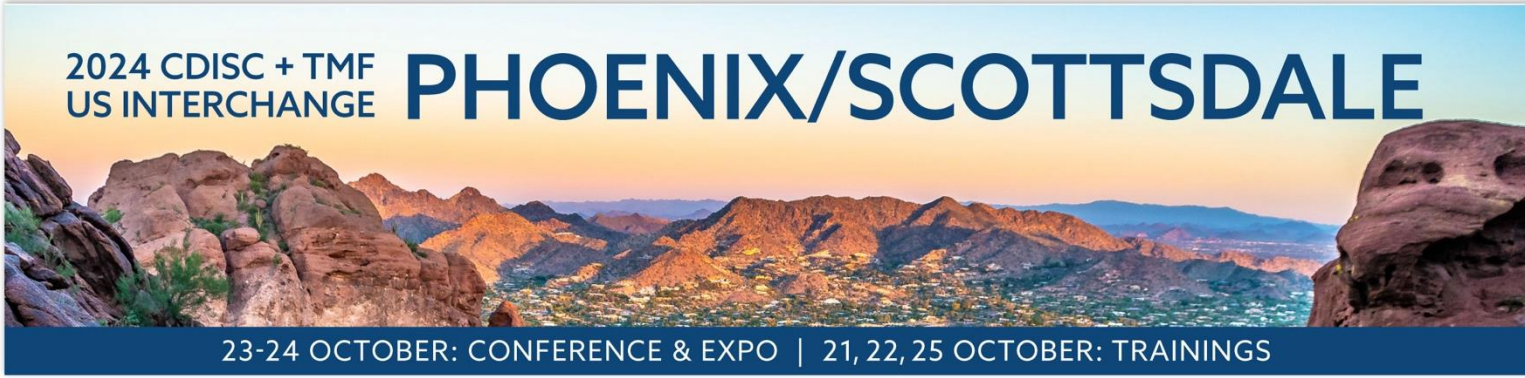

SDTM in Observational Studies: Challenges and Experiences Working in Post-Marketing Observational Study & PASS Study

Presented by Phillip Jackson, Principal Stat Programmer, IQVIA

Meet the Speaker

Phillip Jackson

Title: Principal Stat Programmer

Organization: IQVIA

•Phillip Jackson is a Principal Stat Programmer at IQVIA, where he currently assists clients with data standards, metadata creation, standard control, etc. A firm believer in CDISC standards, he believes that improved interconnectivity with RWD sources and future automation will reshape clinical trials to bring life saving products to the public faster.

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.*
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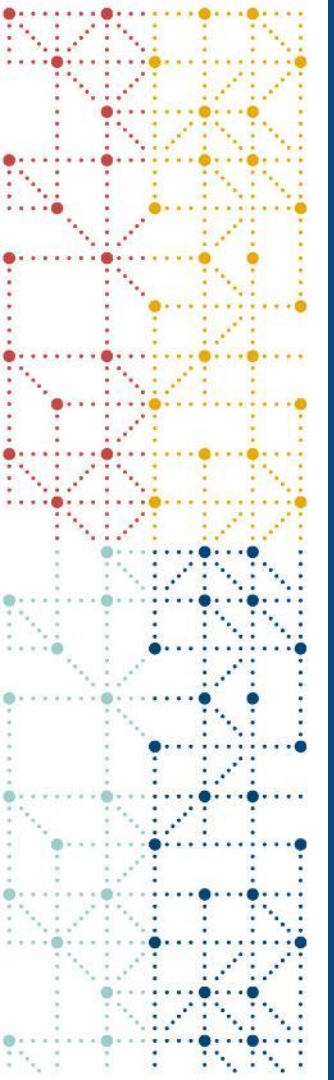
Agenda

1. Introduction
2. EC/EX, or CM?
3. Handling Reference Dates and Study Days
4. Handling Informed Consent



Introduction

Introduction

CDISC's Considerations for SDTM Implementation in Observational Studies and Real-World Data

- Identifies commonly encountered issues with using SDTM for observational studies and RWD.
- Focuses on the following case types:
  - Cohort
  - Case control
  - ECA

This presentation is an attempt to implement a form of sponsor-specific standardization using these considerations as a template for expanding the examples to Registry and Drug Utilization studies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Considerations for SDTM Implementation in Observational Studies and Real-World Data

Version 1.0 (Final)

Prepared by the
CDISC Observational Studies & Real-World Data Standards Development Team

Notes to Readers

- This document is based on SDTM v2.0 and SDTMIG v3.4.

