



2022

JAPAN

INTERCHANGE

13-14 JUNE | VIRTUAL EVENT

The DRAGON Project and the CDISC Observational Studies Document

Kit Howard, CDISC
Jon Neville, CDISC



Meet the Speakers

Kit Howard

Title: Senior Director, Standards Development and Education

Organization: CDISC

Kit Howard spent much of the past 30 years developing data and process standards for clinical trials. She started volunteering with CDISC in 2007, and is now Senior Director of Standards Development and Education for CDISC, co-leads CDISC's Medical Device standards development, and is an authorized CDISC instructor. Kit earned her graduate degree from the University of Michigan's School of Public Health in Clinical Research Design and Statistical Analysis.



Jon Neville

Title: Senior Standards Developer

Organization: CDISC

Jon Neville is Senior Standards Developer at CDISC, where he has worked for almost 5 years. He has over 12 years' experience with both implementing and developing CDISC standards. He has led, co-led, or otherwise participated in many CDISC therapeutic-area data standards projects. He is currently co-leading CDISC's Biomedical Concept Development team. Mr. Neville also serves on the CDISC Global Governance Group (GGG), and the SDS sub-teams for Genomics.





Agenda

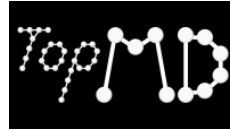
1. The DRAGON Project
2. CDISC Considerations and Examples Document for Observational Study Data

**RapiD and SecuRe AI enhAnced DiaGnosis, Precision
Medicine and Patient EmpOwerment Centered
Decision Support System for Coronavirus PaNdemics**



DRAGON Partners

Data
Artificial Intelligence Modeling
App Development
Project Management
Data Standards
More



