

Bioresearch Monitoring (BIMO) Data Reviewer's Guide

Sample Drug Company, Inc.

Example_Project1

BLA: 00001

List of Studies Included in the BIMO Clinical Data
Application:

Study1 <123456>

Table of Contents	Page No.
1. Introduction	3
1.1 Purpose	3
1.2 Acronyms.....	3
1.3 BIMO Guidance and Supporting Information	4
1.4 Study-related Metadata	4
2. Study Description.....	5
2.1 List of Studies for which BIMO Clinical Data are Submitted.....	5
3. Part I – Request for Clinical Study-level Information.....	6
3.1 Part I (Item A) – List of All Clinical Sites	6
3.2 Part I (Item B) – Entities Contact Information and Trial-related Files Location	6
3.3 Part I (Item C1) – Protocol and Amendments	7
3.4 Part I (Item C2) – Annotated Case Report Form (aCRF)	7
4. Part II – Subject-level Data Line Listings by Clinical Site	8
4.1 Subject-level Listings	8
4.2 Primary and Key Secondary Endpoints	9
4.3 Safety Monitoring	9
5. Part III – Summary-level Clinical Site Dataset.....	11
5.1 Treatment Variables.....	11
5.2 Primary and Key Secondary Endpoints Summary	12
5.3 Clinical Site Dataset Supporting Information	13
5.4 Conformance Inputs.....	14
5.5 Conformance Issues Summary	14
6. External Datasets and Sources	16
7. Site-specific Matters	17
7.1 Site Concerns	17
7.2 Subjects Transferred Between Sites.....	17
7.3 Identical Site ID Used in Multiple Studies	17
8. Site Summary.....	18
9. eCTD Folder Structure Skeleton for BIMO Items in MODULE 5	19
10. Appendix.....	20

1. Introduction

1.1 Purpose

The purpose of the BIMO Data Reviewer's Guide (BDRG) is to provide an overview of sponsor considerations for preparing and submitting 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) to support safety and efficacy in the applications 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 Biologics license application (BLA) containing clinical data.

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

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

Covered in sections 1–10 within this document.

- **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

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

1.3 BIMO Guidance and Supporting Information

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

1.4 Study-related Metadata

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
123456	123456	NCT00808067	10MAY2021	01JUL2021	Study Completed	N/A

2. Study Description

2.1 List of Studies for which BIMO Clinical Data are Submitted

Study Identifier	Study Title	Study Phase	Comments
123456	A Phase III, multicenter, open-label, randomized study to investigate the efficacy and safety of TEST DRUG1 compared with TEST DRUG2 following chemotherapy in patients with STAGE II-III Lung cancer	PHASE III TRIAL	Agreed to be included in the pre-submission meeting with FDA

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

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

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	Current Principal Clinical Investigator Name (Prior Principal Clinical Investigator(s))	Site Address at Time of Clinical Study	Site Contact Information at Time of Clinical Study
SITEID	LASTNAME, FRSTNAME, INITIAL	FACILITY NAME STREET CITY, STATE, POSTAL COUNTRY	PHONE FAX EMAIL
*Site terminated, or clinical investigator changed at the request of the sponsor before study completion.			

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

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

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

3.3 Part I (Item C1) – Protocol and Amendments

Study Identifier	List All Protocol/ Local Amendment Version Numbers	If Local Amendment (List Country)	Date Effective	Location Reference (Items Included In)
123456	Version 2 (FINAL)	N/A	12DEC2008	Appendix 16 of CSR
	Amendment 1	France	05SEP2008	Not submitted [available on request]
	Version 1	N/A	28JUN2008	Appendix 16 of CSR

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

Study Identifier	Annotated Case Report Form (aCRF)	Location Reference
123456	Final aCRF	It is located in the datasets folder (tabulations\sdtm) of the study

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

4.1 Subject-level Listings

The following requested listings are presented using Option A: By Study, By Site and By Listing.

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	
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	Not Provided: No potential efficacy endpoints were 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	Not provided: No additional adjudication beyond the standard study data verification by clinical monitors

Additional information for listings 1 to 10a:

- Splitting logic: N/A

4.2 Primary and Key Secondary Endpoints

The following table provides information about Primary and Key Secondary Endpoints in Part II Listing 8 for each of the major (i.e. pivotal) studies.

