Paper AS07

A Programmer's Journey Through the BIMO Submission Process

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ABSTRACT

In February 2018, the Food and Drug Administration (FDA) published draft guidance on the standardized format for Bioresearch Monitoring (BIMO) documentation in a New Drug Application (NDA). This paper will share the authors' experience in developing a comprehensive BIMO package for a recent NDA submission. It will discuss a programmatic approach to converting clinical study report (CSR) listings into BIMO subject-level site listings. It will describe some of the challenges in deriving the summary-level clinical site dataset, with respect to summarizing variables like treatment arm, the need for additional population variables, the use of screen failure data not in the clinical database, and subjects in satellite sites. It will also cover technical aspects of creating the define.pdf from the define.xml, development of a BIMO reviewer's guide without an industry-defined template, how the BIMO components fit into the electronic Common Technical Document (eCTD), and general recommendations for the BIMO package.

INTRODUCTION

Standardized format for Electronic Submission of NDA and Biologics License Applications (BLA) content for the planning of Bioresearch Monitoring (BIMO) Inspections for Center of Drug Evaluation and Research (CDER) submissions draft guidance [1] was published by FDA and contained binding provisions and nonbinding recommendations. The draft guidance contains details about the content to be provided in standardized format and applies to data submitted from major (i.e. pivotal) studies in the NDA, BLAs and supplemental applications. Following the standards specified in the guidance document helps the review agency in timely selection of sites for on-site inspections, preparation of documents that are provided to Office of Regulatory Affairs (ORA) investigators, and moreover it facilitates good review management practices for the review agency.

BIMO - BACKGROUND

There are three main components that comprise the overall BIMO package described in the BIMO draft guidance.

a.) Clinical Study-Level Information

Clinical Study-Level Information consist of a comprehensive table listing of all clinical sites that participated in the submitted studies, listing of all entities to whom sponsor has contracted clinical study activities, protocol, protocol amendments, and annotated case report forms. More details for the submission of these documents are provided in the BIMO draft guidance.

b.) Subject-Level Data Line Listings by Clinical Site

For all pivotal studies that are part of the application, by-site listings of subjects consented, treatment assignments, efficacy end points, medications, safety monitoring are provided. BIMO Technical Conformance Guide (TCG) [2] provides complete details of the above described data points that need to be included in the by-site listings. These by-site listings can either be grouped by site and by listing of each data type per each protocol or by site and by subject profile per each protocol of the pivotal studies that were included in the submission.

c.) Summary-Level Clinical Site Dataset

Summary-Level clinical Site Dataset contains data from all pivotal studies included in the application. It is intended to support the safety and efficacy data summarized by each study, per clinical site and treatment. This dataset would help to characterize the individual clinical investigator sites, summarize outcomes of the study at the site level.

The above described BIMO components need to be in eCTD format and included in Module 5 of the application. A BIMO study tagging file (STF) is constructed and should be placed in Module 5.3.5.4 – Other study reports and related information.

IMPLEMENTATION
CLINICAL STUDY-LEVEL INFORMATION

As described in the above BIMO background section, there are several individual components that comprise the clinical study-level information. The draft guidance has described all the components that are needed in this section. The first component is the Table listing that contains details of all clinical sites that participated in the submission studies. Following the draft guidance, in Module 5.3.5.1 of study reports within each study, a table listing all clinical sites with site investigator, site number, site address, and site contact information was included. Below is an example table that has details of the sites.

Table 1

APPENDIX 1: CLINICAL STUDY-LEVEL INFORMATION (STUDYID)

SITE IDENTIFIER	INVESTIGATOR NAME (PRIOR CLINICAL INVESTIGATOR(S))	SITE ADDRESS AT TIME OF CLINICAL STUDY (UPDATED SITE ADDRESS WHEN EXISTS AND AVAILABLE)	SITE CONTACT INFORMATION AT TIME OF CLINICAL STUDY (UPDATED CONTACT INFORMATION WHEN EXISTS AND AVAILABLE)	STUDY COORDINATOR CONTACT INFORMATION
001	Last, First Name	Hospital Name Street # City, State Zip code Country	Phone: (XXX) XXX-XXXX Fax: X (XXX) XXX-XXXX Email: xxx.xxx@xxx.xxx	Name: First Last Name Phone: (XXX) XXX-XXXX Fax: Email: xx.xx@xxx.xxx
002[1]	Last, First Name (Prior Investigator Last, First Name)	Hospital Name Street # City, State Zip code Country	Phone: (XXX) XXX-XXXX Fax: X (XXX) XXX-XXXX Email: xxx.xxx@xxx.xxx (Phone: (XXX) XXX-XXXX Fax: X (XXX) XXX-XXXX Email: xxx.xxx@xxx.xxx)	Name: First Last Name Phone: (XXX) XXX-XXXX Fax: Email: xx.xx@xxx.xxx

[1]Site 002 Principal Investigator changed from Investigator A to Investigator B over the course of the study. Contact information has been provided for both investigators.

