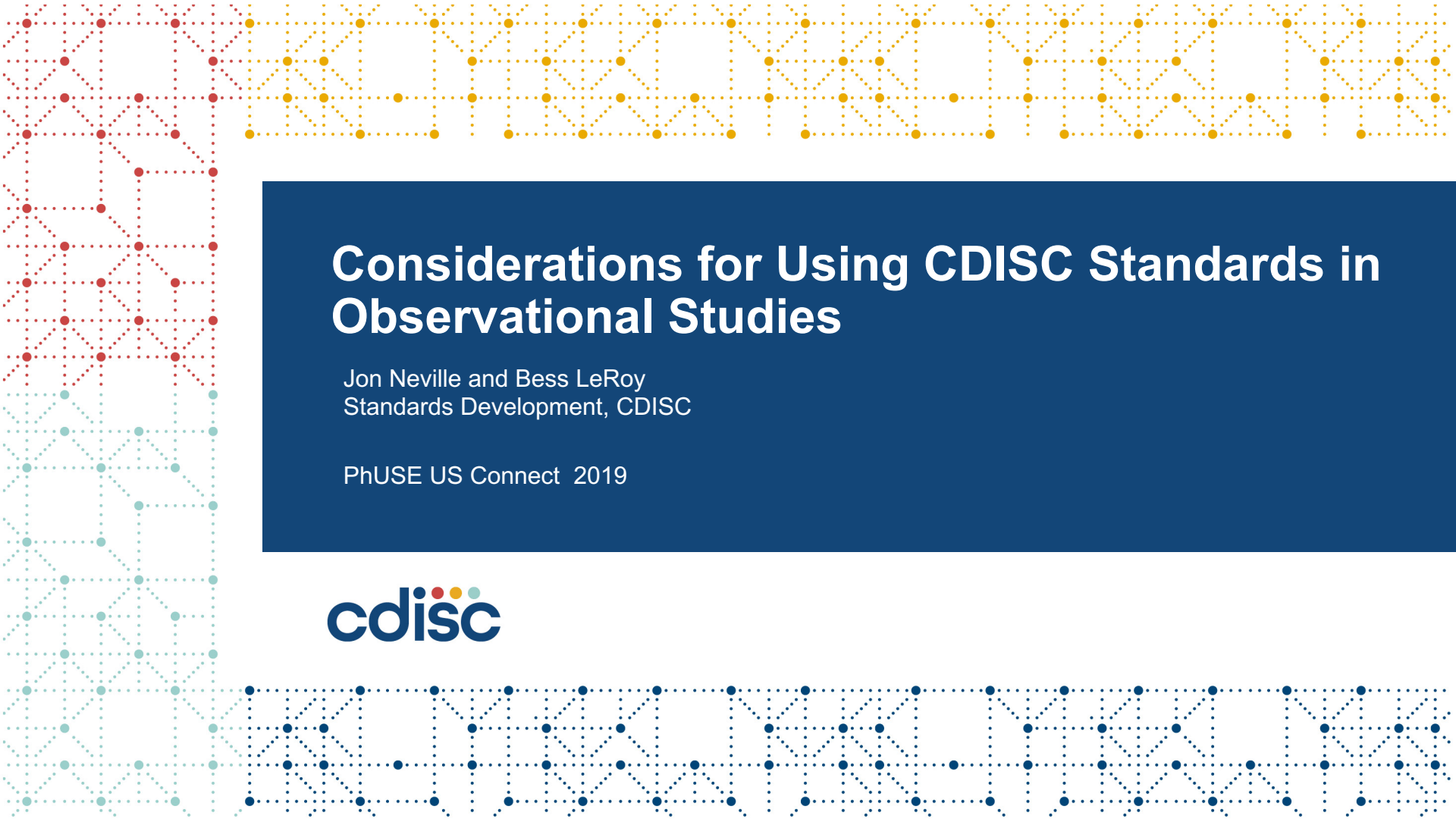




Considerations for Using CDISC Standards in Observational Studies

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PhUSE US Connect 2019





Disclaimer

Some of what you'll see/hear in this presentation is conjecture. If it sounds like a formal CDISC opinion, it's actually just Jon's opinion.

