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Deep Dive into the BIMO (Bioresearch Monitoring) Package Submission

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ABSTRACT

As a part of the review process for regulatory submissions to the Food and Drug Administration (FDA) by both pharmaceutical companies and CROs, the FDA carries out site-level inspections to ensure the integrity of the data submitted, and to verify that the rights, health, and welfare of those who participated in the studies were protected. To efficiently audit the sites, the FDA has established the Bioresearch Monitoring (BIMO) Program for the studies being submitted for their review. Currently, the BIMO package includes three required components: 1. Clinical Study-Level Information, 2. Subject-Level Data Line Listings by clinical site, and 3. Summary-Level Clinical Site (CLINSITE) Dataset, and an optional but important document, called the BIMO Data Reviewer's Guide (BDRG). The scope and format of these components are governed by the BIMO Technical Conformance Guide (TCG) and BDRG template. In this training, the authors clarify the generation of these BIMO components based on the latest TCG and Guidance documents, discuss the potential issues that can surface during the generation and address any questions that the audience brings up during the seminar.

OBJECTIVES OF THIS TRAINING

1. To present a clear view of the contents and the generation of BIMO package in the light of the latest guidance documents, released from both the FDA and PHUSE, and to enable the participants to get a detailed and comprehensive view of a BIMO submission.
2. Participants will receive a copy of relevant governing documents for reference, and will learn the details of these documents while completing practice sheets distributed during the training.
3. Authors will walk through the steps and provide essential clarifications to help the participants gain a thorough understanding of the various components of the BIMO package.

INTRODUCTION AND BACKGROUND

In response to the submissions of New Drug Application (NDA) and Biologics License Applications (BLA) packages for their approval, the FDA carries out site-level inspections to ensure the integrity of the data submitted, and also importantly to confirm that the clinical study investigators, CROs, sponsors and their review committees comply with necessary regulations, as a part of the review processes.

The current format of the clinical data packages and their outputs focuses on the subject-level data, and does not provide enough details about site-level information to enable the FDA to conduct site-level inspections. In order to efficiently conduct audits at the site level, the FDA requires information related to subject data, informed consent, assigned treatment group, and name and contact specifics of investigators at each site. To facilitate these audit objectives at the site level, the FDA has established the Bioresearch Monitoring (BIMO) Program for studies that are submitted for their review process. The FDA Office of Scientific Investigations (OSI) manages the BIMO program for drugs, and the FDA's Division of Inspections and Surveillance (DIS) manages the BIMO program for Biologics.

GUIDANCE DOCUMENTS GOVERNING THE CONTENTS OF THE BIMO SUBMISSION

The FDA develops guidelines for inspections of clinical investigators, sponsors, and institutional review boards (IRBs) and updated versions have been released to cope with the growing requirements that are being witnessed. A draft guidance introducing a standardized format for electronic submission of NDA and BLA content for the planning of BIMO inspections by the Center for Drug Evaluation and Research (CDER) was published by the FDA and contains binding as well as non-binding recommendations. Industry working groups have also published documents to fill in gaps in the FDA publications.

BIMO Technical Conformance Guide (BIMO TCG): In 2011, the FDA published an initial guidance to lay out the expectations and formats for the data elements that reviewers need to investigate at the site level. These efforts finally led to the release of the more established draft guidance and a Technical Conformance Guide (TCG). The first version (v1.0) of the BIMO TCG was published in February 2018. This document contained technical specifications for clinical data submission required for BIMO inspections. The second release (v2.0) of the TCG was published in July 2020, and the current version (v3.0) was issued for public review in August 2022.

BIMO Data Reviewer's Guide (BDRG): While there has been a great deal of knowledge and experience with the generation of the BIMO package in recent years, there was no industry-defined guidance on a Reviewer's Guide for the BIMO package prior to the release of the first draft of the BDRG from PHUSE in 2022. In June 2023, based on the comments received from the users in response to this first release, the current version (v3.0) of the BDRG template was released. Nevertheless, in recent years, sponsors have been assembling BDRGs in their own formats, and the standardized template will be helpful moving forward to have a consistent BDRG format and preparation across the industry.

In order to have a consistent naming convention for this reviewer's guide across the industry, the current BIMO TCG specifically dictates that the BIMO Reviewer's Guide is to be called the "BIMO Data Reviewer's Guide". However, the TCG also indicates that the BDRG is an optional document.

