

Bioresearch Monitoring (BIMO) Data Reviewer's Guide

Sample Drug Company, Inc.

Example_Project2

NDA: 00002

List of Studies Included in the BIMO Clinical Data
Application:

Study1 <234566>

Study2 <234567>

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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 New Drug Applications (NDAs) 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

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
234566	234566	NCT00808067	01MAY2021	01JUN2021	Study Completed	No further recruitment of subjects
234567	234560	NCT00808091	15MAY2021	15JUN2021	On-going	Study Identifier and Protocol Number are different due to merger or acquisition

2. Study Description

2.1 List of Studies for which BIMO Clinical Data are Submitted

Study Identifier	Study Title	Study Phase	Comments
234566	A Phase II, multicenter, 8 week open-label, randomized study to investigate the efficacy and safety of TEST DRUG1 compared with TEST DRUG2 in patients with Mild to Moderate Hypertension	PHASE II TRIAL	N/A
234567	A Phase II, multicenter, 16 week open-label, randomized study to investigate the efficacy and safety of TEST DRUG1 compared with TEST DRUG2 in patients with Mild to Moderate Hypertension	PHASE II TRIAL	Agreement during pre-NDA meeting with CDER OND Review Division that study considered major (i.e. pivotal) study supporting efficacy and safety.

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, MINITIAL	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)
234566	Version 2 (FINAL)	N/A	12DEC2008	Included in the application (refer to section 9)
	Version 1	N/A	28JUN2008	Included in the application (refer to section 9)
234567	Version 2 (FINAL)	N/A	20DEC2008	Included in the application (refer to section 9)
	Version 1	N/A	01AUG2008	Included in the application (refer to section 9)

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

Study Identifier	Annotated Case Report Form (aCRF)	Location Reference
234566	Final aCRF	Included in the application (refer to section 9)
234567	Final aCRF	Included in the application (refer to section 9)

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 Enrolled Subjects	No Screen failed 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	8.1	Listing 8.1: Listing of Efficacy Endpoints (Primary)	Derived OR calculated endpoints are included
ALL	8.2	Listing 8.2: Listing of Efficacy Endpoints (Key Secondary)	Derived OR calculated endpoints are included
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	
234566	10a	Listing 10a: Listing of Safety Monitoring Collected as Clinical Events	Not provided: No additional adjudication beyond the standard study data verification by clinical monitors
234567	10a	Listing 10a: Listing of Safety Endpoints Collected as Clinical Events	
ALL	11	Listing 11: Listing of Blood Pressure Levels	Additional Listing
ALL	12	Listing 12: Listing of All Blood Pressure Measurement Device used	Additional Listing

Additional information for listings 1 to 12:

- Splitting logic: for each of the major (i.e. pivotal) studies, listings 1 to 12 are split into 3 Sub-parts (Part 1: from Site 100000 - 199999, Part 2: from site 200000 – 299999, Part 3: from site 300000 – 399999)
- Refer to section 9 for split files that are submitted in the application.

4.2 Primary, Key Secondary Endpoints and Clinical Events

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.

Study Identifier	Endpoint Category / Clinical Events	Endpoint / Clinical Events Description	Criterion	Listing No.
234566	Primary Efficacy	Change From Baseline at Week 8 in Mean Daytime Diastolic Blood Pressure (DBP) Measured by Ambulatory Blood Pressure Monitoring (ABPM)	Baseline Mean Daytime DBP Measured by Ambulatory Blood Pressure Monitoring (ABPM): ADBP.AVAL, ADBP.AVALU (where ADBP.PARAMCD='BMeanDBP') Week 8 Mean Daytime DBP Measured by Ambulatory Blood Pressure Monitoring (ABPM): ADBP.AVAL, ADBP.AVALU (where ADBP.PARAMCD=' W8AVGDBP')	8.1
234566	Key Secondary Efficacy	Change From Baseline at Week 8 in Mean Daytime Systolic Blood Pressure (SBP) Measured by Ambulatory Blood Pressure Monitoring (ABPM)	Baseline Mean Daytime SBP Measured by Ambulatory Blood Pressure Monitoring (ABPM): ADBP.AVAL, ADBP.AVALU (where ADBP.PARAMCD='B AVGSBP') Week 8 Mean Daytime SBP Measured by Ambulatory Blood Pressure Monitoring (ABPM): ADBP.AVAL, ADBP.AVALU (where ADBP.PARAMCD=' W8AVGSBP')	8.2
234566	Clinical Events	Efficacy Endpoints collected as Clinical Events	Clinical event date of event (ADCE.CESTDTC), adjudicated (ADCE.CEYN=Yes/No by adjudication committee), date of adjudication (ADCE.CEASTDTC) and the outcome of the adjudication process (ADCE.CEAOUT).	8a

Study Identifier	Endpoint Category / Clinical Events	Endpoint / Clinical Events Description	Criterion	Listing No.
234567	Primary Efficacy	Change From Baseline at Week 16 in Mean Daytime Diastolic Blood Pressure (DBP) Measured by Ambulatory Blood Pressure Monitoring (ABPM)	Baseline Mean Daytime DBP Measured by Ambulatory Blood Pressure Monitoring (ABPM): ADBP.AVAL, ADBP.AVALU (where ADBP.PARAMCD='BAVGDBP') Week 16 Mean Daytime DBP Measured by Ambulatory Blood Pressure Monitoring (ABPM): ADBP.AVAL, ADBP.AVALU (where ADBP.PARAMCD=' W16AVDBP')	8.1
234567	Key Secondary Efficacy	Change From Baseline at Week 16 in Mean Daytime Systolic Blood Pressure (SBP) Measured by Ambulatory Blood Pressure Monitoring (ABPM)	Baseline Mean Daytime SBP Measured by Ambulatory Blood Pressure Monitoring (ABPM): ADBP.AVAL, ADBP.AVALU (where ADBP.PARAMCD='BAVGSBP') Week 16 Mean Daytime SBP Measured by Ambulatory Blood Pressure Monitoring (ABPM): ADBP.AVAL, ADBP.AVALU (where ADBP.PARAMCD=' W16AVSBP')	8.2
234567	Clinical Events	Efficacy Endpoints collected as Clinical Events	Clinical event date of event (ADCE.CESTDTC), adjudicated (ADCE.CEYN=Yes/No by adjudication committee), date of adjudication (ADCE.CEASTDTC) and the outcome of the adjudication process (ADCE.CEAOUT).	8a

4.3 Safety Monitoring and Clinical Events

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.

