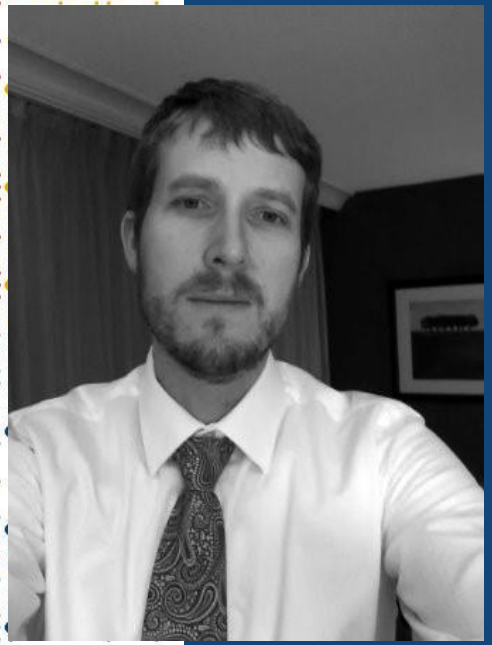
JAPAN ACADEMIC WORKSHOP

Friday, 17 November | 1:00pm -5:15pm

Considerations for SDTM Implementation in Observational Studies and Real World Data

Presented by Jon Neville, Senior Director, Standards Development, CDISC



Meet the Speaker

Jon Neville

Title: Senior Director, Standards Development

Organization: CDISC

Jon Neville has been working in CDISC standards development since 2009. He was worked on a variety of development projects including TAUGs and biomedical concepts. He was been working at CDISC for 6 years.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

Agenda

1. Background
2. Project Framework and Overview
3. Sample Content
4. Current Status and Conclusions

Background

Why CDISC is interested in standards for RWD / Observational research.

Background

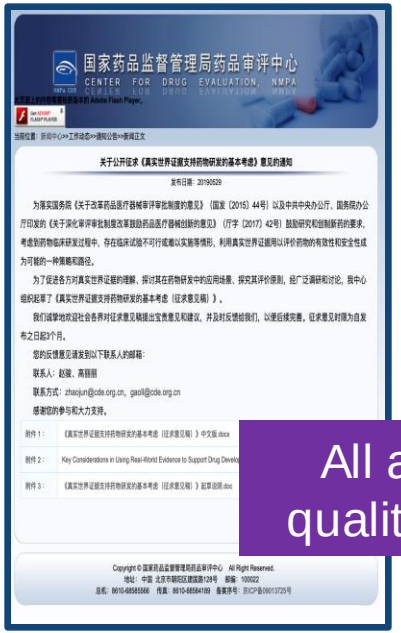
- Historically, CDISC standards were primarily developed for use in studies of regulated medical products
- Increased recognition of the value in using CDISC standards has led to increased interest in using standards in other areas of medical research and other areas of healthcare
- CDISC continues to be approached by research organizations/institutes and members asking for guidance on using our standards for these use cases.

CDISC Mission :

"…enable the accessibility, interoperability, and reusability of data, helping the entire field of clinical research tap into—and amplify—its full value."

