P4 Sponsor Clinical Quality Assurance Audits of Investigator Sites:
Readiness, Response, and CAPAs

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- I have **no conflicts of interest** related to this presentation and **I am not promoting any products or services**
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Agenda

1. Purpose/Authority for site audits
2. Site readiness for sponsor audit
3. Responding to a sponsor audit
4. Corrections and CAPAs

Purpose of & Authority for Sponsor Audits of Investigator Sites

FDA & Bioresearch Monitoring (BIMO) Program

- The Federal Food, Drug, and Cosmetic Act (FD&C Act) is a federal law enacted by Congress. It and other federal laws establish the legal framework within which FDA operates.
- FDA is responsible for protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices. To this end, under its FD&C Act authority, FDA issues regulations which are also federal laws, but they are not part of the FD&C Act. FDA regulations are found in Title 21 of the Code of Federal Regulations (CFR).
- Protecting the rights, safety and welfare of people who participate in clinical trials is a critical aspect of the FDA's mission. FDA oversees clinical trials to ensure they are designed, conducted, analyzed and reported according to federal law and good clinical practice (GCP) regulations
- FDA's bioresearch monitoring (BIMO) program is a comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research.

U.S. Food and Drug Administration (fda.gov)

FDA BIMO GUIDANCE MANUAL

CP 7348.810 Sponsor/CRO

I. QUALITY ASSURANCE ACTIVITIES

- ***Although not required*** by regulations, many sponsors establish quality assurance departments, quality assurance units (QAUs) or similar entity to perform independent audits or data verifications and to critically review processes, procedures, and reports to determine their compliance with protocols and procedures. These quality assurance (QA) activities (e.g., independent audits, data verifications) may be conducted with or without the establishment of a QAU. All QAUs and/or auditing personnel should be independent of, and separate from, routine monitoring or quality control functions. The sponsor is ultimately responsible for the integrity of the study submitted to FDA.

- In general, during routine inspections and investigations, the ORA investigator should review and confirm audit certificates but not request for review or copy reports and records that result from audits, unless directed by the assigning center. For additional guidance on this matter, refer to Compliance Policy Guide (CPG) 130.300: FDA Access to Results of Quality Assurance Program Audits and Inspections. Contact the center POC for further clarification or instruction.

Authority for Sponsor GCP Audits of Sites

	Sponsor CQA Program	Sponsor CQA Site Audits	CQA Site Audits by Sponsor's CRO	Site cooperation with sponsor audits
ICH E6 (R2)	5.1 Quality Assurance and Quality Control	5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see section 1.21) to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor…	5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.	6.10 Direct Access to Source Data/ Documents The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/ institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.
ISO 14155:2020	3.40 quality assurance - planned and systematic actions that are established to ensure that the clinical investigation (3.8) is performed, and the data are generated, documented (recorded), and reported in compliance with this document and the applicable regulatory requirement(s)	9.2.3 Conduct of clinical investigation The sponsor shall be responsible for…g) performing and documenting root cause analysis and implementation of appropriate corrective and Preventive action if noncompliance significantly affects or has the potential to significantly affect subject protection or reliability of clinical investigation results,	9.3 Outsourcing of duties and functions - The sponsor may transfer any or all of the duties and functions related to the clinical investigation…to an external organization (such as a CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical investigation conduct shall reside with the sponsor. The sponsor shall ensure oversight of any clinical investigation-related duties and functions.	7.7 Subject privacy and confidentiality of data - …The principal investigator or investigation site shall provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review and regulatory authority inspections. As required, the principal investigator or investigation site shall obtain permission for direct access to source documents from the subject, hospital administration and regulatory authorities before starting the clinical investigation.
CSA, Protocol, ICF		x	x	x