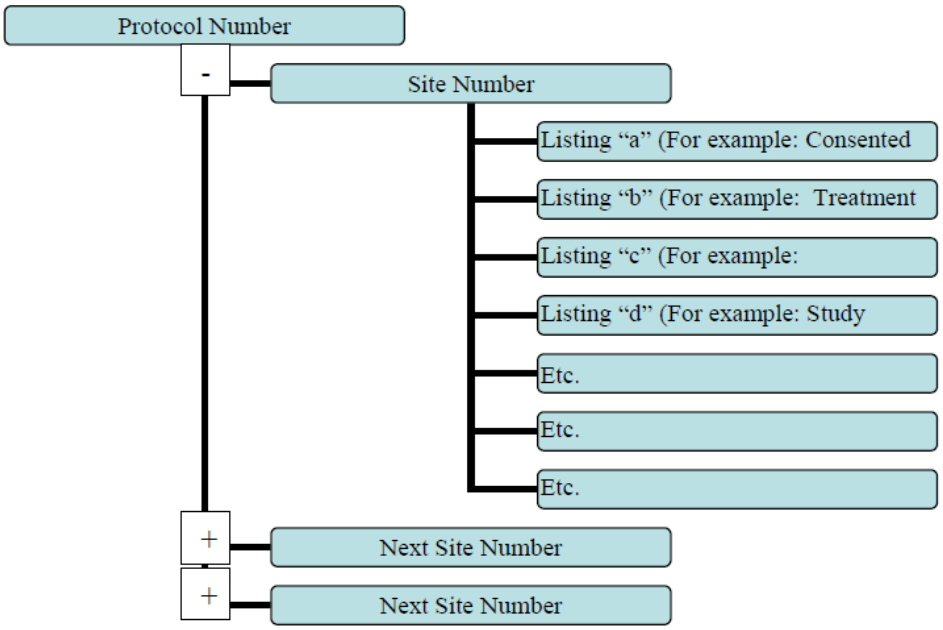
The other components are the details of all the entities to whom the sponsor has transferred responsibility and study functions that were contracted, annotated case report forms, protocol and amendments. As per the BIMO TCG if these entities are included in Appendix 16 of the Clinical Study Report (CSR) for each study it is not required to resubmit again. Since these components were submitted in the CSR in the BIMO Reviewer's Guide (RG) a hyperlink was provided to the location in the eCTD. More details about the BIMO RG are discussed in the later part of the paper.

BIMO LISTINGS

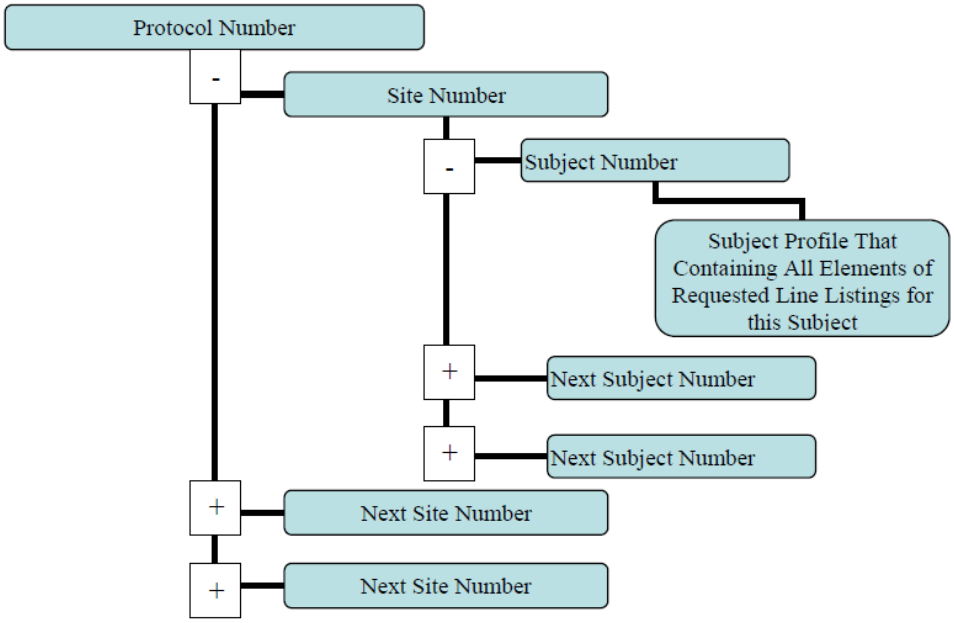
The BIMO TCG provides two options for the creation of listings as seen in Figure 1. Option A is to create all required listings by Site and Option B is to create listings for each subject within each site. This paper describes how we created the listings according to Option A although a similar approach could be taken for Option B.

