

Clinical Development Standards for FDA Bioresearch Monitoring (BIMO) Submissions

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ABSTRACT

The Food and Drug Administration (FDA) published the Bioresearch Monitoring Technical Conformance Guide in February 2018. The document provides specifications for clinical data submission by pharmaceutical companies used in planning of FDA Bioresearch Monitoring (BIMO) inspections. Three types of information are required: clinical study level information, subject level data line listings by clinical site, and a summary level clinical site dataset.

The clinical study level information are PDF files related to the clinical trial. The subject level data line listings by clinical site are typically generated as SAS ® programmed PDF files. The guide states that FDA will be able to generate the listings in the future from submitted clinical datasets compliant with CDISC SDTM and ADaM standards. The summary level clinical site dataset is provided as a SAS V5 transport file named clinsite.xpt with a data definition table named define.pdf. This paper describes the effort to standardize the generation of clinsite.xpt across different therapeutic areas of a pharmaceutical company. Topics include standardizing the SAS variable attributes via metadata, importing clinical site information from Excel to SAS, handling special characters in imported data, and developing standard SAS macros and programs that process data in different formats.

INTRODUCTION

Submission of clinical data to FDA in standard electronic format has been well established as part of the electronic submission (eSub) process of pharmaceutical companies and contract research organizations. The submission of data and listings for FDA planning of inspections has also been in practice; this was formerly known as “OSI submissions” referring to the FDA Office of Scientific Investigations. With the publication of the BIMO Technical Conformance Guide, and concurrently the planning of multiple drug and biologic FDA submissions, a Janssen R&D team was assembled to standardize the process and tools for BIMO submissions.

The BIMO project team was established with global cross functional membership from clinical development standards and statistical programming & analysis experts from multiple therapeutic areas. The BIMO project objective was defined as development of a standard process, standard metadata, and centralized standard tools, SAS programs, and macros to generate a Summary-Level Clinical Site Dataset (clinsite.xpt) and associated documentation (define.pdf) used by FDA for planning of Bioresearch Monitoring (BIMO) inspections.

The development and maintenance of the Janssen R&D BIMO process provides important benefits. First, the Janssen BIMO process provides a sole source of metadata, template, SAS macros/sample programs and documentation that can be utilized by all trial teams needing to provide clinsite.xpt and define.pdf to the FDA. It also ensures compliance in structure and content with FDA guidance. Lessons learned from each BIMO submission are captured in process documents for reference in subsequent submissions across all therapeutic areas.

BIMO DATA FLOW

The BIMO programming process begins with the inputs of study SDTM and ADaM SAS datasets. Some additional site data not included in the SDTM or ADaM datasets, including investigator contact information, is imported as a standard formatted Excel file from clinical trial management systems (CTMS). A statistician, as part of the clinical team planning the FDA submission, provides a data presentation specifications (DPS) document to the responsible statistical programmer. The DPS describes BIMO requirements from FDA discussions, including listings needed and the derivation algorithms for safety and efficacy variables programmed in the clinical site (clinsite) SAS dataset.

The statistical programmer integrates the study SDTM and ADaM SAS datasets and additional site information imported from Excel to create the clinsite dataset using a standard clinsite metadata file. The metadata file contains the variable attributes of the clinsite dataset. A set of standard SAS programs and macros process the input files into the clinsite.xpt SAS V5 transport file and the define.pdf data definition file. The files undergo a quality control (QC) process. After acceptance, the output files are sent to an electronic publishing output drive (EPOD) for FDA submission. Additional files sent to EPOD include any required listings and a reviewer's guide, if requested by FDA.

Figure 1 describes the BIMO data flow.