In our experience, it is highly encouraged to submit this document as a part of the BIMO package due to the following reasons:

1. The BDRG provides a clear overview of all of the components of the BIMO package and serves as the first place that reviewers can go to get an immediate overview of the contents of the BIMO submission.
2. Sponsors can provide additional clarifications that they cannot incorporate in the defined list of listings and the CLINSITE dataset.
3. It is also a document where any potential deviations from the TCG can be recorded.
4. Sponsors may come across unique situations in their clinical trial sites due to the length/complexity of the trials and this document can be used to explain these situations.
5. As the components of the BIMO package mature, industry standards/guidelines and TCGs evolve due to the growing needs, and the validation engines and tools are constantly being updated. The BDRG becomes the document where sponsors can provide information on the challenges and technical issues or gaps that were encountered during the preparation of the BIMO package.

COMPONENTS OF THE BIMO SUBMISSION

For BIMO audits, the sponsors are requested by the OSI to submit three required components and an optional document called BIMO Data Reviewer's Guide (BDRG). Briefly they are as follows:

1. **Clinical Study-Level Information**: This section includes a list of all clinical sites that participated in each pivotal study, a list of external organizations contracted by the sponsor for their clinical research activities, and study specific documents such as the protocol, protocol amendments and annotated case report forms pertinent to the study under review.
2. **Subject-Level Data Line Listings by Clinical Site**: For every site in each pivotal study, subject level data and by-site listings are required under the following categories: consented subjects, adverse events, important protocol deviations, efficacy endpoints, concomitant medications, and safety monitoring. These listings can be organized either by site and then by listing, or by site subject, and listing.
3. **Summary-Level Clinical Site Dataset**: A summary-level clinical site data, called CLINSITE.XPT and containing data for all the sites is required for all pivotal studies. This dataset is to be submitted in SAS transport file format, and is intended to summarize the clinical investigator sites and their relevant administrative information, safety, and efficacy findings.
4. **BIMO Data Reviewer's Guide (BDRG)**: This is an optional component, yet this is highly helpful as it provides a comprehensive view of the BIMO package. It includes well-organized sections to sufficiently cover all components of the BIMO package with links to their locations. Each section provides an

opportunity for the sponsors to provide additional information that could not be accommodated in the other three components.

GATHERING INPUTS AND PREPARING FOR INITIATING BIMO PROGRAMMING

1. The FDA recommends that sponsors follow the latest BIMO TCG version. If a sponsor elects to use the older version of TCG due to study-specific or organizational needs, then the sponsor should discuss this with the FDA prior to the start of the BIMO preparation activities. Also due to study-specific requirements, if the sponsor is unable to follow the current TCG and wishes to deviate from its format and requirements, the study team should discuss these items with FDA prior to starting BIMO programming activities.
2. In order to avoid any last-minute snags while preparing the BIMO package, it is highly advisable to initiate BIMO-related programming tasks in conjunction with the start of the CSR submission programming activities.
3. It is very helpful for the programming team lead to establish contacts with relevant stakeholders such as clinical operations, clinical finance, site management, biostatistics, medical writing, clinical and statistical programming, especially in complex global trials, well ahead of deadlines to allow enough time for compiling all of the necessary inputs.
4. Obtaining clean and user-ready details needed for the CLINSITE data from all of the groups involved in the study has always been challenging. To efficiently handle this process, it is helpful to provide the teams with a template Microsoft Excel sheet with column names matching the variables needed for the site and study level CLINSITE data so that information from the file can be extracted into a SAS dataset with required metadata attributes.
5. Appendix B in the TCG provides two options for the folder structure, and it is important for the programming team to know this plan up front so that necessary structure will be in place during the production of data listings. Hence it will be helpful for the team to have conversations with the regulatory unit that is facilitating the placement of the BIMO listings and other components in the eCTD about the specific options that the team wants to adopt.

WHAT IS NEW IN THE LATEST GUIDANCE DOCUMENTS?

The 40 variables described in the current BIMO TCG (v3.0) are mandatory, and sponsors are encouraged to add additional variables, depending on study requirements. New variables have also been added to replace some of the variables defining populations, treatment efficacy results and censor data and reflect the growing needs and emerging complexities of the trials. These new variables are listed in the Table 1. To effectively address the data related to safety and efficacy populations independently, EFFPOP (Number of Subjects in Efficacy Population) has been added to identify the total number of subjects in the primary efficacy population, as defined in the clinical study report, by site and treatment arm. This is one of the noticeable and important updates in the current TCG. This bifurcation of the population reflects the basis and handling of values for the newly added variables, TRTEFFR1, TRTEFFR2, CENSOR1 and CENSOR2.

The scope of the TRTEFFR variable that was present in the previous TCG versions has been split into two new variables, TRTEFFR1 (Treatment Efficacy Result for SAFPOP) and TRTEFFR2 (Treatment Efficacy Result for EFFPOP) to provide the data separately for the SAFPOP and EFFPOP populations. Values reported in TRTEFFR1 and TRTEFFR2 reflect simple summary statistics for each primary efficacy endpoint by treatment arm at a site, based on subjects in the SAFPOP and EFFPOP populations respectively. Furthermore, in the current TCG, two new variables for censoring-related data have been added: CENSOR1 (Censored Observations in SAFPOP) and CENSOR2 (Censored Observations in EFFPOP). The number of censored observations by site treatment arm for the SAFPOP and EFFPOP are stored in CENSOR1 and CENSOR2 respectively. If a study does not contain a time-to-event endpoint, these variables should still be included in the dataset, but recorded as missing values.

