Overview and Significance of Quality Assurance Process:
You've been selected for a routine QA Review – Now what?

CLINICAL RESEARCH SEMINAR

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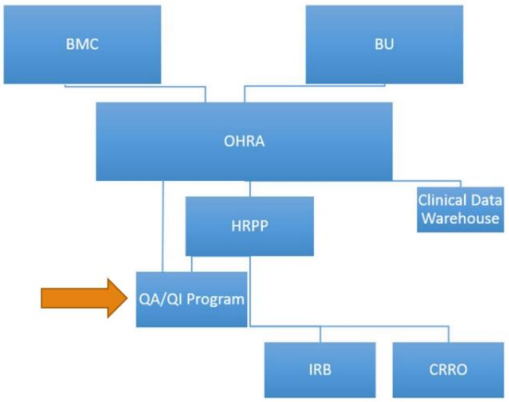
Poll: Name the QA cat!

Poll: Have you ever undergone an OHRA Quality Assurance Review?

About the OHRA Quality Assurance (QA) Program

BMC/BU Medical Campus – OHRA QA Program

- The QA program performs targeted audits and **routine QA reviews** for human research studies being conducted by any investigator at Boston Medical Center/Boston University Medical Campus, including…
  - Ceded studies
  - International studies



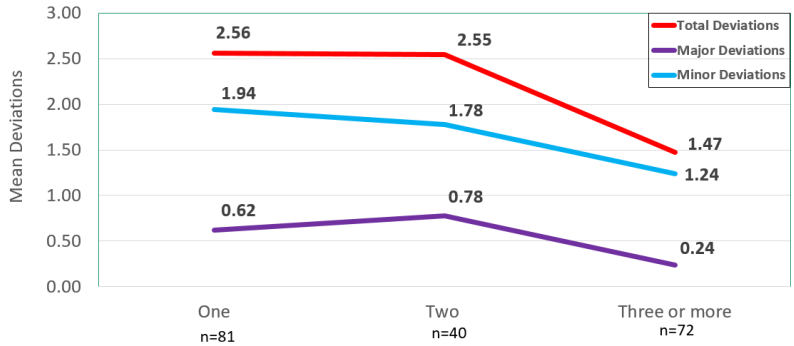
https://www.bumc.bu.edu/ohra/audits-for-research-oversight/

QA Program Objectives

- Help investigators and study staff perform IRB-approved research in compliance with the applicable regulations, policies, and guidance in order to protect the safety of participants or the reliability/validity of study data.
- Intended to be educational and consultative in nature.
  - Identify and help correct potential problems in study conduct or documentation, including problems arising from IRB noncompliance
  - Provide study teams with research best practice recommendations
- Studies are targeted for a QA review during early stages of data collection.

Impact of Multiple QA Reviews on Research Quality

Mean Deviations by Type of Deviation and Number of QA Reviews/PI QA Reviews 2017-Q1 2022 (N=193)



***Total Deviations**, p=0.0165 (**p<0.05**), F=4.19 ANOVA*
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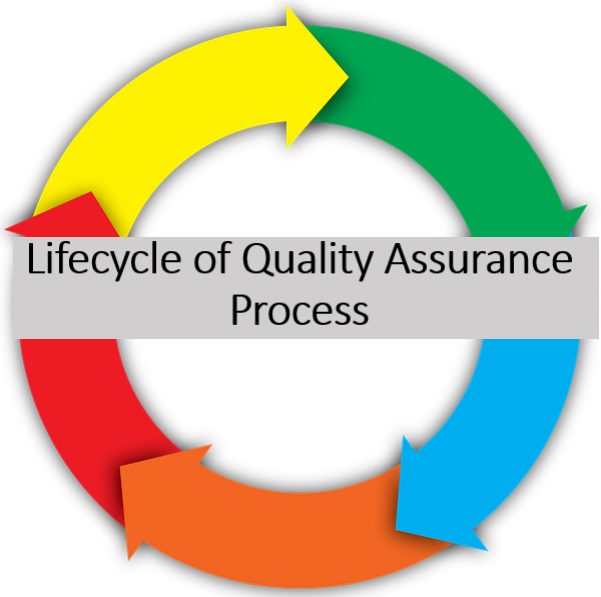


QA REVIEW TIMELINE
STEP 1: A research study is selected based on defined QA criteria.
STEP 2: The QA review is scheduled in the early stages of enrollment when only a few subjects have consented to participate in the study.
STEP 3: The QA review occurs in an in-person, remote or hybrid format.
STEP 4: The QA team compiles findings into the QA report.
STEP 5: The QA report is emailed to the study team, the OHRA Director and the BMC Research Compliance Officer.
STEP 6: The QA team will send a survey to study teams to solicit feedback on the QA review process.
STEP 7: The QA team will follow-up with study teams via email to determine if actionable findings have been addressed.

