Clinical BA/BE – Case Studies

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DISCLAIMER

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Learning Objectives

- Understand the FDA Bioresearch Monitoring (BIMO) Program
- Understand the documentation expectation specified in BIMO Compliance Program 7348.003
- Understand the potential impact of documentation, or lack thereof, on data integrity of BA/BE clinical studies

FDA Bioresearch Monitoring (BIMO) Compliance Programs

- Provide instructions to FDA personnel for conducting compliance activities such as on-site inspections and data audits
- Compliance activities are used to:
  - Protect the rights, safety, and welfare of human research subjects
  - Verify the accuracy, reliability, and integrity of clinical and non-clinical trial submitted to FDA

Program #	Compliance Program Title
7348.003	In Vivo Bioavailability-Bioequivalence Studies - Clinical
7348.004	In Vivo Bioavailability-Bioequivalence Studies - Analytical
7348.007	Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies
7348.808	Good Laboratory Practice (Nonclinical Laboratories)
7348.808A	Good Laboratory Practice Program (Nonclinical Laboratories) EPA Data Audit Inspections
7348.809	Institutional Review Board
7348.809A	Radioactive Drug Research Committee
7348.810	Sponsors and Contract Research Organizations
7348.811	Clinical Investigators and Sponsor-Investigators
7353.001	Postmarketing Adverse Drug Experience (PADE) Reporting Inspections
7353.001C	Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections

BIMO Compliance Program 7348.003

In Vivo Bioavailability-Bioequivalence Studies - Clinical

CHAPTER 48 – BIORESEARCH MONITORING

SUBJECT:	IMPLEMENTATION DATE:
Procedures for FDA Staff: In Vivo Bioavailability/Bioequivalence Studies (Clinical)	05/01/2018
DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Product coding not required for biopharmaceutical establishments	48003A CLINICAL IN-VIVO BA/BE (ANDAS) 48003N CLINICAL IN-VIVO BA/BE (NDAS AND BLAS) 48003P CLINICAL PEPFAR ANDA BA/BE 48003Q CLINICAL IN-VIVO PEPFAR NDA BA/BE 48003B CLINICAL BA/BE - BIOSIMILARS

PART III – INSPECTIONAL

1. Organization
2. Study Administration and Responsibility
3. Subjects' Records and Documentation
4. Test Article Accountability and Disposition
5. Collection, Processing, and Storage of Study Samples Subject to Bioanalysis
6. Randomization
7. Blinding Codes
8. Reserve Samples
9. Review of Electronic Data
10. International Inspections of Clinical BA/BE Study Sites
11. Reporting

www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs

BIMO Compliance Program 7348.003

3. Subject's Records and Documentation

A. Study Source Records

- Determine whether the study subjects met the eligibility criteria (inclusion/exclusion criteria)
- Compare the study source data at the clinical site with the background materials provided by the Center. If discrepancies are found, document them and review the case report forms for accuracy
- Determine whether adverse events (AEs) and the serious adverse events (SAEs) were accurately and adequately documented in the source records
- Describe the study source data files in terms of their organization, condition, accessibility, and completeness. For example, is the information on study source records attributable, legible, contemporaneous, original, and accurate (ALCOA)
- Determine whether there is adequate documentation that all study subjects were alive and actively participated during the study

BIMO Compliance Program 7348.003

B. Informed Consent

- Review the IRB/IEC approval letter for the study. Did the IRB/IEC stipulate any conditions for the informed consent process and, if so, did the clinical site follow those instructions/stipulations?

- Di the subject's legal-authorized representative sign the informed consent document prior to entry into the study (e.g., prior to performance of any study related tests, and administration of the test article)? If the subject did not sign the informed consent document, determine who signed it and that person's relationship to the subject

