FDA BIMO PACKAGE PREPARATION FOR CDER

Robert Tai, 18May2018

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OUTLINE

- WHAT is BIMO?
- FDA BIMO Package for CDER
- HOW to do BIMO Package?
- Future & Challenge
- Reference
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WHAT IS BIMO?

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WHAT IS BIMO?

- BIMO is the acronym of bioresearch monitoring.

- The BIMO program was established in 1977 included by a task force that included representatives from the drug, biologic, device, animal drug, and food areas and provide uniform guidance and specific instructions for inspections of Clinical Investigators, Sponsors, In-Vivo Bioequivalence facilities, Institutional Review Boards, and Non-Clinical Laboratories.

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WHAT IS BIMO?

- BIMO Inspection Metrics – FY'16
- The inspectional data cover all aspects of FDA's BIMO program (i.e., clinical investigators, IRBs, sponsors, bioequivalence, and good laboratory practices) for all Centers, as applicable.

BIMO Inspections Classified FY 2016

Center	CI	IRB	Spon/Mon/CRO[1]	GLP	Total
CBER	93	7	6	0	106
CDER[2]	478	81[3]	58	32	649
CDRH	184	35	46	5	270
CFSAN	1	1	0	1	3
CTP	0	0	0	0	0
CVM	19	n/a	2	6	27
Totals[2]	775	124	112	44	1055

[1] Sponsor/Monitor/CRO inspection totals include Sponsor/Investigator inspections.
[2] In FY 2016, CDER classified 362 inspections of bioavailability/bioequivalence sites (CPGM 7348.001), raising the total BIMO inspections in FY 2016 to **1417**. (1055 + 362 = 1417)
[3] The number of IRB inspections includes 1 Radioactive Drug Research Committee (RDRC) inspection.

- **CBER** = Center for Biologics Evaluation and Research
- **CDER** = Center for Drug Evaluation and Research
- **CDRH** = Center for Devices and Radiological Health
- **CFSAN** = Center for Food Safety and Applied Nutrition
- **CTP** = Center for Tobacco Products
- **CVM** = Center for Veterinary Medicine
- **CI** = clinical investigator
- **GLP** = good laboratory practices
- **IRB** = institutional review board
- **Spon/Mon** = sponsor/monitor

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WHAT IS BIMO?

- The objectives of the BIMO program are:
  - To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials
  - To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications
  - To assess compliance with FDA's regulations governing the conduct of clinical trials
- The FDA's **O**ffice of **R**egulatory **A**ffairs (ORA) is the office responsible for the conduct of the inspections:
  - Has responsibility to select sites for on-site inspection as part of the FDA's BIMO program
  - Each sponsor's help is needed in order to perform this selection quickly and efficiently

