

Bioresearch Monitoring (BIMO) Data Reviewer's Guide

Completion Guidelines

Version 3.0 [28-JUN-2023]

Revision History

Version	Date	Summary
1.0	05-JAN-2022	PHUSE BDRG finalized draft for Public review
2.0	22-JUN-2022	PHUSE BDRG Published version as per BIMO TCG v2.0 [27 th July, 2020] and Public review comments/feedback.
3.0	28-JUN-2023	<p>PHUSE BDRG Published version</p> <p>Section updated for :-</p> <p><u>Alignment with FDA BIMO TCG V3.0 [11th August, 2022]:</u></p> <ol style="list-style-type: none">1. Renamed BIMO Review Guide to BIMO Data Reviewer's Guide2. Renamed TRTEFFR to TRTEFFR1 and CENSOR to CENSOR13. Added EFFPOP, TRTEFFR2, and CENSOR2 Variables4. Deleted reference of TRTEFFS5. Change instructions for use of ISO codes to use of Geopolitical Entities, Names and Codes (GENC) codelist.6. Minor editorial changes. <p><u>Rearranging Section 5 – 11 with new sub-section added and renaming current sub-section:</u></p> <ol style="list-style-type: none">7. Addition of the Sub-Section (“5.3 Clinical Site Dataset Supporting Information”) under Section 5. Part III Summary-level Clinical Site Dataset8. Conformance Section 8 is now placed under Section 5. Part III Summary-level Clinical Site Dataset as Sub-Section 5.4 and 5.5.9. Renaming Section Name 1.2 and 3.2 <p><u>Cosmetic updates:</u></p> <ol style="list-style-type: none">10. Clarity update11. Cascading impact

Bioresearch Monitoring (BIMO) Data Reviewer's Guide

Completion Guidelines

Table of Contents

Page No.

BIMO Data Reviewer's Guide Completion Guidelines Overview	4
BIMO Data Reviewer's Guide (BDRG) Purpose	4
BDRG Overview	5
BDRG Completion Guidelines Purpose	6
Organisation of This Document.....	6
Bioresearch Monitoring Data Reviewer's Guide (BDRG) Template Completion Instructions	7
Cover Page Instructions	7
1. Introduction	8
1.1 Purpose	8
1.2 Acronyms.....	8
1.3 BIMO Guidance and Supporting Information	9
1.4 Study-related Metadata.....	10
2. Study Description.....	12
2.1 List of Studies for which BIMO Clinical Data are Submitted	12
3. Part I – Request for Clinical Study-level Information.....	13
3.1 Part I (Item A) – List of All Clinical Sites	13
3.2 Part I (Item B) – Entities Contact Information and Trial-related Files Location	14
3.3 Part I (Item C1) – Protocol and Amendments	16
3.4 Part I (Item C2) – Annotated Case Report Form (aCRF)	17
4. Part II – Subject-level Data Line Listings by Clinical Site	18
4.1 Subject-level Listings	18
4.2 Primary, Key Secondary Endpoints and Clinical Events	21
4.3 Safety Monitoring and Clinical Events	22
5. Part III – Summary-level Clinical Site Dataset.....	24
5.1 Treatment Variables	24
5.2 Primary, Key Secondary Endpoints Summary	26
5.3 Clinical Site Dataset Supporting Information	28
5.4 Conformance Inputs	29
5.5 Conformance Issues Summary	29
6. External Datasets and Sources	31

7. Site-specific Matters	32
7.1 Site Concerns	32
7.2 Subjects Transferred Between Sites	33
7.3 Identical Site ID Used in Multiple Studies.....	34
8. Site Summary	35
9. eCTD Folder Structure Skeleton for BIMO Items in MODULE 5.....	36
10. Appendix	37
Bioresearch Monitoring Data Reviewer’s Guide (BDRG) Finalization Instructions.....	37

BIMO Data Reviewer's Guide Completion Guidelines Overview

BIMO Data Reviewer's Guide (BDRG) Purpose

The Bioresearch Monitoring Data Reviewer's Guide (BDRG) provides FDA reviewers with an overview of sponsor considerations 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) that are used by the FDA's Center for Drug Evaluation and Research (CDER) for the planning of Bioresearch Monitoring (BIMO) inspections in electronic Common Technical Document (eCTD) format for New Drug Applications (NDAs) OR Biologics License Applications (BLAs) OR supplemental New Drug Applications (sNDAs) OR supplemental Biologics License Applications (sBLAs) OR Investigational New Drug Applications (INDs) containing clinical data.

BIMO Clinical Data

- Part I - Clinical study-level information and Part II - Subject-level data line listings by clinical site are submitted for each major (i.e. pivotal) study to support safety and efficacy in the application.
- Part III - Summary-level clinical site dataset, a single file containing data from all major (i.e. pivotal) studies used to support safety and efficacy in the application should be provided.
- Part I - Clinical study-level information, Part II - Subject-level data line listings by clinical site and Part III - Summary-level clinical site dataset, in electronic Common Technical Document (eCTD) format, should be placed in eCTD Module 5 (M5) — Clinical Study Reports under Module 5.3.5.4 “Other Study Reports and Related Information”.
- The BDRG purposefully duplicates limited information found in other submission documentation (the protocol, statistical analysis plan, clinical study report, analysis data reviewer's guide/Define-XML, etc.) in order to provide FDA reviewers with a single point of orientation to the **BIMO clinical data**. It is advised to avoid redundancy as much as possible between these documents. The submission of a reviewer's guide does not obviate the requirement to submit complete and informative **BIMO clinical data**. For further information about source references used for the BDRG, please refer to the useful FDA resources below.

Useful FDA Resources:

- **OSI (Office of Scientific Investigations)**
<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-scientific-investigations>
- **Bioresearch Monitoring Technical Conformance Guide**
<https://www.fda.gov/media/85061/download>
- **Study Data Standards Resources**
 - <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>
 - <https://www.fda.gov/media/88173/download>
 - <https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/Best+Practices+for+Documenting+Data+Metadata-Define-XML+Versus+Reviewers+Guide.pdf>
- **Geopolitical Entities, Names, and Codes (GENC) – FDA Structured Product Labeling Resources**
<https://evs.nci.nih.gov/ftp1/GENC/>

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).

BDRG Completion Guidelines Purpose

The purpose of this document is to provide sponsors with a clear, concise set of instructions that facilitates the consistent development of the BDRG from the Bioresearch Monitoring Data Reviewer's Guide Template. In addition to the BDRG Completion Guidelines, BDRG examples are available as an additional reference.

Organisation of This Document

This document has three sections: the BDRG Completion Guidelines Overview, the BDRG Template Completion Instructions and the BDRG Finalization Instructions. The section/sub-section number in the BDRG Template Completion Instructions corresponds directly to the BDRG Template. The BDRG Finalization Instructions describe how to format the document for submission after completing the BDRG Template.

Bioresearch Monitoring Data Reviewer's Guide (BDRG) Template Completion Instructions

This section provides supporting instructions while populating information in the BDRG Template. The section numbering corresponds directly to the BDRG Template. **Note: BDRG sections/sub-sections include information in the form of table/standard text format intended to aid FDA reviewers. Provide information in all sections/sub-sections and indicate 'N/A' if not applicable. While finalizing the BDRG document, do not delete any of the sections and/or its sub-sections from the BDRG Template document.**

Cover Page Instructions

- BDRG Name: Bioresearch Monitoring (BIMO) Data Reviewer's Guide
- Provision for <Sponsor's Name>
- Provision for <Compound/Project Name>
- Provision for <Application Type: Application Number>
- Provision to list major (i.e. pivotal) studies used to support safety and efficacy in the application.
List of Studies included in the BIMO Clinical Data Application:
Study1 <DM.STUDYID>
Study2 <DM.STUDYID>
.....
- BDRG Template Version # [DD-MMM-YYYY] <BDRG Template Version used by sponsor and corresponding date>
BDRG Published Date [DD-MMM-YYYY] <Date entered by the sponsor in the BDRG close to their BIMO clinical data application date>
- If the sponsor OR applicant are different, then the applicant reference can be appropriately made instead of sponsor in all sections of the BDRG document.
For example, in Section 1.1 Purpose:
The purpose of the BIMO Data Reviewer's Guide (BDRG) is to provide an overview of applicant considerations when preparing and submitting BIMO clinical data.
- It is optional for sponsors to add confidential text on the cover page just above the BDRG Template Version and the BDRG Published Date.

1. Introduction

1.1 Purpose

This required section states the purpose of the BDRG. The BDRG Template includes standard text.

Sponsors should provide the BIMO clinical data application type using options in the BDRG Template. The section below contains standard text, used without an update in the BDRG Template.

