

SA06: PHUSE Bioresearch Monitoring Data Reviewers Guide

May 3, 2022

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Agenda

- Background about BIMO
- PHUSE BIMO Project
 - Introduction/Scope
 - Project Team
 - Key Deliverables/Timelines
 - Contents
 - Key Points
 - Resources
- Q&A



Bioresearch Monitoring(BIMO) Background



Office of Scientific Investigations (OSI)

OSI administers FDA's Bioresearch Monitoring (BIMO) compliance programs by collaborating with CDER's Office of Study Integrity and Surveillance for planning and conducting SITE inspections/audit.

Ensure:

- Investigators, sponsors and contract research organizations (CROs) conducting nonclinical and clinical studies on investigational new drugs comply with regulations covering good clinical practice, bioavailability and bioequivalence, and good laboratory practice.
- the validity of clinical trial data submitted to FDA in support of applications to demonstrate the safety and efficacy of drugs for human use.

Basically...

- That trial participants are adequately protected
- Submitted data are reliable
 - For regulatory decision making
 - As evidence for instructions for clinical use of the product

Bioresearch Monitoring(BIMO) Background



In 2018, in support of planning and conducting inspections, the FDA's Center for Drug Evaluation and Research (CDER) Office of Scientific Investigations (OSI) developed

- Bioresearch Technical Conformance Guide (updated in 2020)
- Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions Guidance for Industry

This information is requested for each of the major (i.e., pivotal) studies for the following application types:

- New Drug Applications (NDAs)
- Biologics License Applications (BLAs)
- NDA or BLA supplemental applications containing clinical data that are regulated by CDER

Bioresearch Monitoring Background



The guidance includes detailed information for the creation and delivery of the following:

I. Clinical Study-Level Information

- Comprehensive List of All Clinical Sites
- Table Listing All Entities To Whom Sponsor Has Contracted Clinical Study Related Activities
- Protocol, Protocol Amendments, and Annotated Case Report Form

II. Subject-Level Data Line Listing by Clinical Site

- | | |
|------------------------------------|--|
| – Consented Subjects | – Adverse Events |
| – Treatment Assignment | – Protocol Deviations (Minor and Major) |
| – Discontinuations | – Efficacy Endpoints (and corresponding clinical events) |
| – Study Population | – Concomitant Medications |
| – Inclusion and Exclusion Criteria | – Safety Monitoring (and corresponding clinical events) |

Bioresearch Monitoring Background



III. Summary-Level Clinical Site Dataset

- Clinsite.xpt, define.xml
- Variables are described fully in BIMO Technical Conformance Guide
- The variables contain information from SDTM, ADaM and external sources (such as CTMS, etc..)

PHUSE BDRG Project - Introduction

Problem Statement - BIMO Data Reviewer's Guide (BDRG):

- Although mentioned in the TCG, there is No formal FDA Guidance concerning a reviewer's guide. Since there is a lack of clarity, each sponsor has defined their own approach for communication of their interpretation of the BIMO Technical Conformance Guide and BIMO deliverables.
- This could potentially result in Information Requests from the agency for Sponsors to provide additional clarification surrounding BIMO submission content. This could then result in a delay in the approval process.

PHUSE BDRG Project - Introduction



Solution Proposed - BIMO Data Reviewer's Guide (BDRG):

- Develop a Standardized BIMO Data Reviewer's Guide Package (Template, Completion Guidelines and Examples) to allow up front communications regarding the sponsors interpretation of the Bioresearch Monitoring Technical Conformance Guide.
- Form a team of representatives from FDA CDER , FDA CBER, PHUSE Leads, Subject Matter Experts across pharma industry supporting BIMO applications.

PHUSE BDRG Project Scope

Project Phases

- **BIMO Data Reviewer's Guide**

- A comprehensive suite of documents to fully describe the BIMO application to FDA reviewers.
- Introduction and Overview Document
- Template, Completion Guidelines and Examples
 - » Consistency with cSDRG & ADRG but being careful to not duplicate information (with minor exceptions)

Future Phases

- Possible BIMO Frequently Asked Questions (FAQ) Forum



PHUSE BDRG Project Team

Leads

- Katie Warren – PHUSE Project Manager
- Julie Maynard (Janssen R&D) - Project team lead
- Sopan Dharma Kaith (Cytel Inc.) - Project team lead

Team Members

- 50 members representing >24 organizations including active team members from the FDA CDER and CBER divisions