Purpose of sponsor audits of investigator sites

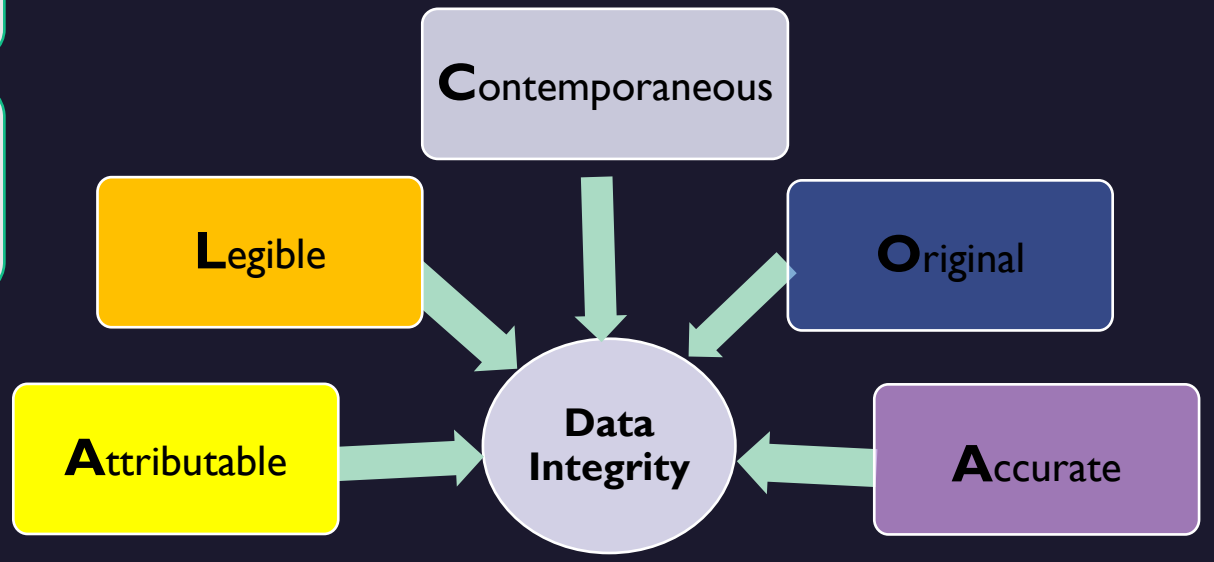
1. **Ensure Good Clinical Practice (GCP) at clinical sites conducting the Protocol**

Subject Safety

rights, safety and welfare of human subjects are protected

Data integrity

reported data is accurate, complete and verifiable from source documents



Goals of sponsor audits of investigator sites

2. **Bring non-compliant sites into compliance**
3. **Manage ongoing/serious noncompliance**
   - Suspend/terminate
   - Comply with reporting requirements
4. **Holistically assess the quality and compliance of the site's study conduct for any appropriate guidance/observations**
5. **Support Inspection Readiness by ensuring the documentation in the record accurately reflects fulfillment of sponsor and site responsibilities**

ISO 14155:2020 Annex J (informative)
Clinical investigation audits – J.3 Investigation site

Regulatory approvals and correspondence

Insurance documents

Site organization of personnel and facilities (DAL, qualifications and experience, training records, agreements, suitable facilities/equipment, equipment maintenance/calibration records, validated site systems)

Financial disclosures

Data integrity, document retention/availability, completeness, storage

Use of approved CIP

CIP deviations, documentation and reporting, management, approval if applicable

Informed consent on correct version approved, consent practices and w/ vulnerable subjects

Source available, organized, condition, GDP/ALCOA

CRF use, recording of data on CRFs, corrections made, compliance

Monitoring records, preservation of pt. privacy

Device handling, accountability, storage, control

Safety reporting

…and more

Site readiness for sponsor audit

Audit Readiness by Design

1. Effective program policies, procedures; documented training and training maintenance, peer checks, self-assessment, corrections, corrective/Preventive actions, continuous improvement, with internal quality and compliance programs to ensure Good Clinical Practice and GDP:
   - **Human Subject Protection** - Protection of the rights, safety and welfare of subjects participating in clinical research
   - **Data Integrity** - Accuracy, reliability of study data submitted in support of research or marketing applications
   - **Compliance** - with applicable regulations and Protocol governing the study
2. Create research program self-audit checklist templates leveraging regs/standards/guidance for content
3. Complete Study-specific compliance assessment, plan, checklist to ensure adequate implementation of GCP with timely identification and correction of errors
4. Complete documented, appropriately approved, signed/dated NTFs and CAPAs as indicated.