Figure 1 Formatting Subject-Level Data Line Listings by Site

By Site, By Listing Option A:



By Site, By Subject Profile Option B:



Source: BIMO TCG Appendix 2

Per the BIMO TCG, subject-level data line listings, by clinical site should include:

1. Consented Subjects
2. Treatment Assignment
3. Discontinuations
4. Study Population
5. Inclusion and Exclusion Criteria
6. Adverse Events
7. Important Protocol Deviations
8. Efficacy Endpoints

9. Concomitant Medications
10. Safety Monitoring

APPROACH

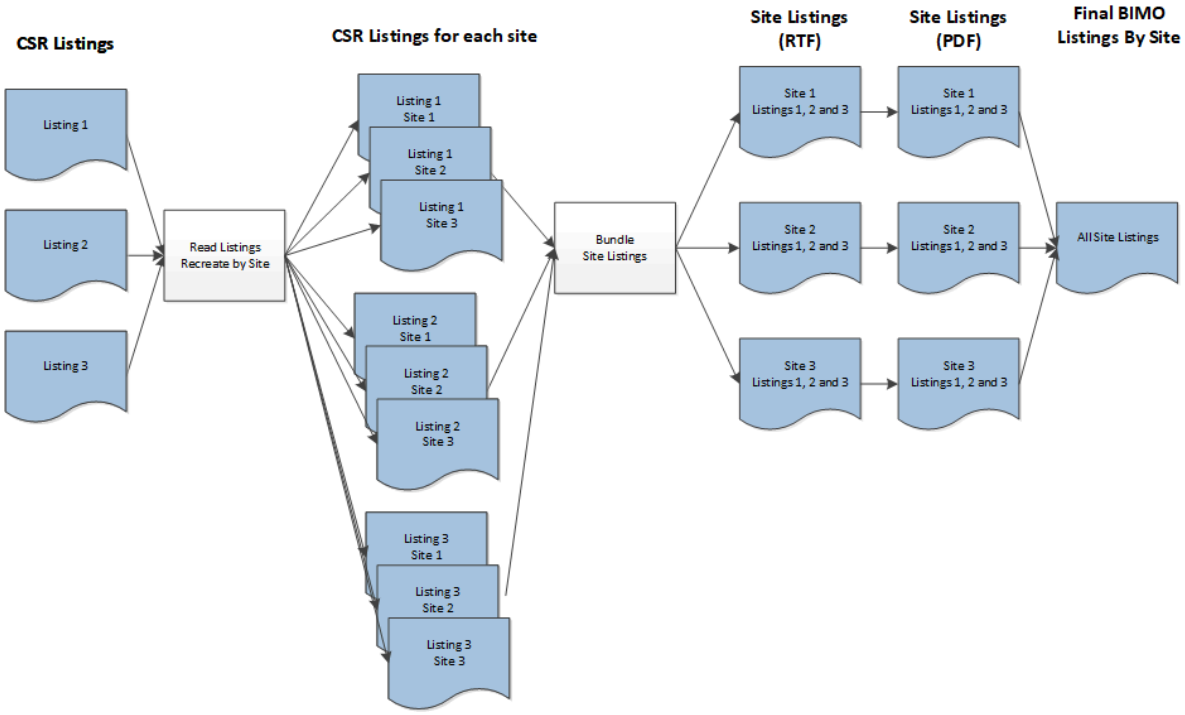
Most of the required listings had already been created for the CSR and were in the same or similar format needed for BIMO. There were multiple CSR listings that would be needed for the Efficacy Endpoints and Safety Monitoring. The Study Population listing was not part of the CSR listings and the Consented Subjects listing was required in a different format for BIMO and these listings were created just for BIMO.

Rather than re-programming the individual listings for BIMO, we wanted to find a method that could utilize the existing CSR listings to create the BIMO listings in a way which could be automated as much as possible and reproduceable for future submissions.

Our CSR listings were created in RTF format using the SAS® ODS RTF destination. There are multiple papers describing in detail how to use SAS to read RTF files and create SAS datasets from them including “Save Those Eyes: A Quality-Control Utility for Checking RTF Output Immediately And Accurately” by Michiel Hagendoorn, Jonathan Squire and Johnny Tai. For this purpose, we needed to extract the titles, footnotes, column headers and widths, listing data and the justifications of the column headers and column values. Each of the CSR listings contained the subject id in the first column so we could take this and use it to find the site for each subject from the SDTM DM domain. The screen failure subjects were not included in the clinical data base and needed to be included from the Interactive Web Response System (IWRS) data. With the site and the information extracted from the RTF file, it was possible to re-generate each of the listings by site.

Using this method iteratively for each of the CSR listings we were able to create a version of each listing for each site. These listings could then be combined into a site-level RTF file containing each of the listings for that site. The site-level RTF files could then be converted to PDF, combined and bookmarks added by site and listing.

Figure 2 Generation of BIMO Listings PDF from CSR Listings Process Flow



READING THE RTF LISTINGS

RTF files created by SAS ODS RTF can be read and parsed programmatically by identifying RTF control words that signify the start and end of the title, footnote, column header and data section of the file. Within these sections, further RTF control words can be found which identify the column widths, justifications and content. Table 2 shows the key RTF control words that were used to identify the sections of the RTF file and extract the information needed to be able to recreate the listings by site.