This document provides the following information to aid navigation and understanding of the BIMO clinical data:

- **Supporting Information, Content and Structure of the Requested BIMO Clinical Data**

Covered in sections 1–10 within this document. Here, sections 1–10 provide information about BIMO clinical data deliverables that assists FDA CDER staff to understand sponsor considerations made in preparing these deliverables.

- **Hypertext Links**

There are no external hyperlinks applied in this document, but the location of deliverables in “eCTD Module 5 (M5) -> Clinical Study Reports -> Module 5.3.5.4 -> Other Study Reports and Related Information” are specified with text in section 9.

1.2 Acronyms

The Acronyms table documents sponsor-specific non-standard acronyms used in the BDRG.

Note: Commonly accepted acronyms do not need to be included in this table. There are two columns in this table: the acronym used and its associated translation.

Example Acronyms Table (Sponsor-specific Non-standard Acronyms):

Acronym	Translation
ARO	Academic Research Center
BDRG	Bioresearch Monitoring Data Reviewer's Guide
TCG	Technical Conformance Guide
SAFPOP	Safety Population
EFFPOP	Efficacy Population

1.3 BIMO Guidance and Supporting Information

The BIMO Guidance **and Supporting Information** table documents the BIMO guidance used to create the BIMO clinical data for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application AND any other supporting information that sponsor would like inform that would be helpful to FDA reviewers.

For Example: Mention of Version of the Summary-level Clinical Site Dataset definition file submitted by sponsor part of **BIMO Clinical Data**.

Sponsors should document the version and/or date used for 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
- Bioresearch Monitoring Technical Conformance Guide (BIMO TCG)
- Summary-level Clinical Site Dataset definition file (define.xml).

Example BIMO Guidance Table:

BIMO Guidance and Supporting Information	Version and/or Date
Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions Guidance for Industry	February 2018
Bioresearch Monitoring Technical Conformance Guide	Version 3.0, 11 th August 2022
Summary-level Clinical Site Dataset Definition File (define.xml)	Version 2.0

Important Note:

- It is highly recommended by the FDA that the most current BIMO TCG be used, but if the sponsor is submitting BIMO clinical data as per earlier BIMO TCG versions, then it should be discussed and agreed upon with the FDA during the pre-submission meeting.
- As per the latest BIMO TCG (e.g. Version 3.0, 11th August 2022), it is highly recommended by the FDA to provide Define-XML. Sponsors may also provide define.pdf (optional) in addition to a define.xml.
- Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions Guidance for Industry February 2018 (Note: Refers to DRAFT GUIDANCE)

For all major (i.e. pivotal) studies used to support safety and efficacy in the application, their BIMO clinical data should follow the same set of guidance in the table. For example, if more than one major (i.e. pivotal) study is included in the application, the same version of the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) is to be followed across all the major (i.e. pivotal) studies' BIMO clinical data in the application.

1.4 Study-related Metadata

The Study-related Metadata table documents important details for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application.

Example of Study-related Metadata table:

1	2	3	4	5	6	7
Study Identifier	Protocol Number	National Clinical Trial (NCT) Number	Data Cut-off Date	Database Lock Date	Study Status (at Time of Data Cut-off Date)	Comments
1234-0001	1234-0001	NCT00808067	01JUL2021	01JUL2021	Study Completed	
1234-0002	1234-0056	NCT00808068	05JUL2021	10JUL2021	On- going	Study Identifier and Protocol Number are different due to merger or acquisition

Details:

- Format for the **Study Identifier** column: DM.STUDYID (unique values in ascending order).
 - If the Study Identifier and Protocol Number are different, document each number and add an explanation to the Comments column as to why they are different (e.g. renamed due to merger or acquisition), otherwise the Comments column can be left blank.

- Format for the **Protocol Number** column: freeform text/numbers referenced in the protocol.

- Format for the **National Clinical Trial (NCT) Number** column: 'NCT' followed by 8 digits.

Hint: To get National Clinical Trial (NCT) Number, Below are the steps to reach the landing page of the respective major (i.e. pivotal) study:

- Go to the clinicaltrials.gov website (<https://clinicaltrials.gov/>).
- Identify each major (i.e. pivotal) study using the 'Find a Study' section (all fields optional) and the Search/Advanced Search option.
- The NCT number can be found on the landing page of the respective study (refer to the below screenshot of the landing page where the NCT number is successfully identified).

The screenshot shows the ClinicalTrials.gov interface for a study record. At the top, the NIH U.S. National Library of Medicine logo and 'ClinicalTrials.gov' are displayed. Navigation links include 'Find Studies', 'About Studies', 'Submit Studies', 'Resources', 'About Site', and 'PRS Login'. The study title is 'pradaxa | Interventional Studies | Phase 3'. Below the title, there are links for 'Previous Study', 'Return to List', and 'Next Study'. The study description is 'RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY Trial'. A disclaimer box on the left states: 'The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.' On the right, a box contains the ClinicalTrials.gov Identifier: NCT00808067 and a table of dates: Recruitment Status: Completed, First Posted: December 15, 2008, Results First Posted: April 8, 2014, Last Update Posted: June 9, 2014. An orange arrow points from the 'First Posted' date to the 'Data Cut-off Date' column in the table below.

4 Format for the **Data Cut-off Date** column: DDMMYYYY, which is based on TS.TSVAL for TS.TSPARMCD='DCUTDTC' and TSPARM="Data Cutoff Date".

- The Data Cut-off Date is the date where all data collected/events up to and including the Data Cut-off Date are only included in the major (i.e. pivotal) study and its analysis. Conversely, data collected following the Data Cut-off Date will not be considered as part of the major (i.e. pivotal) study and its clinical study report analysis submitted in the marketing application.
- This information will help the FDA to understand if there is a Data Cut-off Date applied by the sponsor. If not applicable, add N/A.

5 Format for the **Database Lock Date** column: DDMMYYYY.

- The Database Lock Date is a date after which no further changes can be made to major (i.e. pivotal) study data.
- This information will help the FDA to understand if there is a Database Lock Date applied by the sponsor. If not applicable, add N/A.

6 Format for the **Study Status (at Time of Data Cut-off Date)** column: freeform text.

Provide the study status **at Time of Data Cut-off Date**, e.g. Study Completed OR Study Ongoing. **Note: The Study Status column definition/value should be consistent/aligned with the sponsor's submission documents** such as the Study Data Standardization Plan (SDSP), the Clinical Study Data Reviewer's Guide (cSDRG) and the Analysis Data Reviewer's Guide (ADRG).

7 Format for the **Comments** column: freeform text.

- Example: Provide information as to why the Study Identifier and the Protocol Number are different, or any other comment important for sponsor to communicate to the FDA.

2. Study Description

2.1 List of Studies for which BIMO Clinical Data are Submitted

The List of Studies for which BIMO Clinical Data are Submitted table provides a comprehensive list of all major (i.e. pivotal) studies used to support safety and efficacy in the application.

Example List of Studies for which BIMO Clinical Data are Submitted Table:

1	2	3	4
Study Identifier	Study Title	Study Phase	Comments
1160.71	RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation Who Completed the RELY Trial and a Cluster Randomised Trial to Assess the Effect of a Knowledge Translation Intervention on Patient Outcomes	PHASE III TRIAL	N/A

Details:

1 Format for the **Study Identifier** column: DM.STUDYID (unique values in ascending order).

2 Format for the **Study Title** column:

Option 1) If the value of the TS.TSVAL is less than or equal to 200 characters length: TS.TSVAL for TS.TSPARMCD (Trial Summary Parameter Short Name)= 'TITLE'

ELSE

Option 2) If the value of the TS.TSVAL is more than 200 characters length, i.e. captured in TSVAL1-TSVALn., provide the Title (if <= 200 characters length) as used on clinicaltrial.gov (example: <https://clinicaltrials.gov/> -> Identified Study> Study Design> Official Title <if <= 200 characters length>).

ELSE

Option 3) If both Option 1) and 2) titles are more than 200 characters in length, then shorten the title in Option 1) OR 2) to meet the 200 characters length, using acronyms. These acronyms can be documented in section 1.2 Acronyms of the BDRG document.

3 Format for the **Study Phase** column: based on the value of TS.TSVAL for TS.TSPARMCD (Trial Summary Parameter Short Name) = 'TPHASE'.

4 Format for the **Comments** column: freeform text.

- Example: Sponsors can provide study information important to communicate to the FDA. If not applicable, add N/A.

3. Part I – Request for Clinical Study-level Information

3.1 Part I (Item A) – List of All Clinical Sites

The List of All Clinical Sites table provides **only the information included in the BIMO Part I (Item A) PDF deliverable prepared by the sponsor** to capture a comprehensive list of all clinical sites [sites that participated in the study (i.e. sites that have screened one subject with a signed informed consent)] for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application.