Regulations and Standards for Site GCP

- 21 CFR Part 11 Electronic Records; Electronic Signatures USA
- 21 CFR Part 50 Protection of Human Subjects USA
- 21 CFR Part 54 Financial Disclosure by Investigators USA
- 21 CFR Part 56 Institutional Review Boards USA
- 45 CFR part 46, the "Common Rule"
- 21 CFR Part 812 Investigational Device Exemptions USA
- 21 CFR Part 814 Premarket Approval of Medical Devices USA
- 21 CFR Part 312 - INVESTIGATIONAL NEW DRUG APPLICATION
- ISO 14155 Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice INT'L
- ICH E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) - Guidance for Industry
- Regional requirements

Audit Readiness Resources

1. CP 7348.811 Investigators/Sponsor-Investigators
   - Applies to all FDA inspections of clinical investigators
   - Outlines inspection procedure for ORA investigator ➔ **checklist for site readiness**
   - Authorizes scope expansion if significant deviations are found during inspection that *may have* impact on safety of subjects or accuracy and reliability of the data.
2. Know your applicable regulations
3. Know your applicable GCP standards
   - ICH E6 (R2) – FDA adopted
   - ISO 14155 – FDA has discussed adopting, global device trials and global device manufacturers include in Protocol Statement of Compliance
4. FDA Clinical Trials Guidance Documents - (not the law, assists in interpretation & implementation, good safeguards)

Plan against common FDA Clinical Investigator Inspectional Observations

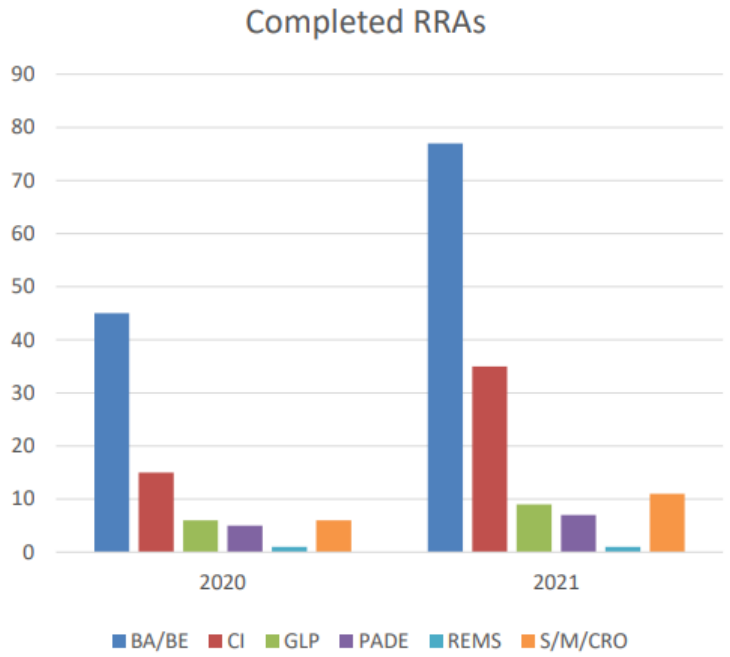
Most common observations collected from issued FDA Form 483s

- Failure to follow the investigational plan; protocol deviations
- Inadequate and/or inaccurate case history records; inadequate study records
- Inadequate accountability and/or control of the investigational product
- Failure to comply with Form FDA 1572 requirements
- Inadequate subject protection; informed consent issues
- Safety reporting; failure to report and/or record adverse events
- Failure to comply with 21 CFR part 56 (IRB) requirements

BIMO Fiscal Year 2021 Metrics (fda.gov)

Be Remote-Ready for RRA

Number of Remote Regulatory Assessments Completed FY 2020-2021



Program area	2020	2021
Bioavailability/Bioequivalence	45*	77*
Clinical Investigator	15	35
Good Laboratory Practice	6	9*
Postmarketing Adverse Drug Experience	5	7
Risk Evaluation and Mitigation Strategies	1	1
Sponsor/Contract Research Organization	6	11

