CDISC Italian User Network 2021

Virtual Event | 3 December 2021

SIMeF
Società Italiana di Medicina Farmaceutica
Italian Society of Pharmaceutical Medicine

IBIG
Italian Blostatistics Group

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Doing Good BIMO

News from the Data Submission Regulatory World

Angelo Tinazzi, Cytel Inc.

VIII CDISC Italian User Network

3 December 2021

Agenda

Doing Good BIMO

- BIMO What?
- BIMO Technical Conformance Guide
- Sponsor(s) Experience
- Conclusions

Data Submission News

BIMO What?

- What is for? Purpose

What is for? Purpose

1977 — FDA granted the right to audit clinical research sites

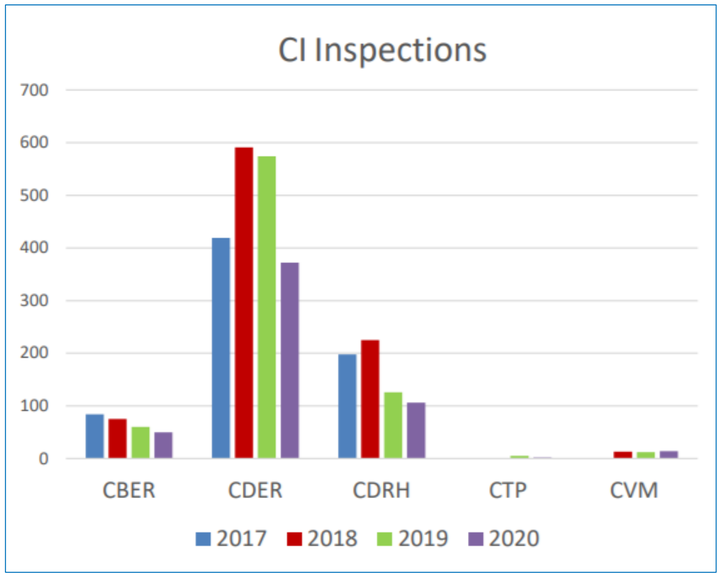
2011 — Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning

Feb-2018 — CDER BIMO Technical Conformance Guide (v1)

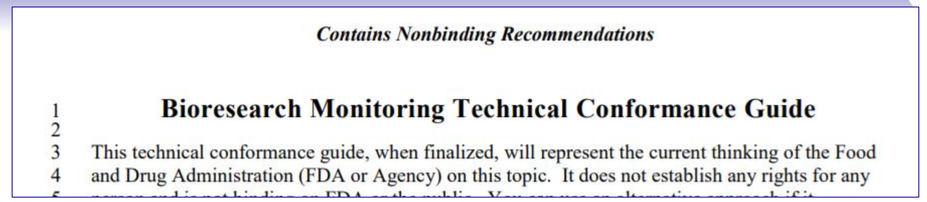
Jul-2020 — CDER BIMO Technical Conformance Guide (v2)

Applicable to NDA and certain BLA only

Bioresearch Monitoring (BIMO) Program, which created guidelines for agency inspections of clinical trial sites



Source: "Bioresearch Monitoring (BIMO) Fiscal Year 2020 Metrics" – FDA Presentation



Contains Nonbinding Recommendations

Bioresearch Monitoring Technical Conformance Guide

This technical conformance guide, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any

BIMO TCG Technical Details

- Content
- Individual Subjects Line Listings
- Site Level Dataset (clinsite.xpt)
- Documentation
- Planning
- eCTD

Content

https://www.fda.gov/media/85061/download

Specifications for preparing and submitting information for planning of Bioresearch Monitoring (BIMO) inspections.

Data from all Pivotal Studies

I. Clinical Study Level Information

- Studies Inventory
- Sites/Investigators locations
- Financial information
- Other study documents in eCTD study folder