UNIVERSITÀ
DEGLI STUDI
FIRENZE



Public Health
England



Imperial College
London



DRAGON

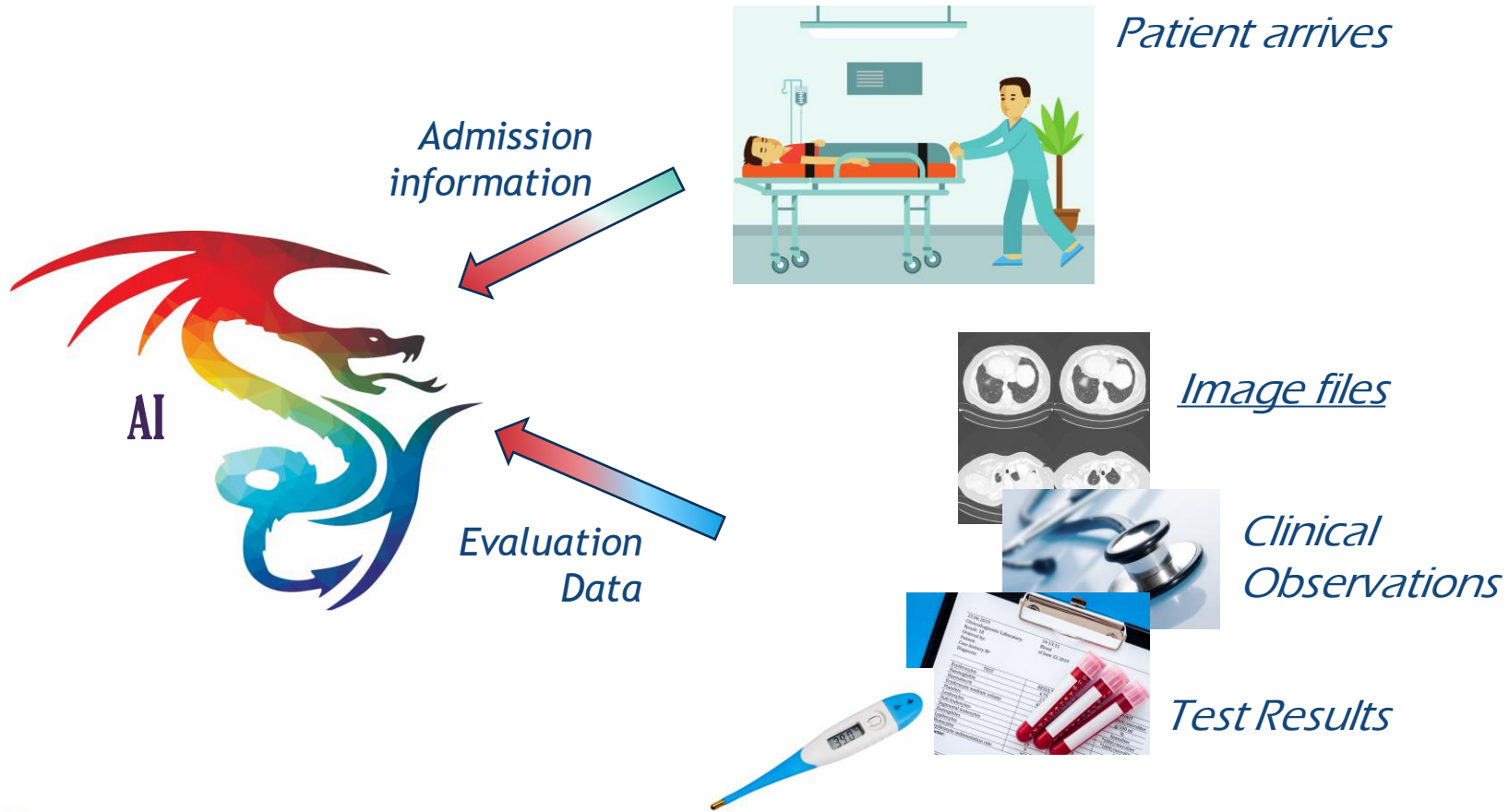


Data
Harmonization for
Artificial
Intelligence (AI)
Modelling

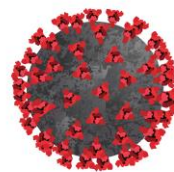
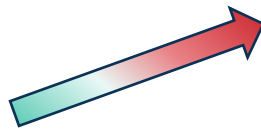
COVID User Guide
v2.0 Imaging Guide

Recommendations
and Considerations
for Using CDISC
Standards with
Observational
Studies

