAPA) be determined? • How will effectiveness be determined and defined? • Who will be responsible for evaluating the effectiveness of the CAPA, and when will this occur?	

7.3.6 Immediate Corrective Actions:

If you become aware of a deviation or unexpected event, take **immediate corrective actions to** protect the rights, safety, and welfare of the participants. This is often done prior to IRB approval because of the immediate action needed.

Immediate corrective actions may be in the form of a phone call, scheduling an unscheduled office visit, ordering a redraw of labs/tests/and/or procedures, etc., to ensure the participant(s) are safe. Document the deviation, the reason it occurred, and all immediate corrections/actions taken and report to the IRB within the required timeframe(s).

Although it is important to take immediate actions to eliminate harm, you should be sure to report the event to all appropriate parties (sponsor, funding entities, CRO, etc.) and to the Mass General Brigham IRB in accordance with their reporting requirements and timeframes (outlined in the table above).

7.3.7 Root Cause Analysis (RCA):

A root cause analysis (RCA) is the process of identifying and documenting the root cause of problems in order to identify appropriate solutions. RCAs should focus on identifying underlying problems that contribute to errors or issues rather than focusing on mistakes made by individuals.

It is important to identify the cause or source of a problem or issue so that it can be resolved to prevent recurrence. There may be multiple reasons or causes that contribute to a problem. Conversely, there may be multiple methods to resolve each cause. The **root cause** is the initiating, most basic cause of a problem that may or may not lead to a chain of causes or other problems. Eliminating the root cause should prevent recurrence.

Steps:

1. Identify/define the problem.
2. Collect data.
    - Interview those impacted by the problem.
    - Interview those people responsible for the problem, if applicable.
3. Identify causal factors.
    - **Keep asking "why" and "how" until you reach the root cause.**
4. Determine the root cause.
5. Develop corrective and preventative actions.
6. Implement actions.
7. Evaluate for effectiveness.

Things to consider:

- Careful review of all study records, including informed consent, to identify similar issues.
- Re-education of study staff (must be documented) Re-education could include completion of relevant courses in HealthStream from the HRA Compliance & Education Office
    - Pages - Education (Human Research) (sharepoint.com)
- Develop an internal study team monitoring plan to periodically assess compliance with approved protocols, research regulations, institutional policies, and compliance with corrective actions.
- If participants need to be notified of any of the errors or there needs to be re-consented – how do you propose to do that, and specifically for which participants?
- Any data/specimens that were collected without consent or from ineligible participants – do you plan to retain or sequester these?
    - Are you able to get consent?
    - If not, how do you plan to move forward with them?
- Are you making changes to the protocol?
    - If so, detail and explain how they should alleviate future errors.
        - You will also need to document when staff will be trained on these changes.
- What, if any, staffing changes are required, and how will they contribute to preventing the issue in the future?
- What if any workflow changes are being made in your lab/clinic/research unit, and how will they contribute to preventing the issue in the future (this can include the creation of new tracking forms, new checklists, any "behind-the-scenes forms" to ensure research procedures are done and documented.
    - It can also include adjusting and identifying what staff are responsible for what actions.
- What, if any, workflow changes are being made between your lab and departments with whom you collaborate, and how will they contribute to preventing the issue in the future?
- How will the above individuals – those involved in the identified process changes or new personnel – be educated on these changes?

Please note that in addition to your outlined corrective and preventative actions, the IRB may impose other required actions. See the next section of this guidance for more details about CAPAs.

7.3.8 Corrective and Preventive Action (CAPA) Plans:

Corrective actions are those taken to resolve a problem, and preventive actions are those actions that keep the problem from recurring.

Corrective actions:

Now that you have assessed the rights, welfare, and safety of the participants and have identified the root cause, you should consider additional reporting to the sponsor and IRB. As a reminder, you should have already submitted your initial report to the IRB, even if only limited or preliminary information is available. Provide as much detail about the event (as detailed below) as possible at the time of initial reporting.

Ensure that the reports to the sponsor and IRB are accurate and thorough and that the CAPA is included. Additionally, there may be actions that should be taken to correct the problem, but that were not required to be taken before IRB review as they were not needed to protect the rights, welfare, and safety of participants and others.

Preventive actions:

Preventive actions are necessary to ensure that the problem does not repeat itself. Preventive actions should be based on the process. Create and document a process or standard operating procedure (SOP). Train on the process, implement the process, evaluate the process, and amend the process as necessary. Consider revising the protocol or informed consent as applicable.

CAPAs must be thorough:

Specific: Identify the actions that will be taken to address the root cause, the individual (role) responsible for taking the actions, and where documentation of the actions will be kept.

Timely: Include the date(s) when the actions will be completed.

Measurable: Include a process of assessment of the action plan's effectiveness and a process by which the plan will be amended if it is found to be ineffective.

CAPAs must be well documented in the research records!

7.3.9 Possible Corrective Actions Required by the Mass General Brigham IRB in Addition to the PI's Plan

1. Requirement to complete Compliance and Education Course(s)
    a. Clinical Research Boot Camp
    b. Good Clinical Practice
    c. Recordkeeping and Record Retention Requirements
    d. Study Team Data Management and Quality Assurance Plans
    e. Informed Consent Including e-Consent
    f. Writing a Clinical Research Protocol
    g. Sponsor-Investigator Responsibilities (IND/IDE/NSR)
    h. Clinical Trials Registration and Reporting Requirements
    i. Virtual Clinical Research
    j. Clinical Research Inspections and Audits

2. Compliance and Education
    a. Consultation with Compliance and Education Office
    b. Audit(s) by Compliance and Education Office
    c. Study Startup Assessment/Consultation for future study with the Compliance and Education Office

3. Changes to the Study or Study Documents
    a. Require Changes to Informed Consent Forms or Process
    b. Require Changes to Protocol
    c. Require Changes to Recruitment Procedures

4. Participant Notification
    a. Require notification of participants about non-compliance
    b. Require Re-Consenting of Participants

5. Staffing
    a. Requirement to add additional staff or co-investigators.
    b. Requirement of a dedicated Research Assistant, Project Manager, or CRO.
    Note: When the noncompliance is directly related to lack of staffing, the IRB and C&E may require additional staffing. Possible options may be discussed with the PI or the department's Research Administrative Director.

c. Requirement to meet with Institutional Research Compliance team, Department Chair, Research Administrative Director, or others as applicable, for assignment of a supervising PI/mentor.

6. Limiting or Restricting Research Activities
    a. Shorten approval time frame for Continuing Review
    b. Restrict approval of additional new protocols
    c. Restriction of PI privileges for a particular type of study (e.g., FDA-regulated, sIRB)
    d. Limit the amount of activity on certain projects (e.g., suspend enrollment of new study participants)
    e. Suspension of Study (or Studies)
        i. The IRB can place a temporary hold on study activity so the investigator and study team can bring study files and documentation into compliance, followed by submission of a status report to the IRB.
    f. Termination of Study (or Studies)
    g. Suspension of PI privileges
    h. Require prohibition on the use of data collected as part of non-compliance.

7. Other Actions
    a. Requirement of independent data monitoring
    b. Requirement of an independent consent monitor to observe the consent process.
    c. Reporting to research integrity officer for assessment of research misconduct
    d. Reporting to IACUC for assessment of impact on preclinical research

7.3.10 Example CAPA:

Description of the Event(s)/Deviation(s):

Four of the five newly hired research coordinators implemented and participated in human subjects research prior to being added and approved by the IRB, prior to completing Mass General Brigham-required human subjects training and prior to receiving protocol-specific training. This was identified during a review by the Compliance and Education Office and is detailed in the attached report.

The Research Manager reviewed the study history and IRB-approved personnel log with the study team history and confirmed that there have only been four occurrences where an unapproved member of the study team participated in research. This was not identified in other studies and specifically occurred in the above-mentioned study.

Root Cause:

There was not a process to ensure that new hires to the research team had all required actions and education taken before participating in Human Subject Research.

Corrective Actions:

The research manager created an SOP for new hire onboarding and a supporting checklist; see attached. The research manager reviewed the SOP with the research staff and PI. This review is documented in a note-to-file, see attached, and

will be kept in the regulatory record. The four research team members completed the Mass General Brigham human subjects training requirements (GCP and Clinical Research Boot Camp), see attached, and a modification to add them to the IRB application and protocol has been submitted to the IRB. The research team members were also trained by the research manager and PI on the above research protocol; see attached. Documentation of their training is filed in the regulatory binder.

Preventive Actions:

The new hire SOP checklist will be utilized by the research manager and the principal investigator to ensure that new hires are appropriately on-boarded before participating in the research. The final step of the onboarding process is the sign-off on the checklist by both the research manager and the principal investigator.

A note-to-file was created by the research manager indicating the start date of the new SOP and checklist; see attached. The completed checklists will be kept in the regulatory record with the delegation of authority log.

The research manager and the principal investigator will review the implementation of the new SOP and checklist after each of the next three new hires and will document the review in a note to file to be kept in the regulatory record. If the result of the reviews is that the SOP and checklist are working as expected, a note to file will be placed in the regulatory record indicating the plan as effective, with an effectiveness check moving to an annual review.

If the SOP and/or checklist require revision, those revisions will be documented in a note to file kept in the regulatory record and the process for evaluating the next three new hires will start again.

