



# Guidance Beyond the SDTM Implementation Guide

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# Agenda

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- 1. Introduction**
- 2. CDISC Guidance**
- 3. PHUSE Guidance**
- 4. Regulatory Guidance**
- 5. Other Guidance**
- 6. Impact of Disregarding Available Guidance**
- 7. Conclusion**

# Introduction

- When preparing SDTM datasets for submission, further guidance may be needed to fill in some of the gaps that are not outlined in the SDTM Model or the SDTM Implementation Guide (SDTMIG)
- Regulatory requirements must also be followed that may differ from what is in the CDISC standards
- Clarifying information is needed but it can be difficult to determine if such documentation exists and where to find it
- Substantial guidance has been published from many different sources (e.g., CDISC, regulatory authorities, etc) to aid implementers in preparing submission deliverables

## CDISC THERAPEUTIC AREA USER GUIDES

- Though the SDTMIG covers much of the data commonly collected in clinical trials, there are some gaps, mostly due to data specific to certain therapeutic areas (TA)
- CDISC Therapeutic Area User Guides (TAUGs) were developed to fill some of these gaps
- Each TAUG contains information specific to a therapeutic area as well as examples of the type of data that might be collected in a study
- All TAUGs contain SDTM examples and most also contain CDASH-compliant CRF representations as well as ADaM guidance
- Most new standards content, such as new variables and SDTM domains, have first appeared in TAUGs
- Like the IGs, each TAUG's content is consensus-based, meaning that each must go through both Internal and Public Review before it can be published

## CDISC THERAPEUTIC AREA USER GUIDES

- Published TAUGs are considered 'Provisional' due to new variables and domains that have not yet been added to the SDTM/SDTMIG
- Examples in TAUGs are considered 'informative' content vs 'normative' content
- When modeling data based on TAUG examples, any new variables should be mapped as non-standard variables (NSVs), i.e. SUPPQUAL
- New domains based on one of the 3 general observation classes are considered custom domains
  - NOTE: Custom Special-Purpose domains are not permitted per the guidance in the SDTMIG
- New versions of the same TAUG will supersede the previous version
  - Vaccines TAUG v1.1 should be referenced versus v1.0

## CDISC THERAPEUTIC AREA USER GUIDES

- If a TAUG was used for a study, the specific TAUG referenced should be listed in the Trial Summary (TS) domain (TSPARMCD/TSPARM = ‘CTAUG’/ ‘CDISC Therapeutic Area User Guide’)
  - Listed in the FDA Study Data Technical Conformance Guide (sdTCG), Appendix B:

|             |       |                                   |                                                                                                                                        |
|-------------|-------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Conditional | CTAUG | CDISC Therapeutic Area User Guide | If applicable, the value should be the exact listing as in section 5.2 of the Technical Conformance Guide. Use as many rows as needed. |
|-------------|-------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|

- FDA sdTCG, Section 5.2 lists those TAUGs that have been evaluated and supported by FDA
  - If the TAUG used is not listed, the rationale should be explained in the Clinical Study Data Reviewer’s Guide (cSDRG)
- In addition to the TAUG names in the sdTCG, there is a CTAUGRS (CDISC Therapeutic Area User Guide Response) codelist in SDTM CT that can be used to populate TSVAL

# CDISC Guidance

## CDISC THERAPEUTIC AREA USER GUIDES

Acute Kidney Injury  
Alzheimer's  
Asthma  
Breast Cancer  
Cardiovascular  
CDAD  
Colorectal Cancer  
COPD  
COVID-19  
Crohn's Disease

Diabetes  
Diabetes Type 1 - Exercise and Nutrition  
Diabetes Type 1 - Pediatrics and Devices  
Diabetes Type 1 - Screening, Staging and  
Monitoring of Pre-clinical Type 1 Diabetes  
Diabetic Kidney Disease  
Duchenne Muscular Dystrophy  
Dyslipidemia  
Ebola  
Heart Failure  
Hepatitis C  
HIV  
Huntington's Disease  
Influenza

Kidney Transplant  
Lung Cancer  
Major Depressive Disorder  
Malaria  
Multiple Sclerosis  
Nutrition  
Pain  
Pancreatic Cancer  
Parkinson's Disease  
Pediatrics  
Polycystic Kidney Disease  
Post Traumatic Stress Disorder  
Prostate Cancer  
Psoriasis

QT Studies  
Rare Diseases  
Rheumatoid Arthritis  
Schizophrenia  
Traditional Chinese Medicine - Acupuncture  
Traditional Chinese Medicine - Coronary  
Artery Disease-Angina  
Traumatic Brain Injury  
Tuberculosis  
Vaccines  
Virology