The column widths in the RTF file are defined in TWIPs where 20 TWIPS is equivalent to 1pt and 1440 TWIPs represents one inch. From this, the widths of each column can be identified and used in generating the proc report code that will recreate the listings for each site.

Table 2 RTF Control Words Used to Programmatically Read SAS-Generated RTF Files

RTF Control Word	Meaning
\footer	Start of the footnote section
\header	Start of the title section
\trhdr	Table row header

RTF Control Word	Meaning
\intbl	Identifies paragraph as part of a table
\cellxnnnn	The right boundary of a table cell where nnnn is a TWIP count Can be used, along with the value for the previous column to identify the column width
\ql, \qr or \qc	Left, right or center justification
\cell	End of a table cell

The RTF file was read to create two SAS datasets, one containing the unique titles and footnotes and the other containing the table data.
The titles and footnotes shown in Figure 3 were converted into a SAS dataset shown in Figure 4 with one row for each title or footnote. Special characters such as superscript and sub-script characters were converted into tokens in the SAS dataset.

Figure 3 CSR Listing Titles and Footnotes

```
My Pharmaceutical Company                                                    Page 1 of 1
BIMO Listings

                                        Listing 1
                                Randomization Scheme and Codes
                                        All Subjects Set

- [1]: F- Female, M- Male.
- [2]: W- White, B- Black or African American, A- Asian, AA- American Indian or Alaska Native, HP- Native Hawaiian or other Pacific Islander,
NC- Not collected per local regulations, and O- Other.
Program: Draft MyStudy\l-rand.sas                                  Creation: 01JAN2019 09:00
```

Figure 4 SAS Dataset Containing RTF File Titles and Footnotes

tf_id	type	count	value
1	TITLE	1	My Pharmaceutical Company
1	TITLE	2	BIMO Listings
1	TITLE	3	Listing 1
1	TITLE	4	Randomization Scheme and Codes
1	TITLE	5	All Subjects Set
1	FOOTNOTE	1	- _super1_: F- Female, M- Male.
1	FOOTNOTE	2	- _super2_: W- White, B- Black or African American, A- Asian, AA- American Indian or Alaska Native, HP- Native Hawaiian or other Pacific Islander, NC- Not collected per local regulations, and O- Other.

The listing body shown in Figure 5 was converted into a SAS dataset shown in Figure 6 containing the column headers (h1-h9), column values (c1-c9), column widths in TWIPs (hw1-hw9) and column header (hj1-hj9) and column (cj1-cj9) justifications.

Figure 5 CSR Listing

				Stratum				
Subject/Sex[1] /Age/Race[2]	Randomized Treatment	Actual Treatment	Randomization Date	Age	Sex	Region	Country	Site
123456789/M/45 /W	Placebo	--	2019-01-01	≥40 Years	Male	North America	United States	(001) Site 001

Figure 6 SAS Dataset Containing CSR Listing Column Headers, Widths, Justification and Body

tf_id	hd_id	page	h1	h2	h3	h4	h5	h6	h7	h8	h9
1	1	1	|Subject/Sex_super1__line_/Age/Race_super2_	|Randomized_line_Treatment	|Actual_line_Treatment	|Randomization_line_Date	Stratum|Age	Stratum|Sex	|Region	|Country	|Site

c1	c2	c3	c4	c5	c6	c7	c8	c9	hw1	hw2	hw3	hw4	hw5	hw6	hw7	hw8	hw9	hj1	hj2	hj3	hj4	hj5	hj6	hj7	hj8	hj9	cj1	cj2	cj3	cj4	cj5	cj6	cj7	cj8	cj9
123456789/M/45/W	Placebo	--	2019-01-01	>=40 Years	Male	North America	United States	(001) Site 001	1623	1776	1481	1481	1185	1185	1185	1481	1776	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c	c

The subject was parsed as the first item from column 1 and then merged with the DM and IWRS datasets to get the site associated with the subject.

MODIFYING THE RTF LISTINGS

Once the listings had been read into SAS datasets, it was possible to make any adjustments where the BIMO listings needed to be different from the CSR listings. CSR Listing numbers in titles were easily replaced by the BIMO listing number and, if needed, CSR listing columns could be dropped from the BIMO listings or rows filtered to show a subset of the information provided in the CSR listing. Column widths could also be changed.

GENERATING THE LISTINGS BY SITE

By using a loop, each listing was created for each site. The proc report code, a sample of which can be seen in Table 3, was generated based on the information extracted from the RTF file. An additional title line (title4) was added to display the site number and name but otherwise, the listing generated was identical to the CSR listing. The only additional information that needed to be provided for each listing that could not be read directly from the RTF file was the columns which would be defined as group rather than display in the define statements and the column after which a blank line would be inserted when the value changed. These can be passed as macro parameters. A sample of the programmatically generated proc report code can be seen in Table 3.