C. Other Study Records

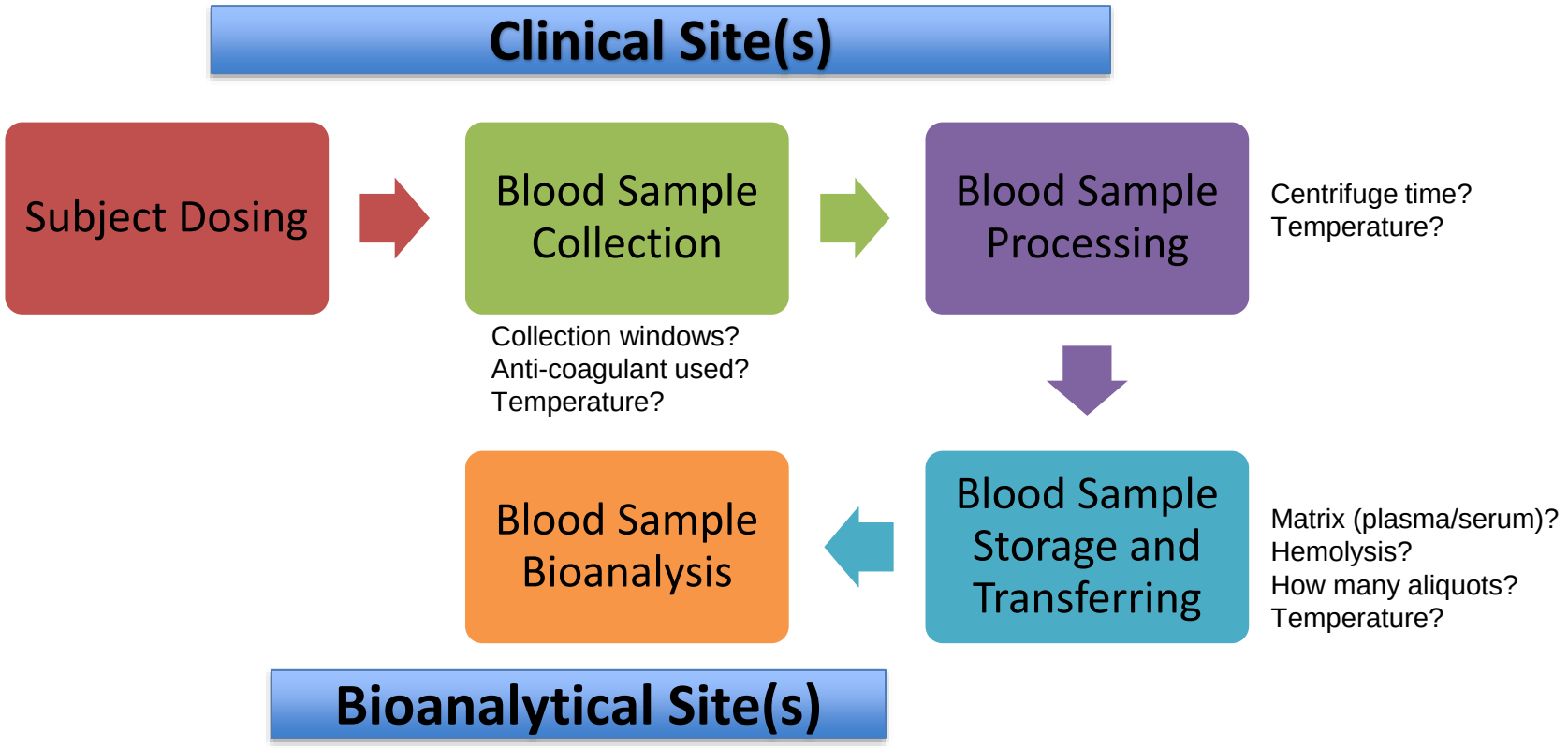
- Determine if the site maintains other records pertinent to the study, such as, but not limited to: administrative study files, correspondence files, sign-in logs, financial disclosure records, written agreements (e.g., transfer of obligations), and third-party storage records. Document anything potentially relevant to the study conduct

BIMO Compliance Program 7348.003

5. Collection, Processing, and Storage of Study Samples Subject to Bioanalysis

- **Review the source documents and determine if sample collection was performed according to the study protocol and the applicable SOPs**
- **Review the SOPs and source documents for sample collection**
  - Determine if samples were collected at protocol-specified time points and within allowable time windows
  - Evaluate if samples collected outside of the protocol-specified range were properly documented and reported in the study report as protocol deviations
  - Determine if missing samples were clearly documented along with an explanation
  - Determine if protocol specific “special handling” procedures were followed and documented
- **Review records for biological sample processing**
  - Verify if samples were handled per the protocol/SOPs
  - Evaluate whether critical steps during sample processing were properly documented. For example, evaluate if the duration and settings of sample centrifugation and the time until freezer storage were consistent with specifications in the protocol
  - Determine if protocol specific “special handling” procedures related to sample processing were performed and documented

