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# Sponsor Considerations for Building a Reviewer's Guide to Facilitate BIMO Review

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## ABSTRACT

CDER's **Bi**oresearch **Mo**nitoring (BIMO) team has responsibility for verifying the integrity of clinical data submitted in regulatory applications and supplements and for determining compliance of trial conduct in accordance to FDA regulations and statutory requirements. In the FDA Draft Guidance for Industry, CDER's BIMO inspectors and Office of Regulatory Affairs (ORA) identifies sites of interest from all major pivotal studies within the submission. BIMO released a Technical Conformance Guide (TCG) in 2018 to facilitate site selection and review, but gave limited information for sponsors to consider when building a BIMO Reviewer's Guide. There is no available reviewer's guide template in industry. In addition, there is insufficient guidance on types of information that should be included in a reviewer's guide. This paper will share a suggested structure and considerations when authoring BIMO Reviewer's Guide.

## ACRONYMS

| | |
|---|---|
| BIMO | Bioresearch Monitoring |
| RG | Reviewer's Guide |
| ORA | Office of Regulatory Affairs |
| OSI | Office of Scientific Investigations |
| CDER | Center for Drug Evaluation and Research |
| eCTD | Electronic Common Technical Document |
| TCG | Technical Conformance Guide |

## INTRODUCTION & BACKGROUND

### BIMO PROGRAM

CDER's 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. The BIMO Program was established to assure the quality and integrity of data submitted to the agency in support of new product approvals, as well as, to provide for protection of the rights and welfare of the thousands of human subjects involved in FDA regulated research. It has become a cornerstone of the FDA preapproval process for new medicines, medical devices, food and color additives and veterinary products introduced to the U.S. consumer. [3]

### BIMO REFERENCES

The BIMO requests, recommendations, and requirements are in the following 2018 FDA references:

Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions Guidance for Industry [1] (DRAFT GUIDANCE)
*"*This guidance applies to electronic submissions of data and information from all major (i.e., pivotal) studies used to support safety and efficacy claims in new drug applications (NDAs), biologics license applications (BLAs) regulated by the Center for Drug Evaluation and Research (CDER), and supplemental applications containing new clinical study reports. It also applies when these data and information are submitted in certain investigational new drug applications (INDs) in advance of a planned NDA, BLA, or supplemental submission*."*

Bioresearch Monitoring Technical Conformance Guide [2]

*"*This document provides current Food and Drug Administration (FDA) specifications for preparing and submitting Clinical Study-Level Information, Subject-Level Data Line Listings by Clinical Site, and a Summary-Level Clinical Site Dataset that are used by the Center for Drug Evaluation and Research (CDER) for planning of Bioresearch Monitoring (BIMO) inspections in electronic form for new drug applications (NDAs), biologics license applications (BLAs), and NDA or BLA supplemental applications containing clinical data that are regulated by CDER. It also applies when these data and information are submitted under certain investigational new drug applications (INDs) in advance of a planned NDA, BLA, or supplemental submission*."*

## BIMO PACKAGE

To accelerate the process of inspection planning, including the identification of inspection sites, FDA CDER relies on the following items in NDAs, BLAs, and supplemental applications containing major (i.e., pivotal) study reports used to support safety and efficacy claims.

## A. Clinical Study-Level Information

1. A Comprehensive and Readily Located Table Listing All Clinical Sites That Participated in Clinical Studies
2. A Table Listing All Entities to Whom the Sponsor Has Contracted Clinical Study Related Activities
3. Protocol, Protocol Amendments, and Annotated Case Report Form

## B. Subject-Level Data Line Listings by Clinical Site

Subject-level data line listings, by clinical site, should include*:*

1. Consented Subjects
2. Treatment Assignment
3. Discontinuations
4. Study Population
5. Inclusion and Exclusion Criteria
6. Adverse Events
7. Important Protocol Deviations
8. Efficacy Endpoints
9. Concomitant Medications
10. Safety Monitoring

The above specified data line listings are anticipated to fit reporting requirements for most applications. However, if a sponsor believes additional listings are needed to permit FDA to verify key study data during inspections, additional listings should be included.