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FDA BIMO PACKAGE FOR CDER

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FDA BIMO PACKAGE FOR CDER

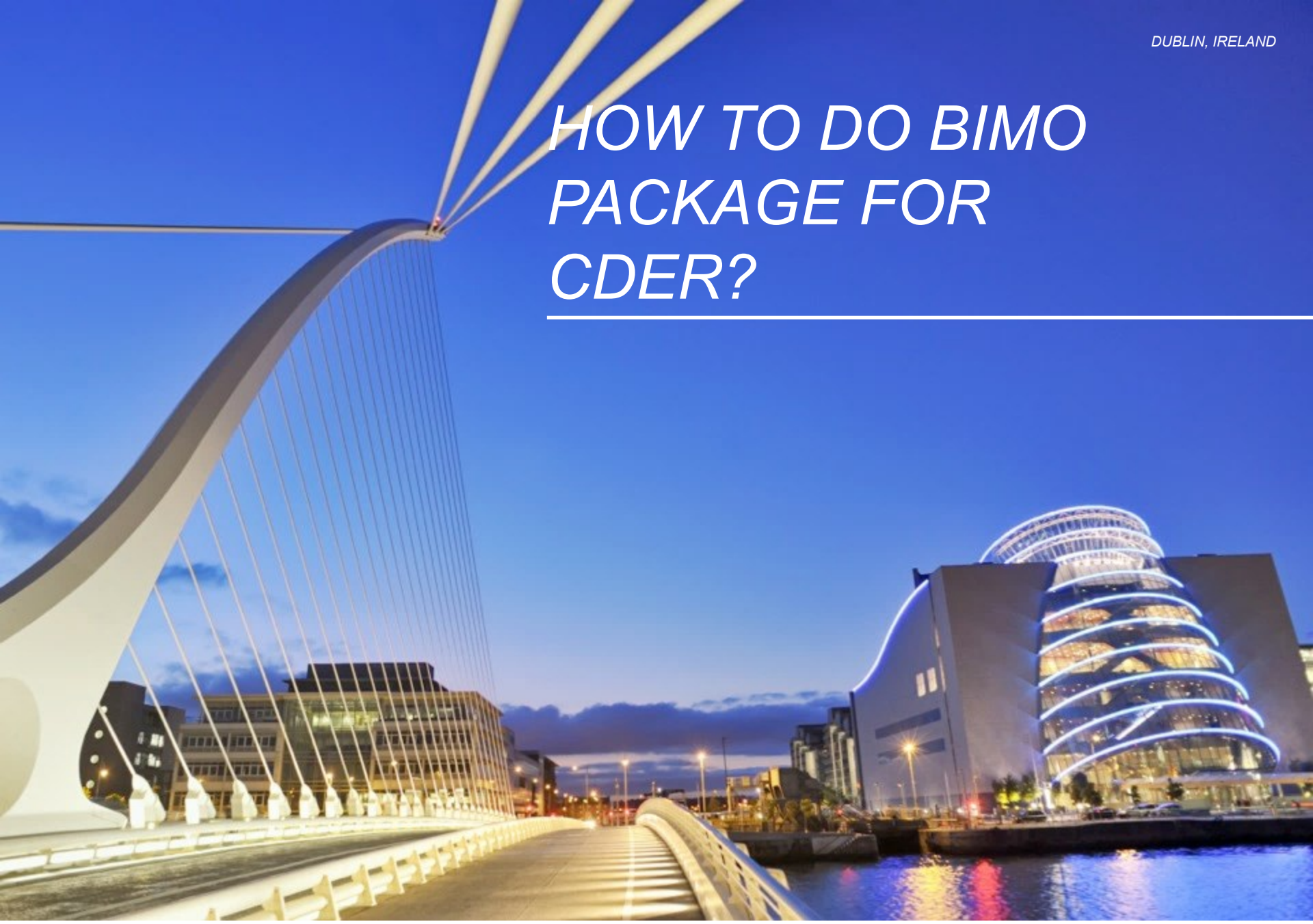
- In Feb 2018, Center for Drug Evaluation and Research (CDER) is released a draft guidance, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of BIMO Inspections for CDER Submissions*.

- This draft guidance supersedes the previous guidance, *Providing 11 Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning.*

- NOTE: Twenty-four months after this draft guidance has been finalized, the data in NDAs and BLAs described in this guidance must be submitted electronically in the format specified in this guidance.

FDA BIMO PACKAGE FOR CDER

- This guidance applies to all major (i.e., pivotal) studies used to support safety and efficacy claims in new drug applications (**NDAs**), biologics license applications (**BLAs**) regulated by CDER and supplemental applications containing new clinical study reports.
  - Also applies for certain investigational new drug applications (INDs) in advance of a planned NDA, BLA, or supplemental submission
- CDER has developed a risk-based model to select clinical investigator sites for inspection. To facilitate site selection, the model uses **a summary-level clinical site dataset** that describes and summarizes the characteristics and outcomes of clinical investigations, both at the study level and at the level of the individual study site.



HOW TO DO BIMO PACKAGE FOR CDER?

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HOW TO DO BIMO PACKAGE FOR CDER?

- BIMO package consist of three main parts referred to as Parts I, II, and III, respectively. In addition, a corresponding define file and reviewer's guide is also required:
  - Part I: Clinical Study-Level Information
  - Part II: Subject-Level Data Line Listings by Clinical Site
  - Part III: Summary-Level Clinical Site Dataset
  - Define File
  - BIMO Reviewer's Guide which is the documentation about the location of above within the submission
- **NOTE:** For clinical investigator sites involved in multiple studies in support of an application, the data independently for each study within the dataset should be provided.