Step 1: QA review selection criteria

- Greater than minimal risk
- Investigator-initiated
- Interventional clinical trials
- First time Principal Investigators
- Studies where Principal Investigator holds the IND or IDE
- Studies having a conflict of interest management plan
- Multi-site studies where the Principal Investigator has the responsibility for overseeing all sites; or
- Other characteristic indicating that a QA review would be appropriate.

The Initial QA Review Notice

An **initial QA review selection notice** will be emailed to the Principal Investigator and key study personnel by a Human Research Quality Manager.

Key details on the QA review process are included in the notice.

Dear Dr. _____,

I hope this email finds you well.

The BU Medical Campus Office of Human Research Affairs (OHRA) conducts routine Quality Assurance Reviews (QA reviews) of human subjects research studies to ensure that the research is being conducted according to the IRB-approved protocol as well as application regulations, policies and best practice guidance.

Your study H-XXXXX: *"Study Title"* has been selected for a QA Review.

QA reviews are performed after a study has begun enrollment. Ideally, a QA review should occur when only a few subjects are enrolled so that any issues can be caught early and addressed before further subjects are enrolled.

QA Review Process Details:
The QA review will focus on the following topics: subject eligibility, informed consent, study procedures, data management, study staff training, the delegation of research responsibilities, and study documentation. The QA review will require access to hard copy records and/or electronic records which document the conduct of the study. Particular attention will be paid to source documentation. Most QA reviews are completed in 4 hours or less. You do not need to be present for the review, but it's helpful if you and/or the study coordinator are available for about 20-30 minutes at the beginning of the review.

During the review, there may be additional questions that require clarification by the study team. These questions may be asked during an on-site review or via email following the on-site review or if the review is performed remotely. After the review is completed, a copy of the QA review report will be provided to you, the OHRA Director, and the BMC Research Compliance Officer. For additional information about the QA Review process, please see the frequently asked questions on the OHRA Website.

Initial QA Review Selection Notice: Requested Information

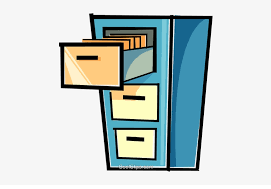
- Enrollment Progress, expected enrollment timeline
  - If no subjects are enrolled, the QA team will follow-up to assess enrollment until subjects are enrolled or the study has closed.
- The date when the first subject was enrolled *(if applicable)*
  - This will help the study team understand which study document versions (protocol, ICFs) are applicable.
- Source Documentation & Regulatory Documentation
  - Format and location of source documentation storage will help the QA determine if the QA review can take place in-person, remotely or in a hybrid format.
    - Format: electronic and/or paper
    - Location: REDCap, BOX, other EDC; on-site

Source documentation is the place where source data is originally recorded.

- A CRF is a source document if study staff directly record participant responses or measurements (such as vital signs) on the form.
- A CRF is not a source document if EMR data is transcribed onto the CRF. The EMR would be the source document in this case.

Step 2: Scheduling & Determining the format of the QA Review

- The QA team will notify the study team if the QA review is ready to be scheduled.
- Potential Format of QA review based on how source documents and regulatory documents are stored:
  - In-person; if documentation is paper
  - Remote; if documentation is electronic and shared with QA team (e.g., BOX)
  - Hybrid (in-person and remote); if documentation is both paper and electronic



Reminder Notice & Request for Study Documents

- Approximately 1-2 weeks before the review, the QA team will email the study team with a reminder of the upcoming QA review.

- The QA team will request the following:
  - Location of QA review
  - Access to electronic databases or documents (e.g., REDCap), if applicable
  - If study is ceded, all IRB-approved protocols, consent forms, other study documents, external IRB approval letters, MOPs, etc.

Step 3: The QA review

Ex. Hybrid QA Review

- In-person on-site visit portion
  - Pre-review discussion with study team (approx. 20 min)
    - Principal Investigator and/or member(s) of research team
  - Review of paper documents
    - Study team does not need to be available for the full review
- Remote portion
  - After on-site visit has concluded, reviewers will review any electronic data storage systems (e.g., REDCap) and the electronic medical record (EPIC)

Step 4: Post-QA review

- Compile findings from on-site and/or remote review
- If necessary, email clarifying questions and/or request additional documents from the research team
- Write the QA review report
- This process can take several weeks as the QA team has multiple simultaneous QA reviews on-going.