## C. Summary-Level Clinical Site Dataset

1. A single summary-level clinical site dataset that contains data from all major (i.e., pivotal) studies used to support safety and efficacy in the application, including studies with different treatment indications, should be provided.
2. A corresponding Define file for Summary-Level Clinical Site Dataset

## D. BIMO Reviewer's Guide (if required)

BIMO RG is a document for providing additional information on clinical study-level information, subject-level line listings by clinical site and clinical site dataset. This document, if submitted, should contain a description of the BIMO components with hyperlinks to Module 5 deliverables.

## CONSIDERATIONS FOR BUILDING AN RG

The assembly of BIMO RG document requires cross-functional effort from stakeholders such as Statisticians, Clinical Scientists, Data Management and Regulatory Affairs. This paper will step through each section of the suggested BIMO RG and outline considerations and recommendations based on Merck & Co., Inc., Kenilworth, NJ, USA experiences and BIMO TCG for authoring an RG. Sponsors may have additional situations for considering an RG beyond the outlined considerations in this paper. The suggested table of contents and potential contents for each section are based out of Merck & Co., Inc., Kenilworth, NJ, USA's template, which can be referenced by the industry for building a BIMO RG. The consideration instructions for the author are shown in *italicized* font.

1. Introduction
2. Protocol Number and Title
3. Clinical Study-Level Information
4. Subject-Level Data Line Listings by Clinical Site
5. Summary-Level Clinical Site Level Dataset (clinsite.xpt)
6. Directory Structure

### 1. INTRODUCTION

This document provides context for BIMO deliverables that benefit from additional explanation beyond the Data Definitions document (define.pdf).

### 2. PROTOCOL NUMBER AND TITLE

*The protocol number and protocol title for all protocols that are part of the BIMO submission should be described in this section.*

### 3. CLINICAL STUDY-LEVEL INFORMATION

A table listing all clinical sites that participated in clinical studies and entities to whom the sponsor contracted clinical study related activities.

The protocol, protocol amendments, and annotated case report form is included in Appendix 16 <hyperlink Appendix 16> of the Clinical Study Report. Refer to the below excerpt from BIMO TCG.
*"*The protocol, protocol amendments, and annotated case report form should be included in Appendix 16 of the Clinical Study Report for each study. When these items are included in Appendix 16, there is no need to resubmit them. If the applicant is submitting a BIMO Reviewer's Guide, the applicant should note that these items are present in Appendix 16 of the Clinical Study Reports and provide hyperlinks to their locations*."* [2]

### 4. SUBJECT-LEVEL DATA LINE LISTINGS BY CLINICAL SITE

Subject-level data line listings are provided to support safety and efficacy in the application. The listings are provided in pdf format.

The following five possible considerations could be addressed in this section.

- **Presenting Multiple PDFs for Data Line Listing:** *If splitting the pdf file of line listings due to the size, then document the criteria on how the files are split (ex: by site ranges).*

- **Identifying Data Line Listing for Exclusion:** *If applicant identifies any criteria(s) that do not apply to the defined line listings, then provide rationale for the exclusion of the line listing(s).*

- **Highlighting Count Differences:** *When count differences exist between the BIMO listings and the individual CSRs, clinsite.xpt, or tabulations data, the reasons for the difference should be provided in BIMO RG.*

- **Adding Non-standard Site Level Listing:** *If the applicant is submitting additional listing(s), apart from the defined listings from the guidance [1], the purpose and description should be documented in the RG. For the ease of navigation, applicant can hyperlink the additional listing(s) in the RG.*

- **Handling the Reporting of Partial Data:** *When screen failure data was not collected in the main study database and from different sources with incomplete data, it should be documented in RG. Additional information on how sites individually documented screen failures, including reason for screen failure in source documentation can be explained in RG.*

## 5. SUMMARY-LEVEL CLINICAL SITE DATASET (clinsite.xpt)

A single summary-level clinical site dataset that contains data from all major studies is provided to support safety and efficacy in the application. The corresponding Data Definition document (define.pdf) for clinsite.xpt is provided.