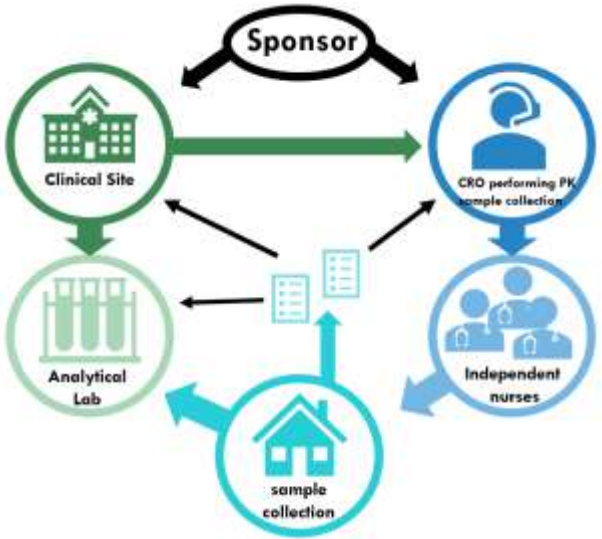
Flow of Subject Samples in BA/BE Studies



Case Study 1

Study Design:

A randomized, open-label, crossover, multicenter, pivotal in vivo bioavailability (BA) study with PK endpoint



Sample Collection and Processing:

- The clinical site was responsible for PK sample collection and processing of the initial timepoints after dosing
- The clinical site was provided relevant sample collection and processing forms for use
- The clinical site enrolled 32 subjects

Case Study 1

Initial observations:

- Subjects were shown to have met inclusion/exclusion criteria for enrollment
- Documentation for study subject PK sample collection and/or processing at certain timepoints were missing or inconsistent
- For 14 subject records, there was at least 1 missing or inconsistent data
- There were 8 subjects that contained missing or inconsistent data across multiple visits or with multiple data collection points in the same visit

Study Number	123ABC	Subject ID	27
Date of Visit	1/2/2023	Visit Number	3

PK Blood Sample Collection	
Scheduled collection time	15:25
Actual collection time	15:30
Out of Window (±3 min)?	Yes
Comments	

PK Blood Sample Processing and Storage	
Centrifuge start time and condition	17:00, 4℃
Centrifuge stop time and condition	
Number of Aliquots	2
Hemolysis	No
Processed sample transfer time to freezer	16:50

PK Blood Sample Shipping to Central Lab	
Shipping date	1/1/2023
Sample condition	Frozen

** Mock form for illustration purpose only.*

Case Study 1

Questions to Consider:

- Are we able to reconstruct the study given the documentation issues at this site?
- Would you be comfortable in relying on the data collected at this site?

Pause for Live Discussion

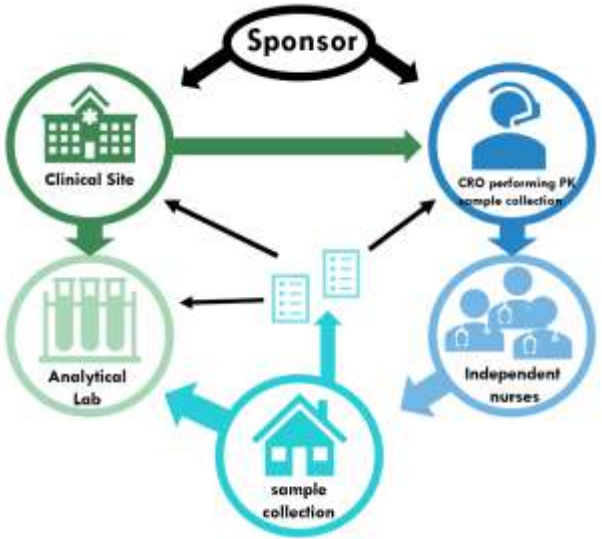
Case Study 1 - Takeaways

- Without accurate documentation, it was impossible to reconstruct the conditions that subject samples underwent during collection and processing
- Given the significant level of documentation concerns, we would have data integrity and reliability concerns with those subjects with missing or inconsistent documentation

Case Study 2

Study Design:

A randomized, open-label, crossover, multicenter, pivotal in vivo bioavailability (BA) study with PK endpoint



Sample Collection and Processing:

- The clinical site was responsible for PK sample collection and processing of the initial timepoints after dosing
- The clinical site was provided relevant sample collection and processing forms for use
- The clinical site enrolled 32 subjects

Case Study 2

Initial Observations:

- Documentation for study subject PK sample collection and/or processing at certain timepoints were missing or inconsistent
- For 14 subject records, there was at least 1 missing or inconsistent data
- There were 8 subjects that contained missing or inconsistent data across multiple visits or with multiple data collection points in the same visit
- It was later discovered that clinical staff used a different set of forms to collect data. Based on these source documents, the data collected were complete and did not contain any missing or inconsistent data elements

Case Study 2

Questions to Consider:

- Are we able to reconstruct the study given the documentation issues at this site?
- Would you be comfortable in relying on the data collected at this site?