Example BDRG Template:

The information below is included in the BIMO Part I (Item A) PDF deliverable for each of the major (i.e. pivotal) studies for sites that participated in the study (i.e. sites that have screened one subject with a signed informed consent).

Site Identifier 1	Current Principal Clinical Investigator Name (Prior Principal Clinical Investigator(s)) 2	Site Address at Time of Clinical Study (Updated Site Address when Exists and Available) 3	Site Contact Information at Time of Clinical Study (Updated Contact Information when Exists and Available) 4	Total Number of Subjects Enrolled at a Site 5
SITEID	LASTNAME, FRSTNAME, MINITIAL	FACILITY NAME STREET CITY, STATE, POSTAL COUNTRY	PHONE FAX EMAIL	Count (number >= 0)
*Site terminated, or clinical investigator changed at the request of the sponsor before study completion.				

Details:

1	2	3	4
---	---	---	---

Columns 1 to 4 are field/column names based on the latest BIMO TCG (e.g. Version 3.0, 11th August 2022), **whose information are populated in the BIMO Part I (Item A) PDF deliverable prepared by the sponsor.**

Columns 1 to 4 field/column names are consistent with the BIMO Part III clinsite dataset variable name (example: LASTNAME, FRSTNAME, MINITIAL).

In case there is any change in the information from the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) that's **included in the BIMO Part I (Item A) PDF deliverable**, then columns 1 to 4 field/column names should be documented by sponsors in BDRG section 3.1 accordingly.

Updated Address refers to address different from the study address of the record during the ongoing study. For inspection planning purposes, the FDA requests current address when known, to permit planning for correct location of Current Principal Clinical Investigator.

5 The **Total Number of Subjects Enrolled at a Site** column: This information will be the sponsor's decision to mention in/exclude from the BDRG and accordingly populate in the BIMO Part I (Item A) PDF deliverable. The BIMO TCG

doesn't have this requirement, but this information helps FDA CDER from a BDRG and BIMO Part I (Item A) perspective for site inspection, as discussed by the PHUSE BDRG Project team. The PHUSE BDRG Project team have proposed to FDA CDER to consider adding it in the future release of the BIMO TCG.

In Part I (Item A) PDF deliverable, if Column 5 is included, then:

- Subjects Enrolled are subjects with a signed informed consent and continued in the study post-screening period by meeting eligibility criteria **OR** Subjects Enrolled are subjects with a signed informed consent and enrolment definition defined by the sponsor in their protocol.

Important Note:

- The List of All Clinical Sites **deliverable content** for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application **should be created as a separate Part I (Item A) PDF deliverable** and placed within the eCTD folder structure (Refer to section 9.). The **table displayed in Section 3.1 of the BDRG document is just to provide FDA reviewers with field/column names, whose information are populated in the separate Part I (Item A) PDF deliverable.**
- The table details in Section 3.1 of the BDRG Template document can be kept without any updates by the sponsor in their BDRG document, if the sponsor is following the same format in their separate Part I (Item A) PDF deliverable for each of the major (i.e. pivotal) studies.

3.2 Part I (Item B) – Entities Contact Information and Trial-related Files Location

The Entities Contact Information and Trial-related Files location table provides **only the information included in the BIMO Part I (Item B) PDF deliverable prepared by the sponsor** to capture a comprehensive list of all entities to whom the sponsor has contracted to conduct/report clinical study-related activities for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application.

From the BDRG Template:

The information below is included in the BIMO Part I (Item B) PDF deliverable for each of the major (i.e. pivotal) studies.

1	2	3	4	5	6	7
Entities Type	Name of Entities	Study-related Activities	Address	Location of Study-related Documents and Records Generated (Physical and/or in TMF)	Contact Information	Responsible for Documentation
					CONTACT NAME (If Available): PHONE: FAX (If Available): EMAIL:	Created by Approved by

Details:

Columns 1 to 7 are field/column names based on the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) and the PHUSE BDRG Project team recommendation, **whose information are populated in the BIMO Part I (Item B) PDF deliverable prepared by the sponsor.**

In case there is any change in the information from the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) that is **included in the BIMO Part I (Item B) PDF deliverable**, then columns 1 to 7 field/column names should be documented by sponsors in BDRG section 3.2 accordingly.

1 Format for the **Entities Type** column: the preferred values recommend populating **Sponsor/CRO/ARO/Vendor** in the **Part I (Item B) PDF deliverable**.

2 Format for the **Name of Entities** column: freeform text. The preferred values recommend populating **Name of the Sponsor/CRO/ARO/Vendor** in the **Part I (Item B) PDF deliverable**.

3 Format for the **Study-related Activities** column: freeform text in the **Part I (Item B) PDF deliverable**.

4 Format for the **Address** column: freeform text. The preferred values recommend populating **STREET, CITY, STATE, POSTAL and COUNTRY** in the **Part I (Item B) PDF deliverable**.

5 Format for the **Location of Study-related Documents and Records Generated (Physical and/or in TMF)** column: freeform text. The preferred values recommend populating **Physical and/or in TMF** in the **Part I (Item B) PDF deliverable, corresponds to the address given in the column.** 4

6 Format for the **Contact Information**: the preferred values recommend populating
CONTACT NAME (If Available): < CONTACT NAME > PHONE: < PHONE No. > FAX (If Available): < FAX No. > EMAIL: < EMAIL ID >.

7 Format for the **Responsible for Documentation (Created by and Approved by)** column: the preferred values recommend populating

Created by: Based on the information in columns 1 and 2 and for each of the identified **Study-related Activities**, identify the 'Sponsor' or 'Entity' who **created** the documentation for **Study-related Activities** mentioned in the **Part I (Item B) PDF deliverable**.

Approved by: Based on the information in columns 1 and 2 and for each of the identified **Study-related Activities**, identify the 'Sponsor' or 'Entity' who **approved** the documentation for **Study-related Activities** mentioned in the **Part I (Item B) PDF deliverable**.

Important Note:

- The Entities Contact Information and Trial-related Files **Location deliverable** for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application **should be created as a separate Part I (Item B) PDF deliverable** and placed within the eCTD folder structure. (Refer to section 9.) **The table displayed in section 3.2 of the BDRG document is just to provide FDA reviewers with field/column names, whose information is populated in the separate Part I (Item B) PDF deliverable.**

3.3 Part I (Item C1) – Protocol and Amendments

The Protocol and Amendments table provides a comprehensive list of all protocol and amendments for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application.

Example Part I (Item C1) – Protocol and Amendments Table:

1	2	3	4	5
Study Identifier	List All Protocol/ Local Amendment Version Numbers	If Local Amendment (List Country)	Date Effective	Location Reference (Items Included In)
1234-0001	Version 2 (FINAL)	N/A	12DEC2008	Appendix 16 of the CSR
	Amendment 1	France	05SEP2008	Not Submitted [available on request]
	Version 1	N/A	28JUN2008	Appendix 16 of the CSR
1234-0002	Version 2 (FINAL)	N/A	10DEC2008	Included in the application (refer to section 9)
	Version 1	N/A	20JUN2008	Included in the application (refer to section 9)
1234-0003	Version 1 (FINAL)	N/A	10NOV2009	Included in the application (refer to section 9)

Details:

- Format for the **Study Identifier** column: DM.STUDYID (unique values in ascending order).
- Format for the **List All Protocol/Local Amendment Version Numbers** column: freeform text. (The preferred values are **Version # (FINAL)/Version #/... Amendment #/... etc.**). Where # is any number >=1, put version/amendment number in descending order.
 - Version # (FINAL)** is the FINAL protocol version number.
 - Version #** is the amended protocol version number.
 - Amendment #** is the amendment version, which is a country-specific amendment version number.
- Format for the **If Local Amendment (List Country)** column: freeform text country name only ELSE N/A (i.e. Not Applicable).
- Format for the **Date Effective** column: DDMMMYYYY, which is based on **Date Effective for the respective protocol and its amendment version number** (Date Effective in descending order).
- Format for the **Location Reference (Items Included in)** column: freeform text. The preferred values are **Appendix # of the CSR/Included in the application (refer to section 9)/Not Submitted [available on request]**.

- Items [Part I (Item C1) – Protocol and Amendments] already included in the Appendix # of the CSR are not included in this application and mentioned as 'Appendix # of the CSR' in the Location reference of the table.
- Items [Part I (Item C1) – Protocol and Amendments] not included in the Appendix # of the CSR should be included in this application and mentioned as 'Included in the application (refer to section 9)' in the Location reference of the table.
- If there are country-specific protocol amendments and the sponsor is not submitting them, then this should be mentioned as 'Not Submitted [available on request]'.
- If there are country-specific protocol amendments and the sponsor is submitting them, then this should be mentioned as 'Included in the application (refer to section 9)'.