Step 5-7: The QA Review Report

- If major deviations are identified, the QA team, including the HRPP Assistant Director, may meet with the study team to review the finding(s).
  - The study team may request to meet with the QA team to discuss the report for any reason, if desired.
- Final report is emailed to study team, the OHRA Director and the BMC Research Compliance Officer
- A survey is emailed to study teams to solicit feedback on the QA review process.
- The QA team will follow-up with study team to determine if any actionable findings have been addressed. Timeframe for follow-up is outlined in the QA report.
  - If report findings require a RENI/CAPA submission, the QA/CRRO team can assist the study team with this process.

Poll: What is the principal method of communication between the QA team and study team?

Scope of the Quality Assurance Review

QA Review Standards: Regulations and Policies

- Applicable federal regulations
  - 45 CFR 46 (The Common Rule)
  - CFR Title 21 (FDA)
- International Council for Harmonization (ICH) Good Clinical Practice (GCP)
- Institutional policies & procedures:
  - BMC/BUMC Human Research Protection Program (HRPP) P&P

    OR
  - P&P of the reviewing institution, if study is ceded
- IRB-approved study plan, as detailed in the protocol and INSPIR application

IRB
Institutional Review Board

QA Review Areas of Focus

- Informed Consent Forms (ICF) & Procedures
- Screening & Eligibility
- Study Activities
- Adverse Events Monitoring & Safety Review
- Confidentiality
- Study Staff
- Regulatory Documentation
- Study Documentation

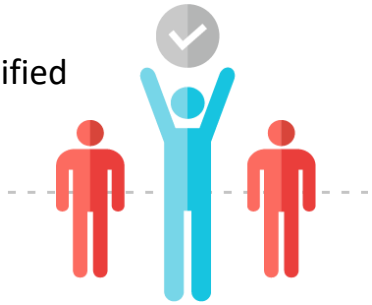
Informed Consent Forms (ICF) & Procedures

- **Informed Consent Form:**
  - ☑ Is the ICF IRB-approved and stamped?
  - ☑ Was the most up-to-date version used?
  - ☑ Did both the participant and the researcher sign and date the ICF?
  - ☑ Is the ICF completely filled out, including any checkbox sections?
  - ☑ Is the ICF free of any hand-written modifications that alter or obscure content?

- **Consent process and documentation:**
  - ☑ Was the consent conducted in accordance with the IRB-approved method?
  - ☑ Was the researcher qualified and delegated to consent participants?
  - ☑ Was the full consent process completed prior to performing any study activities?
  - ☑ Was the participant given a copy of the ICF to keep?

Screening & Eligibility

- ☑ Were recruitment and screening procedures conducted in accordance with the IRB-approved plan?
- ☑ Was participant eligibility assessed/confirmed before any study interventions occurred?
- ☑ Was the eligibility assessment performed by a qualified and delegated researcher?



Study Activities

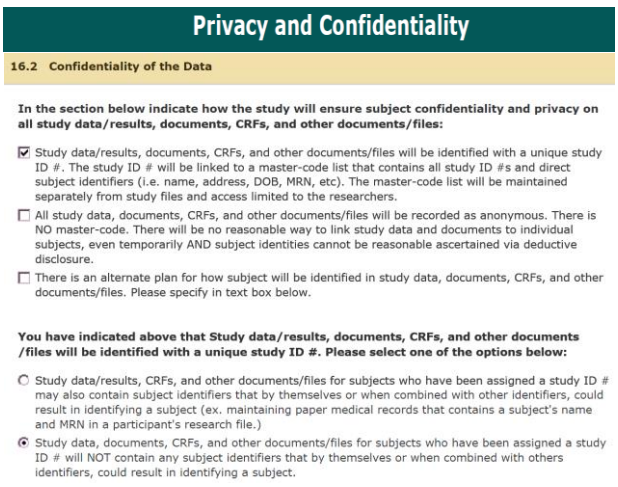
- ☑ Were all and only IRB-approved study activities performed at each participant visit/encounter?
- ☑ Did participant visits/encounters occur within the protocol-specified timeframe (if applicable)?
- ☑ Were study activities performed by a qualified and delegated researcher?