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HOW TO DO BIMO PACKAGE FOR CDER?
PART I: CLINICAL STUDY-LEVEL INFORMATION

- **Comprehensive and Readily Located List of All Clinical Sites**

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)
SITEID	LASTNAME, FRSTNAME, MINITIAL	FACILITY NAME STREET CITY, STATE, POSTAL COUNTRY	PHONE FAX EMAIL

- **Table Listing All Entities to Whom Sponsor Has Contracted Clinical Study-Related Activities**

- **Protocol, Protocol Amendments, and Annotated Case Report Form**

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HOW TO DO BIMO PACKAGE FOR CDER? PART I: CLINICAL STUDY-LEVEL INFORMATION - EXAMPLE

Table 1 General Study xxxxand Clinical Investigator Information

Site Number	Principal Investigator	PI/Site: Name Address Country	PI/Site Contact: Phone Fax (F) Email
1234	Violaine PLANTE - BORDENEUVE	ABC, Department of Oncology No. 200, ABC road, A City, 12345 Country	01 1234 56 78 01 1223 56 89 (F) robert.tai@abc.org

Table 2 Number of Subjects in Study xxxxScreened, Randomized, and Treated who Prematurely Discontinued

Site Number	Principal Investigator (Last Name)	Number of subjects screened	Number of subjects randomized	Number of subjects treated who prematurely discontinued
1234	Plante	10	8	2

3. Location of sponsor trial documentation, Contract Research Organization (CRO), and trial documentation generated by the CRO

a. Sponsor trial documentation (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) is maintained and would be available for inspection at the following location:

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22F, No. 200, Sec. 1, Keelung Road
Taipei, Taiwan, 11071 R.O.C

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HOW TO DO BIMO PACKAGE FOR CDER? PART II: 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 (primary data points in addition to derived data)*
- *9. Concomitant Medications*
- *10. Safety Monitoring*

If a sponsor believes additional listings are needed to permit FDA to verify key study data during inspections, additional listings should be included.

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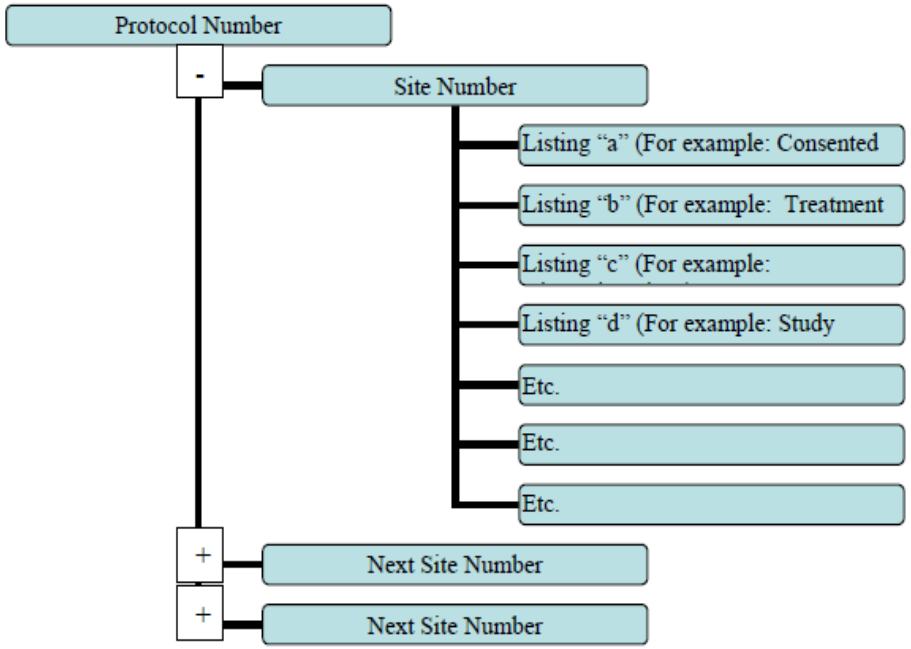
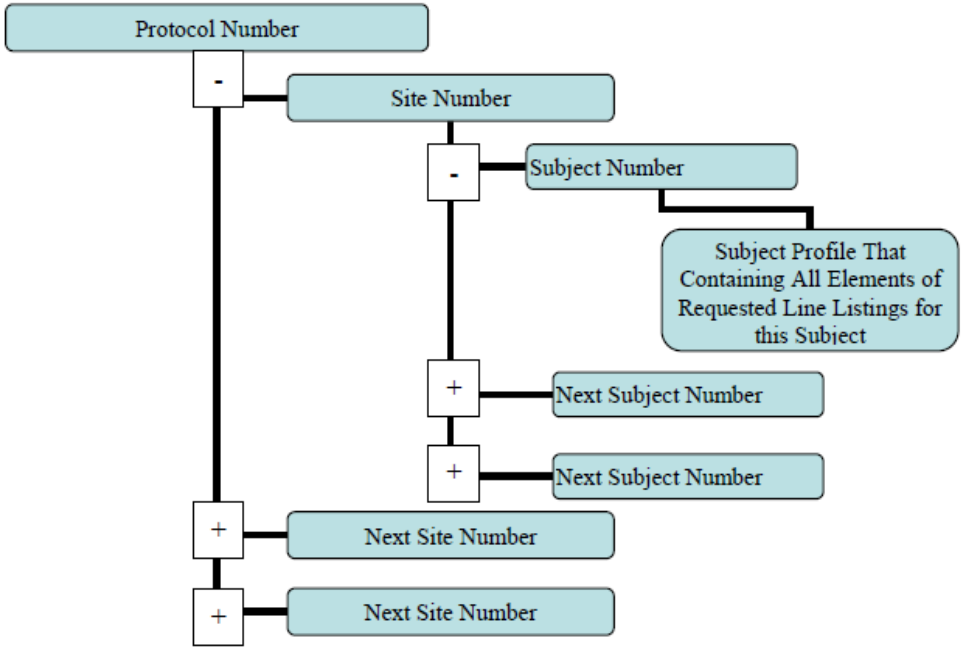
HOW TO DO BIMO PACKAGE FOR CDER? PART II: SUBJECT-LEVEL DATA LINE LISTINGS BY CLINICAL SITE - FORMAT