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8 Remuneration

Research participants may be compensated for the time and effort they devote to clinical studies. Some participants derive medical benefit as a result of their participation; some participants volunteer out of altruism, a desire to further medical research into diseases that affect them and their families, or for other personal reasons.

Even when participants derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Therefore, many investigators reimburse these and similar expenses for research participants routinely, when funding is available, either with or without a small additional stipend as compensation for the individual's time.

Often it is not possible to compensate very ill participants, pediatric participants, or those with rare diseases for their unique and generous contributions to medical research. Sometimes compensation may represent only a small symbolic gesture in recognition of the major contributions that these individuals make to research, and it is hoped, to the health of future patients.

Healthy volunteers who will derive no medical benefit from their participation in the research study are often compensated reasonably for the time they devote to research projects. Monetary compensation is not intended to be the only motivating force to induce participants to participate.

8.1 Prorated Compensation

Compensation for participation in research projects should be pro-rated according to the amount of time devoted to the project. Research participants have the right to withdraw from a study at any time, for any reason.

It is not acceptable to withhold all compensation until the end of the research in order to incentivize participants to complete the research. Compensation should be provided to participants in "installments" based on their participation to that time point. A minor increase in end-of-study payments may be appropriate with justification.

8.2 Compensation for Minors

Appropriate compensation of minor participants involves additional considerations and may be viewed differently for younger children and adolescents. While it may be acceptable to compensate some adolescents monetarily, similar to adults, it may be more appropriate to compensate younger children in another manner.

Monetary compensation for parents may be provided for the time and expenses associated with their child's participation (e.g. expenses for travel, babysitting for siblings, time off work to bring children in for appointments.) However, children are the research participants and normally they should be compensated directly for their participation.

8.3 Chance to Win or Drawings

Research participants may also be paid via Chance to Win methods or Drawings. Participants may be included in drawings where they have an opportunity to receive compensation in return for their participation in research. For instance, a study has $100 for payment and holds two drawings of $50 offered in the form of gift cards. Terms like "raffles" or "lotteries" cannot be used for this type of payment method.

The consent document must describe the Chance to Win or Drawing process, the payment amount and method, and any eligibility criteria to enter into the drawing. If there are conditions associated with the drawing, then those must be described in the study document. Depending on what is required of participants before they are eligible for the drawing or chance to win or if the study imposes a condition before the participants is eligible for the chance to win or drawing, the IRB will determine whether the time and effort required of the participants to complete the procedure justifies the condition. In some cases, the IRB may consider this method unacceptable, if, for instance, the prize is perceived to exert undue influence.

8.4 Parking Vouchers

Parking vouchers should be provided whenever possible so participants do not need to be reimbursed at a later time or be concerned about having enough cash on hand to pay hourly parking rates. Parking vouchers or payments must be described in the IRB protocol and associated study forms or documents.

8.5 Suggested Monetary Compensation for Certain Routine Research Procedures

In an effort to guide investigators, a list of approximate monetary compensation for a variety of frequently performed clinical activities is listed below. This list is meant to guide investigators and is based upon active protocols currently approved by the IRB. Although not every procedure is listed, these amounts may guide investigators by allowing comparison of new procedures with these in terms of time and discomfort. There may be some cases in which no compensation is warranted or needed. There may be special instances where modifications of these procedures might merit additional compensation.

Investigators are welcome to contact the IRB staff if additional guidance is needed.

Suggested Monetary Compensation	
Blood draw for research purposes from healthy volunteer participants	$5 - 25
Noninvasive psychological testing or memory tasks, pencil and paper activities	$5 – 30/hr
Focus groups (1-3 hrs)	$20 – 75
Outpatient visit: depending upon time, discomfort, inconvenience, need to take medications, bringing in timed samples (e.g. 24 h urine collections), diary completion or other activities beyond simply appearing for the visit	$30 – 75
Laser/UV treatments with no direct benefit to participants	$30 – 75/visit
Skin biopsy	$50
Muscle biopsy, at the higher end of the range if special preparation required	$50 - 100
MRI scan, depending upon duration of scan and use of contrast agent	$50 – 200
Oral glucose tolerance test or other infusion tests, more if special preparation or diet required	$50 – 150
Lumbar Puncture	$100
24-hour stay in sleep center or clinical research center, for relatively non-invasive activities: blood draws, IV lines, vital signs or other non-invasive clinical monitoring	$100 – 200/ 24-hour stay
Bronchoscopy with lavage in healthy volunteer participants	$150 – 300
PET scan with radiolabeled material, more if arterial or IV line placed	$200 – 300
Swan Ganz catheter placement in healthy volunteer participants	$200 – 400

9 Vulnerable Populations

9.1 Research Involving Prisoners

9.1.1 IRB Review of Research that Involves Prisoners as Participants

In order for an IRB to review and approve research that involves prisoners, the membership of the IRB must include at least one member who is or has been a prisoner, or a prisoner representative (someone who has a close working knowledge, understanding and appreciation of prison conditions from the perspective of the prisoner). Since the Mass General Brigham IRB does not meet these special membership requirements, Mass General Brigham will utilize the Harvard School of Public Health (HSPH) IRB for review of research involving prisoners. When a protocol involving prisoners as participants is being reviewed by more than one IRB because the protocol is being conducted at multiple sites, only one IRB must satisfy the special membership requirements for research involving prisoners as participants.

9.1.2 Planned Enrollment of Prisoners as Participants

When the study population includes prisoners, the study must undergo review by the HSPH IRB. Prior to submitting an application to the HSPH IRB, Investigators must submit a Cede application in Insight to the Mass General Brigham IRB. A study specific reliance agreement between the HSPH IRB and the MGB IRB must be established. When changes to an ongoing Mass General Brigham IRB-approved protocol include extending the study population to include prisoners, investigators must follow the same process. For questions, contact the Single IRB team at mgbsingleirb@partners.org.

9.1.3 When A Participant Becomes a Prisoner While Participating in an IRB-approved Study

When a participant becomes a prisoner while participating in a research study approved by the Mass General Brigham IRB, all research interactions and interventions with the participant and/or collection of identifiable private information about the participant must cease until the requirements of the federal regulations have been satisfied with respect to the relevant protocol unless the principal investigator asserts and the IRB Chair or designee agrees that it is in the best interests of the participant to remain in the research study while incarcerated. In such cases, the participant may continue in the research until the requirements of the federal regulations are satisfied.

When a participant becomes a prisoner, the investigator must notify the Mass General Brigham IRB immediately of the situation by submitting an Other Event submission in Insight. The notification should include whether the participant's participation will end as a result of their incarceration or whether permission is being requested for the participant to continue in the research because it is in their best interests.

When requesting permission for the participant to continue in the research, address the following:

- the prospect of direct benefit to the individual participant
- the importance of the intervention or procedure to the individual participant's health or well-being
- the availability of the intervention or procedure outside of the research context, and
- how the intervention or procedure can be performed safely while the individual is a prisoner.

The investigator must obtain approval from the HSPH IRB to include the prisoner as a participant in the research. Investigators must also submit a Cede application in Insight to the Mass General Brigham IRB. Once the study is approved at HSPH, the HSPH IRB will become the IRB of record for the study. The Mass General Brigham IRB approved study must be closed once HSPH IRB approval is in place. The Cede application will remain open with the Mass General Brigham IRB.

10 Repositories

10.1 Repository Protocols

10.1.1 Structure and Function of a Repository

Research repositories (e.g., registries, data repositories/banks, tissue repositories/banks) should be designed for three distinct purposes only:

1. Collect data/research materials for *future* research use(s)
2. Store and manage the data/research materials
3. Distribute the data/research materials for use in research activities

Repository protocols are specifically not to be used to obtain IRB approval to conduct analyses, answer research questions, or test hypotheses. A separate IRB protocol, typically called a secondary use protocol, must be submitted by any investigator who wishes to *use* the data/research materials stored in the repository protocol to *conduct research* (e.g., testing hypotheses, conducting analyses to answer specific research questions, etc.). This principle applies even to the investigators who are listed as study team members on the repository protocol, who wish to use the data/research materials in a particular analysis or investigation.

Note that funding linked to a repository protocol should be used only for the management of that repository protocol. Funding that supports secondary use protocols should be linked only to the relevant separate secondary use protocols.

Table 1: Purpose of repository protocols vs. secondary use protocols

	Collect, store, and manage data/research materials for future research	**Collect, store, and manage data/research materials for a specific research study/analysis**	**Have specific research questions to answer**	**May be hypothesis-driven**
Repository Protocols	**YES**	NO	NO	NO
Secondary Use Protocols	NO	**YES**	**YES**	**YES**

Research repositories that hold individually identifiable data/research materials are subject to IRB oversight and require prospective IRB review and approval prior to initiating any activities pertaining to the repository protocol. When data/research materials with no identifiers will be obtained from the repository protocol, a Not Human Research Subjects (NHSR) determination can be made by the IRB. If, however, the investigators requesting the data/research materials are already listed on the repository protocol from which the data/research materials are requested, a human research protocol must be submitted to the IRB for review and approval because the investigators on the repository protocol have access to identifiable data/research materials at the source level.

10.1.2 Repository Study Staff

The study staff on the repository protocol should be limited to only those who are directly working on the repository protocol to collect, manage, and distribute the data/research materials for the repository protocol. Investigators who are only conducting research using the data/research materials obtained from the repository protocol should not be added to the repository protocol as study staff.