EC/EX, or CM?

EC/EX or CM?

CDISC :

CDISC SDTM Implementation in Observational Studies and Real World Data v1.0 Section 2.2

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

Summary	Study Type	Challenge Presented	Recommended SDTM Strategy
Using the Exposure and Concomitant/Prior Medications domains	Cohort or case-control	• 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, nonprescription, 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, nonprescription, historical treatments) should be represented in the CM domain.

EC/EX or CM? Registry Example

- Study A is a Registry study that utilizes data sourced from an established REMS and an associated pharmacovigilance program to check for occurrences of a specific safety event.
- Observational study, so protocol states there is no IMP. However, all patients who are prescribed Med A in routine clinical practice are required to be enrolled in the patient registry.
- Question: Should the Med A be mapped to EC/EX? Or CM?
  - In Study A we decided to use CM
  - Justification:
    - Observational Study with IMP defined as Not Applicable in the protocol
    - No comparators or ECA with which to compare meds.
    - Study is collecting all Med A prescriptions, not just for a specific indication (i.e., there is no defined “disease under study”)
    - Convenient way to avoid determining pre vs post Enrollment exposure to Med A, and the impacts due to that decision.

EC/EX or CM? Registry Example

What if we decided to map to EC/EX instead?

There is a counter argument that this should be in EC/EX due to study enrolment being contingent on starting Med A.

- Mapping to EC/EX would cause the following issues:
  - Some patients entering the registry have already taken Med A prior to enrolment. Where should historical Med A exposures be mapped?
    - Solutions considered:
      - Map ALL Med A exposures to EX
        - Issues:
          - Protocol defines participation in the study as enrolment, so this solution would cause RFXSTDTC<RFSTDTC
          - The datapoints for historical RFXSTDTC may not be complete
      - Map pre-enrolment Med A exposures to CM and post-enrolment Med A exposures to EX
        - Issues:
          - The quality of prescription records is inconsistent, so correctly breaking up the CMs from EX records could be very difficult.
      - **Map all exposures to CM.**

EC/EX or CM? Drug Utilization Example

- Study B is a Drug Utilization study that utilizes retrospective medical chart review of patients treated with Med B per routine medical practice.
- Observational study, so protocol states there is no IMP. However, all patients who are prescribed Med B in routine clinical practice.

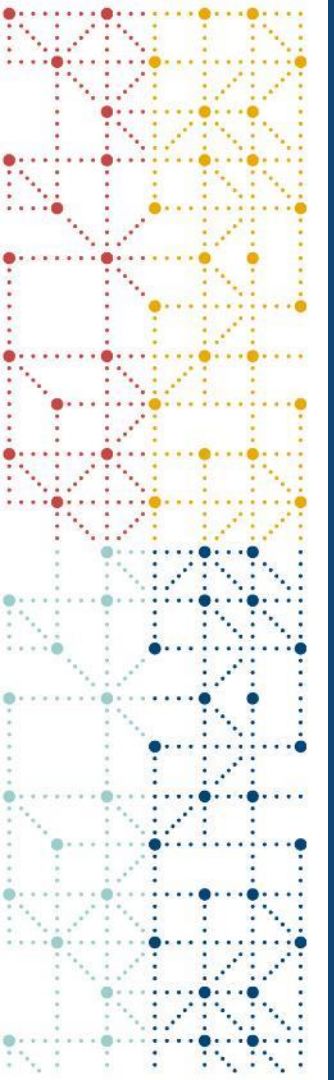
- Question: Should the Med A be mapped to EC/EX? Or CM?
  - In Study B we decided to use CM
  - Justification:
    - Observational Study with IMP defined as Not Applicable in the protocol
    - No comparators or ECA with which to compare meds.
    - Study is collecting all Med B prescriptions, not just for a specific indication (i.e., there is no defined "disease under study")

EC/EX or CM? Drug Utilization Example

What if we decided to map to EC/EX instead?