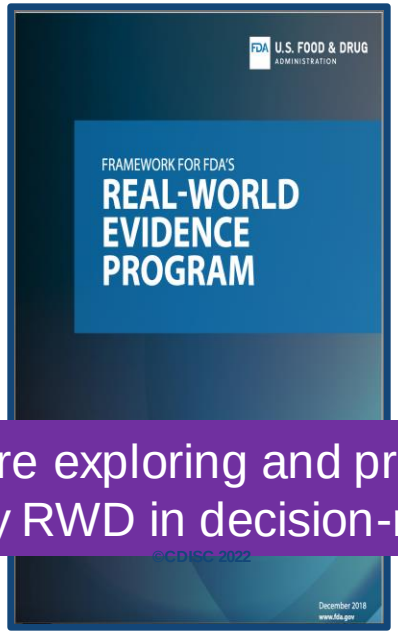
RWD and the Regulatory Environment

China's NMPA



http://www.cde.org.cn/news.do?method=largeInfo&id=23a2b4cbe0807fe2

US FDA

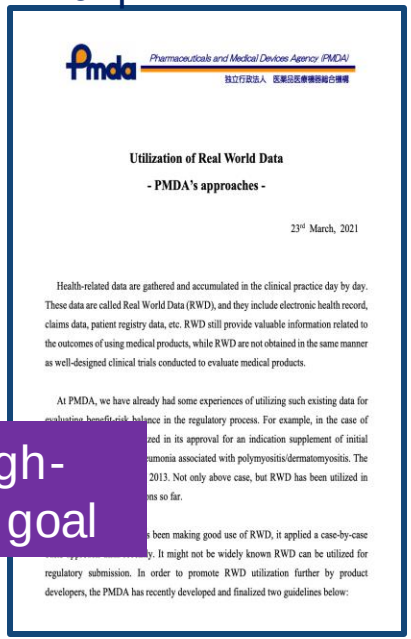


https://www.fda.gov/media/120060/download

EU EMA

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

Japan's PMDA



https://www.pmda.go.jp/english/about-pmda/0004.pdf

All are exploring and promoting the use of high-quality RWD in decision-making as a strategic goal

CDISC RWD Connect Initiative

JMIR Publications
Advancing Digital Health & Open Science

JMIR Medical Informatics

Published on 27.1.2022 in Vol 10, No 1 (2022): January

Preprints (earlier versions) of this paper are available at https://preprints.jmir.org/preprint/30363, first published June 01, 2021.

Use of Clinical Data Interchange Standards Consortium (CDISC) Standards for Real-world Data: Expert Perspectives From a Qualitative Delphi Survey

Rhonda Facile [1]; Erin Elizabeth Muhlbradt [2]; Mengchun Gong [3, 4]; Qingna Li [5, 6, 7]; Vaishali Popat [8]; Frank Pétavy [9]; Ronald Cornet [10]; Yaoping Ruan [11]; Daisuke Koide [12]; Toshiki I Saito [13]; Sam Hume [1]; Frank Rockhold [14]; Wenjun Bao [15]; Sue Dubman [1]; Barbara Jauregui Wurst [1]

Project Framework and Overview

DRAGON

- One of 8 COVID projects funded by the Innovative Medicines Initiative (IMI, via IMI2- Call21)
- 18 partners from Belgium, Italy, the Netherlands, Switzerland, UK, US
- Goal: Apply artificial intelligence and machine learning to deliver a decision support system for improved and more rapid diagnosis and prognosis using imaging and associated clinical care data.
- CDISC was sub-awarded funds to help guide mapping of RWD
- With remaining funds, we produced the considerations document we are discussing today

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imi innovative medicines initiative

Considerations for SDTM Implementation in Observational Studies and Real World Data

Goal

- To publish a CDISC-endorsed approach to working with observational research data
- Provide a “stake in the ground” for future expansion

Limited Scope of Use Cases

- **Observational Research Studies**
  - Cross-sectional studies
  - Cohort studies
- **Clinical trials:** external control arm (ECA) using RWD

Limited Scope of Standards Considered

- SDTM for now
- CDASH, ADaM could come in subsequent version

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Funding is provided by the IMI DRAGON project