*CDER/OSIS Completed RRAs:

- 40 BA/BE RRAs in FY20 (18 Clinical, 22 Analytical)
- 68 BA/BE RRAs in FY21 (18 Clinical, 50 Analytical)
- 7 GLP RRAs in FY21

OSIS: Office of Study Integrity and Surveillance

31

[BIMO Fiscal Year 2021 Metrics (fda.gov)]\

[Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency Guidance for Industry April 2021]

Determine if your site is likely to be audited?

Examples of site selection criteria:

1. Known site compliance issues
2. High enroller / high % of critical data contribution
3. Relative event/deviation rate
4. Event/deviation/data trends
5. Prior site audit observations merit follow up audit
6. Regulatory Authority or IRB/EC inspection findings
7. PI/Sub-I DQ or debarment
8. New site PI/Sub-I/primary RC or new sponsor monitor
9. New Site/no prior sponsor audit
10. Site staff turnover
11. PI participating in numerous trials
12. Study region/population factors
13. Site participation terminated or suspended.
14. Other data trends or concerns
15. For cause audit.

Responding to a sponsor audit

Audit Arrangements

1. **Upon notice**
   - Promptly agree to dates to allow site's ready support of audit activity and in-person meetings with Principal Investigator and primary study team members during opening and closing meetings
   - Arrange primary study team point person for timely responsiveness to planning and execution of audit
   - Advise internal stakeholders (e.g., study team, research manager, quality assurance, investigational pharmacy/device accountability owners, clinic services, IT EMR/research systems owners, etc.)

2. **Set up required prior to the audit day(s)**
   - Direct onsite methods or remote methods depending on audit format (remote not permitted in GDPR regions but used increasingly in US and some other regions)
   - Audit space if onsite, or video conference and file sharing platform(s) if remote
   - Investigator site file and related records access
   - Hospital and facility EMRs read-only access to subject medical records relevant to the study
   - All subject consents and consent process documentation
   - All Subject research records (I/E, source forms, event and deviation logs, etc.)
   - Viewing of all drugs/devices on site and related accountability records
   - Facilities tour for areas used for subject consenting, visits, records storage, drug/device storage

Audit Prep

- ✓ Rely on readiness by design activities and use checklists to re-check records
- ✓ Review monitoring reports for any open issues/action items and try to complete prior to the audit
- ✓ Review ISF and subject records holistically for organization, completeness of essential documents, GDP/ALCOA, DAL start dates are after completing all qualification/training/authorizations, no training/cert gaps for delegated team performing work, logs are complete and accurate, objectively evidences compliant conduct of the study, AE./DD/PD reporting per Protocol and reviewing IRB/EC policy has been met
- ✓ Double check all consents for correct version used, signatures/dates; consent process documentation; timing
- ✓ Be able to provide full case history and ensure source for I/E , endpoint data and AE/PD/DDs readily available for all subjects
- ✓ Be sure any copies of original source placed in subject records are certified by team member sig/date as true, accurate and complete copies of original
- ✓ Investigational product accountability records are current and accurate from receipt through use to return/destruction; temperature logs, installation records, etc.
- ✓ Lab certs/values, other procedure value norms as applicable
- ✓ Ensure any NTFs are well written for issue, clarifications and/or corrections, corrective actions, verifications, as applicable, and appropriately signed/dated by investigator
- ✓ Discuss eSystems and eSignatures validation and Part 11 compliance, back-up and disaster plan for all related systems in play for data collection, recording, reporting, storage, and all involved regulatory documents; know storage and retention period plans
- ✓ Review SOPs for content, currency and have GCP standards on file; ensure all are well understood, compliance met

Review "Essential Documents" for GDP

- ICH E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry - Sec. 8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

- ISO 14155:2020 - Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, Annex E (informative) Essential clinical investigation documents

  - International Organization for Standardization (ISO) issued, approved by CEN (members are the national standards bodies of Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Republic of North Macedonia, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and United Kingdom.