Adverse Events Monitoring & Safety Review

- ☑ Were AEs assessed at the correct timepoints in accordance with the IRB-approved plan?
- ☑ Does AE documentation include adequate information about the event?
- ☑ Were AEs recorded in accordance with the protocol's AE definition?
- ☑ Were AEs, SAEs, and UPs reported to the IRB and/or study sponsor in accordance with reporting requirements?
- ☑ Did safety reviews occur at the correct timepoints and/or frequency in accordance with the IRB-approved plan?

Confidentiality

- ☑ Are study documents stored securely?
- ☑ Are participant identifiers recorded on study documents according to the IRB-approved confidentiality plan?



Privacy and Confidentiality

16.2 Confidentiality of the Data

In the section below indicate how the study will ensure subject confidentiality and privacy on all study data/results, documents, CRFs, and other documents/files:

☑ Study data/results, documents, CRFs, and other documents/files will be identified with a unique study ID #. The study ID # will be linked to a master-code list that contains all study ID #s and direct subject identifiers (i.e. name, address, DOB, MRN, etc). The master-code list will be maintained separately from study files and access limited to the researchers.

☐ All study data, documents, CRFs, and other documents/files will be recorded as anonymous. There is NO master-code. There will be no reasonable way to link study data and documents to individual subjects, even temporarily AND subject identities cannot be reasonable ascertained via deductive disclosure.

☐ There is an alternate plan for how subject will be identified in study data, documents, CRFs, and other documents/files. Please specify in text box below.

You have indicated above that Study data/results, documents, CRFs, and other documents /files will be identified with a unique study ID #. Please select one of the options below:

○ Study data/results, CRFs, and other documents/files for subjects who have been assigned a study ID # may also contain subject identifiers that by themselves or when combined with other identifiers, could result in identifying a subject (ex. maintaining paper medical records that contains a subject's name and MRN in a participant's research file.)

◉ Study data, documents, CRFs, and other documents/files for subjects who have been assigned a study ID # will NOT contain any subject identifiers that by themselves or when combined with others identifiers, could result in identifying a subject.

Study Staff

- ☑ Were researchers added to the study on INSPIR prior to performing any study activities?
- ☑ Are researchers present on the Delegation of Authority log and staff training logs?
- ☑ Do researchers have active CITI certifications, and other required certifications?
- ☑ Do researchers have active medical/nursing licenses (if applicable)?
- ☑ Do researchers have an up-to-date CV/resume on file (if applicable)?
- ☑ Have researchers disclosed Conflicts of Interest and established a management plan (if applicable)?

Regulatory Documentation

- ☑ Are researcher qualifications/certifications filed?
- ☑ Are relevant SOPs/MOPs filed?
- ☑ Are communications with study sponsor, FDA, and/or other entities filed?
- ☑ Are required certifications for institution or facilities filed?
- ☑ Are FDA documents, e.g. 1572 form and IND/IDE documents, filed (if applicable)?
- ☑ Is the Conflict of Interest management plan filed (if applicable)?

Study Documentation

- ☑ Are ALCOA-C standards for source documentation followed?
  - ☑ Attributable, legible, contemporaneous, accurate, and complete
  - ☑ Changes and corrections to source documents follow ALCOA-C standards
- ☑ Is there adequate documentation to prove adherence to the IRB-approved study plan?
  - ☑ Informed consent process
  - ☑ Eligibility assessment and researcher that performed it
  - ☑ Study activities and researcher that performed them
  - ☑ Adverse Event assessment and safety reviews
  - ☑ Deviations
- ☑ Is all source documentation retained?

Poll: Study documentation must be kept in paper/hard copy records.

QA Review Outcomes & Action Items for Research Teams

QA Review Report Findings

Finding type	Definition	Action required by study team (IRB of record: BMC/BUMC IRB)	Action required by study team (IRB of record: External IRB)
Major Deviation *(actionable finding)*	Deviations that may: (1) harm the participant's rights, safety or well-being, (2) significantly damage the overall reliability of the study data, or (3) represent noncompliance with IRB requirements that may be serious or continuing.	Report to the IRB within 7 days of the investigator or research staff becoming aware of the event. The reporting includes a Reportable Events and New Information submission with Corrective and Preventive Action (CAPA) Plan.	Report as directed in QA report; May require follow up with the IRB of record and/or sponsor/main site to determine need for reporting.
Minor Deviation *(actionable finding)*	Any unapproved changes in the research study design and/or procedures that do not have a major impact on the participant's rights, safety or well-being, or on the reliability of the overall study data.	Report in aggregate to the IRB at the time of continuing review or status check-in.	Report as directed in QA report; May require follow up with the IRB of record and/or sponsor/main site to determine need for reporting.
Important Finding *(actionable finding)*	Require some action by the study team, such as submitting an amendment to the IRB or other notification to the IRB and/or sponsor. Does not require a RENI submission to the IRB	Study team should address as described in the QA report. The QA team will follow-up to determine if finding has been addressed.	Study team should address as described in the QA report. The QA team will follow-up to determine if finding has been addressed.
Best Practice Recommendation	Recommendations for study conduct and documentation usually based in ICH-GCP	None	None