Important Note:

- If the sponsor is submitting a BIMO Data Reviewer's Guide, the sponsor should note that when these items are **present** in the Appendix of the clinical study report, then the sponsor should provide the location reference in column 5 of sub-section 3.3 [Appendix # of the CSR], but there is no need to resubmit them in the **BIMO clinical data application**.
- If the sponsor is submitting a BIMO Data Reviewer's Guide, the sponsor should note that when these items are **not present** in the Appendix of the clinical study report, then the sponsor should provide the location reference in column 5 of sub-section 3.3 [Included in the application (refer to section 9)] and should submit them in the **BIMO clinical data application**.

3.4 Part I (Item C2) – Annotated Case Report Form (aCRF)

The Annotated Case Report Form (aCRF) table provides a comprehensive list of all aCRFs for each of the major (i.e. pivotal) studies used to support safety and efficacy in the application.

There are three columns in this table: Study Identifier, Annotated Case Report Form (aCRF), Location Reference (Items Included In). Provide the information by Study Identifier ascending order.

Example Part I (Item C2) – Annotated Case Report Form (aCRF):

1 Study Identifier	2 Annotated Case Report Form (aCRF)	3 Location Reference
1234-0001	Final aCRF	Included in the application (refer to section 9)
1234-0002	Final aCRF	It is located in the datasets folder (tabulations\sdtm) of the study

Details:

- 1 Format for the **Study Identifier** column: DM.STUDYID (unique values in ascending order to reference details specific to the major (i.e. pivotal) studies) OR ALL (to reference details which are the same for all of the major (i.e. pivotal) studies).

Note:

- Multiple DM.STUDYID can be provided separated by a comma (along with 'and') when the entry applies to more than 1 study but not to ALL studies.

2 Format for the **Annotated Case Report Form (aCRF)** column: freeform text. The preferred values are **Final aCRF/Not Provided**.

3 Format for the **Location Reference** column: freeform text. For the **Final aCRF**, the preferred value is **Included in the application (refer to section 9) OR It is located in the datasets folder (tabulations\sdm) of the study**.

Important Note:

- If the sponsor is submitting a BIMO Data Reviewer's Guide, the sponsor should note that when these items are **present** in the dataset folder, then the sponsor should provide the location reference in column 3 of sub-section 3.4 [It is located in the datasets folder (tabulations\sdm) of the study], but there is no need to resubmit them in the **BIMO clinical data application**.
- If the sponsor is submitting a BIMO Data Reviewer's Guide, the sponsor should note that when these items are **not present** in the dataset folder, then the sponsor should provide the location reference in column 3 of sub-section 3.4 [Included in the application (refer to section 9)] and should submit them in the **BIMO clinical data application**.

4. Part II – Subject-level Data Line Listings by Clinical Site

The Part II – Subject-level Data Line Listings by Clinical Site section provides a very 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.

4.1 Subject-level Listings

From the BDRG Template:

The following requested listings are presented using <Choose either Option A: By Study, By Site and By Listing OR Option B: By Study, By Site and by Subject Profile.>.

Study Identifier	Listing No.	Listing Title	Comments
ALL	1	Listing 1: Listing of Consented Subjects	
ALL	2	Listing 2: Listing of Treatment Assignment	
ALL	3	Listing 3: Listing of Discontinuations	
ALL	4	Listing 4: Listing of Study Population	

Study Identifier	Listing No.	Listing Title	Comments
ALL	5	Listing 5: Listing of Inclusion and Exclusion Criteria	
ALL	6	Listing 6: Listing of Adverse Events and Deaths	
ALL	7	Listing 7: Listing of Protocol Deviations (all, i.e. Non-Important and Important, Protocol Deviations)	
ALL	8	Listing 8: Listing of Efficacy Endpoints	
ALL	8a	Listing 8a: Listing of Efficacy Endpoints Collected as Clinical Events	
ALL	9	Listing 9: Listing of Concomitant Medications	
ALL	10	Listing 10: Listing of Safety Monitoring	
ALL	10a	Listing 10a: Listing of Safety Endpoints Collected as Clinical Events	

Additional information for Listings 1 to N <N= No. of listings included in Part II>:

- Splitting logic: provide details of any splitting logic that has been used in presentation of listings, e.g. for labs by site, subject, CAT/SUBCAT
- <Add information as needed>

Details:

- 1 Format for the **Study Identifier** column: DM.STUDYID (reference listing details specific to the major (i.e. pivotal) studies OR ALL (reference listing details which are the same for all of the major (i.e. pivotal) studies).

Note:

- Multiple DM.STUDYID can be provided separated by a comma (along with 'and') when the listing entry applies to more than 1 study but not to ALL studies.

- 2 Format for the **Listing No.** column: the preferred values are **1 to 10a for Mandatory Listings** based on the latest BIMO TCG (e.g. Version 3.0, 11th August 2022), refer to Part II Section A) and **11 to N where N>=11 for Additional Listings** based on the latest BIMO TCG (e.g. Version 3.0, 11th August 2022, refer to Part II Section B).

Note:

- Listing No. 8a is the preferred numbering for "Listing 8a: Listing of Efficacy Endpoints Collected as Clinical Events".
- Listing No. 10a is the preferred numbering for "Listing 10a: Listing of Safety Endpoints Collected as Clinical Events".
- **Additional Listings** are based on the latest BIMO TCG (e.g. Version 3.0, 11th August 2022, refer to Part II Section B)

3

Format for the **Comments** column: freeform text. For any Mandatory Listings **not included and not created** in the application, then the preferred values should be documented as **"Not Provided: <Reason as Freeform text>".** For any Additional listings **included** in the application, the preferred values should be documented as **"Additional Listing"**. Moreover, if there is information specific to the listing that the sponsor needs to mention, the **Comments** column can be utilized accordingly.

Important Note:

Consideration in this section of the BDRG Template:

- All listings recommended are based on the guidance/recommendation in the latest BIMO TCG (e.g. Version 3.0, 11th August 2022).
- All listings recommended are for clinical investigator sites that have consented subjects (clinical investigator sites having screen failed subjects and enrolled subjects OR enrolled subjects only OR screen failed subjects only). For clinical investigator sites with only screen failed subjects, some listings may not be applicable.
- All listings details in BDRG Section 4.1 Table should be aligned with the title and numbering used in the Part II deliverable of the BIMO application by the sponsor.
- Mandatory listings [Listings No. 1 to 10a] are listings based on the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) (refer to Part II Section A. Organization of the Subject-level Data Line Listings).
- Additional listings [Listing No. 11 to N where $N \geq 11$] are listings based on the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) (refer to Part II Section B. Site-specific Listings Format). Moreover, additional listings should be mentioned as "Additional Listing" in the Comments column of BDRG Section 4.1 Table.
- Any mandatory listings not included in the application should be documented in the Comments column of BDRG Section 4.1 Table. For example, if "Listing 8a: Listing of Efficacy Endpoints Collected as Clinical Events" is not included then Comments column of BDRG Section 4.1 Table can mention **Not Provided: no potential efficacy endpoints were collected as clinical events.**
- For each of the major (i.e. pivotal) studies used to support safety and efficacy in the application, mandatory listings (1 to 10a) and additional listings (11 to N where $N \geq 11$) will be part of one PDF file Part II deliverable in the application (and presented as < Option A OR B defined in the latest BIMO TCG (e.g. Version 3.0, 11th August 2022)>). Note: If the size of the PDF file exceeds 500 megabytes, it should be split into smaller components by providing splitting logic in the Additional Information section of BDRG Section 4.1 Table.
- For Listing 8: Listing of Efficacy Endpoints, refer to the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) note **"For derived OR calculated endpoints, the raw data points used to generate the derived or calculated endpoint should be provided."**
- Refer to our PHUSE BDRG 3 examples for the scenarios that can be utilized by sponsors where applicable.

- There is provision at the end of this section for additional information for the overall Part II deliverable of the application.
 - Provide additional information for Splitting logic vs splitting listings: splitting logic is only applicable if the listings are split into parts due to file size/volume/cosmetic issue. If applicable, splitting logic needs to be provided on how the listings are split into parts. Splitting listings are applicable when the display of the listings is affected on a one-page display due to page width or cosmetic reasons. The listings would then need to be divided/split into parts. For example, refer to Listings No. 8.1 and 8.2 along with Additional information for listings 1 to 12: in our PHUSE BDRG Example 2.
 - Another Example for splitting logic: provide details of any splitting logic that has been used in the presentation of listings, e.g. for labs by site, subject, CAT/SUBCAT or parameters etc....
 - If the Additional Information section is not applicable, then just add N/A.