Study Identifier	Safety Monitoring/ Clinical Events	Criterion	Listing No.
234566 and 234567	Labs	Lab Test- ADLB.PARAM [All Lab test], Analysis Visit -ADLB.AVISIT, Result/ Standard Units ADLB.AVALC, ADLB. AVALU>	10.1
234566 and 234567	Vital Signs	VS Test- ADVS.PARAM[All VS Test], Analysis Visit - ADVS.AVISIT, Result/ Standard Units ADVS.AVALC, ADVS. AVALU>	10.2
234566 and 234567	ECG	ECG Test- ADEG.PARAM(All ECG Test), Analysis Visit -ADEG.AVISIT, Result/ Standard Units ADEG.EGSTRESC, ADEG.EGSTRESU>	10.3
234567	Clinical Events	LVEF (Left Ventricular Ejection Fraction) Test- ADVC.PARAM, Analysis Visit- ADCV. AVISIT, Result/Grade ADVC. AVAL, ADCV. GRADE	10a

5. Part III – Summary-level Clinical Site Dataset

5.1 Treatment Variables

For: 234566 and 234567

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 TRT01P are equivalent.

ACTARM versus TRTxxA

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

Yes, ACTARM and TRT01A 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 TRT01P 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
234566	Endpoint Category Primary Efficacy Endpoint Type Continuous Endpoint Description Change From Baseline at Week 8 in Mean Daytime Diastolic Blood Pressure (DBP) Measured by Ambulatory Blood Pressure Monitoring (ABPM)	Refer to clinsite dataset define.xml file	Refer to clinsite dataset define.xml file	Refer to clinsite dataset define.xml file	Refer to clinsite dataset define.xml file
234566	Endpoint Category Key Secondary Efficacy Endpoint Type Continuous Endpoint Description Change From Baseline at Week 8 in Mean Daytime Systolic Blood Pressure (SBP) Measured by Ambulatory Blood Pressure Monitoring (ABPM)	Refer to clinsite dataset define.xml file	Refer to clinsite dataset define.xml file	Refer to clinsite dataset define.xml file	Refer to clinsite dataset define.xml file

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
234567	Endpoint Category Primary Efficacy Endpoint Type Continuous Endpoint Description Change From Baseline at Week 16 in Mean Daytime Diastolic Blood Pressure (DBP) Measured by Ambulatory Blood Pressure Monitoring (ABPM)	Refer to Clinsite dataset define.xml file	Refer to Clinsite dataset define.xml file	Refer to Clinsite dataset define.xml file	Refer to Clinsite dataset define.xml file
234567	Endpoint Category Key Secondary Efficacy Endpoint Type Continuous Endpoint Description Change From Baseline at Week 16 in Mean Daytime Systolic Blood Pressure (SBP) Measured by Ambulatory Blood Pressure Monitoring (ABPM)	Refer to Clinsite dataset define.xml file	Refer to Clinsite dataset define.xml file	Refer to Clinsite dataset define.xml file	Refer to Clinsite dataset define.xml file

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
234566 and 234567	N/A	Refer to clinsite dataset define.xml file

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 clinical site dataset (clinsite.xpt).

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 (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
234566 and 234567	Clinsite	Data and define.xml	For Variable NOIMPDEV, Variable Label in the dataset should match the variable label described in BIMO TCG.	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 requirement and hence we have modified the variable label and kept variable label length ≤ 40 ('Number of Non-Important Protocol Dev')
234566 and 234567	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 safety 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	There are no screen failed subjects for each of the major (i.e. pivotal) studies.
Minor Protocol Deviations	Non-Important Protocol Deviations	CRO system – used to capture this information	For: 234566 - Not collected on the CRF
Minor Protocol Deviations	Non-Important Protocol Deviations	Sponsor system – used to capture this information	For: 234567 - 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
234566	IND: 100304 – site terminated due to compliance issue CHN: 100305 – site terminated due to compliance issue	Compliance issues are documented and related CAPA have been put in place.
234567	N/A	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
234566	234566-200306-1020	200306	200367	20JAN2019	Subject transferred to new job location	N/A
234567	N/A	N/A	N/A	N/A	N/A	No Subjects transferred between sites

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

7.3 Identical Site ID Used in Multiple Studies

Site #	Study Identifiers	Comments
100315	234566 and 234567	For the same SITE, subjects are different between these 2 studies i.e. No roll over subjects between these 2 studies.

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
234566	For BIMO request Part I (item A), II and III there are 150 sites ([100] sites that have enrolled at least 1 subject and [50] sites that have only screen failure subjects).	N/A
234567	For BIMO request Part I (item A), II and III there are 120 sites ([90] sites that have enrolled at least 1 subject and [30] 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) study (234566 and 234567)**
 - 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-Version#<details>.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_split<1, 2 and 3>.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 [bdrbg.pdf]

10. Appendix

N/A