



Development of standard BIMO process to create clinsite dataset

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As a scientist at Janssen, Jeff uses his unique perspective and an array of artistic techniques to express his vision.

Agenda

1 FDA Bioresearch Monitoring (BIMO) Technical Conformance Guide

Janssen BIMO Project Deliverables

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 - Process Documentation
 - Clinsite.xpt metadata
 - Programs/Macros for clinsite dataset and define.pdf
-

3 Current challenges and solution

- Trial and site information not in STDM, ADaM datasets
-

4 Lessons Learned

5 Q&A

BIMO – FDA Requirements

BIORESEARCH MONITORING TECHNICAL CONFORMANCE GUIDE

Containing Technical Specifications
released February 2018



- <https://www.fda.gov/downloads/drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>
- Specifications for preparing and submitting information for planning of Bioresearch Monitoring (BIMO) inspections.
 - I. CLINICAL STUDY-LEVEL INFORMATION
 - II. SUBJECT-LEVEL DATA LINE LISTINGS BY CLINICAL SITE
 - III. SUMMARY-LEVEL CLINICAL SITE DATASET
- APPENDIX 3: CLINICAL SITE DATA ELEMENTS SUMMARY LISTING
Total of 39 variables included

BIMO – FDA Requirements (39 variables)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDYID	Study Identifier	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters). If the title exceeds 200 characters, provide shortened title and define (e.g., use the abbreviated title from Clinicaltrials.gov)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
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
4	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3. If the sponsor name exceeds 200 characters, provide short form sponsor name and define.	DrugCo, Inc.
5	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, leave blank.	010010
6	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND (i.e., a Form FDA	Y
38	STREET	Street Address	Char	String	Street address and office number at which the site is located. (Limit 200 characters)	2005 John Fitzgerald Kennedy Boulevard Northwest, International Technology Center, Department of Medicine and Pharmacokinetics, National Institute of Clinical Research Twin Towers Building.
39	STREET1	Street Address Continued	Char	String	Street address and office number at which the site is located. Use this field when Variable STREET does not permit sufficient space to fully describe street address and office number at which the site is located.	The Executive Wing, Suite # 209

BIMO Submission Requirements

- Purpose:
Planning FDA Bioresearch Monitoring (BIMO) inspections
- Deliverables:
 - I. Clinical Study-Level Information
 - II. Subject-Level Data Line Listings by Clinical Site
 - Currently PDF files – Previously known as OSI listings (FDA office of Scientific Investigations)
 - Future extracted from SDTM, ADaM Datasets
 - III. Summary-Level Clinical Site Dataset
 - clinsite.xpt
 - define.pdf

Janssen BIMO Team and Deliverables

- Multiple FDA NDA/BLA submissions required BIMO/OSI SAS programming efforts
- Cross Functional Team Formed June 2018
 - Clinical Development Standards; Statistical Programming & Analysis; Statistics & Decision Sciences
 - Global Trial Leads; Clinical Trial Management System (CTMS) Specialists
 - All Therapeutic Areas represented across NA / EU / Asia Pacific regions



Janssen BIMO Team and Deliverables (cont'd)



- Scope
 - Summary Level Clinical Site Dataset
 - SAS V5 transport file clinsite.xpt
 - Data definition file define.pdf
- Out of Scope
 - Clinical study-level information
 - Available in PDF documents
 - Subject-level data line listings by clinical site
 - Future generation by FDA from CDISC SDTM and ADaM datasets

Janssen BIMO Team and Deliverables (cont'd)