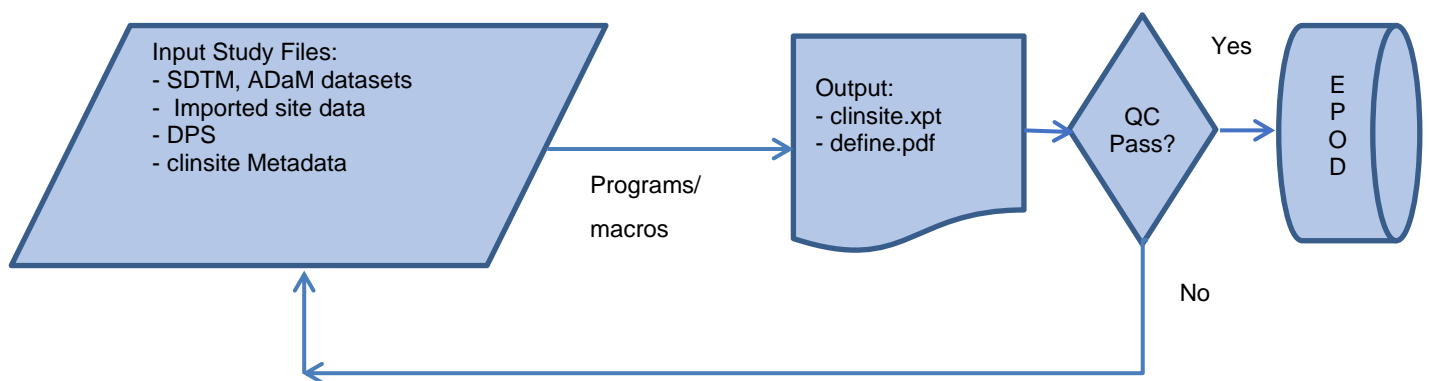


Figure 1. BIMO Data Flow

CLINSITE METADATA

Appendix 3 of the FDA BIMO technical conformance guide contains the clinical site data elements summary table. This table is the source of clinsite metadata. The BIMO team converted Appendix 3 to an Excel file named clinsite_metadata_FDA.xlsx.

We classified the 39 variables into these categories:

- Study information (10 variables, e.g. Study Title)
- Site information (14 variables, e.g. Financial Disclosure Amount)
- Safety results (10 variables, e.g. Number of Serious Adverse Events)
- Efficacy results (5 variables, e.g. Treatment Efficacy Result)

The Excel file contains the following variable attributes:

- Variable index
- Variable label
- Type
- Controlled Terms or Format
- Notes or Description
- Sample Value

This initial metadata file was analyzed for compliance with SAS V5 transport format. We found variables with labels that have lengths greater than 40 characters; these would be truncated.

Table 1 lists variables that would be truncated.

Variable Index	Variable Name	Variable Label	Length of Label
15	DISCTR	Number of Subject Discons from Study Treatment	46
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	44
21	SITEEFFS	Site-Specific Treatment Effect Standard Deviation	49

Table 1. Appendix 3 Variables with Labels Truncated in SAS V5 Transport Format

We contacted the FDA BIMO team for guidance, and promptly received advice to shorten the labels, with documentation in the define.pdf file. An updated metadata file was created, named clinsite_metadata_Janssen.xlsx.

Table 2 lists the updates.

Variable Index	Variable Name	Variable Label	Length of Label
15	DISCTR	Num of Subject Disc from Study Treatment	40
19	TRTEFFS	Treatment Efficacy Result SD	28
21	SITEEFFS	Site-Specific Treatment Effect SD	33

Table 2. Updated Labels

We also have checks in place to look for special characters that should not to be included in the clinsite.xpt file. We found a single sample value containing special characters.

Table 3 lists the special characters in sample values.

Variable Index	Variable Name	Variable Label	Sample Value in Appendix 3	Sample Value in Janssen Metadata
27	FINLDISC	Financial Disclosure Amount	≥ \$25,000	>= \$25,000

Table 3. Appendix 3 Sample Values with Special Characters, with Updates

The sample value was updated in the `clinsite_metadata_Janssen.xlsx` file, which serves as the metadata source for the standard CDISC ADaM compliant metadata file.

SAMPLE SINGLE OBSERVATION CLINSITE DATASET

Our next task was to generate a single observation clinsite SAS dataset with BIMO conforming variable attributes and sample values based on our updated metadata file.

The following SAS code generates a single observation clinsite dataset from the metadata Excel file:

```

***Import clinsite metadata;
proc import datafile = '\\DATACENTER\BIMO\clinsite_metadata_janssen.xlsx'
            dbms = excel
            out = clinmeta replace;

run;

***Use Call Execute to generate dataset;
data _null_;
  set clinmeta end=eof;

  ***Generate data step once at the beginning of the dataset;
  if _n_=1 then call execute('data a_out.clinsite;');

  ***Apply length and assign sample value;
  ***For numeric variables, scan for the first comma-separated sample value;
  if lowercase(type)='char'
    then call execute('length ' || trim(variable_name) || ' $200;' ||
                     trim(variable_name) || ' = "' ||
                     trim(sample_value) || '" ; ');

    else call execute('length ' || trim(variable_name) || ' 8 ;' ||
                     trim(variable_name) || ' = ' ||
                     trim(scan(sample_value, 1, ',')) || ';' );

  ***Apply variable labels;
  call execute('label ' || trim(variable_name) || ' = "' ||
              trim(variable_label) || '" ; ');

  ***Output single observation and the run statement once at end of dataset;
  if eof then call execute(' output; run; ');

```

```
run;
```

This single observation clinsite dataset is used to compare attributes with generated clinsite datasets from clinical trials.

