Clinical Trials Compliance: Planning for Success

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Objectives

- Participants will differentiate between a monitoring visit and an audit.
- Participants will be able to list three advantages of having a study monitored and/or audited.
- Participants will describe the meaning and function of a CAPA

Outline

- What do we mean we say “Compliance”?
- What is monitoring and auditing, is there a difference and why is it necessary?
- How to ensure compliance:
  - Planning for success
  - Who should be responsible
  - Tips and ideas for ensuring compliance.
- CAPAs – a method for identifying and correcting non-compliance
- Common non-compliance findings and examples.

What is Clinical Trials Compliance?

Conducting clinical research in accordance with:

- Ethical principles laid out in the Belmont Report:
  - Respect for Persons
  - Beneficence
  - Justice
- Local and Federal Regulations
  - US FDA-regulated studies: 21 CFR 312, 812, 50 & 56
    - Responsibilities of Sponsors and Investigators
    - Protection of human subjects
    - IRB Board
  - US HHS-funded studies: 45 CFR 56
  - Local regulations over-rule federal regulations (ex. Pregnant minors, wards of the state, etc.)
- International Conference on Harmonization (ICH) Good Clinical Practice (GCP) standards.

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Monitoring Visit vs. Audit

Quick quiz, please match the type of visit with the scenarios below ('you', means you are the auditor or monitor):

The study has been active for 6 months:

1. You are going to a site to review screening, eligibility, and Cycle 1 data for the enrolled subjects on February 22, 2020.

1. You are going to a site to review the study on February 22,2020.

Which scenario is a monitoring visit and which one is an audit?

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Monitoring

Oversight of the progress of a clinical trial; ensuring that a trial is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP and applicable regulatory requirements.

Auditing

A systematic and independent examination of trial-related activities and documents to evaluate whether the trial-related activities were conducted and the data were recorded, analyzed, and accurately reported according to the protocol, SOPs, GCP and applicable regulatory requirements.

Auditing vs. Monitoring

MONITORING	AUDITING
Act of overseeing the progress of a clinical trial	Systematic and independent examination of trial related activities and documents
100% source document verification of participants	Snapshot in time of a subset of participants
Ensures study is conducted in accordance with protocol, SOPs, GCP and regulatory requirements	Determines whether the trial related activities were conducted and data recorded accurately, analyzed and appropriate reported according the protocol, SOPs, GCP and regulatory requirements
Requirements vary by protocol	An audit is

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Why have monitoring and auditing?

The short answer is: history, and unfortunately, history continues to repeat itself.

Historical examples:

- Tuskegee Studies, Nuremburg Trials

Modern Day examples:

- Genetech, Inc: failure to confirm eligibility, failure to conduct approved screening, failure to retain documentation of results and interpretation of all screenings*.
- Physician at NW University: failure to follow investigational plan and protocol contained in the IND, failure to submit a protocol amendment to the FDA when there was a significant change in protocol design*.
- Personal audit experiences reviewing clinical trials conducted at our own institution

*Source: FDA Warning Letters

Why have monitoring and auditing? (Cont.)

What are the Pros?

What are the Cons?

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Why have monitoring and auditing? (Cont.)

Pros: (including but not limited to)

- Verification of study conduct
- Reporting of SAEs and major deviations,
- Ensures approvals and oversight are current
- Verification of data accuracy
- Verification that legally effective informed consent was obtained prior to initiating research procedures
- Confirms adherence to local/internal SOPs

Cons: (including but not limited to)

- Negative dynamic with site reviewer
- Frequent changes to site reviewers leads to inconsistency and less than optimal oversight
- Duplicating query responses due to sponsor disorganization

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FDA BIMO Inspections

- FDA Bioresearch Monitoring Program (BIMO) has the authority to audit or inspect *any* FDA related research

- BIMO Inspectors are focused on 3 things:
  1. Study Conduct and Patient Safety
  2. Data Integrity
  3. ICH GCP Compliance

- 2 Main Types of BIMO Inspections
  1. Planned (Routine)
     - ~80% of yearly inspections;
     - Verification that data submitted is accurate
  2. Unplanned (For Cause)
     - Complaint, sponsor concerts, unexpectedly high accrual rates, results are notably different from other sites etc.