Study Identifier	Endpoint Category	Endpoint Description	Criterion	Listing No.
123456	Primary Efficacy	Progression Free Survival (PFS)	PFS Censor: ADTTE.CNSR (where ADTTE.PARAMCD='PFS') PFS Description: ADTTE.EVNTDESC (where ADTTE.PARAMCD='PFS') PFS Duration (in months): ADTTE.AVAL (where ADTTE.PARAMCD='PFS') converted to months	8
123456	Key Secondary Efficacy	Overall survival (OS)	OS Censor: ADTTE.CNSR (where ADTTE.PARAMCD='OS') OS Duration (in months): ADTTE.AVAL (where ADTTE.PARAMCD='OS') converted to months	8

4.3 Safety Monitoring

The following table provides information about safety monitoring in the Part II Listing 10 for each of the major (i.e. pivotal) studies.

Study Identifier	Safety Monitoring	Criterion	Listing No.
123456	Labs	Lab Test- ADLB. PARAM [all Lab test], Analysis Visit - ADLB.AVISIT, Result/ Standard Units ADLB.AVALC, ADLB.AVALU>	10.1
123456	Vital Signs	VS Test- ADVS. PARAM [all VS Test], Analysis Visit - ADVS.AVISIT, Result/ Standard Units ADVS.AVALC, ADVS. AVALU>	10.2

Study Identifier	Safety Monitoring	Criterion	Listing No.
123456	ECG	ECG Test- ADEG.PARAM (all ECG Test), Analysis Visit - ADEG.AVISIT, Result/ Standard Units ADEG.AVALC, ADEG.AVALU>	10.3

5. Part III – Summary-level Clinical Site Dataset

5.1 Treatment Variables

For: 123456

Use of ADaM Treatment Variables in the CSR Analysis

ARM versus TRTxxP

- Are the values of ARM equivalent in meaning to the values of TRTxxP?

Yes, ARM and TRT02P are equivalent since randomization occurred in the second treatment phase.

ACTARM versus TRTxxA

- If TRTxxA is used, then are the values of ACTARM equivalent in meaning to the values of TRTxxA?

Yes, ACTARM and TRT02A are equivalent.

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

Yes, planned treatment arm is used in efficacy analysis and summarized by (ITT population) while actual treatment arm is used in safety analysis and summarized by (safety population).

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

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

No, only planned treatment TRT02P arm is used for summarizing information within BIMO analysis dataset (clinsite) based on safety population and efficacy population only.

5.2 Primary and Key Secondary Endpoints Summary

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

Study Identifier	Endpoint Category Endpoint Type [ENDPTYPE] Endpoint Description [ENDPOINT]	Endpoint Criterion [TRTEFFR1] Safety Population	Censor Criterion [CENSOR1] Safety Population	Endpoint Criterion [TRTEFFR2] Efficacy Population	Censor Criterion [CENSOR2] Efficacy Population
123456	Endpoint Category Primary Efficacy Endpoint Type Time to event Endpoint Description Duration of Progression Free Survival	Count of the primary efficacy endpoint 1 at a given site for subjects in SAFPOP i.e. Count of (ADTTTE.PARAMC D='PFS' where ADTTE.CNSR=0 and ADSL.SAFFL='Y') per SITEID per ARM per ENDPOINT.	Count of the censored observations for primary efficacy endpoint 1 at a given site for subjects in SAFPOP i.e. Count of (ADTTTE.PARAMC D='DFS' where ADTTE.CNSR=1 and ADSL.SAFFL='Y') per SITEID per ARM per ENDPOINT.	Count of the primary efficacy endpoint 1 at a given site for subjects in EFFPOP i.e. Count of (ADTTTE.PARAMC D='PFS' where ADTTE.CNSR=0 and ADSL.ITTFL='Y') per SITEID per ARM per ENDPOINT.	Count of the censored observations for primary efficacy endpoint 1 at a given site for subjects in EFFPOP i.e. Count of (ADTTTE.PARAMC D='PFS' where ADTTE.CNSR=1 and ADSL.ITTFL='Y') per SITEID per ARM per ENDPOINT.