IMPORTING SITE INFORMATION TO SAS

Some variables required in the clinsite dataset are not available in trial SDTM or ADaM datasets. These variables include site address and contact information, site financial disclosure information, sponsor information, and regulatory information related to IND, NDA, BLA, etc. The information exists in various formats in clinical trial management systems (CTMS), sometimes requiring regulatory interpretation. Our global trial leads (GTL's) download information from CTMS systems to Excel files for import into SAS.

The BIMO team developed a BIMO site information template as an Excel file to standardize the format of data to be imported. The template is the key communication mechanism among the statistical programmer, global trial lead, and statistician for non-SAS information to be imported into SAS. The first tab of the workbook contains detailed instructions for populating every column in the data tab.

The site information template instruction tab contains the following columns:

- A. Variable index
- B. Variable name
- C. Variable label
- D. Type
- E. Controlled Terms or Format
- F. Notes or Description
- G. Sample Value
- H. Notes to Global Trial Lead
- I. Comments from Global Trial Lead

Columns A through G are directly from Appendix 3 of the FDA BIMO technical conformance guide. Column H contains notes from the statistical programmer to the global trial lead, and column I is used by the global trial lead to note comments from data population.

Table 4 displays a single example, using the sponsor count variable.

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
3	SPONCNT	Sponsor Count	Num	Integer	Total count of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, with sponsors as defined in 21 CFR 312.3, enter an integer indicating the total count of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1

Notes to GTL	Comments from GTL
If no change in sponsor during the trial, enter "1". If the value is not provided in the "datasheet" with other individual site information, please reach an agreement with the trial programming group to provide the value in column "Comments from GTL" (i.e., column I of this sheet).	

Table 4. Sample variable from site template instruction tab

The “datasheet” tab is used for data import from CTMS systems and direct entry by the global trial lead. The rows from the instruction tab are transposed to columns for entry in the datasheet tab. The first column is the study id, then columns for sponsor count, sponsor name, and so on. A common issue in Excel to SAS data import is truncation of values, based on SAS assumptions of variable length. To mitigate the truncation risk, the template has populated row 2 with dummy values of very long length. The data are populated starting on row 3 (row 1 contains the column headers translated to SAS variable names).

The statistical programmer converts the populated datasheet into a SAS dataset using a standard SAS macro. Then, an additional standard SAS macro is called to check the imported data for special characters, which need to be resolved prior to conversion to SAS transport format.

Table 5 displays a sample of the data sheet.

BIMO Macro	Purpose
Adclnattrib.sas	Assign metadata attributes to SAS datasets.
Adclngetattributes.sas	Combine multiple metadata datasets, and create macro variables for attributes length, format, and informat.
Adclnmetadaxls2sas.sas	Read Excel metadata workbook and generate SAS metadata datasets.
Adclnxls2sas.sas	Convert Excel files to SAS datasets.
Esdefineclinpdf.sas	Generate define.pdf.
Esspecchar.sas	Check SAS datasets for special characters.

Table 7. BIMO SAS Macros

SAMPLE BIMO SAS PROGRAMS

Sample BIMO SAS programs that call the standard macros were developed.

Table 8 lists the sample programs.

BIMO Program	Macro(s) called	Purpose
Ck_special_char.sas	Esspecchar.sas	Check SAS datasets for special characters and list for updates.
Esclinsite.sas	Adclnattrib.sas	Create clinsite SAS dataset.
Adclnstemetadata.sas	Adclngetattributes.sas	Create clinsite metadata attributes
Escreateaclinxpt.sas	Dtoxpt.sas Eexceptionrpt.sas	Convert clinsite SAS dataset to transport format and run exception report.
Escreatedefineclin.sas	Esdefineclinpdf.sas	Create data definition file define.pdf for clinsite dataset

Table 8. Sample BIMO SAS Programs

BIMO DOCUMENTATION

The BIMO process guide provides the detailed steps that users follow to deliver a BIMO submission, from a statistical programmer's perspective. Additional documents include the clinsite metadata Excel workbook following the ADaM format, site information template Excel workbook, sample BIMO data reviewer's guide, and sample BIMO data presentation specifications document. The documentation and SAS tools provide the framework for FDA compliant BIMO submissions. Collaboration across the functional teams (statistical programming, statistics, clinical trial management, regulatory affairs) and communication with FDA are critical to success. Communication and collaboration have been very constructive to date. Cross-functional issues have been resolved and queries sent to the FDA CDER-BIMO-NDA-BLA request email address have been addressed promptly and comprehensively.

LESSONS LEARNED

The first BIMO submissions utilizing the FDA Bioresearch Monitoring Technical Conformance Guide occurred in the second half of 2018. It has been a continuous learning process as we work on submissions across therapeutic areas. Key lessons learned are summarized below; the list is updated with additional items as they are encountered.