Before proposing the establishment of a repository, an investigator should consider whether the data/research materials they plan to collect would be readily available from already established repositories (either one that already exists within Mass General Brigham or is accessible to the investigator by another means).

10.1.3 Establishing Repositories for Future Research Use

Principal Investigators wishing to create a repository are responsible for establishing and managing the collection, storage, access, and distribution of data/research materials collected under the repository. Therefore, they need to ensure that access to the banked data/research materials is only granted for the appropriate use conducted by the qualified individual/entity.

The primary research mission of the repository protocol, operational scope, and objectives should be well defined and include who will have access to the data/research materials, coding of data/research materials, and the process to ensure that future research projects involving identifiable data/research materials are not conducted without prior IRB approval. The repository protocol should have an established governance structure, as well as policies, best practices, and regulatory and procedural standards that are described in the IRB-approved protocol. Please refer to the Repository Protocol Template for elements that should be included.

10.1.4 Obtaining Informed Consent and HIPAA Authorization

When obtaining data/research materials directly from participants under a repository protocol, written informed consent and HIPAA authorization for research purposes should be obtained to allow the collection of data/research materials to be used for future research. Obtaining consent for broad sharing for future research maximizes the potential downstream use of the data/research materials collected and ensures that future use aligns with established ethical principles relevant to use of research materials. The IRB will consider the acceptability of data/research materials obtained without consent for secondary use on a case-by-case basis. For example, The IRB may consider the following circumstances to allow the use/collection of data/research materials that were obtained without consent/HIPAA authorization:

- Grandfathered collections obtained in research studies conducted prior to 2006, where storage in a repository protocol was not mentioned specifically, may be included under a waiver of consent/HIPAA authorization at the IRB's discretion.
- Completely anonymized data/research materials (i.e., no code nor key to re-identify individuals exists) obtained from clinical procedures, or data/research materials obtained with IRB approval, may be included under a waiver of consent/HIPAA authorization at the IRB's discretion. Contact the IRB to discuss this option before submitting a request for a waiver of consent/HIPAA authorization.

Ensuring that the appropriate consent has been obtained can be done by prospectively obtaining consent from participants for the repository protocol and/or obtaining consented materials from other sources (e.g., participants provided consent for future use under different research studies, sometimes called "feeder" studies). Consent and HIPAA authorization may be obtained in a paper format or electronically (e.g., via REDCap with an electronic signature). The content of the consent/authorization form depends on the purpose of the repository and the permitted future use of the data/research materials.

For a tissue repository, informed consent may be obtained in writing using the Mass General Brigham Research Tissue Bank Consent Form template. For a data repository, informed consent may be obtained in writing using the Mass General Brigham General Research Consent Form template. If the repository is for both tissue and data, use the Mass General Brigham Research Tissue Bank Consent Form template and modify the template language as needed.

If a research study has two components, one to answer research questions and another to collect and store data/research materials for the current research study as well as for future research studies, there are two methods to obtain consent from participants for the repository protocol (see the bullet points below). Regardless of which method of obtaining consent is being used, participation in the repository protocol (i.e., data/research materials collected under the research

study become a part of the repository protocol) should be presented as an option, not a required component of the research study.

- One method of obtaining consent for the repository protocol is to use two separate study-specific consent forms for the research study and the repository protocol, respectively.
  - When this method is used, the consent form for the research study should explain that the data/research materials collected under the research study will become a part of the repository protocol if a participant agrees via a separate consent document.
  - Once a participant agrees, then obtain consent from the participant for the repository protocol using the repository protocol consent form.
- The second method is to prepare one combined consent form under the research study.
  - If the combined method is used, the consent form should provide an option for participants to select whether or not their data/research materials collected under the research study will also become part of the separate repository protocol for future use.
  - When using the combined consent form, this consent form must describe both the research study as well as the repository protocol to the same extent. That is, the descriptions of the repository protocol should include all elements/information that would be required for a stand-alone consent form for a repository protocol.
  - When using a combined consent form, a certified copy of the informed consent for the combined protocol should be placed in the repository records. For more information about certified copies, refer to the *Electronic Storage of Research Documents* section above.

Investigators who will use data/research materials obtained from a repository protocol, as well as investigators releasing data/research materials from a repository protocol, must be cognizant that the proposed research must be consistent with the scope and terms described in the original informed consent document which was used to collect the data/research materials. Any consent terms for future use must be honored, even if the data are de-identified. For example, if the consent form states only de-identified data/research materials will be shared, this MUST be honored in all future uses and cannot be waived by the IRB nor any other entity for downstream use of data/research materials. Note that a Limited Data Set includes certain identifiers (e.g., dates) and is not considered de-identified data. If consent was not obtained for research purposes (e.g., data/research materials obtained for clinical purposes) or the original consent does not adequately include the proposed secondary use, specific informed consent for the new research protocol may be required. If the source consent includes any restrictions (e.g., cancer research only), they must be honored. Aggregating or de-identifying data/research materials does not release the requirement to adhere to the conditions described in the source consent document.

Neither the hospital HIPAA notification nor any clinical procedural consent form replaces the research consent form. Those forms notify patients that their data/materials may be used in research; however, they do not include all the elements/information required by the regulations that must be provided to participants to consent for research purposes.

HIPAA-related language included in the research consent form (i.e., language in the consent form to obtain HIPAA authorization) does not replace information that should be included in the consent form regarding accessing identifiable information or sharing data/research materials for research purposes outside the primary study. That is, HIPAA-related language in the consent form itself is not sufficient to allow sharing of data/research materials for future research.

10.1.5 Re-Consenting Minors or Individuals with Impaired Decision-Making Capacity Who Regain Their Capacity

Minors whose identifiable data/research materials are stored in the repository protocol should be re-consented when they reach age of majority. Information regarding the re-consent process should be included in the protocol and consent form. A typical plan might include language that explains that an attempt, or attempts, will be made to contact the participants after they become an adult for re-consent and will describe the process if contact cannot be made. It is acceptable to include in the plan that either data/research materials will be destroyed if contact cannot be made, or data/research materials will be anonymized (i.e., destroying the code and the key to re-identify participants) at that point. Data/research materials that have already been distributed do not need to be destroyed.

When data/research materials are collected from individuals with impaired decision-making capacity through surrogate consent, investigators should consider whether they will reconsent these individuals if they regain the capacity to consent for themselves, and, if so, the process of obtaining reconsent should be described in the protocol. This population may include participants who were enrolled post-anesthesia, in an ICU, in the ER, or post neurological injury.

10.1.6 Creating a Recruitment Registry

A Recruitment Registry is a special type of repository that is set up for the purpose of collecting and maintaining participants' information for recruitment into ongoing/future research studies. Recruitment Registries are particularly useful in keeping track of participants with an ongoing/long-term medical condition who may be interested in participating in multiple research studies (e.g., migraines, IBS, HIV, hepatitis infections, etc.) within a department or center or for those who are willing to serve as healthy controls in research. Formally consenting participants into a Recruitment Registry allows the retention of participants' contact information even if they do not, at that moment, consent into any other study. The retention of participants' contact information should be compliant with Mass General Brigham IRB Pre-Screening Guidance.

In addition to providing informed consent for the collection and retention of their contact information, registry participants would also typically provide information that could inform future recruitment, such as health conditions or diagnoses, medications, allergies, study visit availability, etc. Such questions should address the common entry inclusion/exclusion criteria of studies which will draw participants from the Recruitment Registry.

Studies wishing to recruit from the Recruitment Registry should specify the Recruitment Registry protocol number in the recruitment section of their study protocols. Study teams who wish to obtain informed consent and/or collect registry data electronically (i.e., using REDCap) should specify their electronic methods in the protocol and submit any participant-facing data collection instruments to the IRB for review and approval.

10.1.7 Appendix: When to Establish a Repository Protocol

Event	Submit Repository Protocol?	Process

You would like to collect and retain contact information and additional demographic and/or health information for the purpose of setting up a registry from which you will recruit participants for future studies.	Yes	• Establish a repository protocol (e.g., recruitment registry) and store the information in the repository. You can open a repository protocol in parallel to a research study or it may stand on its own.
		  ○ Best practice: set up a recruitment registry from the beginning so consent can be obtained upfront.
		• Participants may be asked to sign two separate consent forms for the two protocols or one combined consent form which presents as an option for the collected data/research materials to become a part of the recruitment registry.
		• When using one combined consent form, the consent form must describe both the research study as well as the recruitment registry. The descriptions of the recruitment registry should include all elements that would be required for a stand-alone consent form for a recruitment registry.
		  ○ A certified copy of the combined informed consent should be placed in the repository's records.

You would like to answer a research question but also retain the collected research materials (e.g., biospecimens, images, etc.) for potential downstream research.	Yes	• Establish two protocols – one to answer the research question, and another (a repository) to store collected research materials for potential downstream research. • Participants may be asked to sign two separate consent forms for the two protocols or one combined consent form which presents as an option for the collected research materials to become a part of the repository. • When using one combined consent form, the consent form must describe both the research study as well as the repository protocol. The descriptions of the repository protocol should include all elements that would be required for a stand-alone consent form for a repository protocol. ○ A certified copy of the combined informed consent should be placed in the repository's records.
You would like to have a centralized location for storage of department-wide data/research materials.	Yes	• Establish a repository protocol; present in "feeder" study consent forms as an option for data/research materials collected as part of the research study to become a part of the repository protocol. • If a participant agrees to have their data/research materials to become a part of the repository protocol,

		obtain separate consent form for the repository protocol using the repository protocol consent form. • If using a combined consent form for the feeder study, the combined consent form must describe both the feeder study as well as the repository protocol. The descriptions of the repository protocol should include all elements that would be required for a stand-alone consent form for a repository protocol. ○ A certified copy of the combined informed consent should be placed in the repository's records. • Note that funding linked to a repository protocol should be funding only for the management of that repository protocol.