CDISC is still discussing internally how to approach the broad world of observational data.

Background

- Historically, CDISC standards were primarily designed for use in studies of regulated medical products
- Recent expansion of CDISC standards in therapeutic area development, and the 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 Mission Statement:

The CDISC mission is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare.

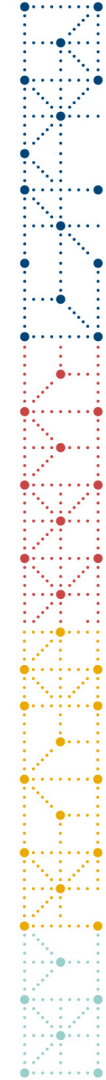
Sources of observational data

- Observational studies carried out in academic or government research settings

- Real world data (RWD) sources including:
 - patient registries
 - mobile / wearable devices
 - electronic health care records
 - claims and billing

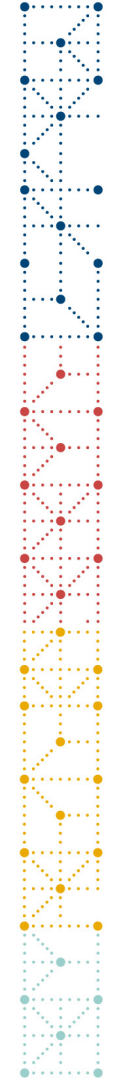
CDISC is currently engaged in internal discussions on vision/direction with respect to real world data

RWD have generally not been collected with the intent of supporting research and thus may be less complete and of lower quality than data collected in a research setting



Observational studies

- Observational studies do not involve an intervention and no attempt is made on the part of the investigator to impact health outcomes
- Goals of these studies are to determine which factors affect disease risk, incidence, prevalence, and/or outcomes
 - Socioeconomics
 - Risk factors or risk-mitigating factors
 - Genetics
 - Behavioral/lifestyle factors
 - Environmental exposures



Observational studies vary significantly from randomized clinical trials

- Studies may have many thousands of patients and may go on for years or even decades
- However, observational data collected in academic or government research settings are often
 - Protocol driven
 - Overseen by an Observational Study Monitoring Board
- Data does not necessarily need to be submitted to a regulatory agency such as the FDA so **there is no strict requirement for data standards**

Commonly identified challenges when using CDISC standards in observational research

Poor data quality



Out of scope

Gaps in
Biomedical
conceptual
content

Conformance/
validation issues



Focus on these issues with
emphasis on SDTM



Biomedical Concepts in Observational Research

Example Case: Mapping a legacy cancer epidemiology study

cnio *stop cancer*

National Center for
Oncology Research
(Spain)

<https://www.cnio.es>



GENETIC & MOLECULAR EPIDEMIOLOGY GROUP

- Special focus on epidemiological studies.

THE AIMS:

- Learn and implement CDISC standards to support development of IMI eTRIKS project for Data Sharing Ecosystem
- To enhance the standardization of data in the epidemiology field

Overview of CNIO Study Materials Received: 4 CRFs

1. Clinical Data Questionnaire (CDQ)

- Biosampling, labs, imaging, diagnostics, and medications



2. Sociodemographic and Epidemiological Questionnaire (SEQ)

- Patients and first-degree relatives: Medical history, smoking, medications, water consumption, hygiene, physical activity



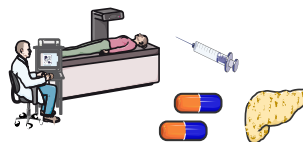
3. Food Frequency Questionnaire (FFQ)