*The QA team will follow up to determine if **actionable findings** have been addressed by the study team.*

QA Review Report Overview

- General Study Information
- Introduction
- Findings, Observations & Recommendations
- Summary of Findings
- Actionable Findings
- Best Practice Recommendations
- Conclusion
- Appendices

QA Review Report Overview: Actionable Findings

1. Screening/Eligibility

1.1 Enrollment of ineligible subject

Description:	Section 7 of the study protocol (v1.2, IRB approved 02/25/2023) indicates that subjects who received a vaccine in the two weeks (14 days) prior to the day of consent are excluded from participating in the study. Subject 05 consented to participate in the study on 04/11/2023. A review of the EPIC EMR record for subject 05 indicated that they received a vaccine on 03/31/2023.
Regulatory Reference:	21 CFR 312.60 ICH GCP 4.5.1
Policy Reference:	BUMC/BMC HRPP Policies and Procedures 6.6.5.2 BUMC/BMC HRPP Policies and Procedures 6.6.1(10)
Protocol/INSPIR Reference:	Study Protocol (v1.2, IRB approved 02/25/2023)
Finding Type:	**Major Deviation**
Action Item:	**This is a major deviation that must be reported to the BUMC/BMC IRB within seven days after receiving this report.** **A Reportable Events and New Information (RENI) form with accompanying Corrective and Preventive Action (CAPA) plan must be submitted to the IRB via the INSPIR II system.** Moving forward, it is recommended that the study team utilize an eligibility checklist to help ensure that all inclusion and exclusion criteria are met and appropriately documented.
CRRO or IRB Resource(s):	CAPA plan template How to create and submit a RENI form Research Subject Eligibility Assessment Form

QA Review Report Overview: Best Practice Recommendations

2. Study Staff

	Best Practice Description	Recommendation	CRRO Resource	Citation
#1	Human subjects protection and GCP training are expired for the following team members: -Emily Crowley -Alyssa Pingitore	Renewal of human subject protection and GCP training is required every three years for those involved in human subjects research. Please ensure the appropriate individuals renew their training.	N/A	BUMC/BMC HRPP Policy 6.2.3.2
#2	The following study staff members are listed on the INSPIR application but not on the delegation of authority (DoA) log: -Emily Crowley -Alyssa Pingitore	All study staff members conducting human subjects research should be listed on the DoA log. We recommend adding the two study staff members to the DoA log. The PI should not back date their initials to the staff members' start dates.	N/A	ICH GCP 4.1.5

Common QA Review Report Findings

Informed Consent	**Study Staff**
• No documentation that participant was provided with a copy of the ICF • Using an unapproved version of the ICF • Using an outdated version of the ICF	• Expired HSP, GCP training • Research staff not listed on INSPIR application and/or delegation of authority log
Screening/Eligibility	**Confidentiality**
• Enrolling ineligible subjects • Insufficient source documentation to support eligibility	• Non-adherence to the Confidentiality section of INSPIR application (PHI maintained in participant files)
Protocol Adherence	**Adverse Event Procedures**
• Procedures not completed as described in INSPIR application or study protocol • Procedures done out of protocol-specified window • Procedures done by staff not qualified, trained or delegated by PI	• AEs documented but not assessed (by qualified staff, in a timely manner, etc.) • AEs not correctly categorized as AEs, per protocol definition • Safety monitoring not occurring at protocol-specified frequency
Study Documentation	**Other**
• Does not adhere to ALCOA-C standards	• Missing regulatory documentation (e.g., training certificates, training logs, FDA Form 1572)

Interpreting the QA Review Report & Using it to improve research conduct

- Thoroughly read the entire report
- Focus on actionable findings (if any) to determine whether prompt action is required
- Reach out to the QA team with questions or to request a meeting to discuss the report, including actionable findings. (The QA team may have already requested a meeting.)
  - The QA team is available to help the study team address required actions (e.g., IRB submissions, CAPA development).
- Adopt best practice recommendations that work best for the research team.
- Research concepts covered are universal.
  - QA reviews may reveal systemic issues with research conduct that apply to other studies.
  - Findings can be used to improve research conduct across multiple studies.