Study Identifier	Endpoint Category Endpoint Type [ENDPTYPE] Endpoint Description [ENDPOINT]	Endpoint Criterion [TRTEFFR1] Safety Population	Censor Criterion [CENSOR1] Safety Population	Endpoint Criterion [TRTEFFR2] Efficacy Population	Censor Criterion [CENSOR2] Efficacy Population
123456	Endpoint Category Key Secondary Efficacy Endpoint Type Time to event Endpoint Description Duration of Overall Survival	Count of the Key Secondary efficacy endpoint 2 at a given site for subjects in SAFPOP i.e. Count of (ADTTTE.PARAMC D='OS' where ADTTE.CNSR=0 and ADSL.SAFFL='Y') per SITEID per ARM per ENDPOINT.	Count of the Key censored observations for Secondary efficacy endpoint 2 at a given site for subjects in SAFPOP i.e. Count of (ADTTTE.PARAMC D='OS' where ADTTE.CNSR=1 and ADSL.SAFFL='Y') per SITEID per ARM per ENDPOINT.	Count of the Key Secondary efficacy endpoint 2 at a given site for subjects in EFFPOP i.e. Count of (ADTTTE.PARAMC D='OS' where ADTTE.CNSR=0 and ADSL.ITTFL='Y') per SITEID per ARM per ENDPOINT.	Count of the censored observations for Key Secondary efficacy endpoint 2 at a given site for subjects in EFFPOP i.e. Count of (ADTTTE.PARAMC D='OS' where ADTTE.CNSR=1 and ADSL.ITTFL='Y') per SITEID per ARM per ENDPOINT.

5.3 Clinical Site Dataset Supporting Information

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
123456	CENSOR1 [Censored Observations in SAFPOP] and CENSOR2 [Censored Observations in EFFPOP]	Study does not contain any time-to-event primary/key secondary endpoint, so these variables value will be missing in the clinical site dataset (clinsite.xpt) and mentioned in its 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).

SAS 9.2

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

FDA BIMO Technical Conformance Guidance Version 3.0, 11th August 2022

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

Manual review

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

FDA BIMO Technical Conformance Guidance Version 3.0, 11th August 2022

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.

Study Identifier	Dataset	Issue (Data and/or define.xml)	Diagnostic Message	Explanation
123456	clinsite	Data and define.xml	For Variable NOIMPDEV, Variable Label in the dataset should	As per the latest BIMO TCG (e.g. Version 3.0, 11th August 2022, the variable label length is 43 which is >=40 and not as per eSub data

Study Identifier	Dataset	Issue (Data and/or define.xml)	Diagnostic Message	Explanation
			match the variable label described in BIMO TCG.	requirement and hence we have modified the variable label and kept variable label length <=40 ('Number of Non-Important Protocol Dev')
123456	clinsite	Data and define.xml	Within the endpoint related variables (ENDPTYPE, ENDPOINT, TRTEFFR1, CENSOR1, TRTEFFR2, and CENSOR2), key secondary endpoint added in addition to the primary efficacy endpoint which deviates from the latest BIMO TCG (e.g. Version 3.0, 11th August 2022.	Sponsor has added key secondary endpoint to support the efficacy analysis of the study drug.

6. External Datasets and Sources

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

External Datasets Sources	Description	Source	Comments
Screen failure file	Consented screen failure subject information file	Sponsor system – used to capture this information	Not collected on the CRF
Minor Protocol Deviations	Non-important Protocol Deviations	Sponsor 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 system – used to capture this information	Not collected on the CRF
Subject Site Transfer Information	Subject Site Transfer Information	Sponsor system –used to capture this information	Not collected on the CRF

7. Site-specific Matters

7.1 Site Concerns

The following table provides site information related to site concerns and site additional information for the 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.

Study Identifier	Site # with Concerns (If any)* <Grouped by Country Code>	Comments
123456	USA: 100203 – site terminated due to compliance issue CAN: 100205 – site terminated due to compliance issue	N/A

Note: *Only sites with site concerns are listed.

7.2 Subjects Transferred Between Sites

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.

Study Identifier	Subject Identifier	Enrolled Site #	Switch Site #	Switch Date <DDMMYYYY>	Reason for Transfer	Comments
123456	123456-100103-1020	100102	100103	15DEC2019	Subject moved to a new location	N/A

Note: For BIMO Requests Part I (Item A), II and III, the sponsor has considered these subjects under their switched site.

7.3 Identical Site ID Used in Multiple Studies

Site #	Study Identifiers	Comments
N/A	N/A	N/A

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.

Study Identifier	Site Summary	Comments
123456	For BIMO Request Part I (Item A), II and III there are 100 sites ([80] sites that have enrolled at least 1 subject and [20] sites that have only screen failure subjects).	N/A

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

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 (123456)**
 - 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
[Appendix 16 of CSR]
 - Part I (Item C2) – Annotated Case Report Form (aCRF)
ALL: [It is located in the datasets folder (tabulations\sdtm) of the study]
 - 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 [define2-0-0.xsl]
 - BIMO Data Reviewer's Guide [bdrg.pdf]

10. Appendix

N/A