Table 3 Programmatically Generated SAS Code to Recreate Listings by Site

```
ods rtf file = "%sysfunc(getoption(work))/site-001-002-l-randomization.rtf" style = odsrtf nogtitle nogfootnote
keepn notoc_data;

proc report data = rtf1_2 nowd headskip missing split = "~" headline;
compute after c1 / style = [just = l];
  line ' ';
endcomp;

title3 j = c "Listing 2(*ESC*){\line}Randomization Scheme and Codes(*ESC*){\line}All Subjects Set";
title4 j = l "Site: (001) Site 001";
footnote1 j = l "- (*ESC*){\super 1}: F- Female, M- Male.(*ESC*){\line}- (*ESC*){\super 2}: W- White, B- Black or
African American, A- Asian, AA- American Indian or Alaska Native, HP- Native Hawaiian or other Pacific Islander,
NC- Not collected per local regulations, and O- Other";

column c1 c2 c3 c4 ("Stratum" c5 c6) c7 c8;

define c1 / order order = data "Subject/Sex(*ESC*){super 1}(*ESC*){\line}/Age/Race(*ESC*){super 2}"
style(header) = {just = c cellwidth = 81.9pt} style(column) = {just = c};
```

EMPTY LISTINGS

There can be cases where a listing, for example Discontinuations, may not contain any records for a site. When this happened, we still wanted to display the titles, footnotes and column headers for the listing but display a message "No data met the criteria for this listing."

This was achieved by identifying when there was an empty dataset for a site, adding a single observation with all missing values so that a report would still be generated and, in the generated proc report code, adding the lines below so that the text will display centered across all columns.

Table 4 Proc Report Code Used to Generate Message for Empty Datasets

```
compute before / style(lines) = [just = c cellwidth = 8in];
  line " ";
  line " No data met the criteria for this listing.";
  line " ";
 endcomp;
```

BUNDLING THE LISTINGS BY SITE

Once individual listings have been created for each site for each of the required BIMO listings, they were combined so there is one file per site with all the required listings for that site.

The RTF listings can be combined programmatically by providing an ordered list of the individual listings for the site, as seen in Table 5, and using that to read the files in, combine them and output to a site-level listings file using the code below. Each RTF file will end with \pard} or {\par}} and the final bracket needs to be removed before appending the next file (except for the final file). The \sectd or \sect\sectd control words are used to identify the start of the relevant information for the next file.

Table 5 Creation of SAS Dataset Containing the RTF File Names to be Bundled

```
data listings;
infile cards truncover;
input fullpath $200.;
fullpath = "%sysfunc(getoption(work))\" || strip(fullpath);
cards;
site-001-001-l-bimo-consent.rtf
site-001-002-l-randomization.rtf
…
;
run;
```

Table 6 Bundling RTF Files

```
data _null_ ;
  retain EndOfFile 0;
  set listings end = lastfile;

  infile filename lrecl = 32767 truncover end = eof filevar = fullpath;
  file "site-001-bimo.rtf" lrecl=32767;

  do while(not eof);
    input;

    * Remove the bracket at the end of the file for all but the last file;
    if not lastfile and _infile_ in('\pard}', '{\par}}') then do;
      _infile_ = substr(_infile_, 1, length(_infile_) - 1);
      EndOfFile = 1;
      put _infile_;
    end;
    else if EndOfFile then do;
      if _infile_ =: '\sectd' then do;
        _infile_ = tranwrd(_infile_,'\sectd','\sect\sectd');
        put _infile_;
        EndOfFile = 0;
      end;
    end;
    else put _infile_;
  end;
run;
```

CONVERTING SITE LISTINGS TO PDF

The Visual Basic code in Table 7, generated via SAS, was executed using the code in Table 8 to automate the conversion of each of the site listing RTF files to PDF.

Table 7 Visual Basic Code Used to Save RTF Files as PDF

```
dim objwd
set objwd = wscript.createobject("word.application")
objwd.visible = false
fname="site-001-bimo.rtf"
objWD.documents.open(fname),false, true
outname="site-001-bimo.pdf"
objwd.activedocument.saveas(outname), 17
objwd.documents.close
objwd.application.quit
```

Table 8 Execution of Visual Basic Code to Automate the Creation of PDF Files from RTF

```
  * Run VB code to convert RTF to PDF;
  filename runvbs pipe "cscript ""%sysfunc(getoption(work))\createpdf.vbs""" console = min;

  data _null_;
  infile runvbs;
  input;
  stop;
  run;
```

COMBINING INTO ONE PDF FILE AND ADDING BOOKMARKS

The individual PDF files can easily be combined into a single PDF within Adobe Acrobat by using the “Combine Files into a Single PDF” option.