You would like to access data/research materials which have been collected as part of a repository.	No	• Establish a secondary use protocol; scope should be consistent with what the participants agreed to in the consent form of the repository protocol.
		  ○ Once the secondary use protocol is approved by the IRB, submit a request/application to the repository operators to receive data/research materials.
		• Note that funding linked to a secondary use protocol should be funding only for the completion of that specific project
		• **DO NOT** add study staff members from the secondary use protocol to the repository protocol solely because they will use the data/research materials from the repository protocol.
		  ○ The study staff on the repository protocol should be limited to those who are directly operating and managing the repository protocol.

10.2 Accessing Tissue from the Tissue Bank or Repository

Investigators may submit the following requests to a tissue bank.

- Recipient investigator requests tissue with identifiable information (directly identifiable tissue): The tissue bank can only release tissue with identifiable information to investigator who have obtained separate IRB approval for a specific research protocol. As part of that review, the IRB must determine whether or not the original consent and HIPAA authorization signed by the participant covers the proposed use.

  If the original informed consent and HIPAA authorization does not cover the scope of research (nature and purpose), the IRB may require the investigators to obtain separate informed consent and HIPAA authorization for this new study or may waive the requirement depending on the specific circumstances. In general, the IRB recommends seeking consent for all future uses at the outset, when tissues are collected for the expected research. Although re-contact of participants for new consent is not impossible, nor prohibited, it may be impractical and bothersome if frequent. Advance planning and description of research plans at the time of initial consent may obviate these difficulties.

- Recipient investigator requests coded tissue with **no** identifiable information (indirectly identifiable tissue): The tissue bank may release tissue that retains a link (code) to identifiable information about the tissue donor without additional IRB review if the following conditions are met:
    a) the recipient investigator will **not** be given individually identifiable information linked to the tissue, and agrees in writing (signs an agreement) **not** to access identifiers or attempt to ascertain the tissue donor's identity; and
    b) the proposed research is consistent with the scope of research described in the consent and HIPAA authorization signed by the tissue donor.

  If these conditions are not met, then the requirements for release of tissue with identifiable information must be followed.

  Note: The tissue bank can release information, such as diagnosis, age, or gender or a HIPAA Limited Data Set (LDS), if the information released cannot be used to "readily ascertain" the identity of the individual from whom the tissue was obtained.A HIPAA LDS Data Use Agreement must be signed.

- Recipient investigator requests tissue with no identifiers or codes (non-identifiable tissue): In accordance with the Common Rule, the tissue bank can release non-identifiable tissue (i.e., tissue that is non-identifiable because it never retained a link to the tissue donor, OR is fully anonymized by the tissue bank before release such that no link to the tissue donor will exist) to the recipient investigator without further IRB review and approval. However, if the tissue was initially collected under a research informed consent and HIPAA authorization, the tissue can only be used for the scope of research described in the consent and HIPAA authorization signed by the tissue donor.

  For information on agreement or contract requirements, please review the Insight Create New page and the **Contracting Guidelines**.

11 Research Participants

11.1 Questions, Concerns, or Complaints from Participants or Family Members

Mass General Brigham is committed to protecting the rights, safety and welfare of participants participating in research conducted by Mass General Brigham. Consistent with this commitment, the Mass General Brigham Research Consent Form template includes a section that addresses whom to contact if participants or family members have questions, concerns, or complaints about the research. This section includes the name of the investigator responsible for the research and their contact information as well as the name and contact information for others on the study team who are available to answer the participant's questions or address any concerns or complaints they might have about the research or their participation in the research. The Mass General Brigham Research Consent Form template also includes the telephone number for the Mass General Brigham IRB should participants wish to discuss their rights as a research participant, their concerns about the research, or a complaint about the research with someone not directly involved in the research. When the Mass General Brigham IRB waives the requirement for the investigator to obtain a signed consent form, contact information for the investigator is included in a study information sheet or other written statement about the research, or in other written materials used during the recruitment and consent process.

Mass General Brigham IRB contact information is available to participants, family members, and the public on the Mass General Brigham IRB website.

Participants are encouraged to ask questions or voice any concerns or complaints they may have about the research or their participation in the research during the consent process and throughout the study period. The investigator is responsible for answering all questions, addressing all concerns, and responding to all complaints raised by participants to the best of their ability.

Participants are also encouraged to contact the Mass General Brigham IRB office if they have any concerns that they do not want to discuss with the research staff, e.g., feeling pressured to take part in the research or, after enrollment, to continue to take part.

11.1.1 Handling Questions, Concerns, or Complaints

Prospective participants and participants enrolled in the research may ask questions or voice concerns or complaints directly to the investigator responsible for the research, a member of the study staff, or to a representative of the Mass General Brigham IRB, verbally or in writing before, during or after taking part in the research.

11.1.2 Complaints Received by Investigators/Study Staff

Investigators are responsible for ensuring that participant complaints are handled in a respectful manner and that participants are not penalized or lose any benefits they are receiving or have a right to receive. Complaints should be resolved and documented thoroughly and in a timely manner.

When, despite their best efforts, the investigator is unable to resolve a complaint thoroughly or in a timely manner, the complaint should be referred to the Director of the IRB Office. The Director will work with the investigator and Senior Chair of the Mass General Brigham IRB (or delegate) and other hospital representatives, such as the Privacy Officer or Accounting and Finance, as appropriate, to resolve the complaint. The IRB Office Director and Mass General Brigham IRB will address the complaint in a timely manner and communicate its resolution to the complainant, generally within 30 days.

A complaint by/on behalf of a research participant that indicates that the rights, welfare, or safety of the participant may have been adversely affected or any complaints that cannot be resolved by the investigator must be reported to Mass General Brigham IRB in an expedited manner per the Reporting Unanticipated Problems policy. In addition, investigators must document all complaints received from participants or family members and their resolution and report them to the Mass General Brigham IRB at continuing review.

11.1.3 Complaints Received by the Mass General Brigham IRB Office

Complaints received by the Mass General Brigham IRB office will be addressed by the Director of the IRB Office (or designee). When the complaint is received by telephone, the IRB staff receiving the complaint will record the information provided by the complainant. The Director or their designee may inform the investigator of the complaint and request a response to the issues raised in the complaint. The Mass General Brigham IRB will maintain privacy of the complainant.

Investigators and study staff are expected to cooperate with internal efforts to investigate and resolve complaints. The Mass General Brigham IRB and/or the investigator will address the complaint in a timely manner and communicate its resolution to the complainant, generally within 30 days of receipt of the complaint. The IRB Office will maintain records of participants' complaints and their resolution.

11.1.4 Remedial Action, Suspension or Termination of Research, and Noncompliance

The Director and Senior IRB Chair will be responsible for determining whether remedial action is necessary. Should the complaint result in an allegation of noncompliance or be cause for suspension or termination of the research, the Mass General Brigham IRB will follow the procedures outlined in the policies related to *Noncompliance in Human Research*, *Suspension or Termination of IRB Approval*, and *Reporting to Authorities*.

12 Single IRB

12.1 Review of Multi-Site Human Research: Investigator-Initiated Collaborative Research

When employees or agents of the applicable Mass General Brigham-affiliated entities conduct non-federally funded investigator-initiated non-exempt human research in collaboration with other institutions or with collaborating individual investigators as defined herein, each collaborating institution and/or collaborating individual investigator engaged in human research must obtain IRB approval for the research they are conducting. 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. Such determinations will be made in collaboration and consultation with authorized representatives of the collaborating institution and/or the collaborating individual investigators, as applicable.

When employees or agents of the applicable Mass General Brigham-affiliated entities conduct federally funded investigator-initiated non-exempt human research in collaboration with other institutions orwith collaborating individual investigators as defined herein, the single IRB review format must be used to obtain IRB approval for the research being conducted.

Investigators must specify in the IRB Application the outside institutions and/or individuals involved in the research.

12.1.1 Collaborating Institutions

Per relevant guidance from OHRP, when multiple institutions are engaged in the same non-exempt human research, the collaborating institutions may rely upon the review of another qualified IRB, or make similar arrangements to avoid duplication of effort. When an institution is engaged in only part of the non-exempt human research, the institution must ensure that the part of the research project in which the institution is engaged is reviewed and approved by the institution's IRB or, on behalf of the institution, by another appropriately qualified IRB or Ethics Committee (EC) listed on the institution's FWA. Alternatively, each institution may decide to review the entire research project, even if the information about the entire project is not necessary to approve the part(s) of the research in which the institution is engaged. See Single IRB Policy for guidance on asking the IRB to be the single IRB for non-MGB collaborating sites, as well as requesting to cede IRB review to a non-MGB IRB.

12.1.1.1 Reliance of Collaborating Institutions on the IRB Office

Collaborating institutions engaged in federally funded non-exempt human research require single IRB review. The Mass General Brigham investigator may request that the IRB serve as the single IRB for review of the research. In such cases, the IRB will consider the request and, if it is granted, an IRB Authorization Agreement (IAA) also referred to as a Reliance Agreement must be executed between the IRB and each relying institution. The relying institution must have an active/approved FWA.