Key Deliverables/Timelines

- **Project Kick-off**
 - 4/21/2021
- **Draft BIMO Data Reviewers Guide (BDRG) Template & Completion Guideline**
 - PHUSE CSS meeting (virtual) 9/13/2021-9/15/2021
- **Final Template/Completion Guideline**
 - 10/2021
- **Examples (3)**
 - 12/2021
- **PHUSE BDRG for Public Review**
 - 1/4/2022 – 2/15/2022

Key Deliverables/Timelines

- **Evaluation of all Public Review feedback**
 - 3/2022
- **Incorporation of Public Review feedback**
 - 4/2022
- **PHUSE BDRG Publication**
- **Roll-out of PHUSE BDRG**
 - 5/3/2022



PHUSE BDRG Contents

- Goal was to have the BDRG look and feel like the other PHUSE reviewer's guides
 - There are differences due to the content of the BIMO submission package. ie listings, clinsite dataset, define
- Every attempt was made to not duplicate information from other submission documents
 - There are deviations in an attempt to aide reviewers in understanding if BIMO used same/differing criteria than what was used for analysis (concerning endpoints, etc...)
- No hyperlinks to other documents found in the electronic common technical document (eCTD)- for consistency with other reviewer's guides
 - As a result of this need for consistency and the fact that BIMO is fairly new, we added a Section to let the agency know what documents are included and where in the eCTD folder structure they reside (as not all submissions are using the same format and naming conventions for listings



PHUSE BDRG Contents- BDRG Template

Bioresearch Monitoring (BIMO) Data Reviewer's Guide	
1. Introduction	
1.1. Purpose	
1.2. Acronyms	
1.3. BIMO Standards	
1.4. Study Related Metadata	
2. Study Description	
2.1 List of Studies	
3. Part I - Request for Clinical Study-Level Information	
3.1 Part I (Item A) – List of All Clinical Sites	
3.2 Part I (Item B) – Entities Contact Information and Trial Related Files	
3.3 Part I (Item C1) – Protocol and Amendments	
3.4 Part I (Item C2) – Annotated Case Report Form (aCRF)	
4. Part II - Subject-Level Data Line Listings by Clinical Site	
4.1 Subject Level Listings	
4.2 Primary, Key Secondary Endpoints and Clinical Events	
4.3 Safety Monitoring and Clinical Events	
5. Part III Summary-Level Clinical Site Dataset	
5.1 Treatment variables	
5.2 Primary, Key Secondary Endpoints Summary	
6. External Datasets and Sources	
7. SITE Specific Matters	
7.1. Site Issues	
7.2. Subjects transferred between sites	
7.3. Identical site ID used in multiple studies	
8. SITE Summary	
9. Conformance Summary for Part III Clinical Site Dataset	
9.1 Conformance Inputs	
9.2 Issues Summary	
10. eCTD Folder Structure skeleton for BIMO Items in MODULE 5	
11. Appendix	

Bioresearch Monitoring (BIMO) Data Reviewer's Guide

<Sponsor's Name>

<Compound/Project Name>

<Application Type: Application Number>

List of Studies included in the BIMO Clinical Data Application:

Study1 <DM.STUDYID>

Study2 <DM.STUDYID>

.....

BDRG Template Version # DD-MMM-YYYY
BDRG Published Date # DD-MMM-YYYY

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PHUSE BDRG Contents- BDRG Template

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- 11. Appendix

BDRG Published Date # DD-MMM-YYYY

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<Sponsor's Name>

BIMO Data Reviewer's Guide

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PHUSE BDRG Contents- BDRG Template

The BDRG has 10 required sections:

Section 1: Introduction - provides information on purpose, navigation and hyperlinks within the BDRG document, Acronyms, BIMO Clinical Data standards and Study Related Metadata used in the application.

Section 2: Study Description – provides summary of study details (Study Identifier, Study Title Study Phase) for each of the major (i.e., pivotal) studies used to support of safety and efficacy in the application.

Section 3: Part I- Request for Clinical Study-Level Information – provides information on structure followed in the Part I (item A and B) deliverables and supporting information for the Part I (item A, B and C [C1 and C2]) deliverables for each of the major (i.e., pivotal) studies used to support of safety and efficacy in the application.

Section 4: Part II Subject-Level Data Line Listings by Clinical Site – provides high level structure and supporting information for the Part II deliverables for each of the major (i.e., pivotal) studies used to support of safety and efficacy in the application.

Section 5: Part III Summary-Level Clinical Site Dataset - provides supporting information for the BIMO Clinical Data (Summary-Level Clinical Site Dataset and a supporting define.xml for each of the major (i.e., pivotal) studies) used to support of safety and efficacy in the application.