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Planning for Compliance Success

- Screening & Eligibility Processes
- Study Conduct
- Adverse Event & Deviation Reporting
- Data Integrity
- CAPAs

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Screening & Eligibility Compliance

- Adherence to Inclusion / Exclusion Criteria
- Minimize use of waivers to Inclusion / Exclusion Criteria
  - Require prior approval from the Sponsor AND the IRB of Record
    - Code of Federal Regulations:
      - 21 CFR 812.150 (a)(4): Deviations from the Investigational Plan
      - 21 CFR 812.35 (a)(1): Changes to the Investigational Plan Requiring Prior approval
      - 21 CFR 312.66: Assurance of IRB Review
    - FDA Biomedical Monitoring (BIMO) Checklist:

"limited prospective exceptions to the protocol (e.g. agreement between the Sponsor and Investigator to enroll a single subject who does not meet all inclusion/exclusion criteria), must be review and approved by the IRB prior to implementation"

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Screening & Eligibility Compliance

- Source Documentation
  - Eligibility Checklists are helpful but are not source.
  - Serve as evidence that no study specific, clinical screening procedures are performed prior to obtaining Informed Consent.[1]
  - Best practice is to document eligibility in the medical record, or if this is not possible, within the research chart.[2]
- Responsibility
  - Some screening and eligibility responsibilities can be delegated to Clinical Research Team Members:
    - Subject medical record review
    - Collection of source / documentation of eligibility
  - It is ultimately the responsibility of the Investigator to verify and document eligibility.
    - Enrolling ineligible subjects is seen as a violation of the Statement of the Investigator (FDA Form 1572).
    - Document Investigator oversight of eligibility and enrollment (e.g. printed/saved email communication, meeting minutes etc.)

1. *FDA Information Sheets: Screening Tests Prior to Study Enrollment (January 19980.*
2. *21 CFR 312.62: Investigator Recordkeeping and Record Retention*

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Screening & Eligibility Compliance: Tips for Success

1. Establish a procedure for processing eligibility waivers (if applicable)
   - Who has the authority to "approve" a waiver of eligibility?
   - Required Documentation: Investigator oversight, rationale for deviation, Sponsor approval, IRB approval, etc.
   - Best practice is to document eligibility in the medical record, or if this is not possible, within the research record

2. Train before Delegating
   - Clinical Research Team members who are delegated screening and eligibility tasks should be appropriately trained *before* engaging in study activities.
     - Training and delegation of tasks should be documented, these logs are requested by auditors.

3. Establish a procedure for ensuring adequate investigator oversight
   - Routine meetings to discuss enrollment and screening:
   - Print or save email communications discussing enrollments

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General Study Conduct Compliance

- Conducting the perfect study

- It's about understanding the process and managing issues along the way
  - Identifying and correcting mistakes and issues along the way
  - Demonstrating compliance with GCP

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General Study Conduct Compliance

Know the protocol

Inconsistencies between the protocol and other materials (schedule of assessment vs. description of procedures, lab manuals, consent forms, standard institutional practice) are common audit findings.

- Document communications with the Sponsor to clarify study requirements and/or expectations.
- Revise protocol / documents if necessary & obtain IRB approval before implementing changes (unless subject safety is involved).

Protocol

Clinical Researchers

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General Study Conduct Compliance

1. Screening: what can be done prior to obtaining consent vs. what can only be done after obtaining consent?

1. Eligibility: each inclusion/exclusion criteria must be supported by source documentation (clinic note, path report, operative report, questionnaire, lab results, radiology reports, etc.).

1. Know and follow the protocol: procedures, evaluations, assessments, follow-up, data entry and AE/SAE reporting. Again, all these things must be supported by source documentation.

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General Study Conduct Compliance (Cont.)

How to manage the study related issues, errors and uncertainty that study teams encounter:

1. Screening and Eligibility:

- Interpretation of protocol eligibility criteria in relation to subject findings is not clear. What should be done?
- Protocol specific screening/baseline evaluation is out of window at the time of registration. How should this be handled?

2. Treatment / Procedures:

- The protocol content and schedule of events are conflicting, how should this be handled?
- The next scheduled clinic visit and research procedures will be out of window, what should be done?

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General Study Conduct Compliance (Cont.)

How to manage the study related issues, errors and uncertainty that study teams encounter

3. A study procedure (lab, infusion, questionnaire, imaging, etc.) was not conducted per protocol, what are next steps?

3. The study requires central review, does this correspondence need to be part of the research file?

3. The investigator has informed you that he/she has spoken to the study chair, and the subject can remain on study. How does this get documented?

3. A new protocol amendment has just been released, what needs to get done?

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Adverse Event Compliance

- The Clinical Research Team is responsible for:
  - Identifying changes in a research subjects health that may qualify as an Adverse Event (AE) or Serious Adverse Event (SAE);
  - Classifying and documenting those events; and
  - Reporting these events to the Sponsor, IRB, FDA, etc. as required.