II. Subject-Level Data Line Listings by Clinical Site

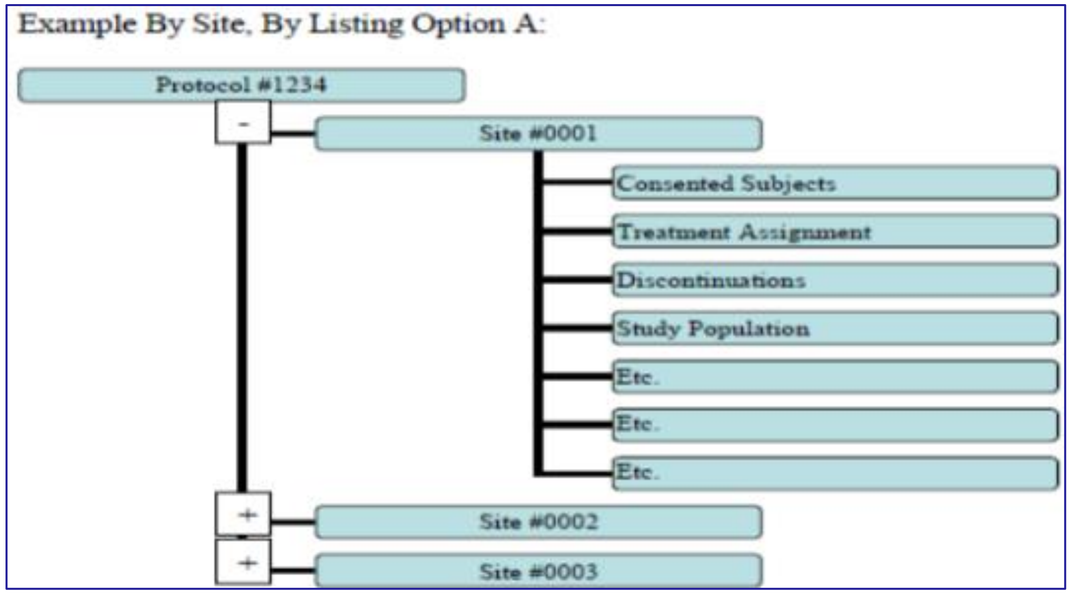
- Organized by Investigator site, listing type

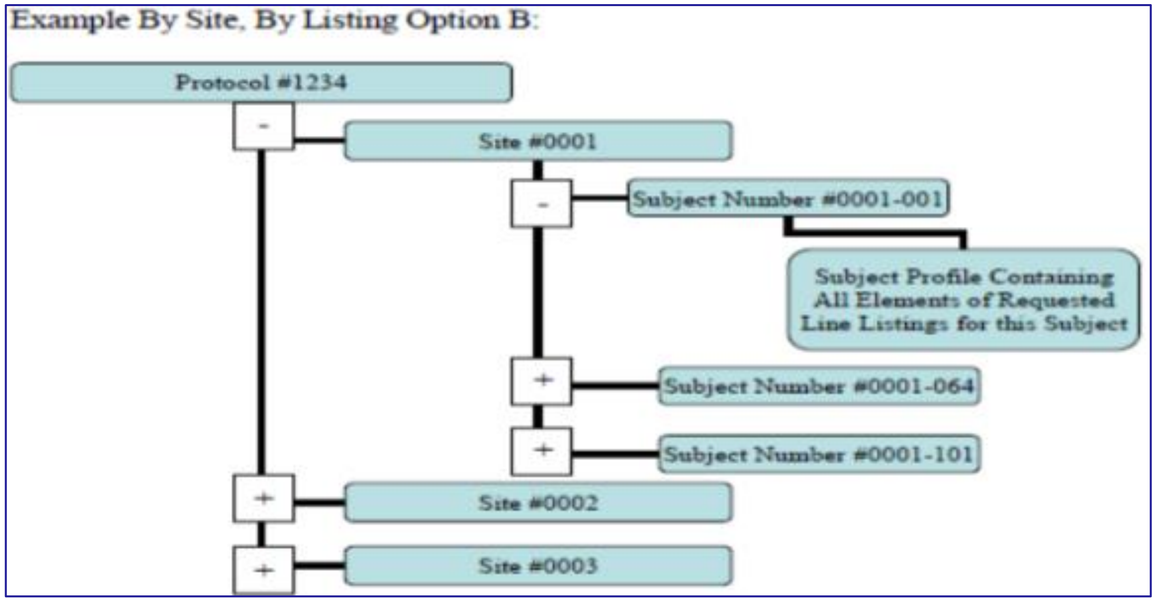
III. Summary-Level Clinical Site Dataset

- **clinsite.xpt**
- summary by study, investigator site, by arm
- Site variables from I.
- 39 standard variables in appendix
- define-xml (pdf)
- Reviewer guide (optional)

Individual Subjects Line Listings - By Clinical Site

- Subject-level data line listings provided for each major pivotal study
- For clinical investigator sites involved in multiple studies, subject listings should be provided independently for each study
- Details about the listings are provided in Bioresearch Monitoring Technical Conformance Guide
- PDF format