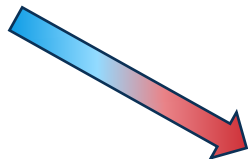
Goal: Gathering Information



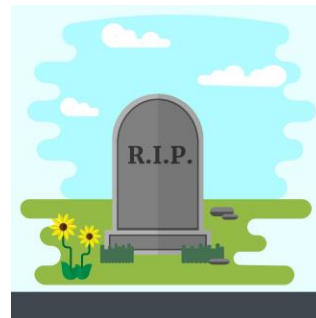
Goal: Providing a Prediction



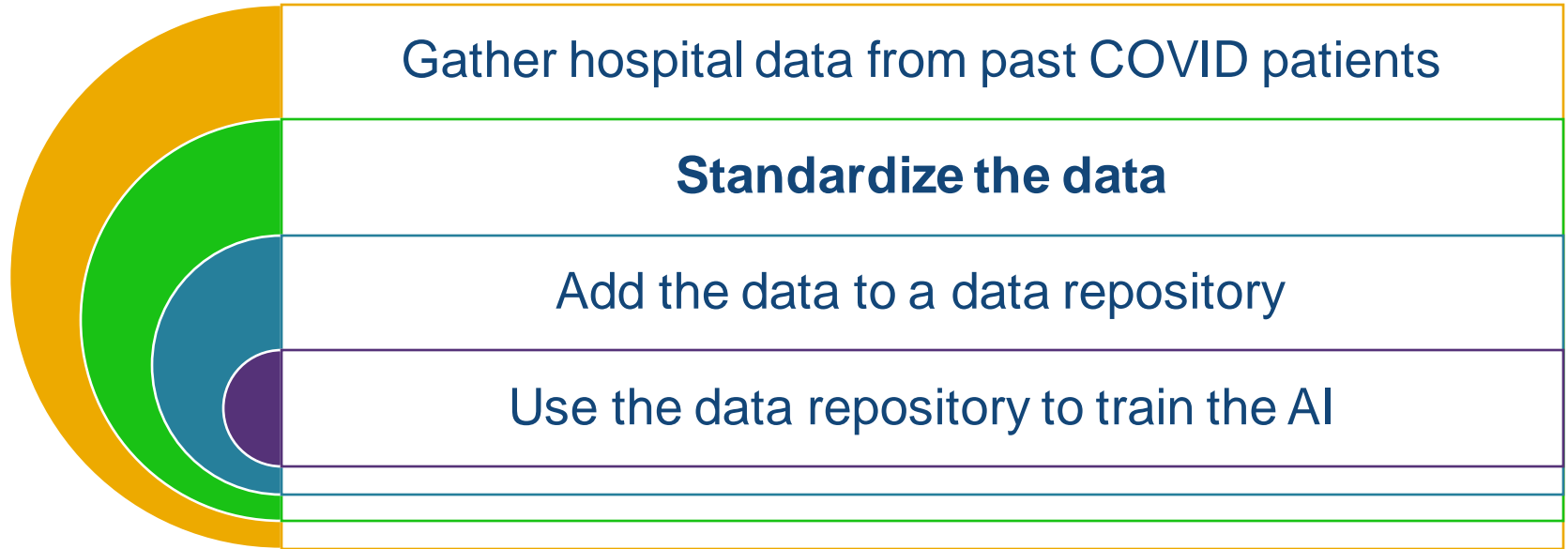
Diagnosis



Prognosis (predicted outcome)



How Can We Do This?



CDISC's Approach?

List of clinical concepts important for DRAGON analyses

- Demographics
- Vital Signs
- Labs
- Comorbidities
- COVID-19 Symptoms
- Medications
- Pregnancy

- Supplemental Oxygen
- Procedures
- Hospitalizations
- Smoking History
- Essential Worker Status
- Death

CDISC Mapping Tool

- Organized by Domain, referencing CDASH & SDTM
- Shows DRAGON Concept(s) represented in that domain
- Shows example(s) of what a conformant SDTM dataset would look like
- Adjusts many CDASH and SDTM requirements to accommodate EHR data

Microbiology Specimen

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

Variable	Units	Explanation	STDM Domain	Notes
COVID-19 proven by PCR	yes / no	If the COVID-19 diagnosis was proven by PCR	Microbiology Specimen (MB)	In CDISC, this item is not handled as Yes/No, rather as Positive/Negative as shown below

← DRAGON Concept

↓ Represented as SDTM

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

STUDYID	DOMAIN	USUBJID	MBSEQ	MBREFID	MBTESTCD	MBTEST	MBTSTDTL	MBORRES	MBSTRESC	MBSTAT
DRAGON	MB	DRAGON-[siteID]-001	1	SP001	SARSCOV2	Severe Acute Resp Syndrome Coronavirus 2	DETECTION	POSITIVE	POSITIVE	
DRAGON	MB	DRAGON-[siteID]-002	1	SP131	SARSCOV2	Severe Acute Resp Syndrome Coronavirus 2	DETECTION	NEGATIVE	NEGATIVE	
DRAGON	MB	DRAGON-[siteID]-003	1	SP067	SARSCOV2	Severe Acute Resp Syndrome Coronavirus 2	DETECTION			NOT DONE

Mapping Tool (cont)

- Provides ability to map partner data to CDISC variables

Microbiology Specimen (MB)						
Study, Site and Patient/Subject/Participant Identification						
No personally identifiable information should be included (e.g., name)						
Observation Class	Domain	CDASHIG Variable	Partner Original Variable Name (if no variable, leave null)	Partner Original Variable Label	Partner Original Controlled Terminology (Code List)	Partner's SDT Algorithm (in n
<i>Findings</i>	MB	MBTEST				
<i>Findings</i>	MB	MBTSTDTL				
<i>Findings</i>	MB	MBORRES				
<i>Findings</i>	MB	MBORRESU				

Navigation bar: > ☰ LB LB Examples RP RP Examples SC SC Examples MB MB Examples SU SU Examples PR PR Examples H +

Data Mapping Guide

- Orients partner sites to using the mapping tool
- Provides more detailed domain- and variable-level notes / rules for DRAGON
- Provides steps and cautions to guide accurate mapping results

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
• Example Formatting	4
Columns	5
• Grey: Observation Class and Domain (prepopulated)	5
• Orange: CDASH Information (prepopulated)	5
• Pink: CDASH to SDTM Conversion (prepopulated)	5
• Green: SDTM Information (prepopulated)	5
• Purple: Correspondence of DRAGON Core Data to SDTM data points (prepopulated)	5
• Blue: Partner Mapping Decisions (partner)	6
Mapping the Data	6
• Steps	6
• Caveats	6
Domain- and Variable-Specific Notes for Populating Patient Data Datasets	7
• All domains	7
• VS - Vital Signs	8
• DM - Demographics	8
• CM - Concomitant and Prior Medications	9
• MH - Medical History	9
• LB – Laboratory Results	11
• RP – Reproductive System Findings	12
• SC – Subject Characteristics	17