- Ensures subject safety and supports principles of beneficence

- Know:
  - The Protocol
  - The requirements of the IRB of Record

Adverse Event Compliance: Tips for Success

- KNOW YOUR PROTOCOL, KNOW THE REQUIREMENTS OF THE IRB OF RECORD
- Collection vs. Reporting
- Establish a baseline prior to any clinical research intervention
- Attribution (the causal relationship to the investigational drug/device/intervention) should be determined by the PI or a qualified Sub-Investigator.
  - This is a medical determination
  - What action was taken regarding the study (off study, dose reduction, delay in treatment)
  - Serves as ongoing documentation of Investigator oversight
- Follow-up appropriately and until resolution and/or all information is provided.

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Deviation Compliance

- Federal Regulations require *prospective* review of any planned deviations from the investigational plan

- Unplanned deviations should be:
  1. Documented (e.g. report to the IRB, cumulative deviation log, research note to file etc.)
  2. Reviewed for consideration of process change

Deviation Compliance: Tips for Success

- Self-identification and reporting is always better
- Don’t make the same mistake twice
- Document corrective actions and efforts to prevent deviations from re-occurring.

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Data Integrity and Compliance

Source documentation forms the foundation for the data that gets transcribed into the CRF, which ultimately gets translated into a clinical study report and in turn determines the treatments that are available to cancer patients.

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Data Integrity and Compliance

Research data management is actually complex, but if done correctly from the start, saves time and resources in the long run.

- It involves daily management of data during the lifetime of the research project
- It involves decisions about the future of a research project
- It involves preserving for long term access and sharing

Data must be obtained within protocol designated time-points

Data must be supported by source documentation (clinic notes, lab results, path and/or radiology reports)

Data entry must be timely AND accurate

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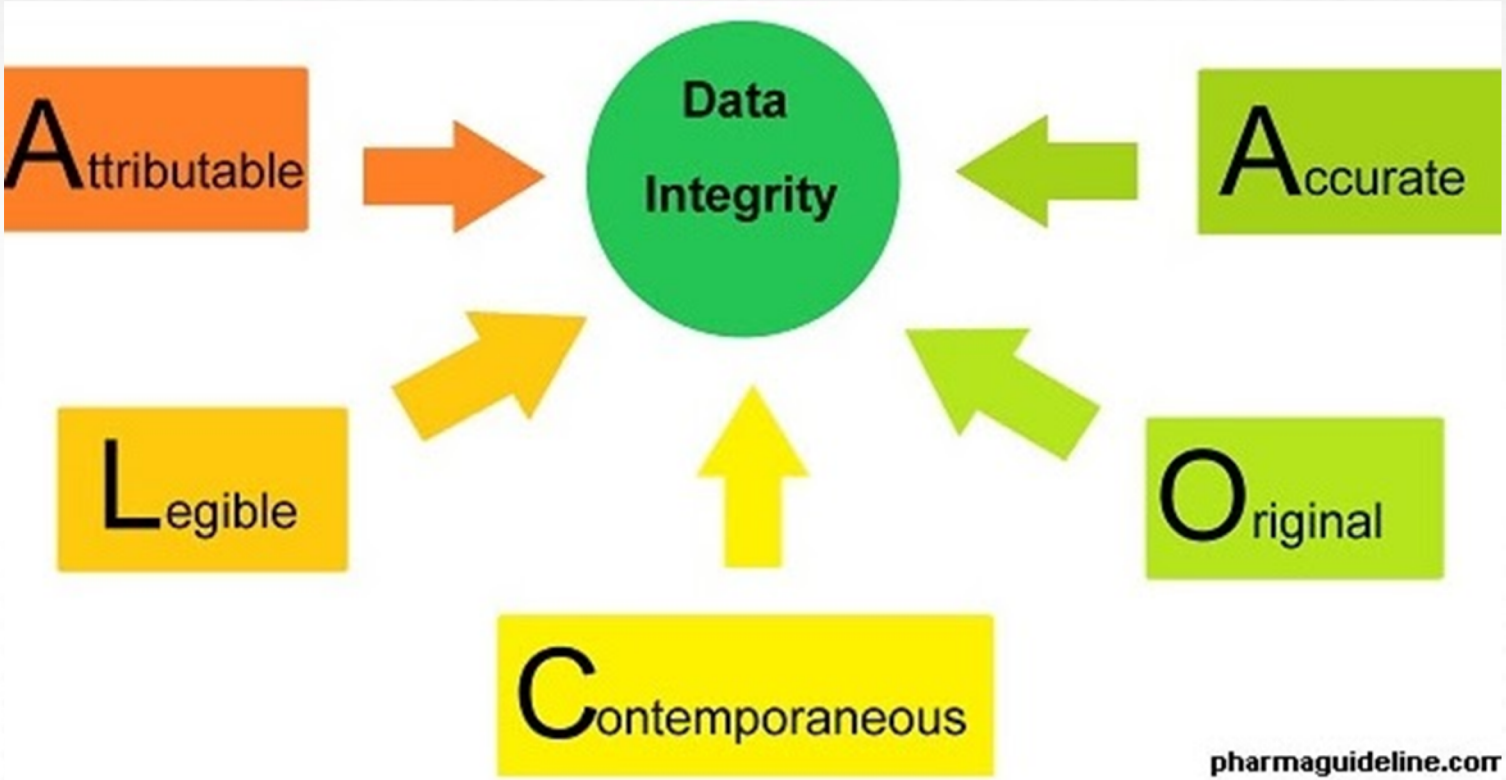
Principles of Good Documentation Practices (GDPs)