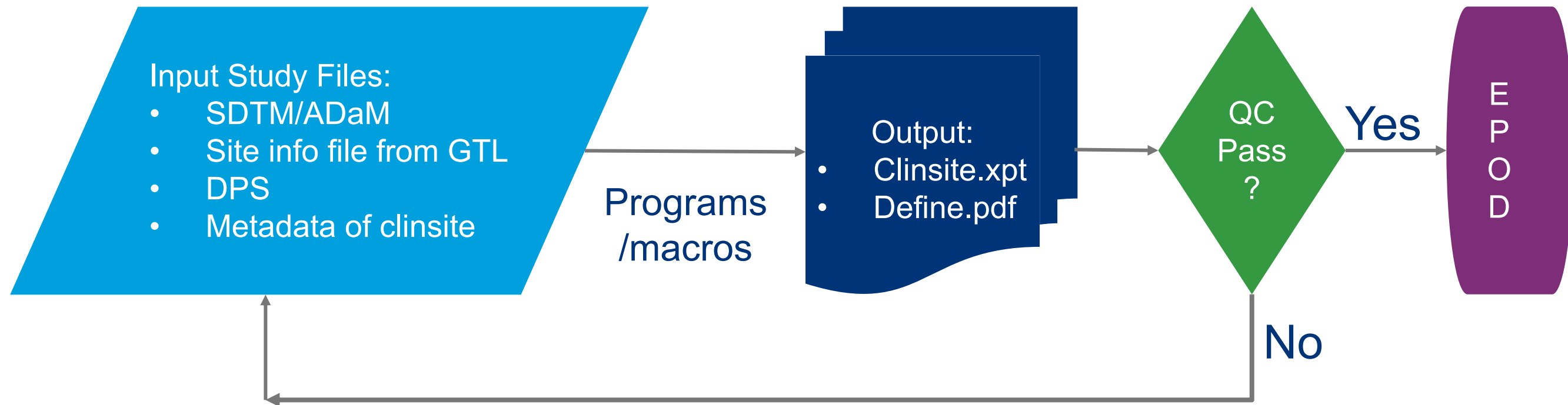


**'Beam me up' into providing
compliant Bioresearch Monitoring
deliverables to the FDA**

- The BIMO project had many challenges to work out with a short timeline and across many functions
... To keep things fun, the team decided to create a BIMO logo
- BIMO Process and tools delivered September 2018

Janssen BIMO Process

BIMO Programming Process/Data Flow



GTL - Global Trial Lead
DPS - Data Presentation Specification
EPOD - Electronic Publishing Output Drive (Regulatory)

Janssen BIMO Project Deliverables

Process documentation

1. BIMO process guidance document
 - Includes detailed steps needed to create the clinsite.xpt, define.pdf and optional reviewers guide to support a compliant BIMO submission
 - Scope, description, process flow
 - Use of metadata templates, sample programs, standard macros
 - Responsibilities by role
2. CLINSITE metadata Excel workbook
 - Excel metadata describing full clinsite dataset
3. Site information template Excel workbook
 - Template to communicate site information not present in SDTM/ADaM:
 - CTMS information, financial information, submission detail



Janssen BIMO Project Deliverables

Process documentation (Continued)



4. Sample BIMO data reviewers's guide

- Not required at this time but helps the reviewer
- If more than one study is included in an application submission, and a BIMO reviewer's guide is included with the submission, please use one BIMO reviewer's guide to include all the studies for which clinsite.xpt files have been provided.

5. Sample BIMO data presentation specifications document (DPS)

- The DPS will include descriptions of the BIMO requirements from FDA discussions
- Listings needed with mockup layouts
 - Derivation algorithms for safety and efficacy variables programmed in the clinsite SAS dataset

CLINSITE metadata Excel workbook

Pre-Work: FDA Conformance Guide APPENDIX 3

- Convert to Clinsite_metadata_FDA.xlsx
39 variables classified
 - Study information (10)
 - Site information (14)
 - Safety results (10)
 - Efficacy results (5)
- Labels > 40 characters truncated in SAS Transport format
DISCTRT, TRTEFFS and SITEEFS
- Special characters in sample values
FINLDISC (Financial Disclosure Amount): $\geq$ \$25,000
- Update to clinsite_metadata_Janssen.xls
 - Labels shortened to 40 char
 - Sample value to ">= \$25,000"

Site information template Excel workbook

[CLINSITE_xxxx_GTLtemplate.xlsx](#)