imi innovative medicines initiative

DRAGON

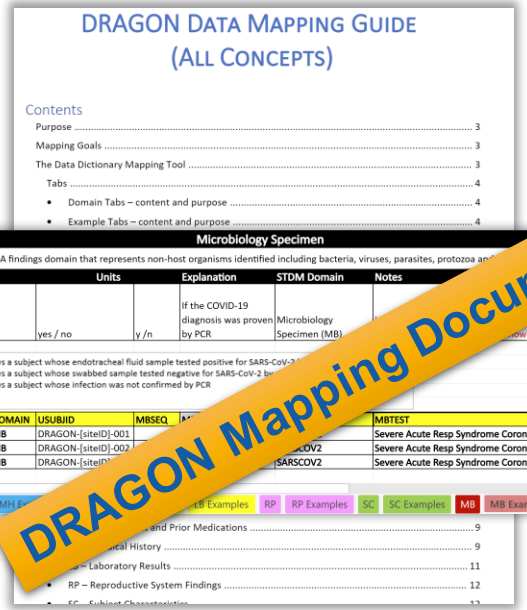
Teamwork Process

- Identified interested parties to participate in development
- Surveyed members about their experience/issues using CDISC in these areas
- Two groups, two weekly calls
  - Japan Group: primarily research-focused
  - US/Europe: Primarily clinical trials/External Control Arm-focused
- Developed document using CDISC Operating Procedures (COP-001, for standards development process)

Survey sent to team members:

- What types of non-interventional studies have you worked with?
- What are the biggest challenges you have experienced when using CDISC standards in observational studies?
- Have you used a model/standard besides SDTM to submit the data to regulatory agencies? In what ways was this easier or more difficult than SDTM?
- What aspects of the CDISC trial design model have and have not worked well for observational data?
- Regarding medications data, how have you handled missing dosing information?
- Have you attempted to create define files for observational study data, and if so, how did you approach define style sheets?
- Have you encountered any issues with CDISC metadata (e.g., origin of data that was imputed whereas CDISC considers it collected)? If so, how did you handle this?

Other Relevant Resources Considered


DRAGON Data Mapping Guide
(All Concepts)

Contents

Purpose 3
Mapping Goals 3
The Data Dictionary Mapping Tool 3
Tabs 4
- Domain Tabs – content and purpose 4
- Example Tabs – content and purpose 4

Microbiology Specimen

A findings domain that represents non-host organisms identified including bacteria, viruses, parasites, protozoa an

Variable		Units		Explanation	STDM Domain	Notes
COVID-19 proven by PCR		yes / no	y /n	If the COVID-19 diagnosis was proven by PCR	Microbiology Specimen (MB)	

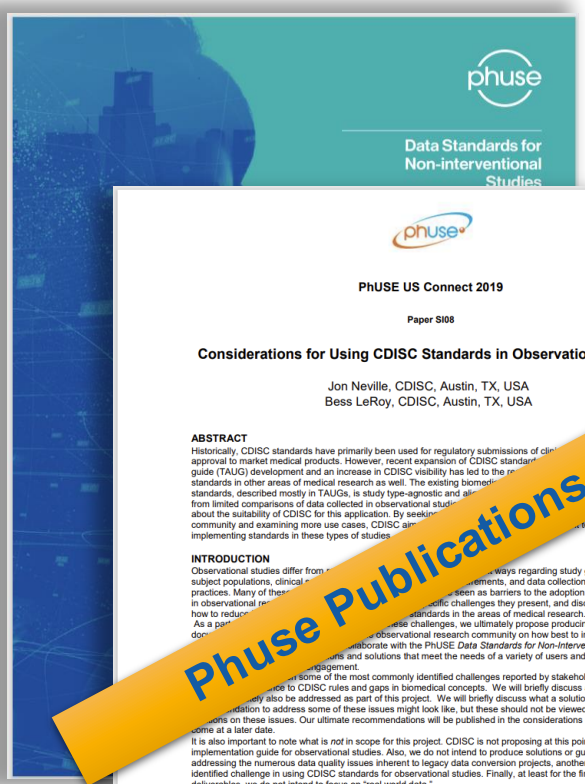
Row 1: Shows a subject whose endotracheal fluid sample tested positive for SARS-CoV-2
Row 2: Shows a subject whose swabbed sample tested negative for SARS-CoV-2 b
Row 3: Shows a subject whose infection was not confirmed by PCR

