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

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ABSTRACT

The FDA Office of Scientific Investigations (OSI) requests that three items (listed below) be provided for all major trials that support the safety and efficacy in a marketing application. This information is used by the FDA OSI to support the identification of clinical sites to be inspected.

I. General Study-Related Information and Comprehensive Clinical Investigator Information
II. Subject Level Data Listings by Site
III. Site Level Dataset (also referred to as bioresearch monitoring (BIMO) dataset)

This paper covers the authors' detailed understanding of these OSI requests and current available guidance from the FDA. Experiences and challenges from recent submissions for planning and creating the Item I and II listings and the BIMO data package will be shared. In addition, programming macros developed for improved efficiency and consistency of the Item II listings will be described.

INTRODUCTION

The FDA Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate the development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II):

I. General study related information and comprehensive clinical investigator information
II. Subject Level Data Listings by Site
III. Site Level Dataset (i.e., bioresearch monitoring (BIMO) dataset)

This information is requested for all major trials used to support safety and efficacy in a marketing application (i.e., phase 2 / 3 pivotal trials). These OSI requests are usually the same or similar across applications. The request also provides instructions for where OSI requested items should be placed within an eCTD submission. The FDA usually makes this request during either a Type C meeting or pre-NDA/pre-BLA meeting before the submission. See Appendix A for an example of the FDA OSI requests from a recent BLA submission.

In the later sections, the authors will provide further details of their understanding of these OSI requested items based on available FDA guidance including examples of data listing outputs. They will also share their experience on how to plan for and create the requested items from a biostatistical programming perspective.

PLANNING FOR OSI REQUESTS

- **Communicate with FDA**

FDA recommends in their draft guidance and their OSI request that applicants should provide the data listings and dataset for all major studies (e.g., phase 2 / 3 pivotal studies) that are used to support safety and efficacy in the application. It is best practice according to the authors' recent experiences that applicants always confirm the list of studies to be included in the OSI request (i.e., a list of studies per Module 5 package) and any unclear details about the request with FDA in a Type C or pre-BLA/pre-NDA meeting prior to the submission.

- **Set up timeline**

CDER recommends that applicants submit OSI requests Item I, II, and III as a part of any NDA/BLA submission (including any supplemental NDA/BLA submission) that contains clinical study data. According to this recommendation, applicants need to plan to complete the OSI requests ideally at least two months prior to the submission date. Accordingly, the biostatistical programming team confirms detailed timelines with the cross-functional filing team ahead of time, e.g., submission timeline, Module 5 publishing timeline, timelines to obtain any additional data elements that are not contained in SDTM and ADaM (e.g., clinical site contact information and financial disclosure) and derivation algorithm for summary of key safety and efficacy by site.

- **Obtain clinical site information**

Clinical site information, such as site ID, principal investigator (PI) first and last name, site or PI contact (address, phone, fax, and email), and site financial disclosure, is needed for preparing the Item I listings and BIMO dataset. Some site information (e.g., site contact and financial disclosures) are usually not included in the clinical study database, SDTM, or ADaM and therefore needs to be provided by the study management. Collaboration with cross-functional team is the most efficient approach to obtain clinical site information and agree on a standard process for data handoff.

Specifically, the standard process should define steps leading to the delivery of the requested data, and the timing of each step. The roles and responsibilities of involved parties need to be clearly defined in the process. Also the standard data formats and the layout of the final deliverable need to be covered by the process. Below are a few lessons learned regarding the data handoffs:

1. The clinical study manager generates the site information report and provide it to programming team after verifying the financial disclosure of the investigators to avoid re-work for the biostatistical programming team.
2. The clinical study manager summarizes financial disclosure amounts (total and maximum amounts) per site per study in US dollars.
3. All sites which screened at least one subject are included.
4. Site information is provided in a format that can be read into SAS® program directly, e.g., Excel format. It is ideal that one single file is provided for all sites per study.

- **Prepare for programming in a central location**

The three OSI items are required for marketing applications only. At the time when a decision is made to submit the application, some of the phase II / III pivotal studies may have been completed and the study level programming activities may have been locked down. Thus, it proves to be efficient to create the OSI listings and datasets in a central location instead of at the study level. This programming setup is similar to other integrated analyses, such as the integrated summary of safety or efficacy.