4.2 Primary, Key Secondary Endpoints and Clinical Events

The Primary, Key Secondary Endpoints and Clinical Events section provides information about primary, key secondary endpoints in the Part II Listing 8 and corresponding endpoints collected as clinical events in Part II Listing 8a for each of the major (i.e. pivotal) studies.

Note: As per latest BIMO TCG (e.g. Version 3.0, 11th August 2022) listing(s) mentioned should contain primary and key secondary efficacy parameters or events. But there is provision for sponsors in this section (for Part II Listing 8/8a) for major (i.e. pivotal) studies which does not have primary and key secondary efficacy parameters or events, so depending on the type of major (i.e. pivotal) study, use primary, key secondary endpoints (safety, PK, etc.) and corresponding clinical events. (Refer to our PHUSE BDRG 3 examples for the scenarios that can be utilized.)

From the BDRG Template:

The following table provides information about Primary, Key Secondary Endpoints in the Part II Listing 8 and corresponding endpoints collected as clinical events in Part II Listing 8a for each of the major (i.e. pivotal) studies.

1	2	3	4	5
Study Identifier	Endpoint Category / Clinical Events	Endpoint / Clinical Events Description	Criterion	Listing No.
<Refer Details below>	<Refer Details below>	<Refer Details below>	<Refer Details below>	<Refer Details below>

Details:

- 1 Format for the **Study Identifier** column: DM.STUDYID (values in ascending order to reference details specific to a major (i.e. pivotal) study OR ALL to reference details which are same for all of the major (i.e. pivotal) studies).

Note:

- Multiple DM.STUDYID can be provided separated by a comma (along with 'and') when the entry applies to more than 1 major (i.e. pivotal) study but not to ALL studies.

2 Format for the **Endpoint Category or Clinical Events** column: freeform text. The preferred values are **Primary Efficacy, Key Secondary Efficacy, Primary Pharmacokinetic, Key Secondary Pharmacokinetic, Primary Safety Key Secondary Safety, Clinical Events**.

Note:

- The latest BIMO TCG (e.g. Version 3.0, 11th August 2022) **mentions** key secondary efficacy endpoints from the **Secondary efficacy endpoints**.

3 Format for the **Endpoint or Clinical Events Description** column: freeform text. For Endpoints the preferred values should be a text that is good representation of the endpoint defined in the study protocol and the same text is recommended to be consistent with the corresponding Part II listing 8/8a column label and value in the 'endpoint' variable **if used in the** Part III Summary-level Clinical Site Dataset.

4 Format for the **Criterion** column: freeform text. The preferred values are <Criteria having dataset and variable reference used for defining columns displayed in the listings 8/8a>. Refer to the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) and our PHUSE BDRG 3 examples for further guidance.

5 Format for the **Listing No.** column: freeform number. The preferred value is the **8/8.1/8.2 etc./8a** number representing the listing no. in the Part II deliverable for the major (i.e. pivotal) studies.

Important Note:

- Row entries common for major (i.e. pivotal) studies can be separated by a comma (along with 'and') when the listing entry applies to more than 1 study but not to ALL studies.
- If the endpoints (Primary/Key Secondary Endpoints and corresponding clinical events) are not collected/not applicable/not provided, then
 - Update BDRG Section 4.2 Name can be modified/updated accordingly.
 - BDRG Section 4.2 Section text "The following table provides information about Primary, Key Secondary Endpoints in Part II Listing 8 and corresponding endpoints collected as clinical events in Part II Listing 8a for each of the major (i.e. pivotal) studies" can be modified/updated accordingly.
 - Update BDRG Section 4.2 Table Header Names can be modified/updated accordingly.

Refer to our PHUSE BDRG example No.1 to 3, for our recommended update.

4.3 Safety Monitoring and Clinical Events

The Safety Monitoring and Clinical Events section provides information about safety monitoring in the Part II Listing 10 and corresponding endpoints collected as clinical events in Part II Listing 10a for each of the major (i.e. pivotal) studies.

From the BDRG Template:

The following table provides information about safety monitoring in the Part II Listing 10 and corresponding endpoints collected as clinical events in Part II Listing 10a for each of the major (i.e. pivotal) studies.

1	2	3	4
Study Identifier	Safety Monitoring / Clinical Events	Criterion	Listing No.
<Refer to Details Below>	<Refer to Details Below>	<Refer to Details Below>	<Refer to Details Below>

Details:

- Format for the **Study Identifier** column: DM.STUDYID (values in ascending order to reference details specific to a major (i.e. pivotal) study OR ALL to reference details which are the same for all of the major (i.e. pivotal) studies).

Note:

- Multiple DM.STUDYID can be provided separated by a comma (along with 'and') when the entry applies to more than 1 major (i.e. pivotal) study but not to ALL studies.

- Format for the **Safety Monitoring or Clinical Events** column: freeform text. The preferred values are **Labs, Vital Signs, ECG, Immunogenicity, etc.**, as defined in the protocol OR **Clinical Events**.

- Format for the **Criterion** column: freeform text. The preferred values are Criteria having dataset and variable reference used for defining columns displayed in the listing 10/10a. Refer to the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) and our PHUSE BDRG 3 examples for further guidance.

- Format for the **Listing No.** column: freeform number. The preferred value is the **10/10.1/10.2, etc./10a** number representing the listing no. in the Part II deliverable for the major (i.e. pivotal) studies.

Important Note:

- Row entries common for major (i.e. pivotal) studies can be separated by a comma (along with 'and') when the listing entry applies to more than 1 study but not to ALL studies.
- BDRG Section 4.3 title text "and corresponding endpoints collected as clinical events in Part II Listing 10a" can be removed if the endpoints are not collected/not applicable/not provided as clinical events which is mentioned also in BDRG Section 4.1, Refer to our PHUSE BDRG example No.1
- If the Safety Monitoring/endpoints (results of tests e.g., **Labs, Vital Signs, ECG, Immunogenicity, etc....** performed for safety monitoring/Endpoints and corresponding clinical events) are not collected/not applicable/not provided, then
 - Update BDRG Section 4.3 Name accordingly can be modified/updated accordingly.
 - BDRG Section 4.3 Section text "The following table provides information about safety monitoring in Part II Listing 10 and corresponding endpoints collected as clinical events in Part II Listing 10a for each of the major (i.e. pivotal) studies." can be modified/updated accordingly,
 - Update BDRG Section 4.3 Table Header Names can be modified/updated accordingly.

Refer to our PHUSE BDRG example No.1 to 3, for our recommended update.

5. Part III – Summary-level Clinical Site Dataset

The Part III - Summary-level Clinical Site Dataset section provides supporting information for the BIMO clinical data (and 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.

5.1 Treatment Variables

This section provides information specific to the comparison of the values of SDTM and ADaM treatment variables and the use of planned and actual treatment variables in the CSR and BIMO analysis. The following questions must be answered. Additional information response may be added beneath these required questions as needed.

From the BDRG Template:

For: <Study Identifier> <<Use DM.STUDYID for each of the major (i.e. pivotal) studies, separated by a comma (along with 'and') >> OR ALL to reference section information which is the same for all of the major (i.e. pivotal) studies.

Use of ADaM Treatment Variables in the CSR Analysis

ARM versus TRTxxP

<<The purpose of this section is to describe/contrast values of ARM vs. TRTxxP. Also, this section should be identical to section **3.2 Treatment Variables** of the ADRG of the respective major (i.e. pivotal) study.>>

- Are the values of ARM equivalent in meaning to the values of TRTxxP?
If yes, state this here.
If no, explain the relationship in text or tabular form.

Table Example:

ARM	Treatment Assignment
TRT01P	ACME Drug 20 mg or Placebo 20 mg
TRT02P	ACME Drug 20 mg

ACTARM versus TRTxxA

<<The purpose of this section is to describe/contrast values of ACTARM vs. TRTxxA. Also, this section should be identical to section **3.2 Treatment Variables** of the ADRG of the respective major (i.e. pivotal) study.>>

- If TRTxxA is used, then are the values of ACTARM equivalent in meaning to the values of TRTxxA?
If yes, state this here.
If no, explain the relationship in text or tabular form.
If TRTxxA was not used, then state this here.

Table Example:

ACTARM	Treatment Assignment
TRT01A	ACME Drug 20 mg or Placebo 20 mg
TRT02A	ACME Drug 20 mg

Are both planned and actual treatment variables used in the analysis?