- Any CDISC TAUG used in this list should be compared to Section 5.2 in the sdTCG

<https://www.cdisc.org/standards/therapeutic-areas>

## QUESTIONNAIRES, RATINGS AND SCALES (QRS) SUPPLEMENTS

- Contain information about the instrument as well as guidance and examples for representing the data in SDTM
- Useful in mapping to the appropriate domain and properly structuring the data
  - Questionnaires (QS)
  - Functional Tests (FT)
  - Clinical Classifications and Disease Response (RS)
- Each TAUG lists QRS instruments that may be used for a specific TA as well as the status of the CDISC QRS supplement, e.g. 'In Progress', 'Final', etc
- Like TAUGs, QRS supplements go through Internal and Public Review
- When authored, the most recent version of the SDTMIG is used but are considered to be version agnostic

[https://www.cdisc.org/standards/foundational/qrs#qrs\\_\\_supplements](https://www.cdisc.org/standards/foundational/qrs#qrs__supplements)

## QUESTIONNAIRES, RATINGS AND SCALES (QRS) SUPPLEMENTS

**RS = Disease Response and Clin Classification**

RSCAT=ECOG

ECOG PERFORMANCE STATUS

Grade

ECOG

☐ 0

Fully active, able to carry on all pre-disease performance without restriction

☐ 1

Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

☐ 2

Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

☐ 3

Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

☐ 4

Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

☐ 5

Dead

RSTRESC/RSTRESN

RSTRESC/RSTRESN

RSTRESC/RSTRESN

RSTRESC/RSTRESN

CDISC believes this instrument to be in the public domain, but you should perform your own assessment. CDISC specifies how to structure the data that has been collected in a database, not what should be collected or how to conduct clinical assessments or protocols.

The ECOG uses a single-status assessment that clinicians may use to evaluate a patient's disease progression, the effect of the disease on daily living abilities, and appropriate treatment and prognosis.

1. The scale point includes a numeric rating (0-5) and a definition of what is represented by the rating (e.g., 0 = "Fully active, able to carry on all pre-disease performance without restriction"). For the ECOG, RSORRES is populated with the text description while the numeric rating is represented in the standardized character and numeric result variables RSTRESC and RSTRESN.

### 3.2 Example for the ECOG RS Domain Model

The ECOG example below shows the terminology used to implement the instrument in the RS domain. This example shows the data for 3 subjects collected at two visits for an ECOG instrument. The example uses CDISC Controlled Terminology for RSTESTCD, RSTEST, and RSCAT. All original results are represented with preferred terminology in RSORRES. This result is then transformed into the standard numeric score in RSTRESC and a character representation of the standard numeric score in RSTRESN.

The table represents the item from the ECOG instrument. The subjects did not fill out the instrument at VISITNUM = 2, so all items are represented as missing.