OSI REQUESTS ITEM I – SITE LISTING

The OSI request Item I covers information that belongs to two main categories, i.e., general study related information and comprehensive clinical investigator information.

The general study related information is usually not supplied by the statistical programming group. The relevant information may be provided in a document called Bioresearch Monitoring Program Reviewer's Guide, as text or links to other sections in the eCTD.

For the comprehensive clinical investigator information, it must be provided in a tabular format for each study separately and the tabulation should contain the following for each site:

- Site identification number, address, phone, fax, and email
- Principal investigator's name and contact information (could be the same as the site contact information)
- Number of subjects screened, number of subjects randomized, and number of subjects treated who prematurely discontinued.

In the eCTD, the site listings are placed in section 5.3.5.1 (controlled studies) or section 5.3.5.2 (non-controlled studies) with the CSR of their corresponding studies. Table 1. shows an example of the site listing for a study generated by the biostatistical programming team as part of the OSI Item I:

Table 1. Listing of Summary Level Clinical Site Data (Study xxxxxxxx)

Site Number	Principal Investigator Name	Site Location	Number of subjects screened	Number of subjects enrolled	Number of subjects treated who prematurely discontinued IP
654321 (99999)	Smith, John	999 West Street,Suite 99, North Jordan, UT, 99999, USA, p: +1-801-100-2000, f: +1-801-100-3000, jsmith@ABChospital.com	99	88	11
…	…	…	…	…	…

OSI REQUESTS ITEM II – SUBJECT LISTINGS BY SITE

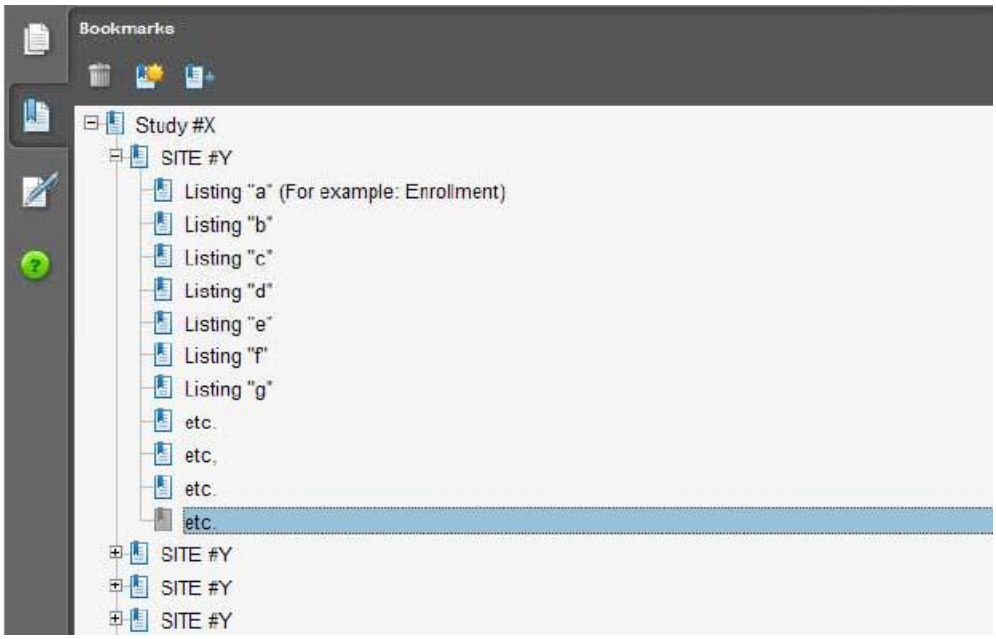
The OSI Item II includes 10 subject level data listings (aka "line listings") by site, as below, for each pivotal study.

a. Subject listing for each subject screened and reason(s) for subjects who did not meet eligibility requirements.
b. Subject listing for treatment assignment (randomization)
c. Subject listing of drop-outs and discontinuations, with date and reason
d. Subject listing of evaluable/non-evaluable subjects and reason not evaluable
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing of laboratory tests performed for safety monitoring

Most of these listings are standard and straightforward. It is well-known that standard departmental listing shells with supporting macros in place greatly improves efficiency and quality for this kind of standard programming work. It is also worthwhile to mention the following lessons learned in the process of generating the listings:

- For the by subject listing of screening and enrollment information, the FDA OSI confirmed that it should include all sites that screened at least one subject, even if the site did not actually enroll or randomize any subjects.
- Even though the FDA didn't specify if the global site ID or study-specific site ID should be included in the listings, the authors' expectation is that it would be useful for the inspection if both are included, as the sponsor usually uses the study-specific site ID while the FDA requests global site ID in the BIMO dataset (see Section for Item III).
- For subjects who changed sites during the study, it is recommended to list the subjects in the final site to be consistent with the BIMO dataset (see Section for Item III).
- For the subject listing of AEs, SAEs, and deaths, it is recommended to include all AEs whether it is before or after first dose of investigational product. A treatment-emergent flag may be included to provide the details. A similar concept applies to the listing of concomitant medications.
- All protocol violations/deviations should be included whether they are important or not.

Meanwhile, FDA requires one PDF with bookmarks for each study to be created by using the following format.



This format is very different from the traditional rtf format for CSR tables, figures, and listings (TFLs). A SAS® macro %m_bimo_listing_004 (…) using PROC DOCUMENT was developed to produce this combined pdf file with bookmarks after individual listings are created.

To generate the combined pdf file with bookmarks using the macro, the three key steps are as follows:

Step 1: BIMOINFO lookup table program creates BIMOINFO SAS® dataset, which will be used for all listings and includes the following information

- The population of all subjects that may appear in the listing including screen failure subjects.
- The population of sites through the variable SITEID and SITEIDSS
- The IDLINE variable(s) used to display subject demographic information in a box at the top of a page.

Step 2: Individual listing programs, which are similar to any CSR TFL programs for the data process part, need to call %m_bimo_listing_004 using the default MODE=REPORT at the end of the listing program. Thus each listing program will create a SAS® file called an item-store. In addition, the macro will create a program specific library to contain other program specific artifacts to be used for generating the combined PDF file.

Step 3: Once all or a few of the individual listings are programmed and producing satisfactory outputs, the combined BIMO document can be created. The program consists simply of a call to the initial programming environment setting program (which varies bycompany) followed by a call to %M_BIMO_LISTING_004 using the MODE=REPLAY parameter, like below.

```
%inc 'init.sas';
%m_bimo_listing_004(mode=replay);
```

In REPLAY mode the macro looks in the output/data directory for the specific type of SAS® files created by ODS DOCUMENT in the listing programs. The macro queries the information in these SAS® files, then combines and sorts the information as needed to produce the BIMO combined document. Finally, the macro generates the PROC DOCUMENT statements needed to create a new combined document from these individual inputs.

OSI REQUESTS ITEM III – CLINSITE.XPT

The BIMO dataset (i.e., clinsite.xpt) requested in OSI Item III is for use in a clinical site selection model being piloted in CDER. In recent submissions, it has become an item in the standard OSI request. In 2012, CDER published *draft guidance for industry* and *draft specifications* for preparing and submitting this summary level clinical site data for CDER's inspection planning. According to the FDA specifications, the BIMO dataset is a single summary level clinical site dataset that contains data from all pivotal studies used to support safety and efficacy in the application. It covers a few categories of information as listed below:

1) Site identification number and contact information
2) Principal investigator's name and contact information
3) Number of subjects screened, randomized, treated but prematurely discontinued at each site
4) Number of serious adverse events, non-serious adverse events and deaths at each site
5) Treatment arm, treatment efficacy endpoint and site-specific treatment effect at each site
6) Total and maximum financial disclosure amounts in US dollar at each site

Although the FDA provides specifications for the data elements to be included in the BIMO dataset, the specifications are not sufficient to be used directly by biostatistical programming. The FDA specifications must be further converted into more detailed data specifications which are specific for the studies included in a given submission. For improved consistency and efficiency, this conversion can be done in two steps. First, convert the FDA specifications into a departmental template. Second, develop submission-specific data specifications based on the departmental template, i.e., create the define file to be included in the submission.

The BIMO dataset has a data structure of one record per study per site per arm per endpoint. For the purpose of this dataset, the OSI confirmed that all clinical sites which screened at least one subject should be included, even if the site did not actually enroll or randomize any subject. The data elements in the BIMO dataset come from different sources, SDTM, ADaM, derived, and additional data collection outside the clinical study database. Data source and derivation algorithms need to be documented in the specifications (i.e., define file).