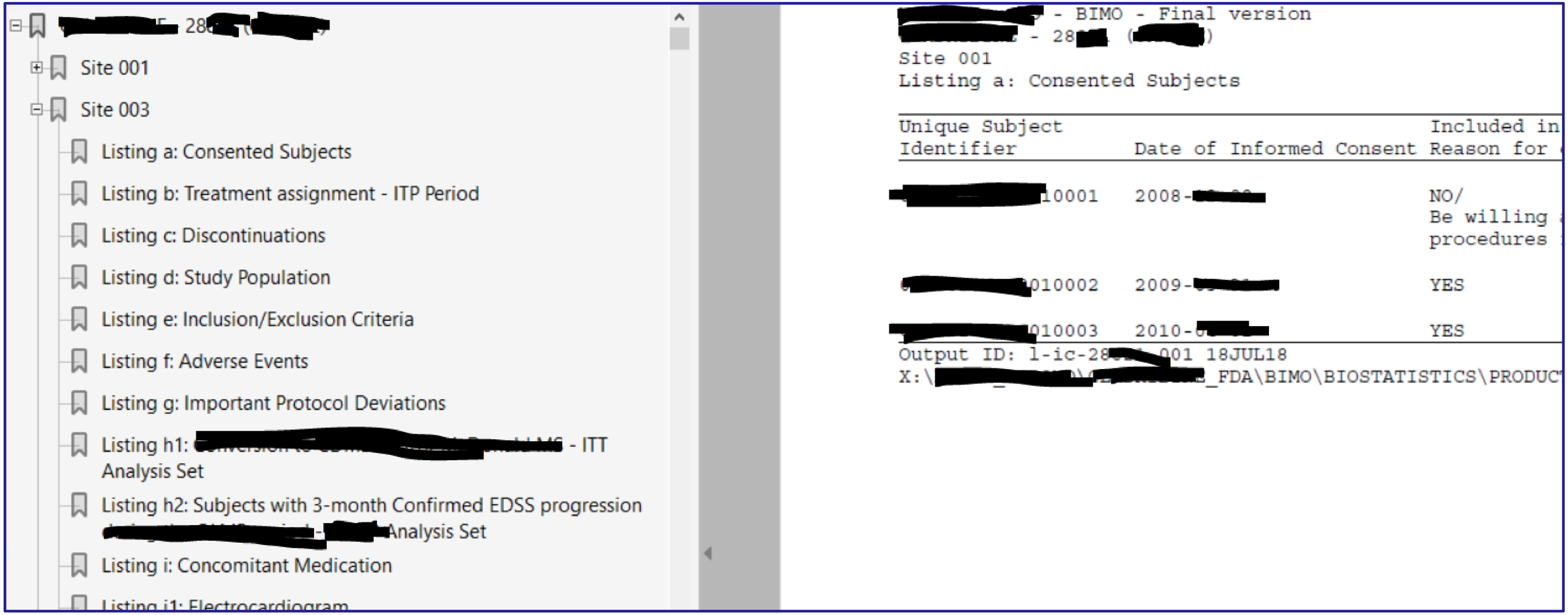




Individual Subjects Line Listings - By Clinical Site [Key Topics]

#	Topic
1	Consented Subjects
2	Treatment Assignment
3	Disposition / Discontinuations
4	Study Population
5	Inclusion/Exclusion Criteria
6	Adverse Events
7	Important Protocol Deviations
8	Efficacy Endpoints
9	Concomitant Medications
10	Other Safety Data e.g., Labs, Ecg, Vital Signs

Individual Subjects Line Listings - By Clinical Site [Key Topics]



Individual Subjects Line Listings - By Clinical Site [Possible Issues]

- 500 MB max file size, if more split
- Generate empty listings when no data are available e.g., no important protocol violations for a site
- If a site has multiple investigators use the most recent

Site Level Dataset (clinsite.xpt)

- One record per Pivotal Study per Clinical Site per Treatment/Arm per Endpoint
- Standard Set of Variables (39)

Study Level

STUDYID, TITLE, SPONCNT, SPONSOR, IND, UNDERIND, NDA, BLA, SUPPNUM, SITEID, ARM, COHORT

Safety & Primary Endpoint

SAFPOP, SCREEN, DISCSTUD, DISCTRT, ENDPOINT, ENDPTYPE, TRTEFFR, TRTEFFS, CENSOR, NSAE, SAE, DEATH, IMPDEV, NOIMPDEV

Site & Investigator

FINLDISC, LASTNAME, FRSTNAME, MINITIAL, PHONE, FAX, EMAIL, COUNTRY, STATE, CITY, POSTAL, STREET, STREET1

Site Level Dataset (clinsite.xpt)