<<The purpose of this section is to describe the use of planned and actual treatment variables in the **CSR analysis**. Also, this section should be identical to section **3.2 Treatment Variables** of the ADRG of the respective major (i.e. pivotal) study.>>

- If no, state this here.
If yes, explain at a higher level (e.g. across safety, efficacy) planned versus actual treatment for each type of analysis.

Use of ADaM Treatment Variables in the BIMO analysis dataset (clinsite)

<<The purpose of this section is to describe the use of planned and actual treatment variables in the **BIMO analysis**.>>

Are both planned and actual treatment variables used in the BIMO analysis?

- If yes, state this here.
If no, explain the relationship in text or tabular form.

Important Note:

Consideration in this section of the BDRG Template:

- The questions in this section of the BDRG Template must be answered and not be deleted.
- Content of this section under the **CSR analysis** (except for the **BIMO analysis**) should be identical to section **3.2 Treatment Variables** of the ADRG of the respective major (i.e. pivotal) study.
- Refer to our PHUSE BDRG 3 examples for the scenarios that can be utilized.
- If Response are major (i.e. pivotal) study specific and not common for all major (i.e. pivotal) studies then prefix response as "For: <Study Identifier> - <Response for specific major (i.e. pivotal) study>"

5.2 Primary, Key Secondary Endpoints Summary

From the BDRG Template:

The following table provides information about the endpoints summarized in the Part III clinsite dataset for each of the major (i.e. pivotal) studies.

1	2	3	4	5	6
Study Identifier	Endpoint Category	Endpoint Criterion	Censor Criterion	Endpoint Criterion	Censor Criterion
	Endpoint Type [ENDPTYPE]	[TRTEFFR1]	[CENSOR1]	[TRTEFFR2]	[CENSOR2]
	Endpoint Description [ENDPOINT]	Safety Population	Safety Population	Efficacy Population	Efficacy Population
<Add more rows if applicable>					

Details:

- 1 Format for the **Study Identifier** column: DM.STUDYID (values in ascending order to reference details specific to a major (i.e. pivotal) study OR ALL to reference details which are the same for all of the major (i.e. pivotal) studies).

Note:

- Multiple DM.STUDYID can be provided separated by a comma (along with 'and') when the entry applies to more than 1 major (i.e. pivotal) study but not to ALL studies.

- 2 Format for the column values are mentioned below.

Format for the **Endpoint Category** column: freeform text. The preferred values are Primary Efficacy, Primary Safety, Primary Pharmacokinetic, Key Secondary Efficacy, Key Secondary Safety, Key Secondary Pharmacokinetic, etc.

Important Note:

- As per the latest BIMO TCG (e.g. Version 3.0, 11th August 2022), for major (i.e. pivotal) studies, endpoints should be defined for only primary efficacy endpoints in the Part III clinsite dataset.
- Sponsors can also additionally provide information about Key Secondary Efficacy endpoints depending on key secondary efficacy endpoints that are critical to approval/support labelling of their application, which was discussed at their pre-NDA/BLA meeting to establish agreement.
- If the major (i.e. pivotal) studies do not have primary and key secondary efficacy endpoints, then the Primary Safety OR Primary Pharmacokinetic, Key Secondary Safety OR Key Secondary Pharmacokinetic, etc. endpoints, depending on the type of major (i.e. pivotal) study part of the application, can be included by the sponsor in the Part III clinsite dataset and in this BDRG Section 5.2 Table accordingly.
- Refer to our PHUSE BDRG 3 examples for the scenarios that can be utilized.

Format for the **Endpoint Type [ENDPTYPE]**: based on the variable [ENDPTYPE] value defined in the Part III clinsite dataset deliverable of the application. **The preferred values are “continuous”, “discrete”, “time to event” or “other”.**

Format for the **Endpoint Description [ENDPOINT]**: freeform text. Based on the variable [ENDPOINT] value defined in the Part III clinsite dataset deliverable of the application.

3 Format for the **Endpoint Criterion [TRTEFFR1]** column: freeform text. The preferred values are <Criteria having dataset and variable reference used for defining variable [TRTEFFR1 **based on Safety Population**] value defined in the Part III clinsite dataset deliverable of the application. Refer to the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) for further guidance>.

4 Format for the **Censor Criterion [CENSOR1]** column: freeform text. The preferred values are <Criteria having dataset and variable reference used for defining variable [CENSOR1 **based on Safety Population**] value defined in the Part III clinsite dataset deliverable of the application. Refer to the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) for further guidance>.

- Only applicable if the **Endpoint Type** is ‘time to event’ ELSE ‘Set to missing’.

5 Format for the **Endpoint Criterion [TRTEFFR2]** column: freeform text. The preferred values are <Criteria having dataset and variable reference used for defining variable [TRTEFFR2 **based on Efficacy Population**] value defined in the Part III clinsite dataset deliverable of the application. Refer to the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) for further guidance>.

6 Format for the **Censor Criterion [CENSOR2]** column: freeform text. The preferred values are <Criteria having dataset and variable reference used for defining variable [CENSOR2 **based on Efficacy Population**] value defined in the Part III clinsite dataset deliverable of the application. Refer to the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) for further guidance>.

- Only applicable if the **Endpoint Type** is ‘time to event’ ELSE ‘Set to missing’.

Important Note:

- Endpoint information added in this table should align with endpoint information in the Part III clinsite dataset.
- If the sponsor has adequate presentation of the endpoint information in the Part III clinsite Define-XML, then in the BDRG Section 5.2 Table only columns 1 and 2 should be filled and columns 3, 4, 5 and 6 can be kept optional and entered values as “Refer to Part III clinsite dataset Define-XML file”.
- Any sponsor-specific non-standard acronyms used here can be mentioned in this BDRG Section 1.2.

5.3 Clinical Site Dataset Supporting Information

From the BDRG Template:

The following table provides supporting information about Part III – Summary-level Clinical Site Dataset for each of the major (i.e. pivotal) studies.

Study Identifier	Variable Name [Variable Label] / General	Description
<Add more rows if applicable>		

Details:

- Format for the **Study Identifier** column: DM.STUDYID (values in ascending order to reference details specific to a major (i.e. pivotal) study OR ALL to reference details which are the same for all of the major (i.e. pivotal) studies).

Note:

- Multiple DM.STUDYID can be provided separated by a comma (along with 'and') when the entry applies to more than 1 major (i.e. pivotal) study but not to ALL studies.

- Format for the column values are mentioned below.

Format for the **Variable Name [Variable Label]/General** column: freeform text. The preferred values are Variable Name [Variable Label] of the Part III – Summary-level Clinical Site Dataset when the entry is for a particular variable OR there is general information entry, etc. that will be helpful for FDA reviewers before/while reviewing summary-level clinical site dataset and a supporting Define-XML.

Important Note:

- Recommended to **provide in brief only key supporting information** about Part III – Summary-level Clinical Site Dataset or its variable that will be helpful for FDA reviewers before/while reviewing summary-level clinical site dataset and a supporting Define-XML.
- The key purpose of this section is not to duplicate any information that is already present in **(Part III – Summary-level clinical site dataset Define-XML document OR in the other sections of the final BDRG document part of the BIMO deliverables)**, but to aid FDA reviewers before/while reviewing summary-level clinical site dataset and a supporting Define-XML.

5.4 Conformance Inputs

The information below describes the validation inputs used to evaluate conformance for the clinsite dataset (clinsite.xpt) and its define.xml for each of the major (i.e. pivotal) studies.

Specify the software name and version used to evaluate conformance on the clinical site dataset (clinsite.xpt).

(Text here) <Choose one from: SAS <Version no.>/Pinnacle 21 <Version no.>/Manual review/<Others specify>

Specify the version of the validation guidance used (i.e. CDISC, the FDA BIMO TCG, with version and date) for the clinical site dataset (clinsite.xpt).

(Text here) <Example: FDA BIMO Technical Conformance Guidance Version 3.0, 11th August 2022>

Specify the software name and version used to evaluate conformance on the clinical site dataset (define.xml).

(Text here) <Choose one from: SAS <Version no.>/Pinnacle 21 <Version no.>/Manual review/<Others specify>

Specify the version of the validation guidance used (i.e. CDISC, the FDA BIMO TCG, with version and date) for the clinical site dataset (define.xml).

(Text here) <Example: FDA BIMO Technical Conformance Guidance Version 3.0, 11th August 2022>

Consideration in this section of the BDRG Template:

- Manual review: refers to conformance checks that are performed without using software/tools/programming/automation but through a manual method by comparing the sponsor's prepared clinical site dataset and Define-XML **versus** the FDA BIMO Technical Conformance Guidance document [Preferred would be latest BIMO TCG (e.g. Version 3.0, 11th August 2022)] used for the BIMO submission.