- Food consumption



4. Follow-up Questionnaire (FUQ)

- Follow-up labs and imaging to assess disease progression



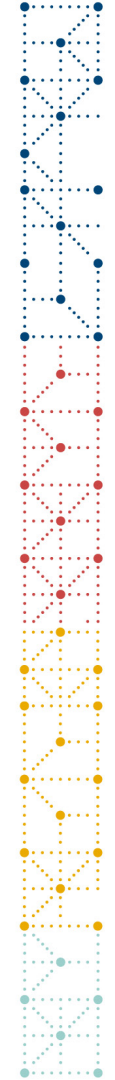
We received from CNIO *only* these CRFs. No data nor protocol received

Conclusions from mapping the CRFs

4 CRFs contained 1137 items

- Some items not mapped– (administrative items such as address)
- Most concepts mapped to SDTM in a straightforward manner
- Approximately 28% were difficult to map; some of these represent possible gaps in *biomedical concepts* for epidemiological studies

	AE	APxx	BS	CE	CM	CO	DM	DS	EC	EX	FA	HO	LB	MH	MI	ML	PE	PR	QS	RELREC	RS	SC	SU	TR	TU	VS	SUPPQUAL	Custom Domains
CDQ	✓		✓	✓				✓	✓	✓	✓	✓	✓		✓			✓	✓	✓	✓			✓	✓	✓	✓	
SEQ		✓			✓	✓	✓							✓		✓						✓	✓					✓
FFQ					✓						✓					✓											✓	
FUQ	✓									✓	✓	✓	✓				✓	✓			✓							



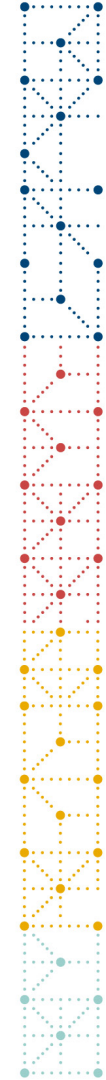
Examples of items placed in custom domains: How would you represent these data?

- Have you been in a swimming pool more than 10 times in your life?
- Have you ever lived in a house without a refrigerator?
- What type of water did you drink at home (tap water, bottled water)?
- How often do you shower and how long do you typically spend in the shower?
- Have you ever had a job where you spent 6 months or more on "night-shifts" or "grave-yard shifts" only?

*Even data that seem conceptually “unusual” will almost always be an **event, intervention or finding.***



Conformance and Validation



Conformance and data validation concerns

- Many expected SDTM domains and variables may not be available nor relevant to observational studies
- Perfectly legitimate observational data records will result in conformance issues and validation errors

Conformance rules are relevant to regulatory submissions and cannot always be strictly adhered to in these use cases

Conformance Rules: SDTM datasets

Conformance Rule	Flag Type	Challenge Presented
Demographics (DM) dataset must be included in every submission.	Error	Inclusion of the dataset should not present a problem. However, some required/expected variables will not be available
Adverse Events (AE) dataset should be included in every submission.	Warning	Depending on study type, these data may not be available
Lab Test Results (LB) dataset should be included in every submission.	Warning	Depending on study type, these data may not be available
Vital Signs (VS) dataset should be included in every submission.	Warning	Depending on study type, these data may not be available
Exposure (EX) dataset should be included in every submission.	Warning	Observational studies are not interventional studies. As such, exposure data will not be relevant.
Disposition (DS) dataset should be included in every submission.	Warning	Subjects will not likely meet formal milestones, nor will they have formal study completion/withdrawal dates.
Subject Elements (SE) dataset should be included in every submission.	Warning	Trial arms and elements are not relevant to observational research. Therefore, neither are subjects' progression through these.
Trial Arms (TA) dataset should be included in every submission.	Warning	Observational studies do not have rigid study designs with planned arms.
Trial Elements (TE) dataset should be included in every submission.	Warning	Without trial arms there are no elements to describe.
Trial Summary (TS) dataset must be included in every submission.	Error	Observational studies are not trials, but investigators could possibly create study parameters to describe here. It would require new controlled terminology and could be burdensome if it were considered a "required" dataset in observational research.