Data entry templates

Some partners cannot export data and are entering data manually

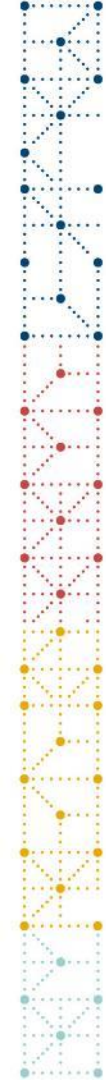
Lab Core Tests ("Blood Gas Deviation")

Core Fields Record structure: one record per test result per time point per

NOTE: the number of tests per patient is unknown; 8 rows per subject w
The conversion factor for converting kPa to mmHg has been included in

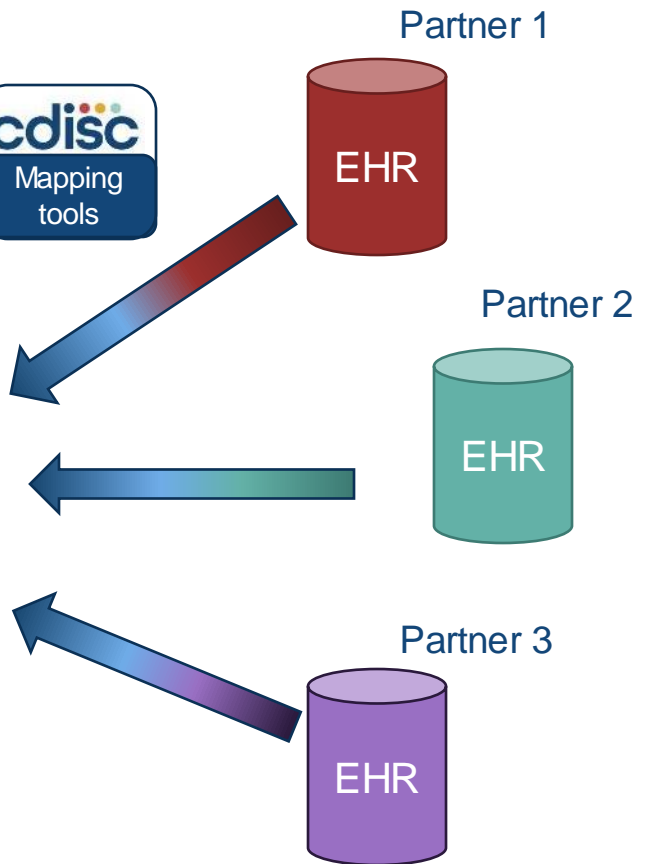
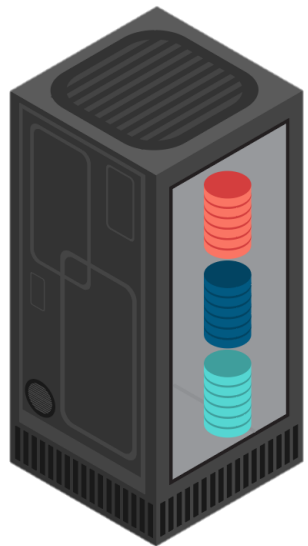
	STUDY	DOMAIN	USUBJID	LBTEST	LBCAT	LBORRES	LBORRESU	LBORNRLO
	[Project]	Domain	Patient ID	Name of the Measurement	Category of lab test	Original Result of the Measurement	Original Result Unit	Lower limit of normal range original result
Codelist/Control	-	DOMAIN C66734	-	C67153 VSTEST			C66770 VSRESU	
Validation Data	DRAGON	LB	DRAGON-YOURSITE-PSEUDOID	PARTIAL PRESSURE OXYGEN	BLOOD GAS PANEL	75	kPa	
Validation Data	DRAGON	LB	DRAGON-YOURSITE-PSEUDOID	PARTIAL PRESSURE OXYGEN	BLOOD GAS PANEL	109	kPa	
Patient Data	DRAGON	LB	DRAGON-YOURSITE-PSEUDOID01	PARTIAL PRESSURE OXYGEN	BLOOD GAS PANEL		kPa	
Patient Data	DRAGON	LB	DRAGON-YOURSITE-PSEUDOID01	PARTIAL PRESSURE OXYGEN	BLOOD GAS PANEL		kPa	
Patient Data	DRAGON	LB	DRAGON-YOURSITE-PSEUDOID01	PARTIAL PRESSURE OXYGEN	BLOOD GAS PANEL		kPa	
Patient Data	DRAGON	LB	DRAGON-YOURSITE-PSEUDOID01	PARTIAL PRESSURE OXYGEN	BLOOD GAS PANEL		kPa	
Patient Data	DRAGON	LB	DRAGON-YOURSITE-PSEUDOID01	PARTIAL PRESSURE OXYGEN	BLOOD GAS PANEL		kPa	
Patient Data	DRAGON	LB	DRAGON-YOURSITE-PSEUDOID01	PARTIAL PRESSURE OXYGEN	BLOOD GAS PANEL		kPa	
Patient Data	DRAGON	LB	DRAGON-YOURSITE-PSEUDOID01	PARTIAL PRESSURE OXYGEN	BLOOD GAS PANEL		kPa	