Pause for Live Discussion

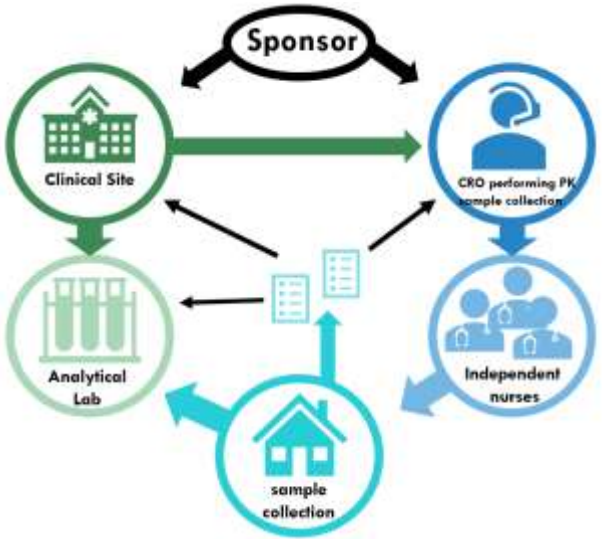
Case Study 2 - Takeaways

- In this scenario, we were able to reconstruct the study using the original forms to collect data so data integrity seems to have remained intact
- However, we were concerned with how the study was conducted and the process at this site that led to the missing and/or inconsistent data observed. We would consider undertaking a variety of options to ensure correction and future compliance relating to site study conduct

Case Study 3

Study Design:

A randomized, open-label, crossover, multicenter, pivotal in vivo bioavailability (BA) study with PK endpoint



Sample Collection and Processing:

- The clinical site was responsible for PK sample collection and processing of the initial timepoints after dosing
- The clinical site was provided relevant sample collection and processing forms for use
- The clinical site enrolled 32 subjects

Case Study 3

Initial Observations:

- 3 out of 32 subjects were missing documentation to show that they met eligibility criteria
- 5 out of 32 subjects were missing a signed informed consent form
- Otherwise, the data collected at each specified visit seem well organized, accessible, and complete

Case Study 3

Questions to Consider:

- Are we able to reconstruct the study given the documentation issues at this site?
- Would you be comfortable in relying on the data collected at this site?

Pause for Live Discussion

Case Study 3 - Takeaways

- Missing documentation to demonstrate subject eligibility is very concerning as it relates to appropriate study enrollment and human subject protections. Without documentation ensuring that each subject enrolled met eligibility criteria, we would be concerned with data integrity and acceptability for those specific subjects.
- Missing documentation of proper informed consent is very concerning as it relates to appropriate study enrollment and human subject protections. We would consider undertaking a variety of options to ensure correction and future compliance relating to site study conduct.

Summary

- Documentation of study related activities is critical during conduct of clinical BA/BE PK studies
- Lack of adequate and/or complete documentation may have negative impact on study data integrity, question the ability of a site to properly conduct a study, and raise concerns about huma subject protections
- BIMO Compliance Program 7348.003 lists examples of documentation that are expected to be reviewed during the BA/BE clinical inspections

References

- Code of Federal Regulations (CFR) Title 21, Part 320 – Bioavailability and Bioequivalence Requirements (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320)
- FDA BIMO program
  https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-bioresearch-monitoring-information/bioresearch-monitoring-program-information
  www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-manual/bioresearch-monitoring-program-bimo-compliance-programs
- BIMO Compliance Program 7348.003: In Vivo Bioavailability-Bioequivalence Studies – Clinical (www.fda.gov/media/112538/download)
- Draft Guidance for Industry: *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application,* 2021 (https://www.fda.gov/media/87219/download)
- Draft Guidance for Industry: *Bioavailability Studies Submitted in NDAs or INDs – General Considerations,* 2019 (https://www.fda.gov/media/121311/download)

Questions?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