Table B: Clinical Site Data Elements Summary Listing

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	TITLE	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 clinicaltrial.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 § 312.3 (21 CFR 312.3), enter an	1
13	SAFPOP	Number of Subjects in Safety Population	Num	Integer	Total number of subjects in safety population at a given site by treatment arm. When a subject has transferred from one site to another, the applicant should handle reporting of such subjects consistently across sites and include in the define file the reporting convention used. The applicant may opt to further explain the reasons subjects transferred between sites in the BIMO Reviewer's Guide, if a guide will be provided.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened (and consented) at a given site (overall number per site as subjects have not yet been assigned to treatment arm). When a subject has transferred from one site to another, the applicant should handle reporting of such subjects consistently across sites and include the reporting convention used in the define file or the BIMO Reviewer's Guide (if provided). The applicant may opt to further explain the reasons subjects transferred between sites in the BIMO Reviewer's Guide, if provided.	100
15	DISCSTUD	Number Subjects	Num	Integer	Number of subjects in the safety population who discontinued from the study by treatment arm at a given	5
27	FINLDISC	Financial Disclosure Amount	Char	String	Total financial disclosure amount (US$) 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 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.	>= $25,000
28	LASTNAME	Investigator Last Name	Char	String	Last name of the clinical investigator as it appears on the Form FDA 1572 or the signed investigator agreement. At sites where the clinical investigator has changed during the	Doe

Study Level Variables

Safety & Primary Endpoint Level Variables

Site and Investigator Level Variables

Site Level Dataset (clinsite.xpt)

STUDYID	SITEID	ARM	SAFPOP	SCREEN	ENDPOINT	ENDPTYPE	TRTEFFR	TRTEFFS	NSAE	SAE	DEATH	PROTVIOL
[redacted]43	019	[redacted] 3.5 mg/kg	4	18	Qualifying relapse rate at 96 weeks	DISCRETE	0.25	0.5	11	0	0	2
[redacted]43	019	[redacted] 5.25 mg/kg	4	18	Qualifying relapse rate at 96 weeks	DISCRETE	0.25	0.5	11	0	0	13
[redacted]43	019	Placebo	4	18	Qualifying relapse rate at 96 weeks	DISCRETE	1.75	2.06155281280883	15	0	0	12
[redacted]43	020	[redacted] 3.5 mg/kg	2	10	Qualifying relapse rate at 96 weeks	DISCRETE	0	0	19	0	0	0
[redacted]43	020	[redacted] 5.25 mg/kg	4	10	Qualifying relapse rate at 96 weeks	DISCRETE	0	0	39	0	0	0

Study/Site/Arm/Endpoint

Study Population Summary

Study Endpoint

Simple Summary Statistics

Key Safety

Summary

DISCRETE

CONTINUOS

TIME-TO-EVENT

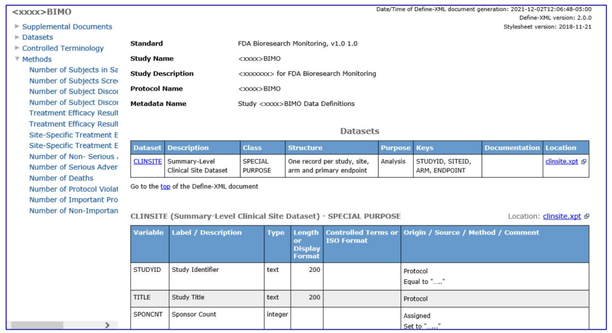
OTHER

Site Level Dataset (clinsite.xpt) – Issues & Challenges

- Trial and Site information not in SDTM → Propose a template to sponsor
  - It includes 22 variables
  - Agree a template
  - Plan a Test Delivery
- Special characters (non-ASCII) not allowed in xpt e.g.,

  FINLDISC (Financial Disclosure Amount): **≥** $50,000 → **>=** $50,000

Documentation [define-xml]



- Only for clinsite.xpt
- Pinnacle21 Enterprise Template
- Key Metadata - CLINSITE/Summary-Level Clinical Site Dataset
  - Standard Name: FDA Bioresearch Monitoring, v1.0
  - Class: SPECIAL PURPOSE
  - Structure: One record per study, site, arm and primary endpoint
  - Purpose: Analysis
  - Key Variables: STUDYID, SITEID, ARM, ENDPOINT
  - 40 Variables, no VLMs
  - 21 P21 Conformance Rules
- Reviewer Guide (optional for now)

Documentation - BIMO PHUSE working Group

https://advance.phuse.global/display/WEL/%28BIMO%29+Bio-research+Monitoring+Data+Reviewers+Guide

- ***Data Reviewer's Guide Template*** *(referenced in the Technical Conformance Guide) and associated documents to allow up front communications regarding the sponsors interpretation of the Bio-research Monitoring Technical Conformance Guide.*
- Public review projected for 15th December 2021 to 31st January 2022.