5.5 Conformance Issues Summary

The following table provides summary from the validation input and checks used to evaluate conformance for the clinsite dataset (clinsite.xpt) and its define.xml for each of the major (i.e. pivotal) studies.

Example Issues Summary Table:

1 Study Identifier	2 Dataset	3 Issue (Data and/or define.xml)	4 Diagnostic Message	5 Explanation
1234-0001	clinsite	Data	Provide Standard text as per the tool mentioned in BDRG Section 5.4 OR <freeform text> as per the manual review mentioned in BDRG Section 5.4	<Freeform text> Provide Explanation to support the information in the diagnostic message column
1234-0001	clinsite	define.xml	Provide Standard text as per the tool mentioned in BDRG Section 5.4 OR	<Freeform text>

1 Study Identifier	2 Dataset	Issue 3 (Data and/or define.xml)	4 Diagnostic Message	5 Explanation
			<freeform text> as per the manual review mentioned in BDRG Section 5.4	Provide Explanation to support the information in the diagnostic message column
1234-0002	clinsite	Data and define.xml	No issues were observed	N/A

Details:

1 Format for the **Study Identifier** column: DM.STUDYID (values in ascending order).

2 Format for the **Dataset** column: freeform text. [The expected value is clinsite].

3 Format for the **Issue (Data and/or define.xml)** column: freeform text. [The expected value is Data OR define.xml OR Data and define.xml].

4 Format for the **Diagnostic Message** column: freeform text. [Provide Standard text as per the tool mentioned in BDRG Section 5.4 OR <freeform text> as per the manual review mentioned in BDRG Section 5.4 OR no issues were observed.]

5 Format for the **Explanation** column: freeform text [Provide Explanation to support the information in the **diagnostic message column**].

Consideration in this section of the BDRG Template:

- Sponsors can provide their manual review findings if no conformance tool/software was used.
- Conformance checking on the Part III clinsite dataset is not mandatory as of now. Currently, there are no validation rules and hence this would not lead to a rejection from the FDA.
- It is highly recommended to refer and align with the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) (which serves as validation guidance).
- If sponsors deviate from the latest BIMO TCG (e.g. Version 3.0, 11th August 2022), this section is an option to raise any deviation to the FDA reviewer.

6. External Datasets and Sources

The External Datasets and Sources table provides a list of all external datasets sources <Example: Screen Failure, Minor Protocol Deviations, Principal Clinical Investigator (Including Prior Principal Clinical Investigator(s)) and Site Contact Information, Financial Disclosure Amount Information> that are used as input for BIMO clinical data applications and not collected on CRF/SDTM/ADaM standard datasets.

From the BDRG Template:

The following table lists all external datasets sources that are used as input for BIMO clinical data for each of the major (i.e. pivotal) studies.

1	2	3	4
External Datasets	Description	Source	Comments
Screen Failure File	Consented screen failure subject information file	<Sponsor/CRO system – used to capture this information>	Not collected on the CRF
Minor Protocol Deviations	Non-important Protocol Deviations	<Sponsor/CRO system – used to capture this information>	Not collected on the CRF
Financial Disclosure Amount	Financial disclosure amount (US\$) by site containing disclosures for the clinical investigator and all sub-investigators	BIMO Module 1: FD Tracker	Not collected on the CRF
Principal Clinical Investigator and Site Contact Information	Investigator Last Name Investigator First Name Investigator Middle Initial Investigator Phone Number Investigator Fax Number Investigator Email Address Country State City Postal Code Street Address Street Address Continued	<Sponsor/CRO system – used to capture this information>	Not collected on the CRF
Subject Site transfer information	Subject Site transfer information	<Sponsor/CRO system – used to capture this information>	Not collected on the CRF
<Add more rows if applicable>			

Details:

- Format for the **External Datasets** column: freeform text. The preferred values are **Screen Failure File, Minor Protocol Deviations, Financial Disclosure Amount, Principal Clinical Investigator (Including Prior Principal Clinical Investigator(s)) and Site Contact Information and Subject Site transfer information etc.**

- 2 Format for the **Description** column: freeform text (describing information in the **External Datasets Sources** column in this BDRG Section 6).
- 3 Format for the **Source** column: freeform text. The preferred values are **<Sponsor/CRO system used to capture this information>**, **BIMO Module 1: FD Tracker**, etc.
- 4 Format for the **Comments** column: freeform number. The preferred values are **"Not collected on the CRF"** OR any additional information added by the sponsor.

Consideration in this section of the BDRG Template:

- If the table row content needs to be major (i.e. pivotal) study-specific, then the Comments column can have values to make these row entries study-specific where applicable, For Example comments column with this scenario will have value as : **"For: <Study Identifier> - <Provide Comments for specific major (i.e. pivotal) study>"**. Refer to our PHUSE BDRG example No.1 to 3, for our recommended update.
- The terms Minor Protocol and Non-important Protocol Deviations are used interchangeably.
- The terms Major Protocol and Important Protocol Deviations are used interchangeably.
- Note:** For BIMO request Part I (Item A) – Investigator Name, Current Principal Clinical Investigator (Including Prior Principal Clinical Investigator(s)) Names are required whereas for BIMO request Part III Only Current Principal Clinical Investigator Name are only required, so it is recommended to have External Datasets to collect Names for Current Principal Clinical Investigator (Including Prior Principal Clinical Investigator(s)).

7. Site-specific Matters

7.1 Site Concerns

From the BDRG Template:

The following table provides site information related to site concerns and additional information for sites that may/may not be present in the 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.

Example Site Concerns Table:

Study Identifier	Site # with Concerns (If any)*	Comments
1	<Grouped by Country Code>	
1234-0001	CAN: 001 – Site terminated due to compliance issue 002 – Site terminated due to compliance issue	< Freeform text>
1234-0002	N/A	N/A

Note: *Only sites with site concerns are listed.

Details:

1 Format for the **Study Identifier** column: DM. STUDYID (unique values in ascending order).

2 Format for the **Site # with Concerns (If any)*** column: freeform text. The preferred values are

<Grouped by Country Code>

<Site #>- <Site Concerns>

- The Country Code is the three-letter from Geopolitical Entities, Names and Codes (GENC) code list [For webpage link refer to Useful FDA Resources: list in this BDRG Completion Guidelines document] for the country in which the site is located.

3 Format for the **Comments** column: freeform text. [Example for site-related additional information: if a study does not have any site concerns, then column 2 and 3's preferred value is N/A which implies Not Applicable.]

Important Note:

- For site good clinical practice compliance concerns, submission of related CAPA is not requested; however, applicants should be aware that additional information related to site non-compliance may be requested and/or reviewed during FDA inspections when considered necessary.

7.2 Subjects Transferred Between Sites

From the BDRG Template:

The following table provides information related only to subjects that transferred between sites. This information is used in the 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.

1	2	3	4	5	6	7
Study Identifier	Subject Identifier	Enrolled Site #	Switch Site #	Switch Date <DDMMYYYY>	Reason for Transfer	Comments
<Refer to Details Below>	<Refer to Details Below>	<Refer to Details Below>	<Refer to Details Below>	<Refer to Details Below>	<Refer to Details Below>	<Refer to Details Below>

Note: For BIMO requests Part I (Item A), II and III, sponsors should consider these subjects under their <enrolled/switched> site.

Details:

1 Format for the **Study Identifier** column: DM.STUDYID (values in ascending order).

- 2 Format for the **Subject Identifier** column: DM.USUBJID (only subjects that transferred between sites).
- 3 Format for the **Enrolled Site #** column: freeform text. **The preferred value is the value of the Enrolled Site #/ID.**
- 4 Format for the **Switch Site #** column: freeform text. **The preferred value is the value of the Switch Site #/ID.**
- 5 Format for the **Switch Date** column: DDMMYYYY.
- 6 Format for the **Reason for Transfer** column: freeform text.
- 7 Format for the **Comments** column: freeform text. **If a study does not have any subjects switch between sites, then the preferred value is 'No Subjects transferred between sites'.**

Consideration in this section of the BDRG Template:

- As per the Table Note: For BIMO Requests Part I (Item A), II and III, if the sponsor has considered these subjects under their <enrolled/switched> site, the sponsor should handle the reporting of such switched subjects consistently and choose one of the approaches in the Table Note, i.e. either enrolled OR switched, as mentioned in the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) for further guidance>.
- When a subject transfer multiple sites and the sponsor has considered these subjects under their switched site, then the sponsor should handle the reporting of such switched subjects switch information consistently under their last switched site.

7.3 Identical Site ID Used in Multiple Studies

This section provides information about sites that appear in multiple major (i.e. pivotal) studies.

