

PHUSE Bioresearch Monitoring Data Reviewer's Guide (BDRG) Introduction and Overview

BIMO OSI Background and Specifications

- About the OSI: the Office of Scientific Investigations (OSI) ensures that CDER-regulated drugs and biologics have reliable evidence of safety and effectiveness and meet post-market safety requirements. The OSI also ensures the rights, safety and welfare of individuals participating in clinical trials are protected. In collaboration with CDER's Office of Study Integrity and Surveillance, the OSI administers the FDA's bioresearch monitoring compliance programs for CDER.
- In 2018, in support of planning and conducting inspections for the FDA's Center for Drug Evaluation and Research (CDER), the OSI developed
 - the Bioresearch Technical Conformance Guide (updated in 2020 and 2022)
 - the 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 type:

- New Drug Applications (NDAs)
 - Biologics License Applications (BLAs)
 - NDA or BLA supplemental applications containing clinical data that are regulated by CDER
- The guidance includes detailed information for the creation and submission of the following deliverables:
 - I. Clinical Study-level Information**
 - Item A: Comprehensive List of All Clinical Sites
 - Item B: Table Listing All Entities to Whom the Sponsor Has Contracted Clinical Study-related Activities
 - Item C1: Protocol, Protocol Amendments
 - Item C2: Annotated Case Report Form
 - II. Subject-level Data Line Listings by Clinical Site**
 - Consented Subjects
 - Treatment Assignment
 - Discontinuations
 - Study Population
 - Inclusion and Exclusion Criteria
 - Adverse Events
 - Protocol Deviations (Minor and Major)
 - Efficacy Endpoints (and corresponding Clinical Events)
 - Concomitant Medications
 - Safety Monitoring (and corresponding Clinical Events)

III. Summary-level Clinical Site Dataset

- clinsite.xpt and Define-XML
 - The variables are described fully in the BIMO Technical Conformance Guide (TCG).
 - The variables contain information from SDTM, ADaM and external sources.

Content summary:

General Application and Study Information

- Study title
- Sponsor information
- Site
- Application type and number: IND/NDA/BLA and number

Study Conduct

- Planned arm
- Cohort
- Enrolment
- Safety population

Safety

- Subject treatment and study discontinuations
- Protocol deviations (important and non-important)
- SAEs, non-SAEs
- Deaths
- Endpoints and censor information

Site Information

- Financial disclosure
- Name, address and contact information of primary clinical investigator
- Site contact information

PHUSE BIMO Data Reviewer's Guide (BDRG)

- **Project:** The PHUSE BIMO Data Reviewer's Guide Project resides under the PHUSE Optimizing the Use of Data Standards Working Group.
- **Objective:** The objective of the BDRG is to help clarify sponsors' consideration, deviations from the BIMO Technical Conformance Guide (BIMO TCG) and to avoid the information requests that are

currently issued by the agency to sponsors to describe inconsistencies. These information requests currently cause delays for submissions and can be avoided through clear description of what was submitted in the BIMO package.

- **Team:** This project team consists of a cross-industry team of approximately 50 members representing over 24 different pharmaceuticals and pharmaceutical-related and health authority organizations, including teams from the FDA's CDER and CBER divisions. This team of BIMO experts, in full collaboration with the FDA, created a comprehensive suite of documents to fully describe the BIMO submission package to FDA reviewers.
- **Package:** The Bioresearch Monitoring (BIMO) Data Reviewer's Guide (BDRG) package, which includes a Template, Completion Guidelines and 3 Examples created by the PHUSE BIMO Project Team.
- **Format:** The BDRG creation began with the Analysis Data Reviewer's Guide format in mind, but, of course, ended up quite different due to the variety of content defined in the BIMO TCG and contained in the BIMO submission package. In order to avoid hyperlinking to external documents and thus the need to use sponsors' regulatory departments, this document includes a section describing the structure of sponsors' BIMO submissions within the eCTD.
- **Expectation:** The BDRG package does require knowledge of the BIMO submission requirements. In order for easy reference, a high-level overview of sections that are part of the BDRG package is explained at the end of this document.

The PHUSE BIMO project team hopes you find this package clear and comprehensive. We have taken special care to ensure that it meets the needs of the organizations submitting BIMO as well as the FDA.

BDRG Overview

The BDRG has 9 required sections:

- **Section 1: Introduction** – provides information on purpose, navigation and hyperlinks within the BDRG document, acronyms, BIMO clinical data guidance, supporting information and study-related metadata used in the application.
- **Section 2: Study Description** – provides a summary of the BIMO study details (study identifier, study title, study phase and any comments) for each of the major (i.e. pivotal) studies used to support 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 any 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 safety and efficacy in the application.
- **Section 4: Part II Subject-level Data Line Listings by Clinical Site** – provides a high-level structure and supporting information for the Part II deliverables for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application.
- **Section 5: Part III Summary-level Clinical Site Dataset** – provides information [Such as Treatment variables, Primary, Key Secondary Endpoints, Clinical Site Dataset Supporting Information, Conformance Inputs and Conformance Issues Summary, etc.] for the BIMO clinical data (Part III - Summary-level clinical site dataset and a supporting Define-XML) for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application.
- **Section 6: External Datasets and Sources** – provides a list of all external dataset sources (<Example: screen failure, minor protocol deviations, principal clinical investigator and site contact information, financial disclosure information>) that are used as input in the submitted **BIMO Clinical Data** (Part I - Clinical study-level information, Part II - Subject-level data line listings by clinical site and Part III - Summary-level clinical site dataset) for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application.
- **Section 7: Site-specific Matters** – provides site information related to site concerns, site additional information <freeform text>, subjects transferred between sites and identical site ID used in multiple studies for the sites used in the submitted **BIMO Clinical Data** (Part I - Clinical study-level information, Part II - Subject-level data line listings by clinical site and Part III - Summary-level clinical site dataset) for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application.
- **Section 8: Site Summary** – provides a site summary (total number of sites, sites that have enrolled at least 1 subject with a signed informed consent, sites that have only screen failed subjects with a signed informed consent and site additional information <freeform text>) for the sites used in the submitted **BIMO Clinical Data** (Part I - Clinical study-level information, Part II - Subject-level data line listings by clinical site and Part III - Summary-level clinical site dataset) for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application.

- **Section 9: eCTD Folder Structure Skeleton for BIMO Items in MODULE 5** – provides an eCTD structural view of BIMO item deliverables (including file naming convention used) placed in eCTD Module 5 (M5).

The BDRG also has 1 optional section:

- **Section 10: Appendix** (for other documentation/supplemental information that would be helpful to FDA reviewers).