12.1.1.2 Reliance of the applicable Mass General Brigham-affiliated entities on Collaborating Institution's IRB

The applicable Mass General Brigham-affiliated entities may rely on the IRB of a collaborating institution when all or the majority of the non-exempt human research is being conducted at the collaborating institution or when the collaborating institution's IRB has more relevant or specialized expertise and/or knowledge of the site where the research will be conducted. In such cases, an IAA must be executed by both institutions.

The institution relied upon for IRB review must have an active/approved FWA.

In the absence of such a reliance arrangement, each institution will independently review theresearch project.

12.1.2 Collaborating Individual Investigators

When a collaborating individual investigator, whether an independent investigator or an institutional investigator, is engaged in non-exempt human research, the applicable Mass General Brigham-affiliated entity may choose to extend its FWA to cover the collaborating individual investigator. In such cases, an Individual Investigator Agreement outlining the terms and conditions of this arrangement must be executed by both parties.

13 Data and Safety Monitoring Plan

13.1 Data and Safety Monitoring Plan (DSMP)

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 Monitor, Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC).

13.1.1 Investigator

The principal investigator could monitor the overall conduct of research by themselves. This type of plan is appropriate when the study involves a small number of participants; the study is conducted only at one site; the study is not blinded; and the range of possible study events that could have an important impact on the risks and benefits of research participants is narrow. In such cases, continuous monitoring of events by the investigator and prompt reporting, when applicable and/or required by policy and regulations, to the IRB, FDA, NIH, or others, may be adequate.

13.1.2 Monitor/Monitoring Group

A qualified and objective individual or group not directly involved with the design and conduct of the study (e.g., safety officer, designated Medical Monitor or Monitoring Group) could perform this advisory function. These individuals may or may not be employees of Mass General Brigham or the study sponsor. However, conflict of interest is an important consideration when employees of the study sponsor have the primary responsibility for monitoring data from the standpoint of scientific integrity and participant safety. Individuals serving in this advisory role do not meet the Sponsor-Investigator regulatory requirement for monitoring as outlined in ICH GCP Section 5.18.

This type of plan is often appropriate to monitor data and safety for clinical trials that involve:

- endpoints that are not serious irreversible events;
- an intervention (for example, to relieve symptoms) that is not high risk and the effects of which would not generally be so compelling as to ethically warrant early termination for effectiveness;
- short term treatments where effects are evaluated over periods of a few days to a few months; and
- a small number of participants where the study is completed quickly, and the risk can be adequately assessed through simple comparisons.

13.1.3 Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)

An independent Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) external to the trial organizers and investigators could perform this function. A DSMB/DMC is a formal committee that is established specifically to monitor data throughout the life of a study to determine if it is appropriate, from both the scientific and ethical standpoint, to continue the study as planned. The DSMB/DMC does not meet the Sponsor-Investigator regulatory requirement for monitoring as outlined in ICH GCP Section 5.18.

In general, an independent DSMB/DMC is the most appropriate way to monitor data and safety for studies that involve:

- **Large numbers of participants** where risk may better be assessed through statistical comparisons of treatment groups;
- **Blinded study treatment groups** where the validity and integrity of the study may be adversely affected by having an individual or group associated with the design and conduct of the study break the blind;
- **Multiple clinical sites** where there is a need for investigators to submit reports of adverse events to a

central reporting entity, such as a coordinating center or statistical center, responsible for preparing timely summary reports of adverse events for distribution among the clinical sites, and to the IRBs;
- **High risk interventions** where death or severe disability is a major risk of research participation; and/or
- **Controlled trials with mortality or major morbidity as a primary or secondary endpoint** where increased morbidity or mortality may better be assessed through statistical comparisons of morbidity or mortality among treatment groups.

13.1.4 DSMB/DMC Membership, Charters, and Responsibilities

DSMBs/DMCs are typically made up of individuals who have expertise in the field, experience in the conduct of clinical trials, and/or statistical knowledge, and who do not have any conflicts of interest, such as financial interests that could be substantially affected by the outcome of the trial, strong views on the relative merits of the interventions under study, or relationship with the sponsor or those in trial leadership positions that could be considered reasonably likely to affect their objectivity.

DSMBs/DMCs typically operate under a written charter that includes well-defined standard operating procedures that address the following:

- Meeting schedule (frequency) and format (in person or virtually)
- Meeting structure and confidentiality (who will attend all or part of DSMB/DMC meetings and who will have access to interim data)
- Format, method and timing of interim reports to the DMC
- Procedures for assessing conflict of interest of potential DSMB/DMC members
- Other issues relevant to committee operations, such as membership, voting, quorum, and handling of minutes
- Responsibilities

The DSMB/DMC charter may be drafted by either the sponsor or the DSMB/DMC; however, both must agree to the procedures outlined in the charter.

Responsibilities of DSMBs/DMCs may be broad or narrow in scope, and include some or all of the following responsibilities:

- Monitoring for effectiveness
- Monitoring for safety
- Monitoring study conduct (rates of recruitment, ineligibility, noncompliance, protocol violations and dropouts; completeness and timeliness of the data; degree of concordance between site evaluation of events and centralized review; balance between study arms on important prognostic variables; accrual within important subsets)
- Consideration of external data, such as release of results of a related study that may have implications for the design of the ongoing study, or even its continuation
- Making recommendations to the sponsor (or other group delegated by the sponsor to make decisions about the trial) concerning continuation of the trial with or without modifications, temporary suspension of enrollment or trial intervention, or termination of the trial based on review of interim data
- Maintaining meeting minutes

Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of participants under their care and for ensuring that the study is conducted at their investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

14 Other Topics

14.1 Blood Sampling Guidelines

The collection of blood samples in the course of research studies is a common practice. Institutional Review Boards (IRBs) are charged with evaluating the rationale, methodology, and risk/benefit ratio to research participants in the collection of these samples.

In some instances, the collection of blood samples may be considered to present no more than minimal risk to research participants and may be reviewed through an expedited review process (45 CFR 46.110). In other instances, the collection of blood samples may be considered as more than minimal risk and must be given full board review.

The following IRB guidance outlines general and specific guidelines for the collection of blood samples from adults and children for research purposes.

14.1.1 General Guidelines

In general, the collection of blood samples meeting the following criteria can be approved by expedited review if the IRB finds that the blood collection poses only minimal risk to participants. Although the removal of blood in these amounts is acceptable, the amount of blood withdrawn should be limited to that needed to meet the goals of the particular study.

Collection of blood samples by finger stick, heel stick, or venipuncture from healthy, non-pregnant adults who weigh at least 110 pounds poses minimal risk if the following parameters are met: Blood may be drawn not more than twice per week, total amount not to exceed 550 cc in an 8-week period.

Collection of blood samples from all other adults (e.g., individuals who are ill or pregnant) and children must take into consideration the age, weight and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. To be considered minimal risk for these participants, blood may be drawn not more than twice per week, and the total amount must not exceed the lesser of 50 cc or 3 cc per kg in an 8-week period.

14.1.2 Adults

- **Blood sampling in amounts of up to 200 cc, drawn at one time:**
    - In general, blood sampling in amounts totaling up to 200 cc may be removed from a participant that upon examination appears healthy, without further precaution.
- **Blood sampling in amounts exceeding 200 cc, drawn at one time:**
    - The following guidelines are suggested when blood sampling in amounts exceeding 200 cc at one time is proposed and should be described in the research protocol as applicable:
        - WEIGHT must be greater than 110 lbs (50 kg);
        - PULSE must be between 50 and 100 beats/minute with no cardiac irregularity;
        - TEMPERATURE must not exceed 37.55°C or 99.5°F;
        - CBC should be drawn before sampling (and at the end of the sampling period if relevant; see below).
        - HEMATOCRIT must be between: 0.36 - 0.48 for females and 0.38 - 0.54 for males;
        - or HEMOGLOBIN must be between 12.5 and 20;
        - TOTAL VOLUME from one participant must not exceed 550 cc for any one sample;
        - THERE MUST BE 8 WEEKS between samples, if multiple samples of 550 cc are required from one participant.

14.1.2.1 Monitoring

Participants should be monitored after large volume phlebotomy to ensure that they are feeling well and able to resume regular activities, as happens after donation at a blood bank, i.e., check vital signs and ensure volume repletion with oral fluids.

14.1.2.2 Iron Supplementation

Iron therapy is not required for healthy adults with normal diets who donate blood infrequently; this is not recommended or required by blood banks. If an individual repeatedly donates blood up to the limits of 550 cc in 8 weeks, or there is other reason to believe it would be medically advisable, the investigators should consider rechecking CBC or hemoglobin at the conclusion of blood drawing (after repletion of volume status). If hemoglobin at the end of the sampling period is at or below the lower end of the normal range, iron therapy should be considered. Usually, 320 mg ferrous sulfate or equivalent three times per day for one month should suffice. If iron therapy is offered, the protocol should describe this as a study procedure, and the consent forms and discussions with the participant should include discomforts and risks of iron therapy (i.e., GI upset, constipation, and black stools). Research funds should pay for repeat lab studies and iron therapy, if needed.