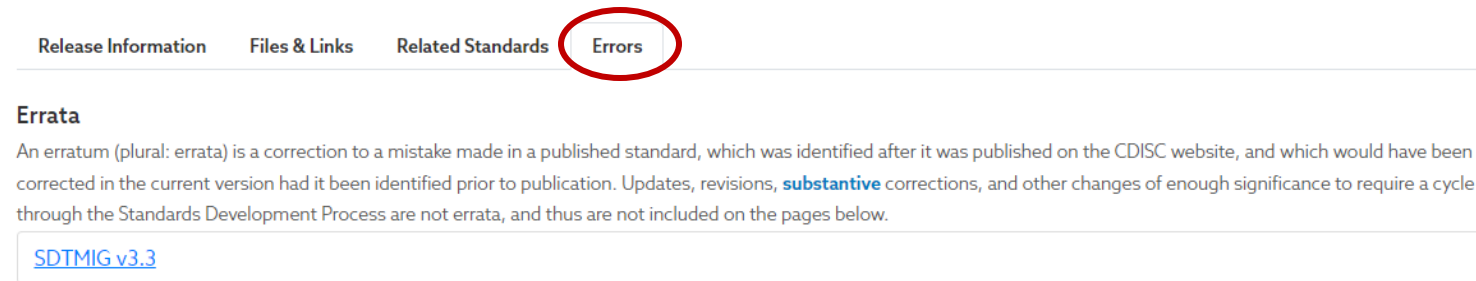
rs.xpt

| Row | STUDYID  | DOMAIN | USUBJID | RSSEQ | RSTESTCD | RSTEST                   | RSCAT | RSORRES                                                                                                                                                   | RSTRESC | RSTRESN | RSTAT    | RSLOBXFL | VISITNUM | RSDTC      |
|-----|----------|--------|---------|-------|----------|--------------------------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------|---------|----------|----------|----------|------------|
| 1   | STUDY001 | RS     | 001-001 | 1     | ECOG101  | ECOG1-Performance Status | ECOG  | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours                                                                  | 3       | 3       |          | Y        | 1        | 2013-04-09 |
| 2   | STUDY001 | RS     | 001-001 | 2     | ECOG101  | ECOG1-Performance Status | ECOG  |                                                                                                                                                           |         |         | NOT DONE |          | 2        | 2013-05-09 |
| 3   | STUDY001 | RS     | 001-002 | 1     | ECOG101  | ECOG1-Performance Status | ECOG  | Fully active, able to carry on all pre-disease performance without restriction                                                                            | 0       | 0       |          | Y        | 1        | 2013-04-09 |
| 4   | STUDY001 | RS     | 001-002 | 2     | ECOG101  | ECOG1-Performance Status | ECOG  |                                                                                                                                                           |         |         | NOT DONE |          | 2        | 2013-05-09 |
| 5   | STUDY001 | RS     | 001-003 | 1     | ECOG101  | ECOG1-Performance Status | ECOG  | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work | 1       | 1       |          | Y        | 1        | 2013-04-10 |
| 6   | STUDY001 | RS     | 001-003 | 2     | ECOG101  | ECOG1-Performance Status | ECOG  |                                                                                                                                                           |         |         | NOT DONE |          | 2        | 2013-05-10 |

## SDTMIG ERRATA

- Sometimes errors are identified after the SDTMIG is published
- Errata are located on the CDISC website and kept on the page for that specific version of the SDTMIG under the 'Errors' tab

### SDTMIG v3.3



The screenshot shows a navigation bar with four tabs: 'Release Information', 'Files & Links', 'Related Standards', and 'Errors'. The 'Errors' tab is highlighted with a red circle. Below the tabs, the heading 'Errata' is followed by a paragraph explaining that an erratum is a correction to a mistake made in a published standard. It also mentions that updates, revisions, substantive corrections, and other changes of enough significance to require a cycle through the Standards Development Process are not errata. A link 'SDTMIG v3.3' is provided below the text.

Release Information Files & Links Related Standards **Errors**

**Errata**

An erratum (plural: errata) is a correction to a mistake made in a published standard, which was identified after it was published on the CDISC website, and which would have been corrected in the current version had it been identified prior to publication. Updates, revisions, **substantive** corrections, and other changes of enough significance to require a cycle through the Standards Development Process are not errata, and thus are not included on the pages below.

[SDTMIG v3.3](#)

### Section 5.2, Demographics

- DM - Specification: The value in the "Controlled Terms, Codelist or Format" column for COUNTRY should be changed from "ISO 3166-1 Alpha-3" to "ISO 3166-1 alpha-3".

<https://www.cdisc.org/standards/foundational/sdtmig/sdtmig-v3-3>

## SDTMIG ERRORS THAT AFFECT CONFORMANCE

- If an error would appear in validation, it is published as an 'Error that Affects Conformance' and not an 'Errata'
  - Also located on the 'Errors' tab for that specific version of the SDTMIG
- The issue is described and coping strategies for handling the error in the standard are provided
  - A coping strategy may include simply explaining the issue in the cSDRG
- Please note that the error is not formally corrected in that version of the SDTMIG, i.e., the standard is not changed

<https://www.cdisc.org/standards/foundational/sdtmig/sdtmig-v3-3>

## SDTMIG ERRORS THAT AFFECT CONFORMANCE

DSDY should be "Permissible", not "Expected"

|                          |                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Short Name               | DSDY should be permissible, not expected                                                                                                                                                                                                                                                                                                                    |
| Affected Standard        | SDTMIG v3.3                                                                                                                                                                                                                                                                                                                                                 |
| Description of Error     | <p>In the DS domain specification, the core value of DSDTC is "Perm" but the core value of the corresponding study day variable, DSDY, is "Exp". The study day variable corresponding to a date/time variable that is "Perm" cannot be "Exp".</p> <p>Note that DSDY was not included in the DS domain specification in previous versions of the SDTMIG.</p> |
| Efforts to Correct Error | The core value for DSDY will be changed to be "Perm" in the next version of the SDTMIG.                                                                                                                                                                                                                                                                     |
| JIRA Issue               | <a href="#">SDS-1417</a>                                                                                                                                                                                                                                                                                                                                    |

| Concerned Published Element | Concerned Published Attribute | Published Attribute Value | Revised Attribute Value |
|-----------------------------|-------------------------------|---------------------------|-------------------------|
| DS.DSDY                     | Core                          | Exp                       | Perm                    |

| Impact of Issue                                                                                                                      | Coping Strategy                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| If DSDTC was not collected, so that DSDY is always null, failure to include DSDY in the DS dataset may result in errors or warnings. | Explain any validation errors or warnings in the Clinical Study Data Reviewers Guide (cSDRG). |