One main challenge in creating the BIMO dataset is that some variables do not exist in the SDTM or ADaM datasets and their derivation involve complex logic and even statistical modeling. Especially for the variables of treatment efficacy endpoints and site treatment effect, which are study specific, the biostatistical programming team must collaborate with study statisticians to define the algorithm and derive them accurately.

The BIMO dataset package usually contains clinsite.xpt and define.pdf. A data reviewer's guide is not required, although recommended by the FDA. The M5 structure in eCTD for submitting the BIMO dataset package can be found in the OSI request (see an example in Appendix A).

CONCLUSION

The FDA has been requesting applicants to include the OSI requests in marketing applications that involve clinical trial data. Although the OSI request is similar across submissions, it usually requires significant programming resources to prepare the package. It is helpful to plan the process and understand the required data elements ahead of a submission.

Currently, the FDA is seeking public comments on their new draft BIMO guidance and technical conformance guide (deadline is April 17, 2018 for public comments), which, when finalized, will supersede the previously issued draft guidance and specifications. Although it is not expected that the BIMO listings and data set contents change dramatically, applicants should prepare the OSI items based on the OSI requests received and the applicable FDA guidance available at the time of submissions.

REFERENCES

Guidance for Industry Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning

Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning

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CONTACT INFORMATION

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APPENDIX A: AN EXAMPLE OF THE OSI REQUESTS

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, by site, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

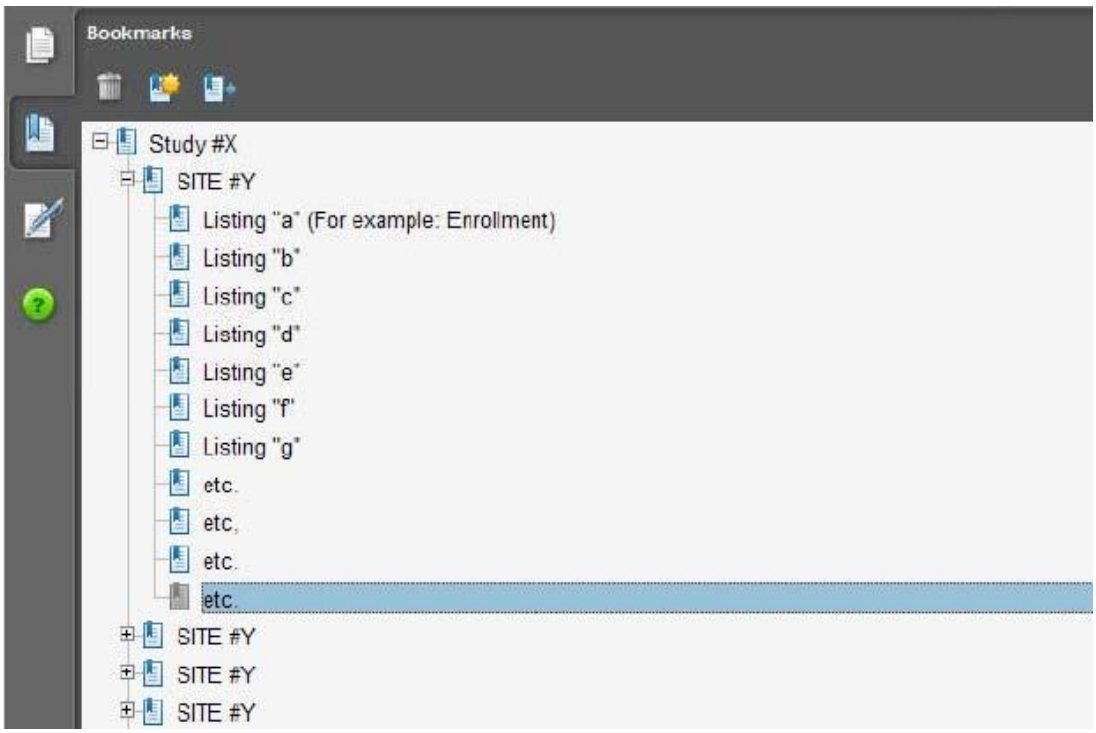
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level

datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

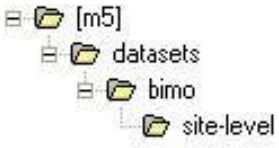
Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 (M5) of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.