Navigation: VS Entry Core | CM Entry Core | **LB Entry Core** | LB Entry Non-Core | SC Entry Core | RP Repro Sys | MB Microbiology | SU S +



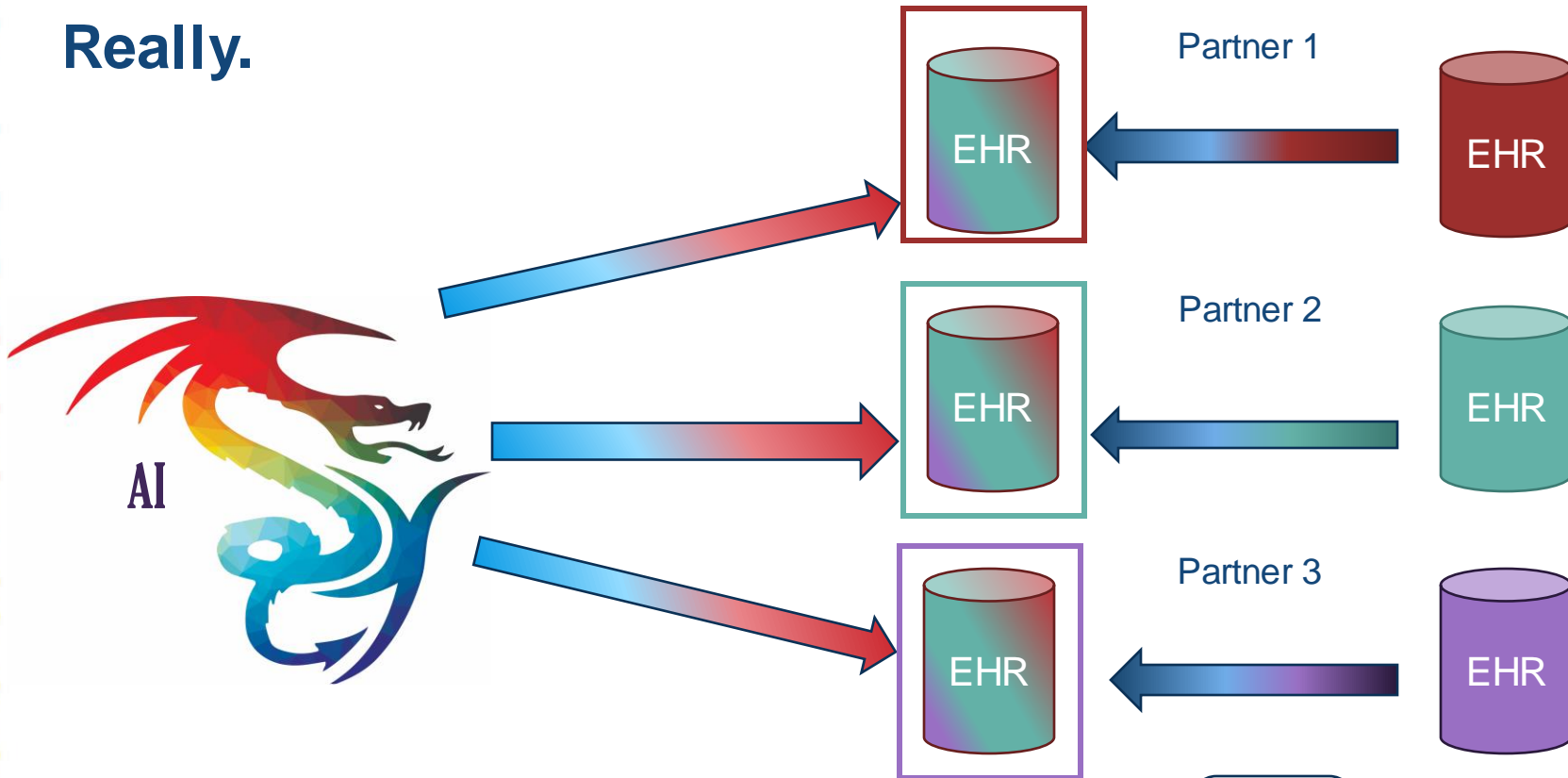
Simple, right?