  - While ISO 14155 is not US law, FDA officially recognized it as a standard in 2012. Current recognition is under FR Recognition Number 2-282 entered 21Dec2020 to recognize ISO 14155:2020. [Transition Period - FDA recognition of ISO 14155 Second edition 2011-02-01 [Rec# 2-205] will be superseded by recognition of ISO 14155 Third edition 2020-07 [Rec# 2-282]. FDA will accept declarations of conformity, in support of premarket submissions, to [Rec# 2-205] until December 18, 2022. After this transition period, declarations of conformity to [Rec# 2-205] will not be accepted.]

Audit Day Response

- ✓ Be on time, available, polite and professional.
- ✓ **Be honest.**
- ✓ Wait to hear the questions so you can be responsive - Ask questions, clarifications if you don't understand the question.
- ✓ Promptly provide requested documents, information, interviewees.
- ✓ If you see or the auditor points out a nonconformance during the audit, proactively work with your team to make appropriately reviewed/approved corrections and consider if corrective actions are needed and can be initiated to avoid an observation.
- ✓ If you reasonably need time to respond/provide records, provide the reason and the reasonable time you expect to respond, understanding that the expectation is to complete the audit during the audit days.
- ✓ Keep track of questions, requests, responses and records produced.
- ✓ Respectfully explain your position if you disagree with an observation, and/or provide documentation in the record to support your position.

Responding to Audit Observations

1. Know and adhere to the response due date
2. Determine if the sponsor monitor will work with you on completing adequate responses
3. Determine if any of the observations or any CAPA require reporting to the IRB/EC
4. Determine if corrections suffice or if corrective action is warranted
5. Be sure written responses are complete sentences
6. Include objective evidence of corrected records and/or corrective actions taken/plan/verification
7. Provide your target date of completion of corrections, of corrective actions and verification of corrective actions

Audit Observation Responses: Corrections and CAPAs

Scale Response to Sponsor's Audit Observation Severity

➔Request End-of-Day meetings each audit day to identify anticipated observations

Critical Observation: A significant non-compliance to regulatory requirement(s), Protocol, and/or GCP that presents risk of or actual harm to subject safety, welfare or rights, and/or compromises study data integrity.

Major Observation: A significant or frequent non-compliance to regulatory requirements, Protocol, and/or GCP that *could* compromise subject safety, welfare or rights, and/or compromises study data integrity if not addressed.

Minor Observation: Non-compliances that are less frequent and less significant for which corrections are readily completed, and which do not compromise data integrity or patient safety, welfare or rights.

Promptly responding to observations demonstrates diligence and commitment to quality

Make corrections such as placing missing records in the ISF or simple data transcription corrections, etc., following GDP, prior to audit closing meeting, if able, and convey corrections to auditor.

During audit, identify likely observations that appear to be due to internal process or training gaps and initiate stakeholder discussions internally to determine if retraining, gap closure can be initiated or completed prior to closing meeting.

After the audit, prepare written responses and return by due date

1. Engage the Investigator (and internal clinical quality assurance if available) and secure Investigator signature on the CAPA Plan
2. State the problem – Who, what, when, where, why, how
3. Determine and indicate scope of issue across site study record
4. Document corrections made to the record (be sure made following GDP)
5. Determine and state the root cause of the non-compliances
6. Plan/Complete and document the CAPA - Corrective and Preventive Action to fix root cause(s) and prevent reoccurrences
7. Plan and state how you will verify effectiveness of the corrective and Preventive actions (e.g., no reoccurrences and compliant outcomes)
8. Indicate your Target Completion Date(s) for corrections, investigation of root cause, corrective and Preventive actions, and verification of effectiveness (and try very hard to meet them!)
9. Provide written response including all above to sponsor in clear, complete, logical sentences with objective evidence of corrections

CAUTION: If the corrective/Preventive action didn't work (or you did not check if it worked), it is worth nothing. Redo!