- If DSDY is not included in DS:
  - SD0057 – SDTM Expected Variable not found
- If DSDY is included in DS:
  - SD1149 - Expected variable with missing value for all records
- Regardless of the approach, this would need to be explained in the cSDRG

<https://www.cdisc.org/standards/foundational/sdtmig/sdtmig-v3-3>

## OTHER GUIDANCE FROM CDISC

- SDTMIG – Associated Persons v1.0
- SDTMIG – Medical Devices v1.1
- Knowledge Base (KB) - <https://www.cdisc.org/kb>
  - Useful articles, Known Issues, Examples Collection, example CRFs in the eCRF Portal
- Define-XML v2.0 and v2.1
  - Both versions are currently supported by FDA
- SDTM Metadata Submission Guidelines (MSG) v2.0
  - Guidance for preparing the different components required for a submission: Annotated Case Report Form (aCRF), SAS v5 XPT files, define.xml, and the cSDRG
  - Informative rather than normative content and should be used in conjunction with CDISC standards
  - An example submission package is included

## BEST PRACTICES FOR SUBMISSION OF EVENT ADJUDICATION DATA

- Provides guidance for handling adjudication data in SDTM
- Adjudication is a committee's blinded evaluation of specific endpoints/events in a clinical trial
- The events that are reviewed are typically subjects' adverse event data collected in a study
- CDISC TAUGs provide some guidance and examples but not enough
- Proposal to standardize how this data is submitted so that sponsors can follow one approach that would help create consistency across industry

# PHUSE Guidance

## BEST PRACTICES FOR SUBMISSION OF EVENT ADJUDICATION DATA

- Event Adjudication (EA) domain

| STUDYID | USUBJID | DOMAIN | EALNKID | EAREFID | EAREPNUM | EATEST   | EATESTCD                                | EAOBJ | EACAT              | EAORRES                            | EAEVAL      | EAEVALID      | EAACPTFL | EADTC      |
|---------|---------|--------|---------|---------|----------|----------|-----------------------------------------|-------|--------------------|------------------------------------|-------------|---------------|----------|------------|
| STUDY01 | 100100  | EA     | 14      | 1       | 1        | ADJOUT   | Adjudication outcome                    | ACS   | FIRST ADJUDICATION | ACUTE MYOCARDIAL INFARCTION        | ADJUDICATOR | ADJUDICATOR 1 |          | 2017-04-04 |
| STUDY01 | 100100  | EA     | 14      | 1       | 1        | ADJDATE  | Evaluated Event Onset date              | ACS   | FIRST ADJUDICATION | 2017-01-01                         | ADJUDICATOR | ADJUDICATOR 1 |          | 2017-04-04 |
| STUDY01 | 100100  | EA     | 14      | 1       | 1        | MICLASS  | Classification of Myocardial Infarction | ACS   | FIRST ADJUDICATION | ST ELEVATION MYOCARDIAL INFARCTION | ADJUDICATOR | ADJUDICATOR 1 |          | 2017-04-04 |
| STUDY01 | 100100  | EA     | 14      | 1       | 1        | MITYPE   | Type of Myocardial Infarction           | ACS   | FIRST ADJUDICATION | TYPE 1 MYOCARDIAL INFARCTION       | ADJUDICATOR | ADJUDICATOR 1 |          | 2017-04-04 |
| STUDY01 | 100100  | EA     | 14      | 1       | 1        | CONF EVT | Confirmation of event                   | ACS   | FIRST ADJUDICATION | FULL DOCUMENT AVAILABLE            | ADJUDICATOR | ADJUDICATOR 1 |          | 2017-04-04 |
| STUDY01 | 100100  | EA     | 14      | 1       | 2        | ADJOUT   | Adjudication outcome                    | ACS   | FIRST ADJUDICATION | ACUTE MYOCARDIAL INFARCTION        | ADJUDICATOR | ADJUDICATOR 2 |          | 2017-04-10 |