From the BDRG Template:

1	2	3
Site #	Study Identifiers	Comments
<Refer to Details Below>	<Refer to Details Below>	<Refer to Details Below>

Details:

- 1 Format for the **Site #** column: DM.SITEID. The **preferred value is sites that appear in multiple major (i.e. pivotal) studies(values in ascending order).**

2 Format for the **Study Identifier** column: DM.STUDYID (values in ascending order) The preferred value is the list of Study Identifiers for each of the major (i.e. pivotal) studies for the identical sites mentioned in the column 1

3 Format for the **Comments** column: freeform text.

Consideration in this section of the BDRG Template:

- Sponsors can make use of this section to inform the FDA if a clinical site is used in more than one major (i.e. pivotal) study.
- Refer to our PHUSE BDRG 3 examples for the scenarios that can be utilized.

8. Site Summary

The following table 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 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.

Example Site Summary Table:

Study Identifier 1	Site Summary 2	Comments 3
1234-0001	For BIMO Requests Part I (Item A), II and III, there are N sites ([n1] sites that have enrolled at least 1 subject and [n2] sites that have only screen failure subjects).	<Freeform text>
<Add more rows if applicable>		

Details:

1 Format for the **Study Identifier** column: DM.STUDYID (values in ascending order).

2 Format for the **Site Summary** column: freeform text. (Please follow the same format as per the template.)

Example: For each of the major (i.e. pivotal) studies: <For BIMO Requests Part I (Item A), II and III, there are N sites (<n1> sites that enrolled at least 1 subject and <n2> sites that have only screen failure subjects).

Important Note:

- Total number of sites that have screened at least 1 subject with a signed informed consent (N) = n1 (sites that have enrolled at least 1 subject with a signed informed consent) + n2 (sites that have only screen failed subjects with a signed informed consent).
- n1: sites that have enrolled at least 1 subject with a signed informed consent. These sites may have either of the combination of signed informed consent subjects, i.e. screen failed and enrolled subjects OR enrolled subjects only.
- n2: sites that have only screen failed subjects with a signed informed consent. These sites will only have screen failed subjects with a signed informed consent.

3 Format for the **Comments** column: freeform text (any comment related to the Site Summary mentioned in the column 2).

9. eCTD Folder Structure Skeleton for BIMO Items in MODULE 5

The eCTD Folder Structure skeleton provides a view of BIMO clinical data deliverable items submitted in MODULE 5 (along with file naming conventions followed by sponsors) for each of the major (i.e. pivotal) studies.

From the BDRG Template:

MODULE 5 – CLINICAL STUDY REPORTS

5.3.5 Reports of Efficacy and Safety Studies (Indication)

5.3.5.4 Other Study Reports

- **BIMO**
 - For each of the major (i.e. pivotal) studies: unique study identifiers from DM.STUDYID in ascending order separated by a comma
 - Part I (Item A) – List of All Clinical Sites
[<Study #> Listing All Clinical Sites.pdf]
 - Part I (Item B) – Entities Contact Information and Trial-related Files Location
[<Study #> Contracted Clinical Study-related Activities.pdf]
 - Part I (Item C1) – Protocol and Amendments
[<Study #> Protocol and Amendments.pdf]
 - Part I (Item C2) – Annotated Case Report Form (aCRF)
[<Study #> Sample Annotated CRF.pdf]
 - Part II – Subject-level Data Line Listings by Clinical Site
[<Study #> Data Line Listings by Clinical Site.pdf]
 - Site-Level Part III – For all major (i.e. pivotal) studies combined
 - Summary-level Clinical Site Dataset [clinsite.xpt]
 - Data definition file [define.xml] and Stylesheet [Stylesheet filename with file extension]
 - BIMO Data Reviewer's Guide [bdrg.pdf]

Consideration in this section of the BDRG Template:

- The skeleton and file naming convention are as per the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) recommendation.
- The sponsor file naming convention is recommended to be aligned with the latest BIMO TCG (e.g. Version 3.0, 11th August 2022) recommendation.

- Sponsors should provide the file naming convention followed for each of the BIMO items in order for FDA reviewers to easily access deliverables. (Important Note: As we are not applying external hyperlinks in the final BDRG document to the deliverables, it is important we provide the correct file naming convention followed in section 9 of this BDRG)
- In case of variability of deliverable items and/or file naming conventions between major (i.e. pivotal) studies, then, in this section 9 of this BDRG skeleton portion **5.3.5.4 Other Study Reports** -> **BIMO**-, next to the BIMO items, mention the study identifier, Refer to our PHUSE BDRG example No.3.
- In case of no variability of deliverable items and/or file naming conventions between major (i.e. pivotal) studies, then skeleton portion **5.3.5.4 Other Study Reports** -> **BIMO**-> should be the same as provided in the BDRG Template, Refer to our PHUSE BDRG example No.1 and 2.
- For certain major (i.e. pivotal) studies, to cross-reference previous submissions, the content mentioned below can be added at the end of section 9 and no external hyperlink needs to be applied. For example:
 - Refer BLA # 001010 submitted to the FDA
 - Date of BLA submission: 10 April, 2020
 - eCTD folder location: <Provide the BLA eCTD folder location by the regulatory submission team of the sponsor/applicant>
- For the Summary-level Clinical Site Dataset Definition File (define.xml) , associated Stylesheet **filename with extension [Stylesheet filename with file extension ~~define2-0-0.xml~~]** should be mentioned here, It is highly recommended to use latest **Stylesheet version that would align with associated** Summary-level Clinical Site Dataset Definition File (define.xml).

10. Appendix

Provide supplemental information in the Appendix. (For example: to support BIMO applications, sponsors can add an inclusion/exclusion criteria list, protocol deviations, i.e. important vs non-important classification and a criteria list (that relates to Part II – Subject-level Data Line Listings by Clinical Site AND Part III Summary-level Clinical Site Dataset).

Bioresearch Monitoring Data Reviewer's Guide (BDRG) Finalization Instructions

This section describes how to format the document for submission after completing the BDRG Template.

1. Page orientation

Page orientation can vary from page to page, as needed, for the most appropriate viewing and printing within a submission. Appropriate page orientation eliminates the need for reviewers to rotate pages or for monitors to read content. For example, setting page orientation of a wide table to **landscape** prior to saving into a document format such as PDF or printing can ensure that all columns fit onto one wide page and that the page is displayed in a top-to-bottom orientation that does not require rotating to read on a monitor. Sponsors can choose **landscape page orientation to accommodate tables which have detailed information**.

2. Applying hyperlinks

Only internal hyperlinks within the final BDRG document are needed and there are no external hyperlinks required in this document.

Select the text that needs an internal hyperlink -> Right click the selected text and choose "Hyperlink" from the menu -> In the left panel of the Hyperlink window, make sure that "Place in this document" is selected.

-> Then, in the right-hand side list of "Place in this document", select the place you need to move and click OK. Ctrl+click the internal hyperlink to test it.

3. Do not remove unused sections from the document

For consistency, it is best to leave unused/not applicable sections in the document and indicate as N/A.

4. Update the table of contents, document header and version date

Edit the left-hand side of the header on Page 2 with the sponsor's name and once the update is done, the rest of the pages will have their left-hand side of the header page updated accordingly.

After all edits have been completed and the BDRG document is final, update the table of contents at the top of the document. Right click on any line in the table and select "Update Field". In the dialog window, select "Update entire table", then click OK.

5. Convert the document to PDF format

These instructions are for Microsoft Word 2003 or newer, using either the Adobe Acrobat plug-in or the MS Office PDF creation feature.

5.1 Using the Adobe Acrobat plug-in for Microsoft Office:

Click the Acrobat tab in the Word menu at the top of the screen. Select "Create PDF". If a dialog window pops up asking you to save and continue, click Yes. In the second dialog window, navigate to the directory in which you want to save the PDF, name the file "bdrg.pdf" and click Save.

5.2 Conversion without the Adobe Acrobat plug-in:

Click the Office button at the top left of your screen. Select "Save As" then "PDF or XPS". Navigate to the directory in which you want to save the PDF, name the file "bdrg.pdf" and click Save.

5.3 Formatting and verifying the PDF

Open the PDF. If bookmarks are not showing, go to the View menu and select "Navigation Panels", then "Bookmarks". If lower-level bookmarks are showing, click on the "Bookmarks Options" icon and select "Collapse Top-Level Bookmarks".

Go to the File menu and select "Properties". Navigate to the Initial View tab. In the drop-down menu for the Navigation tab, select "Bookmarks Panel and Page". In the drop-down menus for both Page Layout and Magnification, select "Default".

Next, navigate to the Description tab and delete the information in the Title, Author, Subject and Keywords boxes. Click OK and then save the file.