Remember?

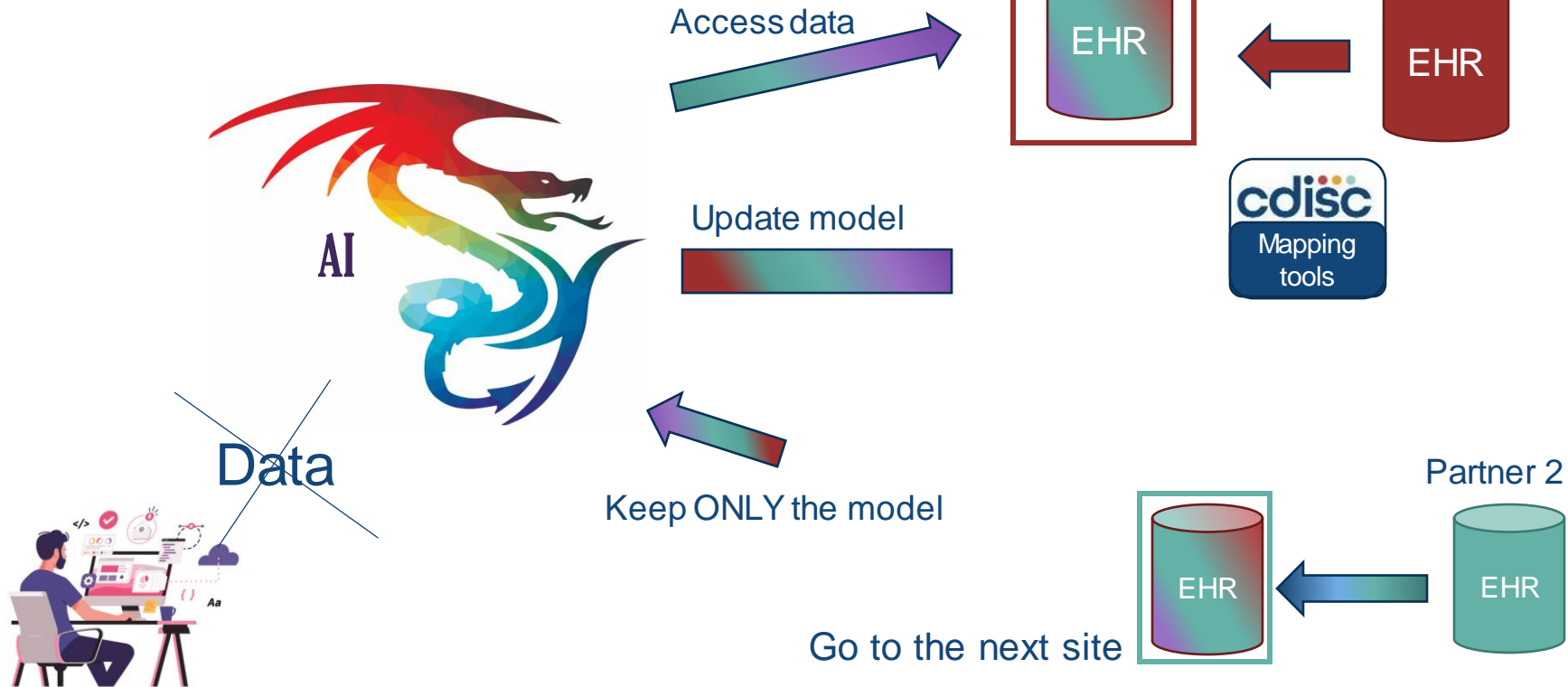


EHR: Electronic Health Record = patients' healthcare data

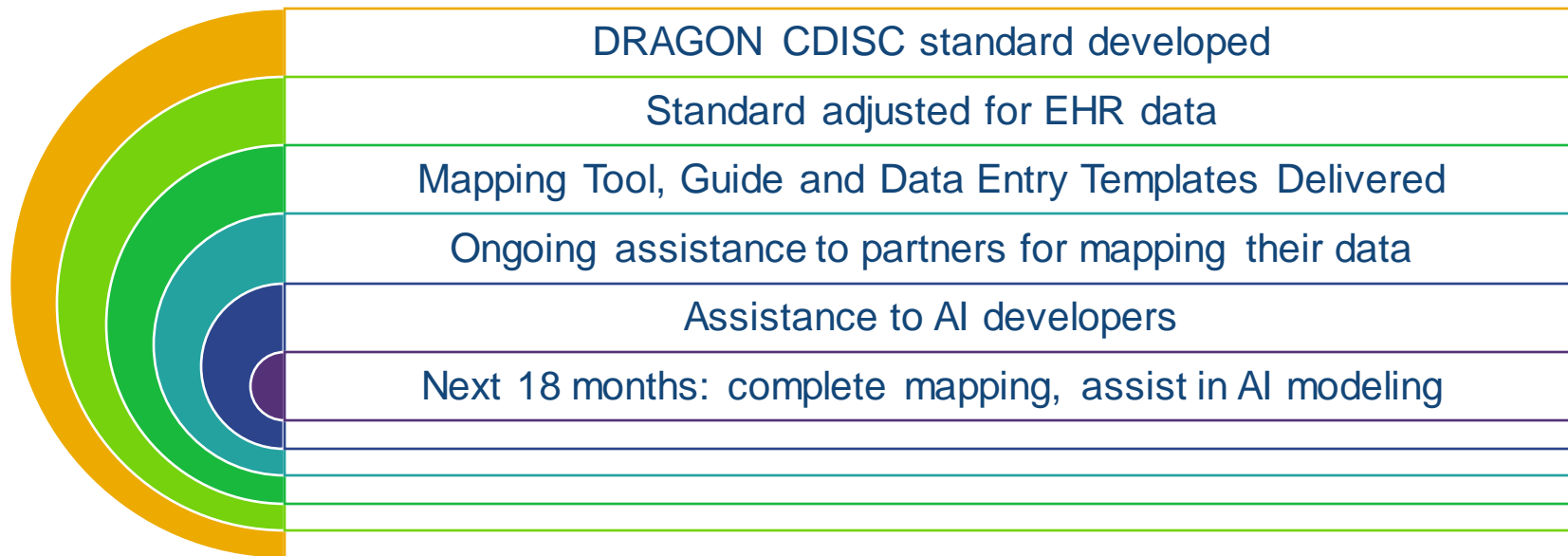
Really.



Actually... Really.



Progress





Using SDTM in Observational Studies: Considerations and Examples Document

Announcing a new standards development project



Overview of Key Points

With funding from the IMI DRAGON project, CDISC is launching a new project to develop a document that will guide users in the implementation of SDTM for observational studies data.

Today we are just announcing and offering a chance to participate.
We plan to kick off in a couple weeks (date TBD)

We have formed a team (though it is not too late participate!)

We are considering holding a separate development call for the Japanese team members at a time that works for Japan so that you're not on the phone in the middle of the night

Proposed CDISC Suite of RWD Guides and Resources

- Basic Implementation Guide
- Basic Study Set-up Guide
- Considerations for Using SDTM for Observational Studies
- REDCap & OpenClinica CDASH eCRFs with rules