Two options for formatting for the PDF of subject-level data line listings

By Site, By Listing



By Site, By Subject Profile



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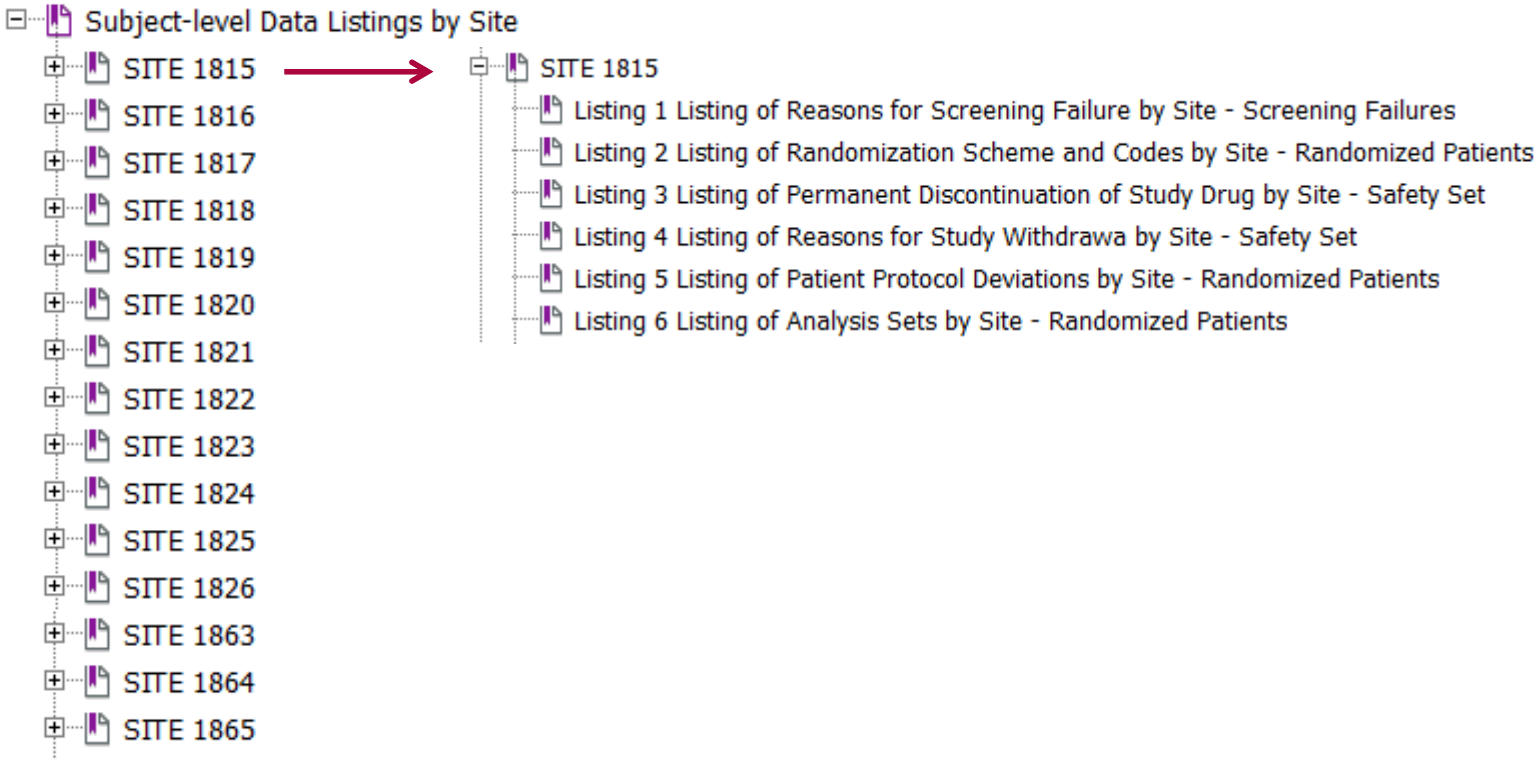
HOW TO DO BIMO PACKAGE FOR CDER?
PART II: SUBJECT-LEVEL DATA LINE LISTINGS BY CLINICAL SITE - EXAMPLE