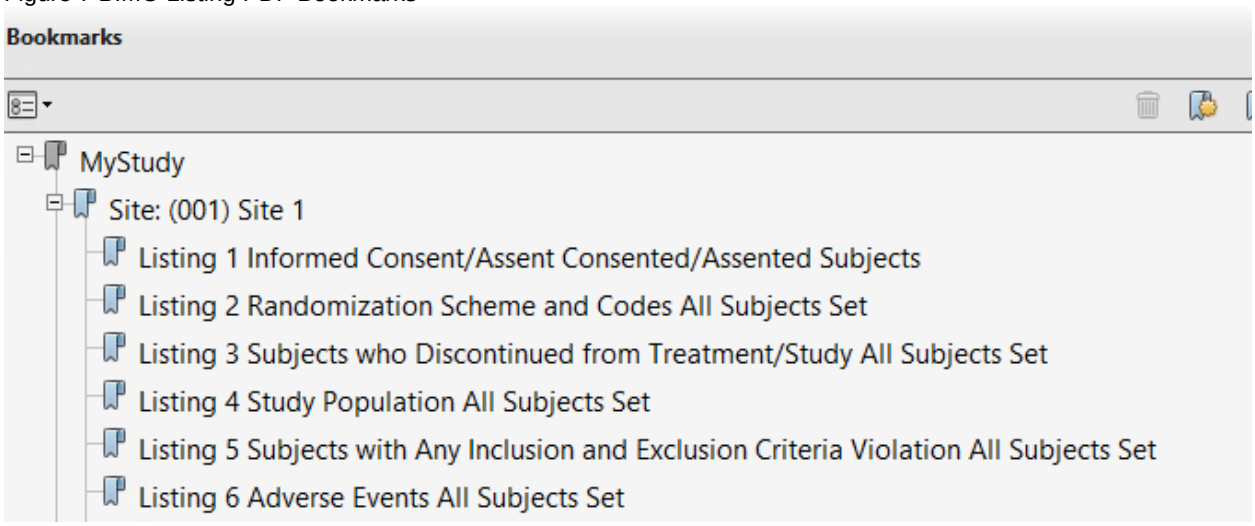
By programmatically reading the site-level RTF files using a similar method to that used in the first step, the cumulative page number, site and listing title can be extracted and used to create a delimited text file containing 3-level bookmarks for the Study, Site and Listing. A sample of the text file used to create the bookmarks with links to the relevant pages can be found in Table 9.

Table 9 Text File Containing the Bookmarks and Associated Page Numbers

```
MyStudy 1
Site: (001) Site 1  1
        Listing 1 Informed Consent/Assent Consented/Assented Subjects          1
        Listing 2 Randomization Scheme and Codes All Subjects Set    2
        Listing 3 Subjects who Discontinued from Treatment/Study All Subjects Set          3
        Listing 4 Study Population All Subjects Set    4
        Listing 5 Subjects with Any Inclusion and Exclusion Criteria Violation All Subjects Set          5
                Listing 6 Adverse Events All Subjects Set      6
```

Using an Adobe Plug-In, the text file was imported to create the bookmarks in the BIMO PDF file which can be seen in Figure 7.

Figure 7 BIMO Listing PDF Bookmarks



BIMO SITE LEVEL DATASET

A summary-level clinical site dataset named as CLINSITE in xpt format, was created in accordance with BIMO TCG published by U.S. Department of Health and Human Services Food and Drug Administration CDER in February 2018. The dataset included two pivotal studies used to support safety and efficacy analysis in the application. The dataset contains information from clinical database for all safety and efficacy related variables, IWRS data for variable SCREEN (Number of Subjects Screened) and from Clinical Operations for financial variable FINLDISC, and variables pertaining to investigator contact information (LASTNAME, FRSTNAME, MINITIAL, PHONE, FAX, EMAIL, COUNTRY, STATE, CITY, POSTAL and STREET). The dataset was structured as one record per pivotal study per clinical site and per treatment arm.

HANDLING ISSUES RELATED TO CLINICAL SITES

Site Transfers: In our clinical database, site ID is an identifier of the site of a subject's current site. Therefore, subjects who transferred from one site to another during the study were summarized under the site ID subject last participated.

Satellite Sites: Satellite sites were used in one of the pivotal studies. These satellite sites were associated with the primary site (based on the SITEID variable).

Screen Failures: SCREEN variable provided the count of number of subjects screened at the site. For sites with only screen failure subjects, a single record was created per site with arm, safety, and efficacy variables set to null. SAFPOP, FASPOP were set to 0.

Financial Disclosure Amount (variable FINLDISC) in $USD by site was calculated as the sum of disclosure for the clinical investigator and all sub-investigators as per the TCG.

Variables related to investigator information including LASTNAME, FRSTNAME, MINITIAL, PHONE, FAX and EMAIL were populated with the most recent primary clinical investigator whenever there were changes in primary clinical investigators.

HANDLING ISSUES RELATED TO TREATMENT ARM (VARIABLE ARM)

According to the Statistical Analysis Plan, a subject was analyzed and summarized per the planned treatment for efficacy and disposition analyses and the actual treatment for safety analyses. In one of the two pivotal studies, there were subjects whose actual treatment was different from the planned treatment.

In the CLINSITE dataset, the ARM variable was used in the concept of both planned (randomized) treatment and actual treatment. The planned (randomized) treatment was used for the efficacy and disposition/study conduct analysis variables (TRTEFFR, TRTEFFS, SITEEFFE, SITEEFFS, DISCSTUD, DISCTRT and PROTVIOL). Whereas, the actual treatment was used for the safety analysis variables (NSAE, SAE and DEATH).