STUDYID	DOMAIN	USUBJID	MBSEQ	MBTEST	MBTSTDTL	MBORRES	MBSTRESC	MBSTAT
DRAGON	MB	DRAGON-[siteID]-001		Severe Acute Resp Syndrome Coronavirus 2	DETECTION	POSITIVE	POSITIVE	
DRAGON	MB	DRAGON-[siteID]-002		Severe Acute Resp Syndrome Coronavirus 2	DETECTION	NEGATIVE	NEGATIVE	
DRAGON	MB	DRAGON-[siteID]		Severe Acute Resp Syndrome Coronavirus 2	DETECTION			NOT DONE

MH Examples | CE Examples | RP | RP Examples | SC | SC Examples | MB | MB Examples | SU | S

... and Prior Medications 9
...ical History 9
... – Laboratory Results 11
- RP – Reproductive System Findings 12
- SC – Subject Characteristics 12

DRAGON Mapping Documents


phuse

Data Standards for Non-interventional Studies

phuse

PhUSE US Connect 2019

Paper SI08

Considerations for Using CDISC Standards in Observational Studies

Jon Neville, CDISC, Austin, TX, USA
Bess LeRoy, CDISC, Austin, TX, USA

ABSTRACT

Historically, CDISC standards have primarily been used for regulatory submissions of cli... approval to market medical products. However, recent expansion of CDISC standar... guide (TAUG) development and an increase in CDISC visibility has led to the r... standards in other areas of medical research as well. The existing biomedi... standards, described mostly in TAUGs, is study type-agnostic and al... from limited comparisons of data collected in observational studi... about the suitability of CDISC for this application. By seekin... community and examining more use cases, CDISC aim... implementing standards in these types of studies.

INTRODUCTION

Observational studies differ from ... ways regarding study goals, study design, subject populations, clinical ... ements, and data collection / data management practices. Many of the... seen as barriers to the adoption of CDISC standards in observational re... ...ific challenges they present, and discuss at a high level how to reduc... ...standards in the areas of medical research. As a par... ...ese challenges, we ultimately propose producing a considerations doc... ...observational research community on how best to implement CDISC ... ...llaborate with the PhUSE *Data Standards for Non-Interventional Studies* ...ons and solutions that meet the needs of a variety of users and use-cases as will ...engagement.

...some of the most commonly identified challenges reported by stakeholders interested in ...ce to CDISC rules and gaps in biomedical concepts. We will briefly discuss analysis challenges ...ly also be addressed as part of this project. We will briefly discuss what a solution or ...dation to address some of these issues might look like, but these should not be viewed as CDISC's official ...ons on these issues. Our ultimate recommendations will be published in the considerations document that will ...come at a later date.

It is also important to note what is *not* in scope for this project. CDISC is not proposing at this point to produce a full implementation guide for observational studies. Also, we do not intend to produce solutions or guidance for addressing the numerous data quality issues inherent to legacy data conversion projects, another commonly-identified challenge in using CDISC standards for observational studies. Finally, at least for the first phase deliverables, we do not intend to focus on "real world data."

OBSERVATIONAL DATA

Unlike a randomized controlled trial, observational studies do not involve an intervention and no attempt is made on the part of the investigator to impact health outcomes. When collected in an academic or government research setting, observational data are often of high quality; these studies are protocol driven and subject to oversight by an Observational Study Monitoring Board. Like randomized controlled trials, observational studies vary in the study design employed and can be generally categorized as case-control, cohort, or cross-sectional studies. The intent of a randomized controlled trial is to determine the safety and/or efficacy of an intervention. In contrast, observational studies seek to relate potential risk factors to disease outcomes. Because of the lack of randomization, observational studies are more prone to bias and thus potential confounding factors must be collected in order to control for bias during analysis. Beyond research driven studies, observational data may also be generated from real world data sources including electronic health care records, claims and billing, patient registries, and mobile devices. These data have generally not been collected with the intent of supporting research and thus may be less complete and of lower

1

Phuse Publications

Considerations for Using SDTM for Observational Studies/RWD - Overview

Discussion on common issues encountered when implementing SDTM in observational data

Provide implementation strategies or guidance to address these issues.