Variable Name	Variable Label	Type	Controlled Terms or Format	Note or Description
Population Variable(s)				
EFFPOP	Number of Subjects in Efficacy Population	Num	Integer	Total number of subjects in primary efficacy population as reported in the Clinical Study Report at a given site by treatment arm.
Treatment Efficacy Result Variables				
TRTEFFR1	Treatment Efficacy Result for SAFPOP	Num	Floating Point	Summary statistic for each primary efficacy endpoint by treatment arm at a given site for subjects in SAFPOP
TRTEFFR1	Treatment Efficacy Result for SAFPOP	Num	Floating Point	Summary statistic for each primary efficacy endpoint by treatment arm at a given site for subjects in EFFPOP
Censor Variables				
CENSOR1	Censored Observations in SAFPOP	Num	Integer	Total number of censored observations in SAFPOP at a given site by treatment arm for primary endpoint (e.g., applicable to time-to-event). If not applicable, leave blank
CENSOR2	Censored Observations in EFFPOP	Num	Integer	Total number of censored observations in EFFPOP at a given site by treatment arm for primary endpoint (e.g., applicable to time-to-event). If not applicable, leave blank.

Table 1. List of new variables included in the current TCG

In addition to the inclusion of new variables listed above, the current TCG has also replaced the format for the values in the COUNTRY variable with the GENC (**G**eopolitical **E**ntities, **N**ames and **C**odes Terminology) format for country names. The decision to use the GENC format is line with the FDA's announcement in their publication dated July 19, 2019 which states, "*The Food and Drug Administration (FDA or Agency) is announcing the adoption of the current version of the Geopolitical Entities, Names, and Codes (GENC) Standard on December 17, 2020. The GENC Standard is the U.S. Government profile of International Organization for Standardization (ISO) 3166 "Codes for the Representation of Names of Countries and Their Subdivisions." It specifies an authoritative set of country codes and names for use by the U.S. Government for information exchange, using ISO 3166 names and code elements wherever possible, with modifications only when necessary to comply with U.S. law and U.S. Government recognition policy. Adopting the GENC Standard will enable FDA to be in conformance with U.S. Government naming and recognition policies.*"

BIMO Data Reviewer's Guide (BDRG): The current version (v3.0) was finalized to reflect the updates in the current BIMO TCG (v3.0) by the PHUSE working group and was released in June 2023. Details of the contents and some of the practical perspectives and challenges will be discussed in the subsequent sections of this paper.

GENERATION OF THE BIMO PACKAGE

CLINICAL STUDY-LEVEL INFORMATION:

Ideally information needed for this section must be available in the CSR folders of the study. The study team should ensure that the study documents such as the protocol, CRF, aCRF, SAP, etc. are the most updated versions. Importantly, if external vendors were involved in any of the data management and SDTM tasks, steps must be taken to confirm that the latest versions of these documents were transferred to the external vendors, and the final

deliverables reflect the use of these updated documents. Figure 1 and Table 2 provide an overview of the BIMO generation process flow that is ideally followed by an organization and the respective stakeholders of this process.

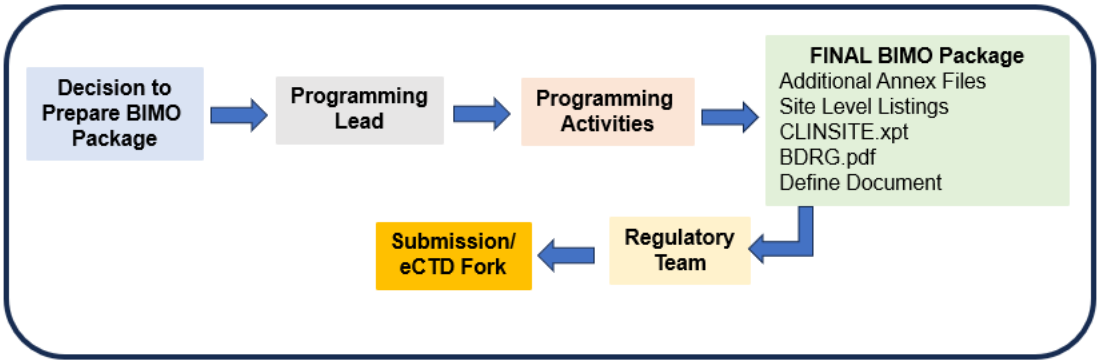

Figure 1. BIMO Generation - Process Flowchart.