Planning – Write a mini-SAP

- Planned Studies
- List of Listings
  - Key Instructions for Programmers
  - Ad-hoc derivations
  - List of Variables to be included
  - Reference to CSR listings if applicable
  - Decide how they will be organized, by subject vs by listings
- clinsite.xpt
  - Identify study endpoints e.g., efficacy
  - Specify type of endpoint e.g., continuous vs binary vs time to event

eCTD

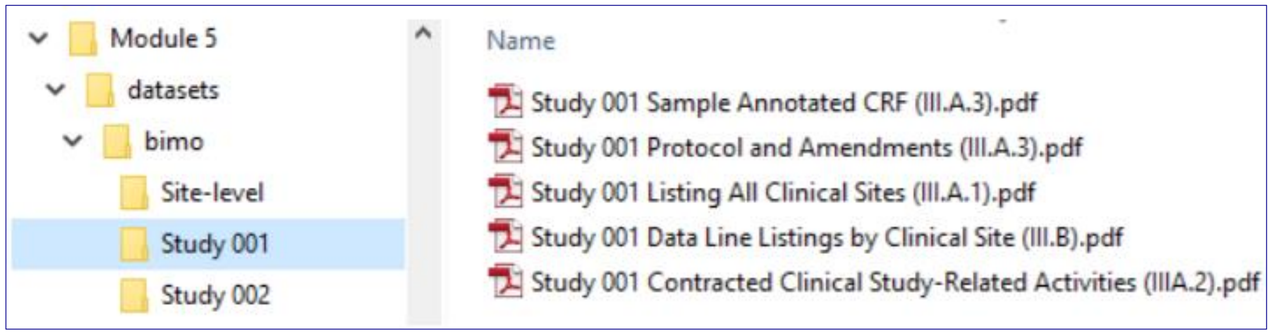
- The three items should be placed in eCTD Module 5
- Module 5.3.5.4 with specific “BIMO” study tagging file (STF)

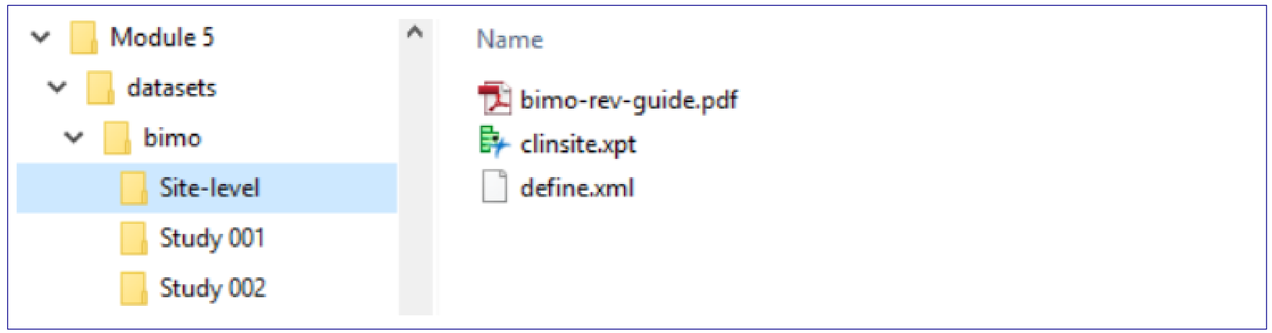
Module 5 clinical Study Reports

└ 5.3 Clinical Study Reports

└ 5.3.5 Reports of Efficacy and Safety Studies

└ 5.3.5.1 Study Reports of Controlled Clinical Studies…….