- Will be published in SDTMIG v4.0 to make EA a standard Findings About-structured domain

## OTHER GUIDANCE FROM PHUSE

- Define-XML v2.0 Completion Guidelines
  - Clarifies some of the more challenging metadata items in the define.xml file
  - Not meant repeat what is already outlined in CDISC's Define-XML standard
  - Geared towards Define-XML v2.0 but could also be applied to Define-XML v2.1
- Best Practices for Documenting Dataset Metadata: Define-XML Versus Reviewer's Guide
  - Guidance on documenting the dataset metadata for a trial with recommendations on where to best add this information: define.xml vs cSDRG
  - Best practices for explaining validation results in the cSDRG

# Regulatory Guidance

## DATA STANDARDS CATALOGS

 **U.S. FOOD & DRUG**  
ADMINISTRATION

[Home](#) / [For Industry](#) / [FDA Data Standards Advisory Board](#) / [Study Data Standards Resources](#)

### Study Data Standards Resources

This page provides quick links to key guidances to support the submission of study data to FDA's Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and Center for Veterinary Medicine (CVM) and provides a common site where guidances and technical documents related to study data standards are displayed together. Every guidance listed below may not apply to all centers. Each link provides more complete information on the document.

**Quick Links**

- [eCTD Resources](#)
- [Data Standards Catalog](#)
- [Study Data Technical Conformance Guide](#)

Content current as of:  
12/08/2023

Regulated Product(s)  
Drugs

 独立行政法人 医薬品医療機器総合機構  
Pharmaceuticals and Medical Devices Agency

**New Drug Review with Electronic Data**

**Data Standards Catalog and Study Data Validation Rules**

- [Data Standards Catalog \(2023-02-28\)](#)

### Notable Differences:

- SEND - FDA lists many versions as supported, but PMDA lists none
- SDTM - FDA lists new(ish) v3.4 as supported, but latest version supported by PMDA is v3.3

# Regulatory Guidance

## STUDY DATA TECHNICAL CONFORMANCE GUIDES AND FAQs

- FDA's Study Data Technical Conformance Guide

- 1.2 Purpose

- This Guide provides technical recommendations to sponsors<sup>4</sup> for the submission of animal and human study data and related information in a standardized electronic format in INDs, NDAs, ANDAs, and BLAs.<sup>5</sup> The Guide is intended to complement and promote interactions between sponsors and FDA review divisions. However, it is not intended to replace the need for sponsors to communicate directly with review divisions regarding implementation approaches or issues relating to data standards.

- PMDA's Technical Conformance Guide on Electronic Study Data Submissions

- 1.1 Purpose

- Handling of the submission of electronic study data for new drug applications has been described in the notification on gateway application, notification on electronic study data and its question and answer guide. More detailed matters and precautions regarding the submission of electronic study data are provided in this guide.

- In addition, detailed matters and precautions concerning the submission of related electronic files, including the eCTD, shall be described together in this guide.

- PMDA's FAQs on Electronic Study Data Submission

- FAQs on Electronic Study Data Submission**

- This document summarizes inquiries on electronic study data submission received by the PMDA in a Q&A format.

# Regulatory Guidance

## TECHNICAL SPECIFICATION DOCUMENTS

### 5.3 List of FDA Technical Specification Documents

Technical specification documents provide detailed information for content on specific topics, where applicable, submitted to FDA for an application. Sponsors should consult with the review division early in the process to discuss issues with trial design or conduct that may affect the content of the study data being submitted. Technical specifications can be found [here](#).<sup>51</sup>

5.3.1 Submitting Nonclinical Datasets for Evaluation of Rodent Carcinogenicity Studies of Pharmaceuticals, Guidance for Industry **SEND guidance**

5.3.2 Submitting Next Generation Sequencing Data to the Division of Antiviral Products **Data Collection and Reporting guidance**

5.3.3 Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs **ADaM guidance**

5.3.4 Bioanalytical Methods Templates **Summary Table guidance**

5.3.5 Submitting Select Clinical Trial Data Sets for Drugs Intended to Treat Human Immunodeficiency Virus-1 Infection **ADaM guidance**

✓ 5.3.6 Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review **SDTM guidance**

5.3.7 Technical Specifications-Comparative Clinical Endpoint Bioequivalence Study Analysis Datasets for Abbreviated New Drug Applications **ADaM guidance**

✓ 5.3.8 Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH) **SDTM (and ADaM) guidance**