Conformance Rules: Variables that may present issues

Variable(s)	Domain	Core	Challenge Presented
RFSTDTC / RFENDTC	DM	Expected	Study reference periods will not always be relevant. Defining these dates can be challenging. Sometimes dates will be missing altogether.
RFXTSDTC / RFXENDTC	DM	Expected	Observational research does not include regimented exposure to a protocol-defined drug. Phase IV studies / Post-marketing surveillance could possibly provide these
SITEID	DM	Required	Observational research includes observations from across healthcare and clinical settings. These will likely vary and not be available in the data anyway
ARM / ARMCD ACTARM / ACTARMCD	DM	Required	There are no arms to describe in observational research.
VISITNUM	Multiple	Sometimes Required	The concept of “visit” may not be relevant in observational research

SPECIAL CASES FOR OBSERVATIONAL STUDIES

Some CDISC definitions do not apply directly to studies without a treatment intervention

Typical CDISC	HBGD <i>ki</i> Usage
AE vs MH dichotomy	Using CE in all cases to avoid implying a pre/post distinction where one does not exist.
RFSTDTC defines the study Baseline	Relative days important, but use DOB as the milestone. e.g., LBDY=1 is day of birth.
VISITNUM, VISIT reflect study design	Many observational studies still have visit schedules.
Study epochs	Used to reflect pregnancy or developmental milestones rather than study design characteristics. • Prepregnancy, T1, T2, T3, intrapartum, postpartum. • In utero, delivery, neonatal, infancy, childhood.
Study arm describes randomization	Study arm describes different cohorts that were enrolled (e.g., case-control studies).

Where we are today: workarounds / coping strategies

Gaps in Biomedical concepts

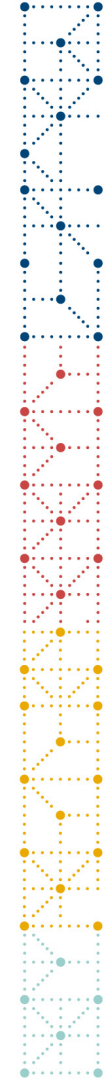


- Custom domains
- Non-standard variables

Conformance/validation issues



- Ignore irrelevant errors
- Repurpose datasets and variables to analogous use cases



Coping strategies are not permanent solutions!
Can we do better going forward?

Many users have probably developed many disparate workarounds.
Can CDISC weigh in?

Considerations document: a better way forward
Develop a formal, CDISC-vetted, consistent, harmonized strategy for addressing these challenges in observational research.

Maybe, eventually...

- address concept gaps in existing SDTM; new development (COP-001*)
- address specific study-type conformance and validation rules

Data Standards for Non-Interventional Studies:

Collaboration on common goals



Yuliia Bahatska, PRA Health Sciences
Vladlen Ivanushkin, DataFocus



Jon Neville, CDISC



CDISC and PhUSE workstreams for non-interventional studies



Gather inputs from research groups



Focus on end-to-end standards



Produce “considerations” document



Much interest in RWD



Gather inputs from programmers



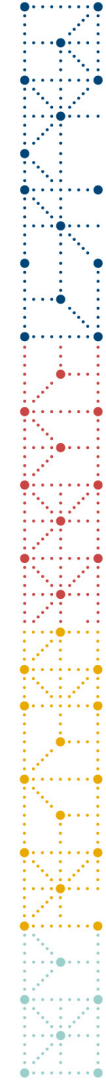
Focus on ADaM-based solutions to common problems



Publish white paper

Next steps – Considerations document

- Develop a work plan and timeline
- Brainstorm on actual and potential challenges and discuss them (PhUSE group has completed programmers' survey)
- Seek broader input from the research community
- TBD- Produce a scope for a white paper/ considerations document



Interested?

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Thank You!

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