PHUSE BDRG Contents- BDRG Template

Section 6: External Datasets and Sources - provides a list of all external data sources <Example: -Screen failure, Minor Protocol Deviations, Principal Clinical Investigator and SITE contact information, financial disclosure information etc...> that are used as input in the Part I, II and III deliverables for each of the major (i.e., pivotal) studies used to support of safety and efficacy in the application.

Section 7: SITE Specific Matters - provides SITE information related to SITE issues, SITE additional information < Freeform text>, Subjects transferred between sites and Identical site ID used in multiple studies for the SITES used in the BIMO Clinical Data (Clinical Study-Level Information, Subject-Level Data Line Listings by Clinical Site, and a Summary-Level Clinical Site Dataset) for each of the major (i.e., pivotal) studies used to support of safety and efficacy in the application.

Section 8: SITE Summary - provides SITE summary (Total number of SITES, SITES that has enrolled at least 1 subject with a signed informed consent, SITES that has only screen failed subjects with a signed informed consent and SITE additional information < Freeform text>) for the SITES used in the BIMO Clinical Data (Clinical Study-Level Information, Subject-Level Data Line Listings by Clinical Site, and a Summary-Level Clinical Site Dataset) for each of the major (i.e., pivotal) studies used to support of safety and efficacy in the application.

PHUSE BDRG Contents- BDRG Template

- **Section 9: Conformance Summary for Part III Clinical Site Dataset** – Provides an overview of validation checks and inputs used to evaluate conformance summary/findings on the Part III (Summary-Level Clinical Site Dataset) deliverable while using BIORESEARCH MONITORING TECHNICAL CONFORMANCE GUIDE (Version 2.0, 27th July 2020).
- **Section 10: eCTD Folder Structure skeleton for BIMO Items in MODULE 5** – Provides an eCTD structural view of BIMO Items deliverables (Including file naming convention used) placed in MODULE 5 of the eCTD

The BDRG also has 1 optional section:

Section 11: Appendix (for other documentation/supplement information that would be helpful to the FDA Reviewers)

PHUSE BDRG Contents- BDRG Completion Guide/Examples

- Completion Guideline
 - Comprehensive Instructions on how to populate the BDRG Template
 - Possible scenarios, deviations
- 3 Examples - containing:
 - a Single pivotal study
 - Multiple pivotal studies
 - Studies with safety ,Time to event endpoints and PK endpoints...etc..
 - Many different options/scenarios mentioned in the Completion Guidelines are laid out in the examples to provide clarity

PHUSE BDRG – Key Points

- **The BIMO Technical Conformance Guide (BIMO TCG) and the BDRG mentions FDA CDER. What about submissions to FDA CBER?**
 - At this time, the BIMO TCG and PHUSE BDRG are CDER initiated guidance. However, we have CDER and CBER representation on our PHUSE BIMO initiative team. It is recommended that you discuss BIMO needs for CBER at your pre-submission meetings.
- **The Conformance section of the BDRG Template is mandatory. Why is that, when there are no official validation rules nor rejection criteria for BIMO at this point in time?**
 - If sponsors deviate from the BIMO TCG, this is a perfect section to describe those deviations. Additional details are included in the Completion Guidelines

PHUSE BDRG – Key Points

- **Is the BDRG mandatory?**
 - As with the Study Data Technical Conformance Guidance which provides specifications and **recommendations** for, as well as general considerations on, submitting SDTM and ADaM data, the Bioresearch Monitoring Technical Conformance Guidance provides specifications/recommendations for submitting BIMO Clinical Data.
 - We have proposed that a new version of the BIMO TCG.
 - Reducing Information Requests from the agency that hold up submissions
 - CDER and CBER were active members of the team to define the PHUSE BDRG
- **Are you expecting us to duplicate tables in the body of the BDRG? See table 3.1, 3.2 (Part I item A and B)**
 - The expectation is to provide the format/information of what is presented in the listing in the submission package not to duplicate the table. It is a place to let the agency know if you added any additional fields that you felt are key to the agency. i.e., total enrolled patients

PHUSE BDRG – Resources

Available at a portal (PHUSE Advanced Hub) near you...

PHUSE BDRG Publication



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Thank You

All of our attendees for participating in today's roll-out and taking this information back to your organizations

FDA CDER & CBER BIMO Team Members

PHUSE BIMO Team - all members listed on the Advanced HUB

PHUSE Staff

Optimizing the Use of Data Standards Leads - Janet Low and Jane Lozano

PHUSE Steering Committee

Industry Public Reviewers

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