The variable SAFPOP represented the number of subjects in the safety population. As the planned treatment differed from the actual treatment for some subjects, the number of subjects who contributed to efficacy and disposition/study conduct analysis variables was not identical to the number of subjects in the safety population. To clearly establish the logical relationship among efficacy analysis treatment arms, efficacy analysis population and efficacy analysis variables, sponsor defined custom variable FASPOP was added. This variable was based on the Full Analysis Set (FAS) population in each pivotal study and was associated with the derivation of efficacy variables of the primary endpoint (TRTEFFR, TRTEFFS, SITEEFFE and SITEEFFS), the discontinuation variables (DISCSTUD and DISCTRT) and important protocol deviations (PROTVIOL).

HANDLING ISSUES RELATED TO BIMO TCG

In the BIMO TCG, the variable labels for DISCTRT, TRTEFFS, and SITEEFFS exceeded 40 characters. The variable labels used in the dataset were abbreviated to be within 40 characters.

The BIMO TCG had variable TRTEFFS labelled as “Treatment Efficacy Result Standard Deviation” and furthered explained as “Standard deviation of the efficacy result (TRTEFFR) for each primary efficacy endpoint by treatment arm at a given site”. Since the efficacy result (TRTEFFR) for each primary efficacy endpoint was the mean of treatment effect pertaining to the primary efficacy endpoint, TRTEFFR was calculated as the standard deviation of the mean of the primary endpoint by planned treatment at a given site based on FAS population. Similarly, the variable SITEEFFS was derived as the standard deviation of the site-specific efficacy effect size given by square root of (TRTEFFS**2 for the investigational study medication arm + TRTEFFS**2 for the control arm).

DEFINE.PDF

Per the BIMO TCG, define.pdf should be included along with the CLINSITE dataset. Our existing programming set up only supported the creation of define.xml using the metadata specifications of the CLINSITE dataset so define.xml was generated first and then converted to define.pdf. In order to ensure hyperlinks work correctly between the define.pdf and BIMO RG, the XML code was modified and the below steps were followed to convert define.xml to define.pdf.

a) define.xml was opened in edit mode and blank spaces in the named destinations were removed.
b) Base font size was set to 10, and in page layout tab Orientation was set to Landscape, Page Size was set to Letter with W=11in, H=8.5in, margins was set with Top=1in, all other sides=0.375in and scaling was set to Check Scale Wide Contents.
c) Once the define.xml was updated with the above preferences, it was converted from web page to pdf by selecting convert web page to pdf using the convert icon located on the top of define.xml file.
d) Finally, in define.pdf file properties in the Initial View tab, Navigation Tab was set to Bookmarks Panel and Page (Page Only*), Page Layout and Magnification was set to Default and Open to Page was set to 1.

BIORESEARCH MONITORING REVIEWER’S GUIDE (BIMO RG)

The Reviewer’s Guide is recommended but not required as per the BIMO TCG. It is indeed a recommended component of the BIMO package for the following reasons outlined.

a) It provides a good overview of all the BIMO components in the package.
b) It can be a good starting point for the reviewer to identify all the BIMO components located in the eCTD.

c) Per the TCG, some of the BIMO components submitted in Appendix 16 of the Clinical Study Report need not be submitted again, hyperlinks were provided to the locations in the eCTD.
d) It provides additional guidance/clarification for the BIMO components

Since there was no industry-defined template for the reviewer's guide, we have built a custom template keeping in scope of the BIMO submission components. The contents of the BIMO RG include four major sections: Introduction, Clinical Site-Level Listings of Investigator Information, Subject-Level Data Line Listings by Clinical Site, and Summary-Level Clinical Site Dataset and Date Definition File.

In the Introduction section of the BIMO RG, a brief overview of study design of the pivotal studies included in the submission package was described. As described earlier, hyperlinks were provided in the BIMO RG for some of the components of BIMO that were included in Appendix 16 of the Clinical Study Report of each pivotal study included in the submission. Figure 8 displays section 2.2 of the BIMO RG that shows clinical sites, investigator financial disclosure, list of vendors, protocol, protocol amendments, annotated case report forms, statistical analysis plan with hyperlinks to the respective eCTD locations.