NOTE: Technical issues while combining too many rtf files into one PDF
(XXX subject listings x YYY clinical sites)

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HOW TO DO BIMO PACKAGE FOR CDER?
PART III: A SUMMARY-LEVEL CLINICAL SITE DATASET

The summary level clinical site dataset is intended:

- To characterize individual clinical investigator sites
- To describe aspects of the studies associated with those clinical investigator sites
- To present the characteristics and outcomes of the study at the site level
- **Name:** clinsite.xpt
- **Format:** SAS transport file
- **Structure:** one record per pivotal study, per clinical site, per treatment arm. 39 pre-defined variables with specific names, labels, definitions and formats.

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HOW TO DO BIMO PACKAGE FOR CDER?
PART III: A SUMMARY-LEVEL CLINICAL SITE DATASET

Variables for general information and information about included studies

Variables for site information

Variables for characteristics and outcomes by study, site and treatment arm

Variable Index	Variable Name	Variable Label
1	STUDYID	Study Identifier
2	STUDYTL	Study Title
3	SPONCNT	Sponsor Count
4	SPONNAME	Sponsor Name
5	IND	IND Number
6	UNDERIND	Under IND
7	NDA	NDA Number
8	BLA	BLA Number
9	SUPPNUM	Supplement Number
10	SITEID	Study Site Identifier
11	ARM	Description of Planned Treatment Arm
12	SAFPOP	Number of Subjects in Safety Population

Variable Index	Variable Name	Variable Label
13	SCREEN	Number of Subjects Screened
14	DISCSTUD	Number of Subject Discons from Study
15	DISCTRT	Number of Subject Discons from Study Treatment
16	ENDPOINT	Primary Endpoint
17	ENDPTYPE	Primary Endpoint Type
18	TRTEFFR	Treatment Efficacy Result
19	TRTEFFS	Treatment Efficacy Result Standard Deviation
20	SITEEFFE	Site-Specific Treatment Effect
21	SITEEFFS	Site-Specific Treatment Effect Standard Deviation
22	CENSOR	Number of Censored Observations
23	NSAE	Number of Non-Serious Adverse Events
24	SAE	Number of Serious Adverse Events

Variable Index	Variable Name	Variable Label
25	DEATH	Number of Deaths
26	PROTVIOL	Number of Protocol Violations
27	FINLDISC	Financial Disclosure Amount
28	LASTNAME	Investigator Last Name
29	FRSTNAME	Investigator First Name
30	MINITIAL	Investigator Middle Initial
31	PHONE	Investigator Phone Number
32	FAX	Investigator Fax Number
33	EMAIL	Investigator Email Address
34	COUNTRY	Country
35	STATE	State
36	CITY	City
37	POSTAL	Postal Code