✓ 5.3.9 Submitting Patient-Reported Outcome Data in Cancer Clinical Trials **SDTM (and ADaM) guidance**

✓ 5.3.10 Submitting Clinical Trial Datasets and Documentation for Clinical Outcome Assessment Using Item Response Theory **SDTM (and ADaM) guidance**

#### Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review

- Reactogenicity Data, Unsolicited AEs, Lab Assessments, MAAEs, Deaths
- Clinical Disease Endpoint Efficacy Data
- Immunogenicity, Concomitant Medication, Maternal Immunization Data

#### Submitting Clinical Trial Data Sets for Treatment of NASH

- Guidance for SDTM domains: BE, BS, MI/SUPPMI, RS, ZI, ZA, and others
- Guidance for ADaM datasets: ADSL, ADAE, ADLB, ADDILI, ADMI, ADRS, ADTTE

#### Submitting Patient Reported Outcome Data in Cancer Clinical Trials

- Guidance for SDTM domains: QS, TS
- Guidance for ADaM datasets: ADQS
- Handling of missing PRO data, data not collected due to skip logic or CAT
- Guidance for tables and figures

#### Submitting Clinical Trial Datasets and Documentation for COAs Using IRT

- Guidance for SDTM domains: ZQ (item dataset), QS, TS
- Guidance for ADaM datasets: ADQS
- Handling of missing data, data not collected due to skip logic or CAT

\*From the FDA's Study Data Technical Conformance Guide, December 2023

# Other Guidance

## HOW TO USE WHODRUG FOR COMPLIANCE WITH CM DOMAIN IN THE SDTM STANDARD



### Background

The CDISC SDTM (Study Data Tabulation Model) standard describes how to report data from a clinical trial and includes guidance for reporting of concomitant medications. The CDISC implementation guide does not state how to retrieve the concomitant medication data from a drug dictionary; **this guide aims to give data managers and SAS programmers detailed information for how to retrieve the correct data from WHODrug for inclusion in the Concomitant medication (CM) domain and as a result be fully compliant with the CDISC SDTM standard.**

This guide is based on the CDISC SDTM standard version 1.4<sup>1</sup> and implementation guide version 3.2. There are five variables within the CM domain that are most relevant with relation to WHODrug: CMTRT, CMMODIFY, CMDECOD, CMCLAS and CMCLASCD.

# Impact of Disregarding Available Guidance

## DISREGARDING REGULATORY GUIDANCE

### Guidance for Industry

#### Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act

##### IV. ISSUANCE AND USE OF INFORMATION REQUEST AND DISCIPLINE REVIEW LETTERS

###### A. General

CDER and CDER will use IR letters to obtain clarifying information to assist in completing a review. Because the Agency issues IRs to obtain clarification, it is normally expected that the applicant will respond as quickly as possible. FDA reviews such responses (if they are of a clarifying nature) as part of the current review cycle of the application. However, if the response is of a significant nature, the response could constitute a major amendment. Major amendments to an original application received in the last three months of the review cycle may extend the Action Due date by three months. Only one such extension is permitted. FDA may defer the review of a response to the next review cycle, if the review team believes that the new information cannot be fully reviewed in the time remaining in the current review cycle or is ready to issue an action letter.

# Impact of Disregarding Available Guidance

## DISREGARDING SDTMIG ERRATA AND ERRORS THAT AFFECT CONFORMANCE

### Errors that Affect Conformance

Core Values for MIBLFL, MILOBXFL, MOBLFL, and MOLOBXFL

|                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Short Name               | Core Values for MIBLFL, MILOBXFL, MOBLFL, and MOLOBXFL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Affected Standard        | SDTMIG v3.3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Description of Error     | <p>The --LOBXFL (Last Observation before Exposure) variable was introduced as a Findings Domain qualifier with the intent of eventually replacing --BLFL (Baseline Flag).</p> <p>In findings domains in which --BLFL was expected, its core value was to be changed to permissible, while --LOBXFL became expected. This was not carried out as intended for the MI (Microscopic) and MO (Morphology) domains.</p> <p>In the MI domain, MIBLFL is expected but should be permissible and MILOBXFL is permissible but should be expected.</p> <p>In the MO domain, MOBLFL is expected but should be permissible and MOLOBXFL is permissible but should be expected.</p> |
| Efforts to Correct Error | The core values will be corrected in the next version of the SDTMIG.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Sponsor explanation for resulting validation issue:

### 4.2 Issues Summary

| Check ID | Diagnostic Message                        | Dataset | Count (Issue Rate) | Explanation                                                                                   |
|----------|-------------------------------------------|---------|--------------------|-----------------------------------------------------------------------------------------------|
| SD0057   | SDTM Expected variable MILOBXFL not found | MI      | 1 (100.00%)        | MILOBXFL is a permissible variable in SDTMIG 3.3. Pinnacle 21 is flagging this incorrectly. ❌ |

False explanation

# Impact of Disregarding Available Guidance

## DISREGARDING UPPSALA MONITORING CENTRE GUIDANCE

### CMDECOD is longer than 200 characters

For drugs with many ingredients, the generic name is longer than 200 characters. The SAS export format has a limitation to 200 characters per field, if this format is used for submission, the supplemental dataset needs to be utilised. Note that the guidelines state that **the text should be truncated between words, in the case for long generic names the text should be truncated after the semicolon closest to 200 characters**. Illustrations of the ordinary and supplemental datasets are shown in table 1 and 2.

Table 1. Illustration of SDTM dataset where CMDECOD is longer than 200 characters.

| USUBJID  | CMSEQ | CMTRT | CMMODIFY | CMDECOD                                                                                                                                                                                                  | CMCLAS | CMCLASCD |
|----------|-------|-------|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|----------|
| AB-21-01 | 1     | ....  | ...      | Ascorbic acid;Biotin;Calcium;Carbohydrates nos; Chloride;Choline;Chromium;Colecalciferol; Copper;Cyanocobalamin;Docosahexaenoic acid; Fats nos;Folic acid;Fructooligosaccharides; Iodine;Iron;Magnesium; | ....   | ....     |

Table 2. Illustration of supplemental dataset for CM domain where CMDECOD is longer than 200 characters.

| USUBJID  | RDOMAIN | IDVAR | IDVARVAL | QNAM     | QLABEL                         | QVAL                                                                                                                                                                    |
|----------|---------|-------|----------|----------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AB-21-01 | CM      | CMSEQ | 1        | CMDECOD1 | Standardized Medication Name 1 | Manganese;Nicotinic acid;Pantothenic acid;Phosphorus;Phytomenadione; Potassium;Proteins nos;Pyridoxine; Retinol;Riboflavin;Selenium;Sodium; Thiamine;Vitamin e nos;Zinc |

← This guidance from Uppsala Monitoring Centre

Is used in this validation rule algorithm

version 1.6, finalized December 2022

| FDA Validator Rule ID | Publisher | Publisher ID | FDA Validator Rule Message                        | FDA Validator Rule Description                                                                                                                                      |
|-----------------------|-----------|--------------|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SD1344                | FDA       | FDAB017      | Value for --DECOD not found in WHODrug dictionary | Value for the Standardized Medication Name (--DECOD) variable must be populated using a Drug Name from the WHO Drug dictionary version specified in the define.xml. |

# Impact of Disregarding Available Guidance

## DISREGARDING CDISC TAUGS AND PHUSE GUIDANCE

✖ Study 1:

|                  |          |                                                                    |
|------------------|----------|--------------------------------------------------------------------|
| Type of receptor | LBSCAT   | ER                                                                 |
| Test method      | LBMETHOD | IHC<br>FISH<br>CISH<br>ISET<br>VERIDEX<br>NISH<br>SISH<br>Not Done |
| Receptor result  | LBORRES  | Negative<br>Positive                                               |

✖ Study 2:

|                                                                                                |         |                      |         |
|------------------------------------------------------------------------------------------------|---------|----------------------|---------|
| 2. Estrogen Receptor Status<br>[Estrogen Receptor Status]                                      | PFTTEST | Positive<br>Negative | PFORRES |
| 3. Pathological Diagnosis Progesterone Receptor Status<br>[Patholog Diag Progester Recep Stat] | PFTTEST | Positive<br>Negative | PFORRES |
| 4. Pathological Diagnosis HER2 Status<br>[Pathological Diagnosis HER2 Status]                  | PFTTEST | Positive<br>Negative | PFORRES |