Provide examples illustrating these strategies (where applicable)

- Reuse existing standards; create new domains and variables only if necessary

Discussion on adjusting conformance rules to better fit these data

- New conformance rules as needed
- Note irrelevant conformance rules for validation checks of observational studies.

Resulting document will be CDISC-endorsed by having gone through our development process.

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What the document does *not* address…

- **SDTM implementation basics**
  - The document will supplement SDTMIG knowledge
- **How to handle dirty or missing data, such as imputing missing values**
- **Source-to-target mapping guidance**
  - Legacy data/RWD are too highly variable
- **How to improve a "validation score" on third-party validation software like P21**
  - We focus on impact of CDISC conformance rules
  - Any changes proposed *may* eventually be incorporated into such vendor software

Please also be aware…

This document is NOT a standard.

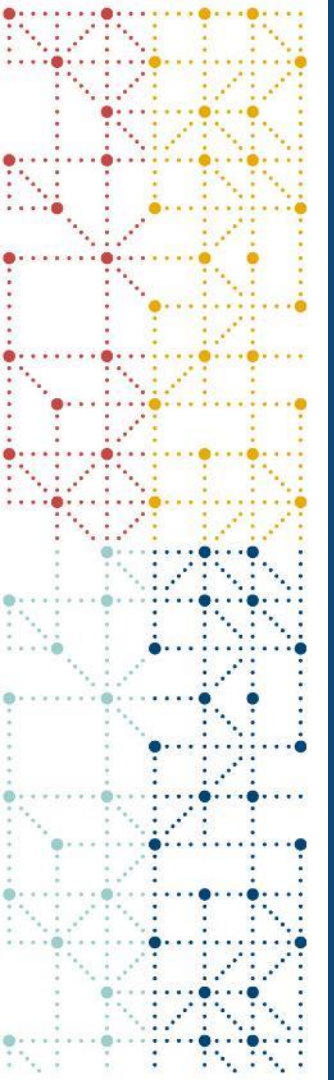
It is a white paper discussing how CDISC proposes to address commonly encountered issues implementing SDTM when working with observational data.

Contents

- Most common issues identified from community input
- Presented in table format, addressed by use case

- Conformance rules likely to be broken by working with observational data
- Coping strategies and proposed changes to conformance rules discussed

- Minimal examples provided
- Section 2 discussion of how to arrive at SDTM is more informative



Sample Content

(Conformance rules and SDTM example content is part of the document but not included here)

Example of Issue Discussion Table – EX vs CM

2.2 Using the Exposure and Concomitant Medications Domains [Go]

The exposure domains are used for protocol-defined treatments that may not be applicable to observational or ECA studies. OBVS-55 UNDER GGG REVIEW

Summary	Study Type	Challenge Presented	Recommended SDTM Strategy
Using the Exposure and Concomitant Medications Domains	Case-Control or Cohort	• No protocol-defined treatment • Distinction between therapies for disease under study vs all other treatments may not be relevant to observational studies	Any medications used to treat the disease under study should be represented using the EC/EX domains, if the investigator deems it appropriate. All other treatments (e.g., prescription, non-prescription, historical treatments) should be represented in the CM domain. Alternatively, the sponsor may choose to represent all medications in the CM domain.
	External Control Arm	• No protocol-defined treatment • Treatments for the disease under study vs all other treatments are important to distinguish	The medication deemed by the investigator to be the comparator to the experimental drug (i.e., used to treat the disease under study) should be represented using the EC/EX domains. All other treatments (e.g., prescription, non-prescription, historical treatments) should be represented in the CM domain. OBVS-59 UNDER GGG REVIEW

- Issue(s) are summarized, and challenges are discussed by use case
- Recommended strategy for implementing in SDTM is provided
- Where useful, SDTM examples are provided.