Figure 8

2.2 Clinical Study-Level Document Links

2.2.1 A Comprehensive and Readily Located Table Listing All Clinical Sites That Participated in Clinical Studies and Site Investigator Financial Disclosure

- Clinical Site Information

Study <*studyid*> All Clinical Sites

Study <*studyid*> All Clinical Sites

- Site Investigator Financial Disclosure

Study <*studyid*> Investigator Financial Disclosure

Study <*studyid*> Investigator Financial Disclosure

2.2.2 A Table Listing All Entities to Whom the Sponsor Has Contracted Clinical Study-Related Activities

Study <*studyid*> List of Vendors

Study <*studyid*> List of Vendors

Study <*studyid*> V1

Study <*studyid*> V2

Study <*studyid*> V3

- Annotated Case Report Forms

Study <*studyid*> Annotated Case Report Forms

Study <*studyid*> Annotated Case Report Forms

- Statistical Analysis Plans

Study <*studyid*> SAP

Study <*studyid*> SAP

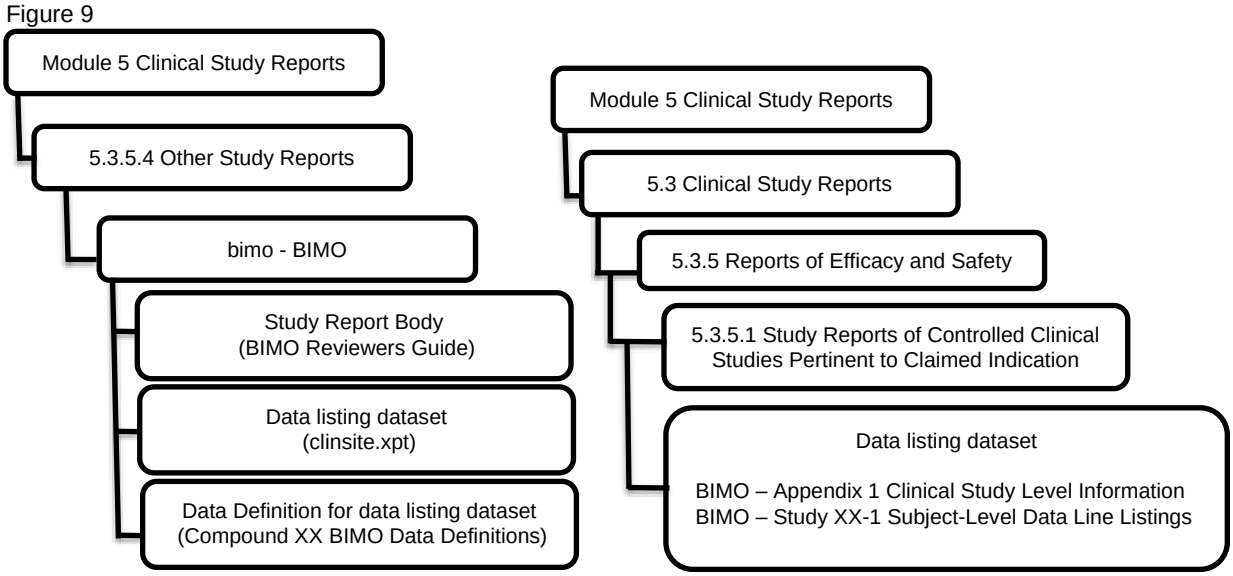
In section 3 of the BIMO RG, for each pivotal study subject level data listing topics were listed along with the Office of Scientific Investigations (OSI) subject level listing topic to help reviewer navigate through the site listings based on the OSI topic listed in the BIMO TCG along with additional details about the listing content that would help reviewer. A hyperlink for the site listing location in the eCTD was also provided for ease of access to the reviewer. In the final section of the document, details about the Summary-Level CLINSITE Dataset and Data Definition File were described. Hyperlinks for the cliniste.xpt and define.pdf to the eCTD locations were also provided. Additional algorithm details that were not described in the define.pdf were clarified in the document. For some of the CLINSITE variables like Treatment Arm, Site Transfer, Satellite Site, and Screened Subjects additional clarifications were provided for better understanding of the CLINSITE dataset data points. For

example, additional explanations were provided about handling of the satellite sites, and the inclusion of the screen failures in the CLINSITE dataset from IWRS source, since screen failure subjects were not present in the clinical database.

SUBMISSION OF BIMO IN ECTD

Following the guidance of the BIMO TCG, the study tagging file was constructed with STUDYID BIMO under eCTD module 5.3.4.5 - Other Study reports and related information. Within this directory, clinsite.xpt data was submitted and linked into the BIMO STF using data-listing-data-set file tag, define.pdf was linked into the same BIMO STF using data-listing-data-definition file tag, and BIMO RG also included and linked with Study Report Body file tag as shown in below Figure 9. Subject-Level line listings, Clinical Study-Level information were submitted within module 5.3 Clinical Study Reports, using the data-listing-dataset file tag. Below Figure 9 summarizes the submission of entire BIMO package for an NDA application.

Figure 9



CONCLUSION

Not limiting to clinical database, multiple sources of data were required to create a BIMO package per BIMO submission guidance. It involved cross function team collaboration with regulatory, clinical, publishing to ensure required data points were obtained as needed to create the BIMO package. While working on the CLINSITE dataset, we realized the need for additional variables for proper interpretation of the dataset. For the site-level listings, we took advantage of the existing CSR listing and created site-level listing and hope this approach can save significant time and ensures complete alignment between the listings. Finally, without an industry defined template for BIMO RG we hope the information summarized in this BIMO RG should assist the agency. Overall, in this paper we shared the entire process involved in creating a BIMO package along with other considerations that should be taken while working on each of those individual sections of the BIMO package.

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