Sponsor(s) Experience

- Sponsors Sharing their BIMO Experience
- Cytel Sponsor(s) Experience

Sponsors Sharing their BIMO Experience

- Pfizer 2018
- Janssen 2019
- Merck & Co 2019
- Vertex 2020
- Regeneron Pharmaceuticals 2021

See “References” Slide

Cytel Sponsor(s) Experience

Sponsor	Number of and Type of Trials	Details
1 [2016] Pain	2 Pivotal Ph III/Ph II	Only Listings; FDA Request post submission **ClinSite not provided (pilot not mandatory at that time)**
2 [2018] Neurology	2 Pivotal Ph III	define.xml; No reviewer Guide; By Site, Listings ClinSite with Efficacy Data, Binary. **Site Treatment Effect Size**
3 [2019] Neurology	1 Pivotal Ph III	define.pdf; No reviewer Guide; By Site, Listings ClinSite with Efficacy Data, Continuous. **Site Treatment Effect Size**
4 [2020] Multiple Sclerosis	3 1 Ph II 2 Ph III 1 Ph IV	define-xml / define.pdf; No reviewer Guide; By Site, Listings ClinSite with Efficacy Data, Continuous / Binary Old Studies, Cytel not involved in the Submission
6 [2021] Oncology	1 Pivotal Ph III	**define-xml; Reviewer Guide**; By Site, Listings ClinSite with Efficacy Data, Binary Old Studies, Cytel not involved in the Submission
5 [2021] Fertility	3 2 Pivotal Ph III 1 Bioequivalence	define-xml / define.pdf; Reviewer Guide; By Site, Listings ClinSite with Efficacy Data, Continuous / Binary **Discussed during FDA meeting (SDSP)**

Cytel Sponsor(s) Experience – Unnecessary Effort

From BIMO TCG

Treatment Efficacy Result (TRTEFFR) — The summary statistic for each primary efficacy 190 endpoint, by treatment arm at a site. Values reported in TRTEFFR generally reflect ***simple summary statistics*** *for the primary efficacy endpoint(s).*

Sponsor 3 → endless discussion on PROC MIXED model to apply for Lsmeans calculation , **this is not needed!!!**

Site-Specific Treatment Effect variables also removed from TCG Version 2

- Site-Specific Treatment Effect (SITEEFFE) — The treatment effect should be reported using the same representation as reported for the primary efficacy analysis.
- Site-Specific Treatment Effect Standard Deviation (SITEEFFS) — The standard deviation of the SITEEFFE. The method used to calculate standard of deviation should be included in the data define table.

BIMO - Conclusions

BIMO - Conclusions

- Plan ahead, **it is not optional.** Integrate into submission activity priorities
- Get confirmation from the reviewer (**SDSP**)

> **4.4 BIMO Outputs**
>
> [redacted] also plans to submit the following information that will be used by the Center for Drug Evaluation and Research (CDER) for planning of Bioresearch Monitoring (BIMO) inspections in electronic format:
>
> I. Clinical Study-Level Information
> II. Subject-Level Data Line Listings by Clinical Site
> III. Summary-Level Clinical Site Dataset
>
> This will be provided for the two studies that will be pooled into the ISS/ISE, study [redacted]008 and [redacted]009, as well as for [redacted] (Bioequiavelence Study).
> For item III a define-xml and a light reviewer guide will be provided in the submitted package.

- Re-use existing study material e.g., ADaM, CSR listing programs
- Standardize the process
- Future: **FDA using "our" SDTM/ADaM to generate BIMO elements?**