There is a counter argument that this should be in EC/EX due to study enrollment being contingent on starting Med B.

- Mapping to EC/EX would cause the following issues:
  - The indication/reason for taking Med B can vary. –INDC is technically allowed (not explicitly excluded) in EC/EX per SDTMv2.0, but mapping TSPARMCD=INDIC for each indication possible related to Med B if mapped to EC/EX is burdensome.



Handling Reference Dates and Study Days

Reference Dates and Study Days

CDISC :

CDISC SDTM Implementation in Observational Studies and Real World Data v1.0 Section 2.4

Summary	Study Type	Challenge Presented	Recommended SDTM Strategy
Defining Reference Start Date (RFSTDTC) and Reference End Date (RFENDTC)	Cohort	Study reference periods may not be relevant.	• Use registration date as RFSTDTC. • Set the date of occurrence of the evaluated event as RFENDTC. • Document how the RFSTDTC and RFENDTC were defined/populated in the Define.XML or study data reviewer's guide (SDRG).
	Case-control	Study reference periods are not relevant.	• Both RFSTDTC and RFENDTC should be left null. • If validating the SDTM data, explain the error in the SDRG.
	External control arm	Study reference periods may not be relevant.	• The index date[a] or another appropriate milestone date should be used as RFSTDTC. Choose the latest observation in the data as RFENDTC. • Document how RFSTDTC and RFENDTC were defined/populated in the Define.XML.
Handling study day (--DY) variables when complete dates (month, day and year) are not available.	All	• The investigator may have limited information on which to base RFSTDTC (e.g., only birth year, only month and year of participation start). • Dates associated with other observations/records may be incomplete or missing.	Study day variables (--DY) are based on RFSTDTC and --DTC. If either is not a complete date, --DY cannot be used.

Reference Dates and Study Days – Registry Example

- Example Study A's protocol defines registry participation as beginning at enrollment in a REMS program.

- Decided on the following:
  - RFSTDTC=Date of enrollment in the REMS program.
  - RFENDTC=Last Date in the study
  - RFXSTDTC/RFXENDTC=null (no EX mapping)

Reference Dates and Study Days – Drug Utilization Example

- Example Study B's protocol defines the Index Date as the first prescription of Med B for the patient.

- Decided on the following:
  - RFSTDTC=Index Date (first prescription of Med B)
  - RFENDTC=Last observation date
  - RFXSTDTC/RFXENDTC=null (no EX mapping)

Handling Informed Consent

Informed Consent – Registry Example

- In Study A, the protocol states that Informed Consent is not expected to be required for the study since all data will be collected via established REMS and pharmacovigilance programs.
- However, the patients ARE required to agree to enrollment into the REMS program.
- Question: If informed consent is not required for this study, then can we use REMS program enrollment date?

- Our Decision:
  - Date of patient REMS enrollment signature = RFICDTC
  - Justification:
    - The protocol defines the start of participation in the study as the patients enrolling into the REMS program. Only patients who enter the REMS program are included in the registry. No separate informed consent is expected to be required of the patients.

- Considerations:
  - Discuss this with the FDA FIRST
  - Must be documented in cSDRG

Informed Consent – Drug Utilization Example

- In Study B, the protocol states that Informed Consent is not required but may be required depending on local country regulations.

- Informed consent, if obtained, will be prior to chart abstraction. RFICDTC will therefore be AFTER RFSTDTC (first retrospective dose of Med B).
  - This will need to be explained in the cSDRG.

In Conclusion..

Conclusion

The CDISC Considerations document includes many great examples which can be used as a launching point for strategies related to other observational study types.

Sponsors will need to remain flexible in their use of CDISC standards for observational studies, while at the same time creating comprehensive documentation to assist with review of the programming choices made.

Additional use cases from the industry would go a long way to assisting CDISC add to this “stake in the ground”.

Thank You!

Phillip Jackson

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References / Additional Reading

- Info on REMS studies:
  - https://www.fda.gov/media/77846/download
  - What's in a REMS? | FDA
- Informed Consent for Registries (NOT regulatory guidance, just some info): Informed Consent for Registries - Registries for Evaluating Patient Outcomes - NCBI Bookshelf (nih.gov)
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (fda.gov)
- Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products Guidance for Industry (fda.gov)