- The pre-submission meeting with FDA (BLA, NDA, supplement) should include BIMO planning.
 - Confirm major (pivotal) trials to include in BIMO submission / consistent with NDA/BLA/ supplement submission.
 - What subject-level data line listings are required to optimize inspection?
 - Is a BIMO reviewer's guide needed?
- Document the BIMO programming requirements.
 - Specify listings needed and any programming algorithms.
 - Safety and efficacy variables in clinsite.xpt match clinical trial analyses / clinical study report.
- Clinsite metadata ensures compliance.
 - Convert Appendix 3 of the FDA conformance guide to metadata for clinsite variables and update to standard metadata format.
 - The metadata approach mitigates risk of data being flagged as invalid by FDA tools, which assume implementation of the conformance guide without exception.
- Importing clinical site information from CTMS systems is challenging.
 - Check consistency of study id and site id variable format for merging information with clinical database.
 - Special characters are common in global trials, especially in names and addresses. Use SAS programs to check for and replace special characters. No characters outside 32-126 ASCII code range can be in clinsite.xpt variables. The preference for encoding is UTF-8.
- Include ALL sites that have any consented subjects, even if all site data (safety and efficacy) are excluded from clinical study report.
- Ensure that safety and efficacy variables in clinsite.xpt match those in the clinical trial analyses / clinical study report.
- A clinical site is expected to have a single investigator in clinsite.xpt.
 - Multiple investigators with the same site id will cause duplication of safety and efficacy data; this will be flagged as error by FDA tools. Clinsite.xpt "should" be unique based on study id, site id, and treatment arm.
 - In cases of multiple primary endpoints, there will be additional rows for the endpoint data.
 - If site has multiple investigators due to transitions, use most recent clinical investigator, that is, the current responsible investigator at the site.
- In some cases, an investigator may have multiple sites. For example, main site and satellite sites with DIFFERENT subjects enrolled.
 - Clinsite dataset is to include each site separately with unique assigned site number and unique site address.
- Check for SAS version 5 transport file compliance.
 - Ensure the clinsite dataset has no character variable with length > 200 before converting to clinsite.xpt.

NEXT STEPS

The FDA technical conformance guide has enabled the development of standards to enhance the BIMO process. The document articulates that the listings process will be updated as extracted below:

Although listings are currently requested in PDF format, CDER is in the process of developing tools to extract site-specific listings, needed for inspectional purposes, from submitted Clinical Data Interchange Standards Consortium, Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM) datasets and intends to make those tools available in the future. FDA intends to update these technical specifications to include details for the submission of SDTM and ADaM datasets, including controlled terminology standards. In anticipation of development of CDER tools for extraction of by-site, by-subject data listings, sponsors should ensure that they are prepared to submit clinical study data using standards specified in the Data Standards Catalog.

As FDA is updating the listings process, there are opportunities for sponsors to improve the BIMO process. The most challenging element has been importing site data not contained in CDISC SDTM or ADaM datasets. The current process of importing CTMS data using Excel to SAS is manual and prone to error. The ideal future solution would involve updating CDISC SDTM datasets to include all of the clinsite variables. This would eliminate the import processing and special character issues.

CONCLUSION

Bioresearch Monitoring (BIMO) electronic submissions are key to the planning of FDA inspections. The technical conformance guide was used as specifications to standardize BIMO statistical programming across therapeutic areas, specifically the generation of clinsite.xpt dataset and define.pdf. Standardization of the BIMO process provided a single source of metadata, template, SAS macros/sample programs and documentation that can be utilized by all trial teams needing to provide clinsite.xpt and define.pdf to the FDA. The standards also ensure compliance in structure and content with the FDA guidance. Compliance is key to successful FDA acceptance of the submission; tools are in place to confirm specifications were followed. The site information import from external systems is challenging, and continuous improvement efforts are in progress.

REFERENCES AND RECOMMENDED READING

Bioresearch Monitoring Technical Conformance Guide

<https://www.fda.gov/downloads/drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>

Providing Regulatory Submissions in Electronic Format — Standardized Study Data

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>

Programming Support for BIMO Deliverable

<https://www.lexjansen.com/pharmasug-cn/2018/CD/Pharmasug-China-2018-CD77.pdf>

BIMO Listings – Check That Off Your NDA To-Do List

<https://www.lexjansen.com/phuse-us/2018/rg/RG07.pdf>

Preparing the Office of Scientific Investigations (OSI) Requests for Submissions to FDA

<https://www.lexjansen.com/pharmasug/2018/EP/PharmaSUG-2018-EP15.pdf>

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