Data Submission News

Data Submission News – FDA Technical Rejection Criteria for Study Data

https://www.fda.gov/media/100743/download

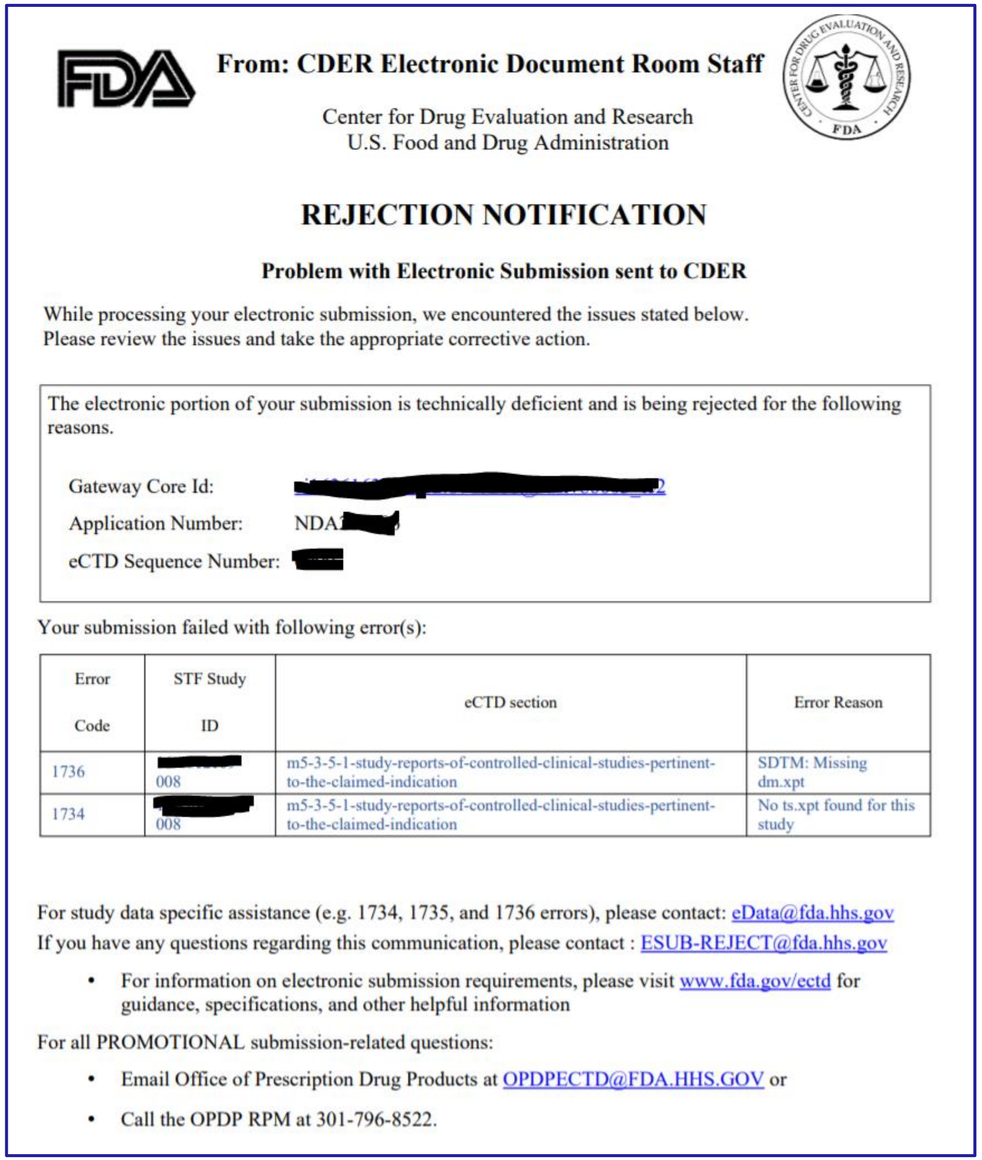
- Version 1 released January 2019
- Few Criteria so far
  - Presence of **ts.xpt** also for legacy studies if legacy datasets submitted
  - **eCTD STF file-tag matching STUDYID** in submitted datasets
  - **Presence of dm.xpt** if TS.SSTDTC>2016-12-16*
  - **Presence of adsl.xpt** if TS.SSTDTC>2016-12-16 when ADaM is submitted*
  - Presence of dm.xpt if TS.SSTDTC>2016-12-16
- September 15, 2021 **Final Implementation**

* Presence of define-xml

Data Submission News – FDA Technical Rejection Criteria for Study Data

A Recent Sponsor/Cytel Experience

- Datasets submitted prior to September 15, 2021
- Several SDTM/ADaM Packages submitted for the same study e.g., key study endpoint analysis at 24, 48, 72 months
- Re-submission after September 15
- Sponsor got a “Rejection Notification”



From: CDER Electronic Document Room Staff

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

REJECTION NOTIFICATION

Problem with Electronic Submission sent to CDER

While processing your electronic submission, we encountered the issues stated below. Please review the issues and take the appropriate corrective action.

The electronic portion of your submission is technically deficient and is being rejected for the following reasons.

Gateway Core Id: [redacted]
Application Number: NDA[redacted]
eCTD Sequence Number: [redacted]

Your submission failed with following error(s):

Error Code	STF Study ID	eCTD section	Error Reason
1736	[redacted] 008	m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication	SDTM: Missing dm.xpt
1734	[redacted] 008	m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication	No ts.xpt found for this study

For study data specific assistance (e.g. 1734, 1735, and 1736 errors), please contact: eData@fda.hhs.gov
If you have any questions regarding this communication, please contact : ESUB-REJECT@fda.hhs.gov

- For information on electronic submission requirements, please visit www.fda.gov/ectd for guidance, specifications, and other helpful information

For all PROMOTIONAL submission-related questions:

- Email Office of Prescription Drug Products at OPDPECTD@FDA.HHS.GOV or
- Call the OPDP RPM at 301-796-8522.

Data Submission News – FDA Technical Rejection Criteria for Study Data

Full package SDTM/ADaM re-submitted for additional data cut-off, What went wrong?