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Common Audit Findings

I. **Regulatory**: binders missing some sponsor and/or IRB correspondences or submissions, 1572 needs to be revised, new Sub-I CV needed, etc., lack of- or poorly documented training for study staff.

I. **Consents**: scanned copy not found in the CTMS or EMR

I. **Re-consents**: not always done, documentation of re-consent note often lack the reason for re-consent (i.e. PA4, correction of injury language)

I. **Inconsistencies** between protocols, manuals, consents and standard practice (ex. IV vs. Oral premedication, Oral vs. Temporal temperatures, screening within 7days vs. 28days)

Common Audit Findings (Cont.)

V. **Deviation reporting missing**

V. **CRFs**: missing pagination, signatures, entries, blank fields

V. **Data Entry**: not done, entry error, incorrect, chose wrong response un-intentionally “assessment not done” vs. “N/A per protocol”

V. **Queries not completed** since last visit

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CAPAs

What is this 4-letter word and what impact does it have?

- CAPA: **C**orrective **A**nd **P**reventative **A**ction
- Can be self identified and initiated to show due diligence
- Required by regulatory authorities as a result of findings from a site visit

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CAPA (Cont.)

A CAPA plan is a series of actions taken to focus on the immediate noncompliance and the broader scope of the problem, it requires:

- Investigating and understanding the issue
- Reporting what was done to immediately correct the issue
- Identifying the root cause of the issue
- Implementing plans to prevent the root cause

CAPA (Cont.)

When is a CAPA required?

- When subject safety issues have been identified
- When data integrity issues have been identified (data cannot be validated or confirmed by source documentation, frequent errors in data entry).

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CAPA (Cont.)

CAPA plans must be documented, maintained, and demonstrate that the corrective and preventative actions have effectively resolved the issue.

It’s an on-going assessment, and CAPAs may need to be re-assessed when events continue to occur, or re-occur.

The hematologic laboratory tests for both protocols include hematocrit and hemoglobin; red blood cell count; total and differential white blood cell counts, including neutrophils, lymphocytes, monocytes, eosinophils, and basophils; platelet count; prothrombin time; partial thromboplastin time; and international normalized ratio.

These hematologic laboratory tests are safety assessments in the studies, because they are used to monitor for **(b)(4)**- related adverse events such as neutropenia for which subjects will have their doses interrupted or discontinued, depending on the severity.

Failure to diagnose neutropenia in a timely manner places subjects at increased risk for developing serious infection and sepsis.

Therefore, missed protocol-required hematologic laboratory tests compromise subject safety.

Specifically:

a. Subject 033-008-03 in Protocol **(b)(4)** missed hematologic laboratory tests at Week 20
b. Subject 033-008-04 in Protocol **(b)(4)** missed hematologic laboratory tests at Weeks 5, 6 and 7
c. Subject 033-008-05 in Protocol **(b)(4)** missed hematologic laboratory tests at Week 20
d. Subject 1302 in Protocol **(b)(4)** missed hematologic laboratory tests at Week 1

In your October 2, 2017, written response for the Form FDA 483, you indicated that these missed laboratories were mainly due to subject noncompliance.

You stated that orders for laboratory tests were given to the subjects at each visit

You noted that corrective measures to address subject non-compliance taken at the time included phone calls to subjects and oral reminders during the following clinical visit.