The following three possible considerations could be addressed in this section.

- **Highlighting Count Differences:** *When count differences exists between the clinsite.xpt and tabulation data, then describe the differences and reason for the differences*.

- **Transferring of subjects between sites:** *In situation when subject(s) transferred from one site to another, identify the transferred subject and document the applied convention for counting the safety population and/or screened subjects in RG. Additionally, sponsor may opt for further explain the reasons for subjects transferred between sites. Refer to the below excerpts from BIMO TCG.*

  - ***SAFPOP Clinsite Dataset Variable****: "*Total number of subjects in safety population at a given site by treatment arm. When a subject has transferred from one site to another, the applicant should handle reporting of such subjects consistently across sites and include in the define file the reporting convention used. The applicant may opt to further explain the reasons subjects transferred between sites in the BIMO Reviewer's Guide, if a guide will be provided*." [2]*
  - ***SCREEN Clinsite Dataset Variable:*** *"*Total number of subjects screened (consented) at a given site. When a subject has transferred from one site to another, the applicant should handle reporting of such subjects consistently across sites and include the reporting convention used in the define file or the BIMO Reviewer's Guide (if provided). The applicant may opt to further explain the reasons subjects transferred between sites in the BIMO Reviewer's Guide, if provided*." [2]*

- **Pooling Multiple Pivotal Studies with Multiple Endpoints:** *Irrespective of number of pivotal studies within the submission, only one clinical site (clinsite) dataset is submitted for the program. When multiple studies are included to support BIMO, some studies may have multiple end points while others pivotal trials may have a single endpoint. The definition of each trials' endpoint can be described in the RG.* An illustration of multiple pivotal studies with multiple endpoints is shown in Table 1.0.

| STUDYID | SITEID | ENDPOINT |
|---|---|---|
| ABC-123 | 001 | Hypertension |
| XYZ-456 | 002 | Hypertension |
| XYZ-456 | 002 | Percent Responders |
| XYZ-456 | 002 | Change from Baseline |

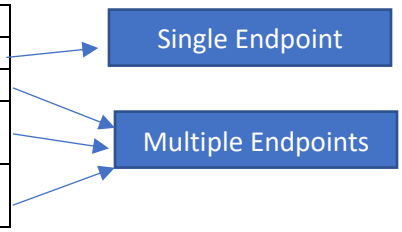


**Table 1.0**

## 6. DIRECTORY STRUCTURE

Study dataset and their supportive files are organized in accordance to Study Data Technical Conformance Guide [4] (March 2019).

| | | |
|---|---|---|
| module | 1 | Refers to the eCTD module in which clinical study data is being submitted. |
| datasets | 2 | Resides within the module folder as the top-level folder for clinical study data being submitted for m5. |
| bimo | 3 | Contains Subject-Level Data Line Listings, Site-level clinsite.xpt, define.pdf and bimo-reviewers-guide.pdf |

## CONCLUSION

The BIMO RG is an optional document submitted with the CDER BIMO package. There is currently no template available for industry to adopt. The BIMO RG should be considered when a sponsor opts for providing additional information on clinical study-level information, subject-level line listings by clinical site, and clinical site dataset. Since the BIMO TCG provides limited information for sponsors to consider when building an BIMO RG, this paper shares the experiences that encountered in authoring a BIMO RG. A step by step structure and guidance built on BIMO TCG and draft BIMO industry guidance is outlined with considerations and recommendations to help industry for referencing when building a BIMO RG.

## REFERENCES

[1] Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions Guidance for Industry (DRAFT GUIDANCE)
[2] BIORESEARCH MONITORING TECHNICAL CONFORMANCE GUIDE
[3] Bioresearch Monitoring Program
[4] FDA Study Data Technical Conformance Guide March 2019

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