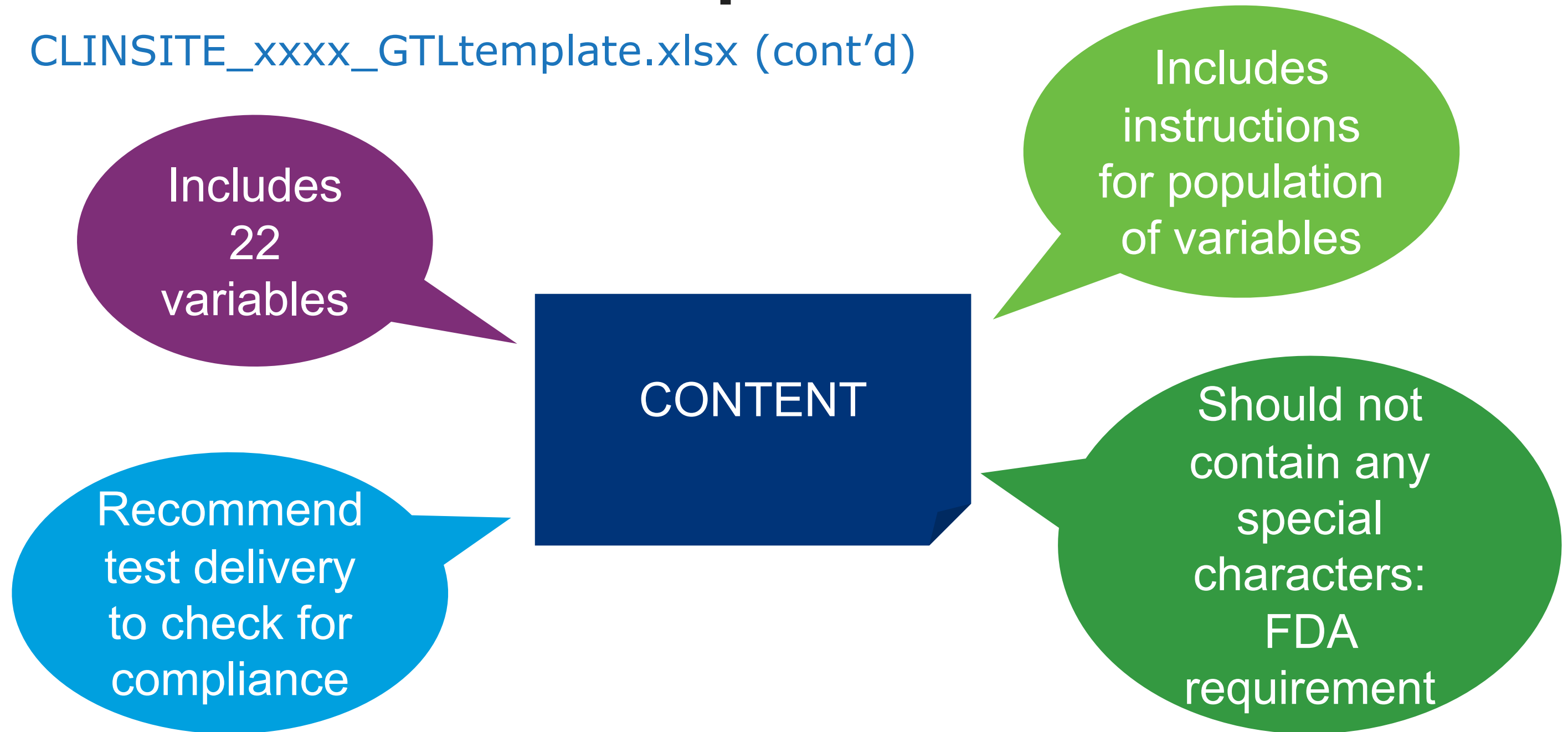
Purpose:

- Communicate information not currently present in SDTM/ADaM
- Programmer <-> Global Trial Lead (GTL)
 - Site details
 - Site financial disclosure
 - Sponsor information
 - Submission details



Site information template Excel workbook

CLINSITE_XXXX_GTLtemplate.xlsx (cont'd)



Site information template Excel workbook

[CLINSITE_xxxx_GTLtemplate.xlsx \(cont'd\)](#)

Workbook with 2 tabs:

- Readme – Detailed instructions for each variable
 - From Appendix 3:
Variable index; Variable name; Variable label;
Type; Controlled terms or format; Notes or description;
Sample value
 - For communication:
Notes to GTL; Comments from GTL
- Datasheet – For data entry by Global Trial Lead
 - Rows from Readme tab transposed to columns for data entry
 - Row 1: column headers as valid SAS variable names
 - Row 2: dummy values of very long length – prevent truncation
 - Data entry starts at row 3

Site information template Excel workbook

[CLINSITE_xxxx_GTLtemplate.xlsx \(cont'd\)](#)

Study Information examples

- SPONCNT “Sponsor Count”

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”.

- IND “IND Number”

Investigational New Drug (IND) application number. If study not performed under IND, leave blank.

Site information template Excel workbook

[CLINSITE_xxxx_GTLtemplate.xlsx \(cont'd\)](#)

Study Information examples (cont'd)

- UNDERIND “Under IND”

Value should equal “Y” if study at the site was conducted under an IND (i.e., a Form FDA 1572 was signed by the investigator) and “N” if study was not conducted under an IND at the site (i.e., a Form FDA 1572 was not signed by the investigator).

- FINLDISC “Financial Disclosure Amount”

Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the clinical investigator and all sub-investigators to include all required parities under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). Enter “>= \$25,000”, “< \$25,000”, “unknown” if a proper value is applicable but is not known (i.e., unable to obtain information from investigator at site), or “masked” if information on this item is available but it has not been provided by the sender due to security, privacy or other reasons.

Program/Macro code for clinsite.xpt and define.pdf

BIMO standard macros

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.

Program/Macro code for clinsite.xpt and define.pdf (continued)

eSub standard macros

eSUB Macro	Purpose
dtoxpt.sas	Convert SAS datasets to SAS V5 transport files.
esconvertmetadata.sas	Convert metadata to value level structure for define.pdf.
esexceptionrpt.sas	Generate eSub exception report (variables > 8 characters, labels >40 characters, etc.).

Program/Macro code for clinsite.xpt and define.pdf (continued)

BIMO sample programs (call standard macros)

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.
Adclinstemetadata.sas	adclngetattributes.sas	Create clinsite metadata attributes.
Escreateaclinxpt.sas	dtoxpt.sas esexceptionrpt.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.

BIMO Current Challenges and Solutions

- Challenge:
Trial and site information not currently in SDTM, ADaM datasets
- Solution
CDISC could help by defining structure for trial and site information needed.
-> Include in existing SDTM/ADaM or add new clinsite domain.



BIMO Lessons Learned

- BIMO is a **Must Do** for FDA submission.
 - Risk to file acceptance due to importance of FDA inspection planning
 - Integrate into submission activity priorities
- FDA does a thorough review of clinsite.xpt including use of tools.
- Include **all** sites that have any consented subjects, even if all site data (safety and efficacy) are excluded from CSR.
- Collaboration between **Statistical Programmer – Statistician – GTL** is key.
Regulatory advise for some information.



BIMO Lessons Learned (continued)

- Pre-submission meeting with FDA.
 - Clarify BIMO requirements leading to BIMO Data Presentation Specifications (DPS)
 - Is a reviewers's guide needed?
- Initiate site data collection early.
 - At least 1-2 months prior to Pivotal trial DB lock
 - Provide template
- Prepare listings.
DPS required from Statistician for clinical site and related listings.



BIMO Lessons Learned (continued)

- Multiple Investigators per Site.
 - Clinsite dataset **should** be unique by study, site and treatment arm
 - When more than one primary efficacy endpoint exists, additional rows should be added to the dataset to report additional ENDPOINT, ENDPTYPE, TRTEFFR, TRTEFFS, SITEEFFE and SITEEFFS values by arm for each site.
 - FDA tool cannot accept duplicate site records
 - If site has multiple investigators, use most recent clinical investigator.
- Multiple Sites per Investigator.
 - Main site and satellite sites
 - Different subjects at the sites
 - Clinsite dataset is to include each site separately with unique assigned site number and unique site address



Questions & Answers

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