14.1.2.3 Children

Children can participate in research if the research involves minimal risk or, if more than minimal risk, the research presents the prospect of direct benefit to the participant. Blood sampling is considered a risk, albeit usually a small one. To be considered minimal risk, blood volume taken from children must be either less than 50 cc or less than 3 cc/kg body weight, whichever is smaller, in an 8-week period and collection may not occur more frequently than 2 times per week. In studies where the direct benefit outweighs this volume restriction, the full IRB committee can consider approval as a more than minimal risk study. The full IRB committee will consider the blood volume, frequency of blood draws, and age, weight, and health of children and make determinations regarding approval on a case-by-case basis.

14.1.2.4 Recommendations

- The use of EMLA cream is recommended to minimize pain related to blood draws in young children. When used, this should be described in the protocol, consent documents, and it should be listed as an ancillary drug in Insight.
- Whenever possible, blood As for all research procedures, assent of children should be taken from children at the same time that a clinically needed blood draw is performed to avoid "extra" needle sticks,

14.1.2.5 Consent/Assent

- for research blood draws needs to be collected and documented per the IRB's Informed Consent policy and as outlined in your IRB application and IRB approved protocol.

14.2 Research Involving Investigational Devices

14.2.1 Background

The Mass General Brigham IRB Office assesses the use of investigational devices in research studies and makes a device determination when a study plans to test the safety and/or efficacy of an investigational device (non-FDA approved/cleared device, or in some instances for an FDA-approved/cleared device being used off-label).

When a device is used within the context of a research study but its safety and/or efficacy are not being directly investigated within the proposed research, the device may be considered an "Ancillary Device" or the IRB may determine that the IDE regulations do not apply.

The Investigational Device Exemptions (IDE) regulation (21 CFR 812) describes three types of device studies: significant risk (SR), nonsignificant risk (NSR), and exempt studies. This guidance outlines the IRB's decision-making process pertaining to the two types of studies that are subject to the IDE regulation – the SR and NSR studies, as well as device studies that are exempt from the IDE requirements, and devices to which the IDE regulations do not apply.

The following section outlines the regulatory considerations and possible IRB device determinations.

14.2.2 Is my Device Considered a Medical Device?

Investigators must determine whether the device that is being proposed for use in a research study meets the following definition of a medical device:

> An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is: intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body.

The device is considered "investigational" if it is a device, including a transitional device, that is the object of an investigation. Transitional devices are devices that were regulated by the FDA as drugs prior to the May 28, 1976, the date the FDA Medical Device Amendments were signed into law. Any device that was approved by the FDA New Drug Application process is now governed by the FDA PMA regulations.

If the device in question does meet this definition of a medical device, it must be determined if researchers will be collecting safety and/or efficacy data on the device itself. Safety or effectiveness data are considered to be collected if the study plans to evaluate the device's safety and/or ability to diagnose (predict), treat, prevent, cure mitigate a disease, OR affect the structure or function of the body. This is true regardless of whether or not the device is FDA approved. In contrast, devices used as tools to collect data to examine a physiological principle are not subject to FDA regulations.

14.2.3 What is a Significant Risk (SR) Device Study?

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. For all clinical evaluations of investigational devices, unless exempt or deemed a Nonsignificant Risk (NSR), the IDE must already be in place with the FDA before the study is initiated.

Under 21 CFR 812.3(m), 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. B.

14.2.4 What is a Nonsignificant Risk (NSR) Device Study?

An NSR device is an investigational device that does not meet the definition of a significant risk device. If an IRB finds that an investigational medical device study poses a NSR, the sponsor does not need to submit an IDE to FDA before starting the study. If the IRB determines that the proposed study is an NSR study, the IRB may proceed to review the study under 21 CFR 56.109 and 21 CFR 56.111. FDA considers an NSR device study to have an approved IDE when the IRB concurs with the nonsignificant risk determination and approves the study and when sponsors meet the abbreviated requirements at 21 CFR 812.2(b). Consequently, in most cases, FDA is not aware of non-significant risk device studies.

14.2.5 Device Studies that are Exempt from the IDE Regulations

In accordance with 21 CFR 812.2(c), sponsors and investigators of certain studies are exempt from the requirements of 21 CFR Part 812:

> *Exempted investigations. This part, with the exception of § 812.119, does not apply to investigations of the following categories of devices:*
>
> (1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
>
> (2) 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 part 807 in determining substantial equivalence.
>
> (3) A diagnostic device, if the sponsor complies with applicable requirements in § 809.10(c) and if the testing:
>
> (i) Is 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.

Studies of a cleared device for a new use must comply with the human subject protection (informed consent and additional safeguards for children in research), IRB, and IDE regulations. Similarly, studies of a PMA (post market approval) approved device are exempt from the IDE requirements if the device is being studied for the indications in the approved labeling.

14.2.6 What are Ancillary Devices?

Ancillary devices are devices that are used in the context of a research study to perform tasks such as obtain measurements, collect data or monitor research participants, but whose safety and/or effectiveness are not being investigated for the purposes of the research study.

Ancillary devices that are FDA approved/cleared, are considered standard hospital inventory, to be used in a manner consistent with their labeling and how they are used in standard clinical practice do NOT need to be accounted for on either a Device Form OR the Ancillary Device Form in Insight.

Ancillary devices that are FDA approved/cleared but are considered NON-hospital inventory must be listed on the Insight Ancillary Device Form.

NOTE: A non-FDA approved/cleared medical device, irrespective of whether or not it is standard hospital inventory, cannot be used within a research protocol to facilitate or support ancillary procedures performed strictly for research purposes because the safety and/or effectiveness of such a device has not been properly vetted for clinical use. Therefore, it cannot be assumed that it would be safe and effective to use in the context of a research study. This applies to devices that are used to collect data or study human physiology as those data or physiological results cannot be relied upon.

14.2.7 Devices to Which the IDE Regulations Do Not Apply

The IRB may determine that the IDE Regulations do not apply to a particular device when that device's safety and/or effectiveness are not being investigated within the proposed research study, or the device does not meet the definition of a medical device.

14.2.8 How do I reflect the use of my Device in my Insight submission?

A Device Form must be completed in Insight to account for any device(s) that are being used in an investigational nature within a particular research study. Investigators are to complete the Form in the manner that best represents their intended use of the device but note that the IRB will make the ultimate device determination and may therefore require changes to the Device Form.

The Device Form is organized in a manner that first assesses whether the investigator plans to test the safety and/or efficacy of the device, if the device will be used as a Humanitarian Use device, OR if the device will be used as a tool to measure data or study human physiology. Sub-sections become open depending upon which option is chosen.

14.2.9 IRB Office Review and Determination

The IRB Office initiates this assessment at the time of Screening and aims to identify and communicate any additional requirements related to the use of the device to the Investigator *before* the full IRB review takes place. This includes the possibility of identifying that an investigational device may be considered a Significant Risk device and requiring that the investigator query the FDA in order to obtain their input about whether or not an IDE should be sought for the use of the device in this particular research study.

Any supporting documents, such as Device Brochures, must be provided to the IRB Office by being uploaded to the "Attachments" page of the Insight submission.

The investigator may provide information to support their independent assessment of the various possible device determinations but per Mass General Brigham policy the IRB Office may or may not concur with this assessment and will make a device determination.

14.2.10 Software as a Medical Device (SaMD)

Software as a Medical Device" (SaMD) is defined as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device. When software meets the definition of a medical device the IRB applies the medical device determination process to the software and must determine whether the software is considered a Significant Risk (SR) or Nonsignificant Risk (NSR) device (see above for definitions of Significant Risk (SR) and Nonsignificant Risk (NSR) devices).

Note that an "NSR" Determination must be made by the full board. Therefore, studies that propose to use software that may be considered to be "nonsignificant risk" still require initial review by the full board.

Under changes from the 21st Century Cures Act, Section 520(o)(1) of the FD&C Act was revised to **exclude certain software functions** from the definition of "medical device", in particular "Clinical Decision Support" (CDS) software.

14.2.11 What is Clinical Decision Support (CDS) Software?

A variety of software tools may be considered to be CDS, including, but not limited to:

- Computerized alerts and reminders for providers and patients;
- Clinical guidelines;
- Condition-specific order sets;
- Focused patient data reports and summaries;
- Documentation templates;
- Diagnostic support; and
- Contextually relevant reference information."

Examples of CDS Software include:

- The code that generates Epic BPAs
- Laboratory information systems that highlight critical care values
- Differential diagnosis websites like Diagnosaurus or WebMD
- Tools to complete drug dosing calculations
- Software that presents filtered reference information for a specific disease or condition

Note: Software does not need to be AI-related to be CDS Software.

A CDS Software function must meet **ALL FOUR** of the following statutory criteria to be excluded from the medical device definition (to be "Non-Device CDS"):

Criterion 1: Not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system

- Examples of acquiring, processing, or analyzing:
  - Software that enhances, manipulates, measures, or identifies structures
  - Software generating a clinical test result from an IVD
  - Software identifying genetic variants or clinical implications from Next Generation Sequencing
  - Software measuring repeated complexes or detecting arrhythmias in an ECG

Criterion 2: Intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information

- Examples of medical information include:
  - A blood pressure result from a legally marketed device
  - A lab test result in an electronic health record
  - An ECG report annotated by a physician with a description of an abnormal heart rhythm
  - The report from a radiology study

Criterion 3: Intended for the purpose of supporting or providing recommendations to a health care professional (HCP) about prevention, diagnosis, or treatment of a disease or condition

- If the recommendation is made **to patients or caregivers**, rather than to an HCP, the software does not meet this criterion.
- Automation bias leads people to over-rely on suggestions from an automated system, so the FDA makes a distinction between software that provides a specific output/directive and software that provides a list (including a prioritized list) of options or next steps for consideration.