- CDASH to SDTM Guide
- HL7-FHIR to CDISC Mapping
- Brief Overview of CDISC Model, Library and QRS

RWD Resources Draft Timeline

Phase 1

Instantiate eCRFs:

- CDISC eCRF Portal
- OpenClinica
- REDCap

Phase 2

- Develop CDISC Basic Implementation Guides, Basic Study Set-up and Considerations for Observational Data
- Review of draft guides (EAB), follow CDISC Standards Development Process
- Develop Educational Content > Publish as Ready
- Publish on Microsites > Publish as Ready

Ongoing

- Review
- Community Feedback
- Curation & Maintenance
- Communications



Q3 2022

Instantiate eCRFs



Q3 2023

CDISC Basic Implementation Guide



Q3 2023

CDISC Basic Study Set-up Guide



Q3 2023

Considerations Using SDTM for Observational Studies

ONGOING



RWD and the Regulatory Environment

China's NMPA

国家药品监督管理局药品审评中心
CENTER FOR DRUG EVALUATION, NMPA
CHINA

关于公开征求《真实世界证据支持药物研发的基本考虑》意见的通知

发布日期: 2019/02/29

为落实国务院《关于改革药品医疗器械审评审批制度的意见》(国发〔2015〕44号)以及中共中央办公厅、国务院办公厅印发的《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》(厅字〔2017〕42号)鼓励研究和创新药的要求,考虑药物临床研发过程中,存在临床试验不可行或难以实施等情形,利用真实世界证据以评价药物的有效性和安全性成为可能的一种策略和途径。