- Due to several study folders created for the same study, the STUDYID was not matching the eCTD STF file-tag
- Solution in the FDA TCG “7.1 eCTD Specifications”

The study identifier (STUDYID in trial summary (TS) and [study-id] in the study tagging file (STF)) should be identical wherever possible.[59] For studies where alignment of the study identifier across TS and STF is not feasible, the value for [study-id] used in the STF should be included in TS using the parameter SPREFID. Though SPREFID is not in the SDTM controlled terminology for TSPARMCD, please use SPREFID to reconcile study identifiers where necessary for SEND or SDTM studies. FDA will use SPREFID to match study identifiers across STF and TS to establish the study start date where necessary for evaluation against the eCTD validation criteria.

Data Submission News – Other FDA Update

- Study Data Technical Conformance Guide

Last Update October 2021 – No major changes

https://www.fda.gov/media/153632/download

- Data Standards for Drug and Biological Product Submissions Containing Real-World Data (October 2021 draft version, Comments by January 22nd, 2022)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-drug-and-biological-product-submissions-containing-real-world-data

- Use of “Simplified ts.xpt files (November 2019)

https://www.fda.gov/media/132457/download

Data Submission News – EMA

Submission of Raw Data to EMA

What Might the Future Landscape of Submitting Data Look Like in 2025

PHUSE 2021

Presented by Eftychia-Eirini Psarelli on 15 November 2021
Methodology Workstream, Data Analytics and Methods Task Force, EMA

- The **purpose** of the project is to **determine the regulatory benefit of access to raw data** via **pilots of analysis of raw data** from clinical trials, before coming back with **recommendations to the Committee for Medicinal Products for Human Use** (CHMP).
- Ultimate aim is for the **Network to understand and take informed decisions** on the place of analysis of **raw data for future regulatory submissions.**

The way ahead…what the future would look like?

- **Data landscape**
  - Quality and manufacturing structured data
  - Veterinary data
  - Combine submission data with external data
- **Data standards** and **analytical software**
  - Beyond CDISC data format (e.g. HL7 FHIR)
  - Beyond SAS (e.g. R, R-shiny)
  - Visualisation software
- **EMA: Working for every patient in Europe** → working for every agency in Europe
  - **IT solution** should be working for all 27 EU Member states providing fair access to raw data

Proof-of-concept raw data pilots

- **Design phase** ongoing
- **Selection** of procedures
  - Raw data analysis for approximately 10 Marketing Authorisation Applications
  - Clinical (including modelling & simulation, Good Clinical Practice data) and non-clinical
  - Initial marketing authorisations and variations
  - Different types of applicants (large pharmaceutical companies, small/medium-size enterprises)
  - Parallel submission to FDA or PMDA can be considered

References

References

- **BIMO Listings – Check That Off Your NDA To-Do List**, C. Singh Kahlon, D. Tirumalasett, B. Busa; PHUSE-US, 2018
- **Programming Support for BIMO Deliverable**, R. Zhang; PharmaSUG-China, 2018
- **Programmer's Guide for OSI Deliverables – Creation of Site Level Summary Dataset and Automation of BIMO Listings Generation**, C. Kahlon, D. Tirumalasetti, B. Busa, K. Achaogen;PharmaSUG, 2018
- **Clinical Development Standards for FDA Bioresearch Monitoring (BIMO) Submissions**, D. Michel and J. Maynard; PharmaSUG, 2019
- **Development of standard BIMO process to create clinsite dataset**, H. Delanghe; PHUSE 2019
- **Multiple Studies BIMO Submission Package – A Programmer's Perspective**, R. Valluru, H. Dyavappa ; PharmaSUG, 2019
- **Sponsor Considerations for Building a Reviewer's Guide to Facilitate BIMO Review**, K. Kundarapu, J. Low, M. Haloui; PharmaSUG 2019
- **Preparing a Successful BIMO Data Package**, E. Li; PharmaSUG, 2020
- **A Programmer's Journey Through the BIMO Submission Process**, R. Ranga, PHUSE-US, 2020
- **BIMO SAS® Macros and Programming Tools**, R. Kamath, M. Young Kwon; PharmaSUG 2021
- **BIORESEARCH MONITORING TECHNICAL CONFORMANCE GUIDE**, FDA, July 2020, https://www.fda.gov/media/85061/download
- **From Before to After_ Preparing and Concluding your FDA Data Submission**, A. Tinazzi, Cytel Blog; https://www.cytel.com/blog/preparing-and-concluding-your-fda-data-submission

Thank you.

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