Criterion 4: Intended for the purpose of enabling a health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make clinical diagnosis or treatment decision regarding an individual patient.

- The intended use, HCP user, and patient population should be clearly identified.
- The software should give enough information for the HCP user to make their own judgement based on what is provided to them and to understand why the recommendations/information were given to them.
- The intended HCP should be expected to have enough time and training to review the information presented; use should not be time-critical.

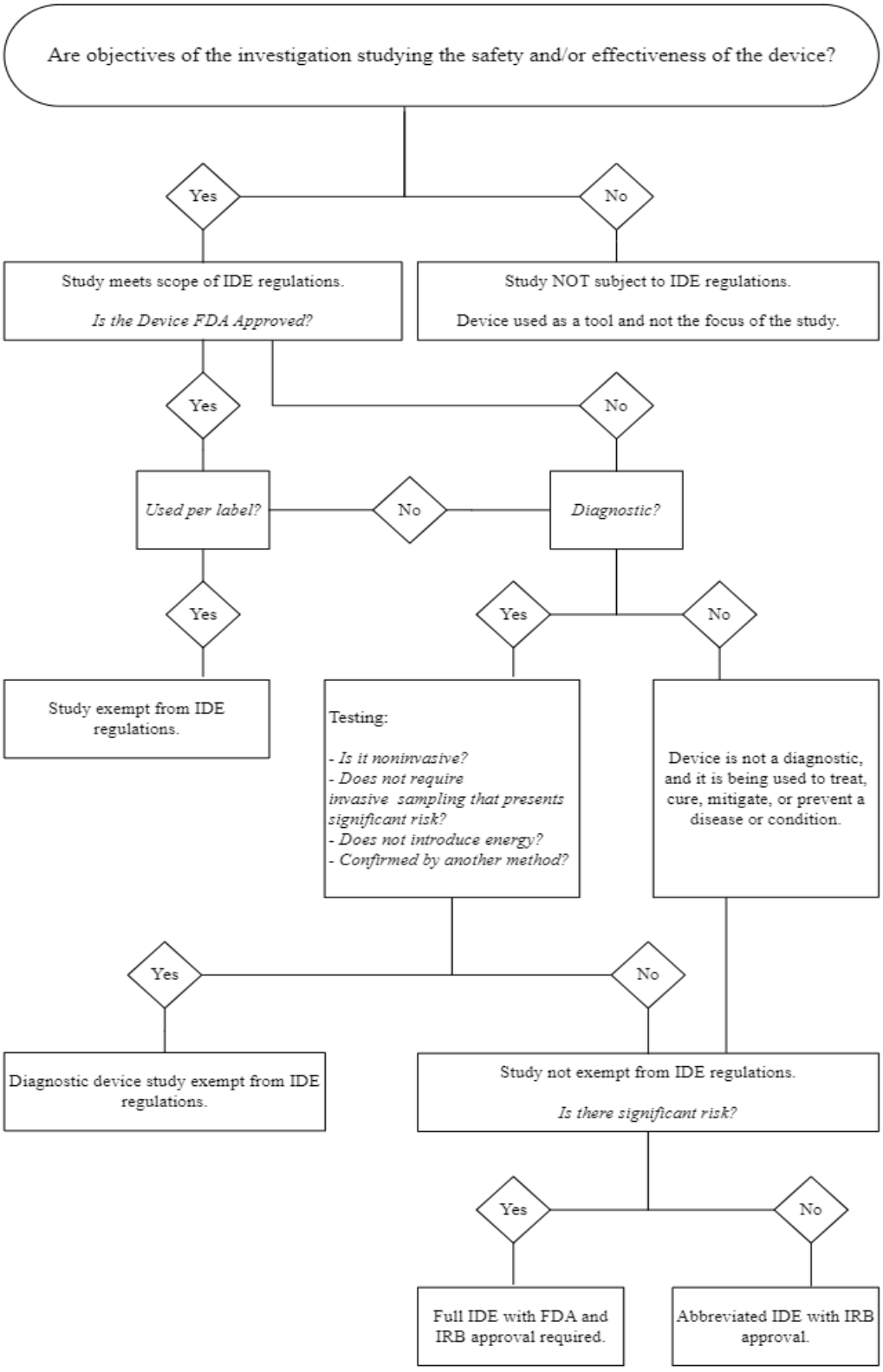
Examples of software functions that are EXCLUDED from the definition of a "medical device":

1. Administrative support of a healthcare facility (section 520(o)(1)(A));
2. Maintaining or encouraging a healthy lifestyle and unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition (section 520(o)(1)(B));
3. Serving as electronic patient records, including patient-provided information, to the extent that such records are intended to transfer, store, convert formats, or display the equivalent of a paper medical chart, so long as such records were created, stored, transferred, or reviewed by healthcare professionals or by individuals working under supervision of such professionals; such records are part of health information technology certified under section 3001(c)(5) of the Public Health Service Act; and such function is not intended to interpret or analyze patient records, including medical image data, for the purpose of diagnosis, cure, mitigation, prevention, or treatment of a disease or condition (section 520 (o)(1)(C); or
4. Transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results, findings by a healthcare professional with respect to such data and results, unless such function is intended to interpret or analyze clinical laboratory test or other device data, results, or findings (section 520(o)(1)(D)); or
5. Clinical decision support software, if certain criteria are met (section 520(o)(1)(E)

Link to FDA Decision Tree:

https://www.fda.gov/medical-devices/software-medical-device-samd/your-clinical-decision-support-software-it-medical-device

14.2.12 DEVICE DETERMINATION DECISION TREE



14.3 HIPAA Privacy Rule

The Privacy Rule is a Federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that protects certain health information. The Privacy Rule was issued to protect the privacy of health information that identifies individuals who are living or deceased. Investigators who are part of a covered entity conducting research using protected health information (PHI) must comply with HIPAA regulations. Definitions of key HIPAA Privacy Rule terms are included in the IRB policy.

PHI is individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium.

Here is the list of 18 identifiers under HIPAA:

1. Names;
2. All geographical subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; or (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
4. Phone numbers;
5. Fax numbers;
6. Electronic mail addresses;
7. Social Security numbers;
8. Medical record numbers;
9. Health plan beneficiary numbers;
10. Account numbers;
11. Certificate/license numbers;
12. Vehicle identifiers and serial numbers, including license plate numbers;
13. Device identifiers and serial numbers;
14. Web Universal Resource Locators (URLs);
15. Internet Protocol (IP) address numbers;
16. Biometric identifiers, including finger and voice prints;
17. Full face photographic images and any comparable images; and
18. Any other unique identifying number, characteristic, or code (note this does not mean the unique code assigned by the investigator to code the data)

The HIPAA Privacy Rule requires that researchers obtain signed authorization from individuals to use and/or disclose PHI for research purposes. In some cases, the IRB may grant a Waiver or Alteration of HIPAA Authorization.

14.3.1 HIPAA Authorization

The HIPAA Privacy Rule seeks to protect the privacy of PHI by generally giving individuals the opportunity to agree to the uses and disclosures of their PHI by signing an Authorization form for uses and disclosures not otherwise permitted by the Rule. An Authorization focuses on privacy risks and states how, why, and to whom the PHI will be used and/or disclosed for research. The Privacy Rule establishes the right of an individual, such as a research participant, to authorize a covered entity to use and disclose their PHI for research purposes. This requirement is in addition to the informed

consent to participate in research required under the HHS Protection of Human Subjects Regulations and other applicable Federal and State law. The Authorization must include core elements and required statements. Participants must sign and date the Authorization, and a signed copy of the Authorization must be provided to the participant.

When an Authorization is obtained for research purposes, the HIPAA Privacy Rule requires that it pertain only to a specific research study, not to nonspecific research or to future, unspecified projects. The Privacy Rule considers the creation and maintenance of a research repository or database as a specific research activity, but the subsequent use or disclosure by a covered entity of information from the database for a specific research study will require separate Authorization unless the PHI use or disclosure is permitted without Authorization. If an Authorization for research is obtained, the actual uses and disclosures made must be consistent with what is stated in the Authorization. The signed Authorization must be retained by investigators for 7 years in accordance with the Recordkeeping guidance.

Mass General Brigham IRB includes HIPAA Authorization in the combined consent and HIPAA templates. A standalone Authorization form may also be used in limited circumstances.

14.3.2 Waiver or Alteration of HIPAA Authorization

For certain types of research (e.g., medical record review), it may not be feasible to obtain a signed Authorization from participants. Please refer to the *Pre-Screening* section above for information about waiver or alteration of HIPAA Authorization.

Documentation of the waiver or alteration of Authorization must satisfy the following criteria:

1. The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
    a. An adequate plan to protect health information identifiers from improper use and disclosure.
    b. An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so).
    c. Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
2. The research could not practicably be conducted without the waiver or alteration.
3. The research could not practicably be conducted without access to and use of the PHI

14.3.3 Minimum Necessary Standard

The HIPAA Privacy Rule requires Mass General Brigham and its affiliated hospitals and providers to make all reasonable efforts to use or release only the "minimum necessary" identifiable health care information to achieve the intended purpose.