Processes	Clinical Trial Operations	Finance	Data Management	Statistics	Programming Team
List of Sites	X		X		
Enrolled Subjects/Site List	X		X		
Randomized Subjects/Site List	X		X		
Investigator Contacts List	X		X		
Finance Details		X			
Listings Generation & Validation			X	X	X
Specification File				X	X
CLINSITE Generation & Validation				X	X
Pinncle21 Usage & Compliance Report					X
Define.XML Generation					X
BDRG Preparation				X	X

Table 2. BIMO Generation: Key Processes and their stakeholders

SUBJECT-LEVEL DATA LINE LISTINGS BY CLINICAL SITE:

A good number of publications are available on the logistics and methods for the efficient generation of the site-specific subject data line listings. Indeed, some sponsors have created an exclusive team to oversee the development of macros for generating these listings very efficiently to capture the data on consented subjects, adverse events, important protocol deviations, efficacy endpoints, concomitant medications, and safety monitoring. These subject-level by-site listings are required for every site of each pivotal study. It is important to follow the TCG's guidelines and include the listings under the categories shown in the TCG. However, in addition to these recommended listings, sponsors are encouraged to include additional listings based on the study requirements.

SUMMARY-LEVEL CLINICAL SITE DATASET (CLINSITE.XPT):
As stated earlier, over 40 variables are defined for each study site, and these variables cover information ranging from administrative to specific site-specific safety and efficacy findings. These variables can be grouped under the following five categories:

1. Study level and scope of the application: Study title, sponsor details, site, application type (IND/NDA/BLA), and relevant reference numbers

2. Study Conduct: Arm, cohorts, enrollment and study populations

3. Safety: Subject treatment, study discontinuations, important and non-important protocol deviations, SAEs, non-SAEs, death details

4. Efficacy Details: Population-wise endpoints, efficacy results and censoring details

5. Site-level Information: Primary clinical investigator contact information, financial disclosure and site details.

There have not been major differences between the previous and current versions of TCG in terms of the overall structure of the CLINSITE dataset. The BIMO TCG provides detailed guidelines for each variable. A few variables from the previous version were dropped, and some additional variables have been incorporated in the current TCG.

While preparing the specifications file for this dataset, it is important for the team to work with the project statistician to define the algorithms for the endpoint and censoring variables to avoid any last-minute ambiguity. It can also happen that the study team may not want to include certain sites because of a lack of enrollment, enrollment by non-randomized subjects, or other issues. In this case, these situations can usually be reported in the BDRG, or also described in a separate file in the Appendix. These decisions should be made and documented with agreement from the statistician and the relevant stakeholders of the study. The specification file is a as much of a key element for the development of CLINSITE data as it is for the SDTM and ADaM datasets.

BIMO DATA REVIEWER'S GUIDE (BDRG):

As emphasized earlier in this paper, inclusion of the BDRG in the BIMO package has several advantages. For one, the current version reflects all of the changes that occurred in the current BIMO TCG, and therefore both the TCG and BDRG are in agreement. To add a historical perspective, in the middle of 2022, the first version of formalized BDRG was released for the industry use. Almost at the same time, the latest version of the TCG was released. Hence this first version of BDRG reflected v.2.0 of TCG.

Table 2 depicts the organization of the contents of the current version of the BDRG.

1	Introduction
1.1	Purpose
1.2	Acronyms
1.3	BIMO Guidance and Supporting Information
1.4	Study-related Metadata
2	Study Description
2.1	List of Studies for which BIMO Clinical Data are Submitted
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 Location

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 and Key Secondary Endpoints Summary
5.3	Clinical Site Dataset Supporting Information
5.4	Conformance Inputs
5.5	Conformance Issues Summary
6	External Datasets and Sources
7	Site-specific Matters
7.1	Site Concerns
7.2	Subjects Transferred Between Sites
7.3	Identical Site ID Used in Multiple Studies
8	Site Summary
9	eCTD Folder Structure Skeleton for BIMO Items in MODULE 5
10	Appendix

Table 2. Organization of contents of the current version of the BDRG (v3.0).

CONCLUSION

There have been many publications providing valuable insights for different components of the BIMO submissions in recent years. The past two years have seen valuable updates in both the BIMO TCG and BDRG templates to cater to the growing needs of the industry. Undoubtedly these documents are helpful for improving quality and clarity in BIMO submissions. With the current release of the BDRG template, both the BIMO TCG and the BDRG are in agreement. Just like any other standards, both of these documents will witness additional updates due to evolving requirements, and as we learn more from the complexities of the trials. This training highlights the important updates from these regulatory guidance documents, and collectively presents them to the participants, along with the clarifications and explanations that are helpful for the completion of the BIMO submissions.

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