Mass General Brigham

Institutional Review Board (IRB)

GUIDANCE ON REPORTING EVENTS:

When and How to Report

Research Guide

This is a comprehensive research guide for those conducting Human Subjects Research and provides a summary of what events require reporting to the IRB or other Mass General Brigham Research Offices, details on how to submit/report, and the required reporting timeframes.

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Guidance for Reporting Events: When and How to Report

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, 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.

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.

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.

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Event Type	Mass General Brigham Reporting Timeframes			How to Report
	5 Working Days (of becoming aware of the event)	**Continuing Review**	**Other**	
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 subjects.	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

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	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

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Event Type	Mass General Brigham Reporting Timeframes			How to Report
	5 Working Days (of becoming aware of the event)	**Continuing Review**	**Other**	
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 humanresearchqi@partners.org Pages - Audits & Inspections (sharepoint.com) Microsoft Word - FDA Inspection SOP_January 2022 FINAL (sharepoint.com)

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	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. humanresearchqi@partners.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.**

Submitting Other Events (OEs) 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**.

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?	
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?	☐Yes ☐No ☐N/A-Event was not an AE or UP	
	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)
  ○ Re-education could include completion of relevant courses in HealthStream available from the HRA Compliance and 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 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.
  ○ 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:
  ○ 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?		

Immediate Corrective Actions:

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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).

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.

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!

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. Subject Notification
    a. Require notification of subjects about non-compliance
    b. Require Re-Consenting of Subjects

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

Example:

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.

Resources:

Other Event Reporting Document (Document to submit with your other events)

Corrective and Preventive Actions (CAPA) | FDA

Resolving and Preventing Repetitive Problems in Clinical Trials - SOCRA Blog

Bridging the Gaps in CAPA Planning in Clinical Trials (appliedclinicaltrialsonline.com)

Navigating CAPA in Clinical Development: Ensuring Compliance and Quality Assurance (advarra.com)