The minimum necessary standard does not apply to the following:

- Disclosures to, or requests by a health care provider for treatment
- Situations in which an individual has signed an authorization for the use or disclosure of identifiable information (e.g., for research)
- Uses or disclosures required by law
- Disclosures to the individual
- When required for compliance with other HIPAA rules (e.g., to fill out required or situationally required data fields in standard transactions).

14.3.4 Limited Data Set

The Privacy Rule allows the use and disclosure of select identifiers with only limited HIPAA Privacy Rule requirements. A Limited Data Set refers to PHI that excludes 16 categories of direct identifiers but may include: city, state, zip code, elements of date (e.g., birth date, admission and discharge dates), and other numbers, characteristics, or codes not listed as direct identifiers.

Limited Data Sets can be used for research, healthcare operations, and public health purposes. A covered entity may use and disclose a limited data set for research activities conducted by itself, another covered entity, or a researcher who is not a covered entity if the disclosing covered entity and the limited data set recipient enter into a data use agreement (DUA). Because limited data sets may contain identifiable information, they are still PHI.

Important requirements/restrictions for use and/or disclosure of limited data set:

- Limited data sets may NOT be used to reidentify or contact an individual.
- The "minimum necessary" standard applies to the limited data set, which means a researcher must explain that the data elements requested are necessary for the research.
- A Data Use Agreement must be signed by the covered entity and the recipient of the Limited Data Set.
- The requirement of accounting for disclosures of protected health information (PHI) does not apply.

Contact Research Management for questions about DUAs.

14.3.5 Research on Decedents' PHI

To use or disclose PHI of the deceased for research, the HIPAA Privacy Rule does not require covered entities to obtain Authorizations from the personal representative or next of kin, a waiver or an alteration of the Authorization, or a data use agreement. However, the covered entity must obtain from the researcher who is seeking access to decedents' PHI (1) oral or written representations that the use and disclosure is sought solely for research on the PHI of decedents, (2) oral or written representations that the PHI for which use or disclosure is sought is necessary for the research purposes, and (3) documentation, at the request of the covered entity, of the death of the individuals whose PHI is sought by the researchers.

For research involving decedent PHI, contact the Privacy Office for any submission requirements. If research involves human participants and decedent PHI, the IRB will make determinations as part of the human participants research study.

14.3.6 Accessing Medical Records from non-Mass General Brigham Sites

If the research involves accessing medical records from non-Mass General Brigham sites, investigators must obtain approval from the sites. Documentation of approval from the site indicating their approval must be submitted as part of the application in Insight.

14.4 External Monitoring

External monitors or sponsor representatives at Mass General Brigham (MGB) may be individuals engaged by federal and non-federal sponsors, including industry sponsors, Data Coordinating Centers, MGB Sponsor-Investigators, or other parties external to the study team responsible for assessing site facilities or monitoring the conduct of and documentation for a clinical research protocol to verify that:

- The rights and well-being of human subjects are protected.
- The reported study data are accurate, complete, and verifiable from source documents.
- The conduct of the protocol is in compliance with the currently approved protocol, GCP, and with applicable regulatory requirements.

Monitoring activities may be done remotely or onsite. If coming onsite, the external monitor or sponsor representative must comply with applicable MGB institutional policies in effect at the time of the onsite visit, including but not limited to the Visitor Policy. It is the responsibility of the employee-host (PI/study staff) to ensure compliance with this policy.

External monitors or sponsor representatives are subject to local laws and regulations and may not audio- or video-record any aspects of their visit without prior review and approval by the IRB and appropriate agreement of the recorded individuals, whether they are site study staff, research participants, hospital staff, or patients.

14.4.1 Advance Notification

The external monitor or sponsor representative must notify the PI generally within at least two weeks in advance of the visit to provide specific information regarding the expectations for the visit including details such as the anticipated date(s) of the visit, nature and scope of the visit, whether the visit will be onsite or remote, the source documents/data, essential documents, and study files to be reviewed, if access to electronic systems is desired, if visits to the research pharmacy or other clinical area are desired, and which individuals from the study team need to be available for the visit.

Other relevant information regarding the visit should also be included in the notification as needed. It may not be possible for the PI to meet all requests of the monitor or sponsor representative due to local restrictions and policies and/or insufficient advance notice from the monitor or sponsor representative.

14.4.2 Access to Protocol-Related Source Data and Documents

The Principal Investigator (PI) has to make available the requested clinical research protocol-related source documents, essential documents, and study files to monitors, auditors, or regulatory authorities as required by applicable research regulations and institutional policy. Investigators may use various electronic platforms approved by the institution and, if appropriate, limited access may be granted to the external monitor or sponsor representative.

If access to study regulatory and/or subject documents is required for the the external monitor or sponsor representative, then the PI and study staff must use an MGB-approved HIPAA compliant and secure method to provide access to those documents.

External monitor access to MGB-approved HIPAA-compliant systems should be removed as soon as the monitoring visit is complete.

> **Electronic Medical Record:** External monitors or sponsor representatives will not be given unrestricted access to the electronic medical record. Investigators and study staff must follow institutional policy for requesting external user read-only access to the electronic medical record.
>
> Requests must be submitted at least two weeks in advance to the Digital Health team as outlined in the eCare Research FAQs > Release of Information To Research Study Monitors instructions.

External monitors or sponsor representatives should be instructed to respond immediately to the email sent to them with login instructions and requirements in order to get access.

If access is not granted in advance, then the investigator/study staff and the external monitor or sponsor representative must make alternative arrangements to review source data in the electronic medical record. It is not possible for the PI or study staff to request access for the external monitor or sponsor representative on short notice.

Electronic Regulatory and/or Study Participant Files: If the investigator/study staff maintain protocol regulatory documents electronically using Mass General Brigham approved electronic platforms such as REDCap or Veeva SiteVault Free, then it may be possible to grant the external monitor or sponsor representative access as appropriate.
Typically, read-only access is granted to these records, and this is arranged by the investigator/study staff. External user access to other platforms may be restricted per institutional policy.

Electronic Data Capture (EDC) System: If the PI is using an EDC platform available at Mass General Brigham (e.g., REDCap), then the PI/study staff may facilitate getting an external monitor or sponsor representative access as an external user. Each platform has specific instructions for the PI/study staff related to external user access.

Electronic IRB platform: External monitor or sponsor representative user access to the MGB IRB electronic platform Insight is not permitted.

Instructions for granting external monitors and sponsor representatives access to MGB-approved electronic systems:

- Mass General Brigham REDCap
- Veeva SiteVault Free
- DropBox Business
- Microsoft OneDrive for Business
- Microsoft SharePoint Online
- Secure File Transfer
- Syncplicity

External monitors or sponsor representatives should not personally duplicate any study-related or confidential documents, including documents with PHI/PII. If a copy is needed, the external monitor or sponsor representative should request that an electronic copy be provided by the PI/study staff via an approved secure process (e.g., Secure File Transfer).

The PI/study team must ensure that all study documents and files are secure at all times during the onsite visit and, if applicable, returned to the appropriate secure storage location when the external monitor or sponsor representative leaves at the end of the day. Again, access to any MGB electronic systems should be removed at the conclusion of the monitoring visit.

14.4.3 Access to Secured or Clinical Areas

External monitors and/or sponsor representatives are not allowed access to secured, restricted, or clinical areas without the assistance of appropriate authorized personnel. The employee host must obtain permission from the manager of the secured or clinical area prior to any visit. Permission is granted at the discretion of the manager of the secured or clinical area. The employee host must coordinate the visit with the manager of the secured or clinical area and escort the external monitor or sponsor representative.

External monitors and/or sponsor representatives may not observe clinical visits and/or study staff performing study visit procedures such as (but not limited to) phlebotomy, processing specimens, or preparing drugs, for example. These activities may involve patients and/or study participants, or they may be done in restricted areas. There may also be additional safety and regulatory concerns.

14.4.4 Involvement in Onsite Study Activity

In general, external monitors and/or sponsor representatives are not allowed to interact with study participants, be present during study visits or procedures, or actively take part in a study visit. Requests of this nature are considered on a case-by-case basis and may require additional permissions and approval from the IRB, including prior consent of the study participant.

14.4.5 Requests for Copies of FDA Warning Letters, Untitled letters, or Form 483s

Mass General Brigham does not provide information regarding FDA inspections of investigators or the institution directly to external monitors and/or sponsor representatives. FDA Form 483s and Untitled Letters are available from the FDA with a Freedom of Information Act request.

Sponsors interested in this information for our investigators or the IRB may submit requests directly to the FDA. Warning Letters issued by the FDA are posted publicly on the FDA website: (https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters). Please refer to the Mass General Brigham Research Compliance Office's Audits and Inspections Audits & Inspections – Research Hub (mgb.org).

14.4.6 Requests for Copies of Mass General Brigham Policies, Guidance, and/or SOPs

Sponsors, external monitors, and/or sponsor representatives may be provided copies of Mass General Brigham Public facing Policies and Guidance as appropriate for conducting their business activities.

Mass General Brigham Human Research Affairs'
internal policy/guidance/and/or SOPs should NOT be provided.

Research team's internal SOPs can be shared as appropriate.

Applicable regulations include:

- International Conference on Harmonization Good Clinical Practice Guidelines E6 (R2), Section 5.18
- 21 CFR 312.50 and 21 CFR 312.56
- 21 CFR 812.40 and 21 CFR 812.46