Variable Index	Variable Name	Variable Label
38	STREET	Street Address
39	STREET1	Street Address Continued

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HOW TO DO BIMO PACKAGE FOR CDER?
PART III: A SUMMARY-LEVEL CLINICAL SITE DATASET – EXAMPLE

STUDYID	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	SAFPOP	SCREEN	DISCSTUD
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	'	'	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	'	'	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	'	'	001	Placebo	25	61	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	'	'	001	Placebo	25	61	4

DISCTRT	ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLDISC	LASTNAME	FRSTNAME
3	Percent Responders	Binary	0.48	0.0980	0.34	0.1405	'	0	2	0	1	< $25,000	Doe	John
2	Change from Baseline	Continuous	0.74	0.0861	0.60	0.1502	'	0	2	0	1	< $25,000	Doe	John
3	Percent Responders	Binary	0.14	0.0694	0.34	0.1405	'	2	2	0	1	< $25,000	Doe	John
4	Change from Baseline	Continuous	0.14	0.0699	0.60	0.1502	'	2	2	0	1	< $25,000	Doe	John

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET	STREET2
M	555-123-4567	555-123-4560	John@mail.com	RUS	Moscow	Moscow	103009	Kremlin Road 1	
M	555-123-4567	555-123-4560	John@mail.com	RUS	Moscow	Moscow	103009	Kremlin Road 1	
M	555-123-4567	555-123-4560	John@mail.com	RUS	Moscow	Moscow	103009	Kremlin Road 1	
M	555-123-4567	555-123-4560	John@mail.com	RUS	Moscow	Moscow	103009	Kremlin Road 1	

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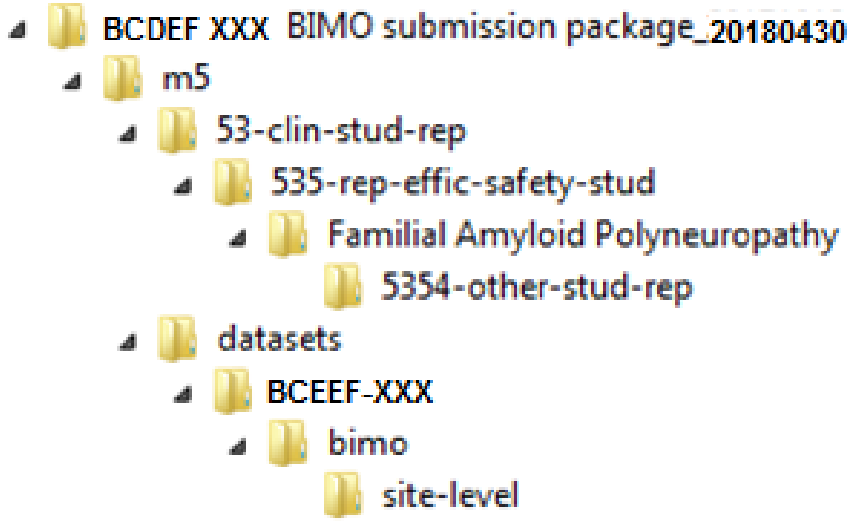
HOW TO DO BIMO PACKAGE FOR CDER?

- **Documentation:** Define file, Reviewer Guide
- **Location:** Within the directory structure, place the site-level dataset in the M5 folder



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FUTURE & CHALLENGE

- CDER is in the process of developing tools to extract site-specific listings, needed for inspectional purposes, from submitted CDISC, Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM) datasets.

- FDA intends to update these technical specifications to include details for the submission of SDTM and ADaM datasets, including controlled terminology standards.

- Now, only CDER have this guides but it may expend to other centers, e.g. CBER, CDRH, etc.

- I believe that more regulatory agencies will follow this way to standardize those data to facilitate the timely identification of sites for inspection and full information to conduct the inspections.

REFERENCE

- BIORESEARCH MONITORING TECHNICAL CONFORMANCE GUIDE https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/ucm332468.pdf

- Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions Guidance for Industry *(DRAFT GUIDANCE)* https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/ucm332466.pdf

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Q & A

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THANK YOU