Example of Issue Discussion Table – TS

Trial Summary Issues

Created by Alana St. Clair, last modified by Jon Neville a minute ago

Summary	Study Type	Challenge Presented	Recommended SDTM Strategy
How to Define Study Start Date	Observational studies	Study Start Date (TSPARMCD = SSTDTC) for SDTM is defined as "The earliest date of informed consent among any subject (Date/Time of Informed Consent, RFICDTC) that enrolled in the study." Informed consent may not be available for observational studies.	• Sponsors should set the study start date to the earliest reference start date for any subject. • Document how the study start date was defined/populated in the Define.XML or a study data reviewer's guide if Define.XML is not used.
	ECA studies	Study Start Date (TSPARMCD = SSTDTC) for SDTM is defined as "The earliest date of informed consent among any subject (Date/Time of Informed Consent, RFICDTC) that enrolled in the study." Informed consent may not be available for RWD.	It is recommended to use the earliest start date of any subject's first line of therapy.
Study Type	Observational studies	None identified	Use "OBSERVATIONAL" from Study Type Response codelist
	ECA studies	No controlled terminology available at this time. Study Type Response codelist is non-extensible.	Use "EXTERNAL CONTROL ARM" and explain the error in the SDRG.

External documentation is an integral part of the strategy

- The use and derivation of some variables will need to be explained
  - For ECA studies / regulatory submission:
    - A study data reviewer's guide
    - Define.XML
  - For basic observational research:
    - Something like a study data reviewer's guide will be necessary and helpful

Status and Conclusions

Timeline

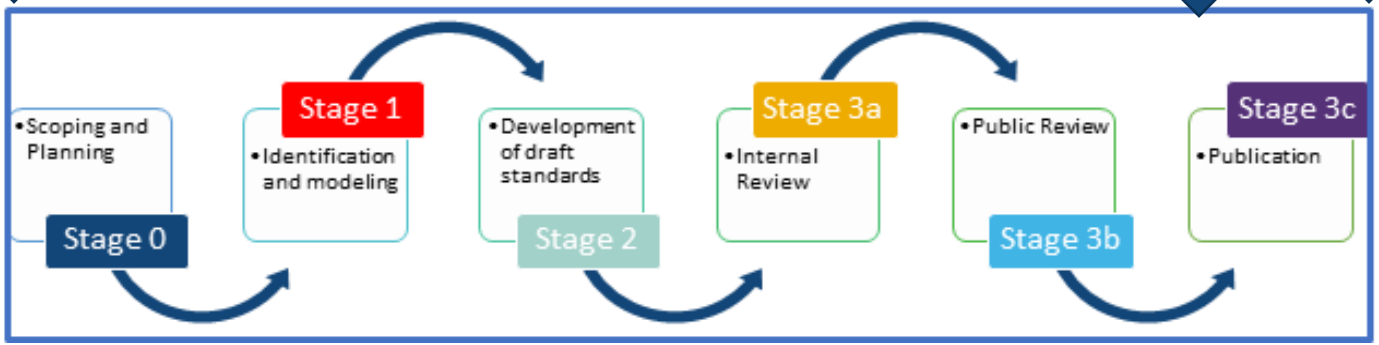
62 issues reported in Jira from beginning of internal review to end of public review

Kick-off: 6/29/22

Development phase: OCT 2022- MAR 2023

Public review Completed 09/2023

Publication by end of year



Lessons learned

Most conformance rules can be followed. Some failures will have to be explained in an external reviewer's guide or define.XML

Existing SDTM domains cover what we need for the use cases we've examined.

Existing variables can also be used as-is or repurposed

- e.g., ARM can be used to represent cohorts

SDTM Examples are less informative than discussions of considerations

- Examples look like normal SDTM examples
- Discussing how we arrived at the modeling, and how to explain that to reviewers is more impactful

Conclusions

- The “Considerations for SDTM Implementation in Observational Studies and Real World Data” document is on schedule for publication by end of 2023
- It was produced with limited funding and has a limited scope.
- It is not an “implementation guide” (terminology reserved for standards) It is not a standard but was developed using COP-001
- This document could serve as the foundation for future development with expanded use cases and broader input
- With input from regulators, it *could* evolve into a standard in the future, but…
- As of today, no follow-up project is planned.

Thank You!

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