Sample content

Consider:

- Who discovered the problem, how was it discovered, and when?
- Who/what is involved in and/or impacted by the problem or event?
- What is the scope of the problem – i.e., how many times did it happen? Which subjects are involved? Is it systemic or isolated problem?
- What happened? What process was not followed, or failed?
- What regulation or Protocol section or internal procedure was violated because of what happened?
- Who did you tell? Investigator, sponsor, IRB…? What did they tell you to do?
- Then what was done?
- Why did it happen? E.g., root cause such as lack of training, the consent version control is not adequate because old versions of the consent remain accessible, misunderstood the Protocol, too much time elapsed between the visit and the collection/reporting of source data to sponsor…?
- What did you do about the problem's root cause, so it won't happen again? If many occurrences and/or systemic cause, engage internal Compliance/Quality.
- How will you know in the future that it hasn't happened again?

Briefly describe above in narrative format, clear sentences. Reference objective evidence or attach to the written CAPA plan.

Sample Self-initiated CAPA format:

Study Protocol Name: _____
Sponsor:_____
Date Site CAPA Initiated:_____
Date Site CAPA Closed:

Principal Investigator / Site #:
Sponsor Monitor:
All CAPA Items completed (Investigator signature/date):
_____

#	Date Issue Occurred	Issue Description	Itemized list of errors to be corrected	Root Cause	Corrective and Preventive Actions	Responsible Person	Target/Actual Completion Date	Verification effective	Investigator Initial/Date Confirming Issue Resolved

Sample Sponsor Required Site CAPA format:

Study Protocol Name: _____
Sponsor: _____
Date Site CAPA Initiated: _____
Date Site CAPA Closed: : _____

Principal Investigator / Site #: _____
Sponsor Monitor: _____
All CAPA Items completed:
_____
(Investigator signature/date)

Issue #1: *describe the nonconformance issue* _____

Itemized occurrences:

1. Xyz
2. Xyz

Sponsor expectations/Requirements:

- Corrections to be completed:
- Corrective Action and Preventive Action Plan to fix the cause and prevent recurrence:
- Objective evidence required:
- Verification of effectiveness:
- Expected completion date:

Site Response:

- Itemized Corrections completed:
  1. Xyz, completed: *sig/date*
  2. Xyz, completed: *sig/date*
- Corrective/Preventive Action(s) to be taken/implemented by Site:
  1. Xyz, responsible person/Planned completion date:
  2. Xyz, responsible person/Planned completion date:
- Verification of effectiveness plan:
  1. Xyz Verified by: (Sponsor Monitor or other verifier name, sig, date)
  2. Xyz Verified by: (Sponsor Monitor or other verifier name, sig, date)
- Expected completion date for Issue #1 all items:
- Completion Date:

A “good Note to File”?

1. Clarifications/explanations that are not errors
2. Errors - It is never acceptable to document the error without:
   - how the error was corrected if correctible
   - how it was reported to sponsor/IRB, as applicable
   - what activity was completed as a result of the reporting, such as additional corrections and/or corrective action plan imposed by the IRB
   - what was done to determine root cause, what root cause is, what retraining and/or process change was completed
   - how you’ll ensure it does not occur again in the future
   - Investigator sign-off as responsible for all study conduct and oversight of the team

Better to have proactive compliance and quality plan for each Protocol:

- Proactively map out your Protocol workflow
  - Include scheduling for protocol visits and potential challenges, backup plans
  - Identify source to be used for each data point, check protocol for specificity of requirement such as "12-lead EKG" for rhythm source, not wearable device or telemetry monitoring
  - Determine where SOC differs from Protocol procedure and data collection requirements and plan how to ensure Protocol compliance
- Establish Consent version control and consent documentation practices, consider if time of consent may end up being relevant given time of procedure
- RC Peer review against quality checklist including GDP, such as:
  - ISF content, organization, GDP
  - Consent signatures and process documentation for first 2 subjects
  - Subject binder content and data reported for first subject
- Reassess whether workflow map is adequate

The way to get started is to quit talking and begin doing.

Walt Disney

Thank you for your commitment to clinical quality and the work you do!

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