Re-Visiting: QA Review Process Goals and Effectiveness

- To help research teams perform IRB-approved research in compliance with the applicable regulations, policies, and guidance in order **to protect the safety of participants** and **the reliability or validity of study data**.
- To educate study teams about best practices in Good Clinical Practice
- To consult on methods to correct potential problems with study conduct

- Like IRB review, QA reviews are a **required** component of the BUMC/BMC human research protection program.

- QA reviews are **effective** in reducing the number of actionable findings – just look at the data!

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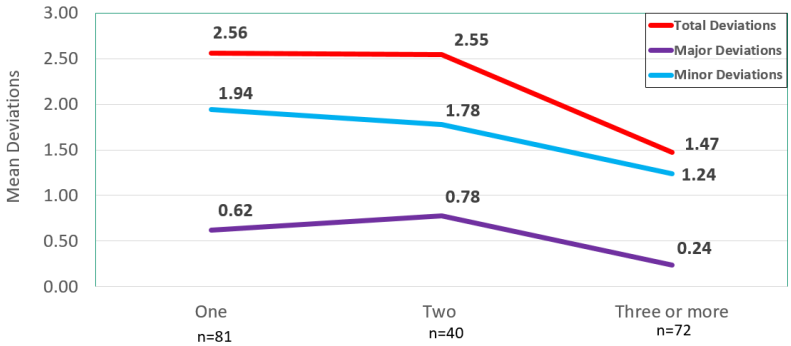

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Poll: The findings from a QA review are only useful for improving the specific study that was reviewed.

Don't want to wait to be selected for a QA review?

- Contact a Human Research Quality Manager to request a QA review at any point in the study lifecycle!
  - Alyssa Pingitore (aping@bu.edu)
  - Emily Crowley (eacrow@bu.edu)

- Conduct a Self-Assessment Review:
  - A research team's planned review of their own study documents and processes to verify protocol adherence and compliance to policy and regulations
  - Benefits include:
    - Supports participant safety and rights protection
    - Strengthens data integrity and reliability
    - Recommended as best practice
  - See the March 2023 Clinical Research Seminar for further guidance on conducting self-assessments

Check out these resources!

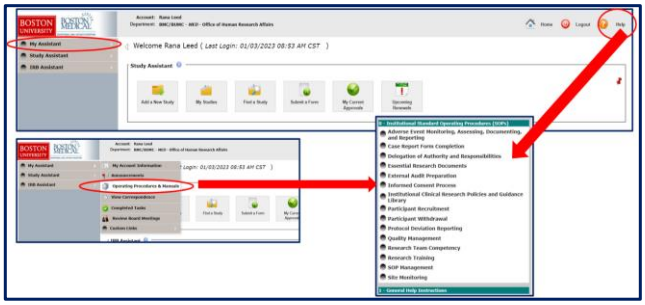
- Office of Human Research Affairs
  - Quality Assurance Reviews
  - Contact us
- Institutional Review Board
  - IRB Templates
  - INSPIR II Instructions for Investigators
- Clinical Research Resources Office
  - Study Documentation Tools
  - Self-Assessments
  - Education/Training Portfolio

Check out these resources!

Institutional Standard Operating Procedures (SOPs)

- Cross-institutional collaboration between BU Medical Campus and Boston Medical Center

Adverse Event Monitoring, Assessing, and Reporting
Case Report Form Completion
Delegation of Authority and Responsibilities
Essential Research Documents
External Audit Preparation
Informed Consent Process
Institutional Research Policies and Guidance Documents
Participant Withdrawal
Protocol Deviation Reporting
Quality Management
Research Team Competency
Research Training
Site Monitoring Visits
SOP Management
Subject Recruitment



Access SOPs within INSPIR:
My Assistant → Operating Procedures & Manuals – only available within the "home screen"

Check out these resources!

CAPA-Specific Resources

- **RPN Workshops**
  - Corrective and Preventive Action Plans: What they are and why you should care (11/17/22)
  - Developing Effective Corrective and Preventive Action (CAPA) Plans (6/18/19)
- **Clinical Research Seminar**
  - How to develop a Corrective and Preventative Action Plan (CAPA) that even the FDA will love (4/11/18)
- **CR Times**
  - Developing a Corrective and Preventive Action Plan (5/25/22)
- **BU Med Campus/BMC CAPA Template**