Your response is inadequate because:

- You have not proved sufficient details about your corrective action plan.
- You have not provided adequate documentation of your efforts to address subject noncompliance (e.g. phone calls, oral reminders during the following visit) in the source records. Without those details in the records, we are unable to determine whether your corrective action plan is adequate to prevent similar violations in the future.

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3. You failed to ensure that the investigation was conducted according to the Investigational Plan [21 CFR 312.60].

Your general responsibilities as a clinical investigator include ensuring that the clinical trial is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety and welfare of subjects under your care; ensuring control of drugs under investigation [21 CFR 312.60]. Protocol **(b)(4)** outlines the types and timing of required assessments in Section 6.3 and Table 2, Assessments During Study Treatment.

You failed to ensure that Protocol (b)(4) was conducted according to the Investigational Plan in that you failed to ensure that all assessments required by Protocol (b)(4) were performed.

Examples of your failure to follow the investigational plan include, but are not limited to, the following:

a. Subject 089002, November 18, 2009 (Cycle 1, Day 1): circulating tumor cells, pharmacokinetics, and pharmacogenomics were not performed
b. Subject 089002, December 9, 2009 (Cycle 2, Day 1): Quality of Life FACT-O Questionnaire and circulating tumor cells were not performed
c. Subject 089002, December 30, 2009 (Cycle 3, Day 1): Quality of Life FACT-O questionnaire was not performed

We acknowledge that in your January 10, 2011, response to From FDA 483 you describe the corrective actions taken in response to the above-listed violations.

These corrective actions include: hiring additional staff, providing additional training for research staff on Research SOPs, GCP and HSP, and updating existing SOPs. However, as the clinical investigator is was your responsibility to ensure that study related-procedures were performed in accordance with the protocol requirements.

Failure to perform study-related procedures has the potential to jeopardize subject safety and welfare, and to compromise the interpretation and validity of the investigational endpoints.

Although the assessments listed above are not primary endpoints of the investigation according to the protocol, the conduct of the investigation and conformance with the protocol must be taken as a whole.

The inclusion of subjects who have been diagnosed with ovarian cancer in this study indicates that the collection of valid data on circulating tumor cells, pharmacokinetics and pharmacogenomics is valuable for the complete evaluation of the study results. In addition, Protocol **(b)(4)** states that a secondary endpoint of the study is to asses health related quality of life, thus indicating that valid QOL data are necessary.

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You failed to ensure that the investigation was conducted according to the signed investigator statement, in that you failed to personally conduct or supervise the clinical investigation [21 CFR 312.60]

When you signed the Statement of the Investigator (Form FDA 1572) for the above-referenced clinical trials, you agreed to take on the responsibilities of the clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trial is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation.

By signing Form FDA 1572, you specifically agreed to personally conduct the clinical trial, or to supervise those aspects of the trial that you did not personal conduct.

While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that Protocol **(b)(4)** and Protocol **(b)(4)** were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety and welfare of human subjects.

Specifically, we note that your failure to adequately supervise a study coordinator for Protocol **(b)(4)** and Protocol **(b)(4)** led to problems with the conduct of these investigations as described below, which included failure to maintain adequate and accurate case histories, and failure to conduct assessments required by the protocols.

We note that in your January 10, 2011 respond to the Form FDA 483, you state that:

- The study coordinator who was delegated the tasks led to the violations cited below, admitted her wrongdoing and resigned in February 2010.

We also acknowledge that your response described corrective and preventative actions that you have taken, including the

- Appointment of a Director of Clinical Research with at least 8 hours per week designated to work on oversight of the clinical trials program, who will meet at least weekly with clinical trial coordinators and data managers.

However, your response is inadequate because you have not submitted the revised SOPs referenced in your response, or specifically identified how changes in those procedures will serve to prevent the recurrence of this type of violation in the future. Please provide this documentation. Without the submission of this information, the Agency is unable to undertake and informed evaluation of the potential use of your actions in preventing the recurrence of these violation.

Summary

The key to a successful clinical research enterprise is to have successful regulatory authority visits. These are directly related to the quality of the work that is produced.

Clinical Research Teams have members from varying backgrounds should be committed to supporting an environment that enhances the success of the research effort, which reflects in the research provided to our subjects and the data we submit to our sponsors. We all need each other to be successful.

We can achieve this through on-going review of audit/monitoring outcomes, and identify which is the best method(s) to address our needs: education, change in operations, or methods to enhance investigator/research staff collaborations.