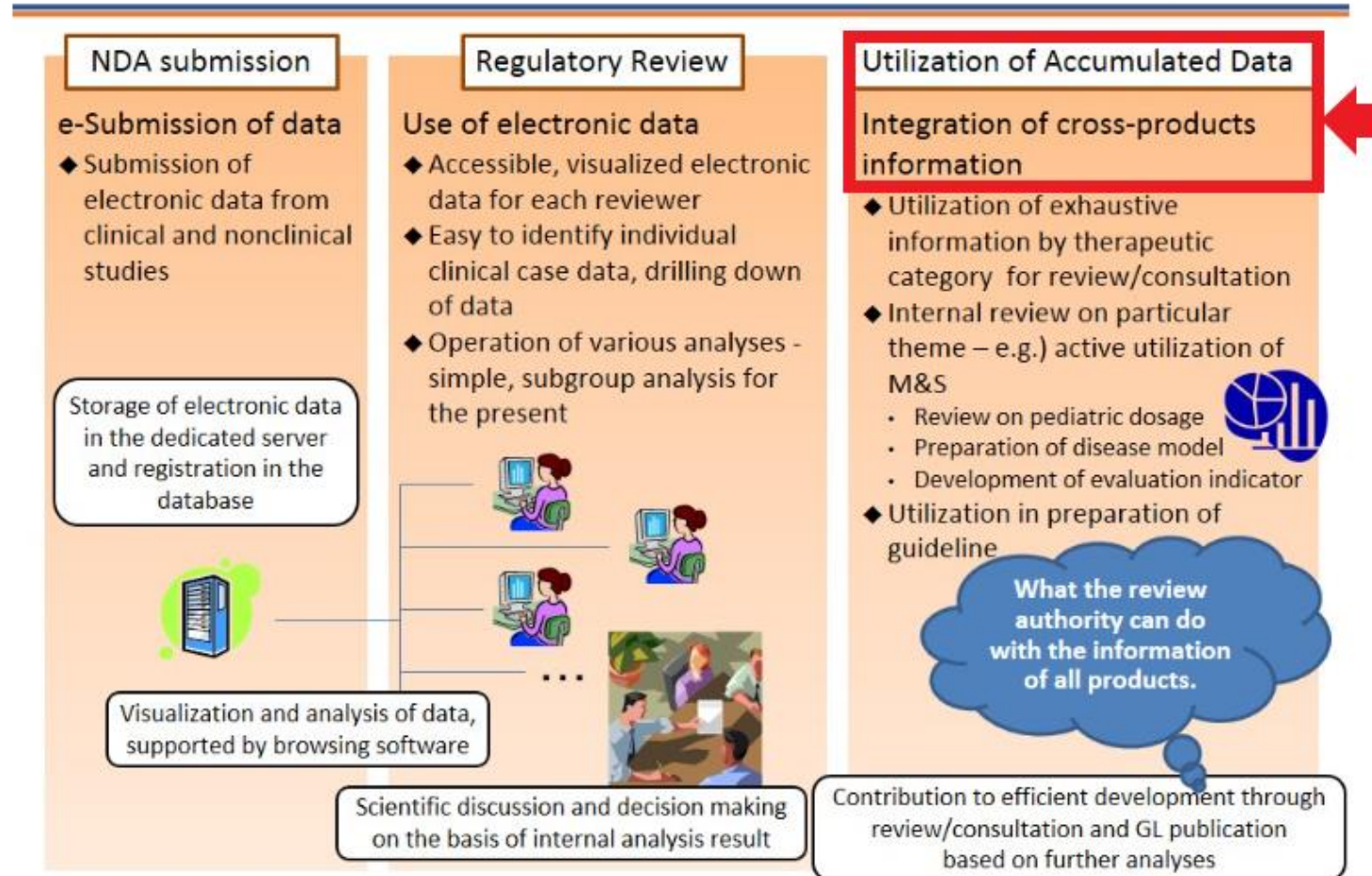
✔ Study 3 (This is the approach that matches the example in the Breast Cancer TAUG):

|                    |                                 |                       |  |
|--------------------|---------------------------------|-----------------------|--|
| MITESTCD = ESTRCPT |                                 | Progesterone Receptor |  |
|                    |                                 | Estrogen Receptor     |  |
|                    |                                 | ErbB2                 |  |
| Date of Sample     | MIDTC                           |                       |  |
| Qualitative Result | Positive<br>Negative<br>Unknown |                       |  |
| MIORRES, MISTRESC  |                                 |                       |  |

# Impact of Disregarding Available Guidance

## DISREGARDING CDISC TAUGS AND PHUSE GUIDANCE

### Accumulation and utilization of data



\*<https://www.pmda.go.jp/english/review-services/reviews/0002.html>

# Conclusion

- Relying solely on the SDTM Implementation Guide is not sufficient
- Preparers of SDTM datasets need to be aware (and follow) guidance from:
  - Regulatory Agencies
  - CDISC (such as TAUGs, QRS Supplements, errata, etc.)
  - PHUSE
  - Other organizations
- There are real impacts to disregarding guidance from these organizations



# Questions?

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