为了促进各方对真实世界证据的链接,探讨其在药物研发中的应用场景,探究其评价的便利,经广泛调研和讨论,我中心组织起草了《真实世界证据支持药物研发的基本考虑(征求意见稿)》。

我们诚挚地欢迎社会各界对征求意见稿提出宝贵意见和建议,并及时反馈给我们,以便后续完善。征求意见稿自发布之日起2个月。

您的反馈意见请发到以下联系人的邮箱:
联系人: 赵俊
联系方式: zhaojun@cde.org.cn, gaoli@cde.org.cn
感谢您的参与和大力支持。

附件 1: 《真实世界证据支持药物研发的基本考虑(征求意见稿)》中文版.docx
附件 2: Key Considerations in Using Real-World Evidence to Support Drug Development.docx
附件 3: 《真实世界证据支持药物研发的基本考虑(征求意见稿)》起草说明.doc

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电话: 010-66583666 传真: 010-66583409 电子邮箱: 33333333@132.com

December 2018
www.fda.gov

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

US FDA

FDA U.S. FOOD & DRUG ADMINISTRATION

FRAMEWORK FOR FDA'S
REAL-WORLD EVIDENCE PROGRAM

December 2018
www.fda.gov

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

EU EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Regulatory Science to 2025
Strategic reflection

December 2018
www.fda.gov

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

Japan's PMDA

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

Utilization of Real World Data - PMDA's approaches -

23rd March, 2021

Health-related data are gathered and accumulated in the clinical practice day by day. These data are called Real World Data (RWD), and they include electronic health record, claims data, patient registry data, etc. RWD still provide valuable information related to the outcomes of using medical products, while RWD are not obtained in the same manner as well-designed clinical trials conducted to evaluate medical products.

At PMDA, we have already had some experiences of utilizing such existing data for evaluation benefit-risk balance in the regulatory process. For example, in the case of approval for an indication supplement of initial remission associated with polymyositis/dermatomyositis. The 2013. Not only above case, but RWD has been utilized in many cases so far.

It has been making good use of RWD, it applied a case-by-case approach. It might not be widely known RWD can be utilized for regulatory submission. In order to promote RWD utilization further by product developers, the PMDA has recently developed and finalized two guidelines below:

<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

What will the observational data document contain?

Discuss common issues encountered when implementing SDTM for observational data

Develop implementation strategies that address these issues.

Illustrate these strategies in examples

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

Discover and develop new concepts as needed, with examples

Adjust conformance rules to better fit these data

- New conformance rules as needed
- *Remove* irrelevant conformance rules from validation checks of observational studies.

Resulting document will be CDISC-endorsed by going through development process.

What will be identified in scoping?

What types of studies will we accommodate, and how are these studies designed?

What are the common issues encountered while using SDTM for observational research data?

What domains/variables/conformance rules are not relevant?

New concepts, if any, for which will have to develop implementation strategies

Relevant Resources


DRAGON DATA MAPPING GUIDE (ALL CONCEPTS)

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COVID-19 proven by PCR	yes / no	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									
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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]-003		Severe Acute Resp Syndrome Coronavirus 2	DETECTION	NEGATIVE	NEGATIVE	NOT DONE	

DRAGON Mapping Documents


PHUSE US Connect 2019
 Paper S108
Considerations for Using CDISC Standards in Observational Studies
 Jon Neville, CDISC, Austin, TX, USA
 Bess LeRoy, CDISC, Austin, TX, USA

ABSTRACT
Historically, CDISC standards in other areas, described from limited comparisons about the suitability of CDISC standards in observational research.

INTRODUCTION
Observational studies of subject populations, clinical practices. Many of these in observational research how to reduce barriers to implementation. As a part of CDISC's on document designed to go standards in their studies Workgroup to produce a that will ultimately also be recommendation to address positions on these issues come at a later date. It is also important to not implementation guide for addressing the numerous identified challenge in us deliverables, we do not

OBSERVATIONAL DESIGN
Unlike a randomized controlled trial, observational studies are conducted in the real world setting, observational studies are conducted in the real world setting, observational studies are conducted in the real world setting.


Data Standards for Non-interventional Studies

Phuse Publications

phuse.eu

Examples of conformance issues discussed in PHUSE Paper

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 (See table 2 below)
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 won't 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 trials 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.

Examples of required/expected variables that may not be relevant to observational data

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
EPOCH	Multiple	Sometimes Required	Use cases for observational research have not been explored. Existing controlled terminology is specific to clinical trials

Other Problems we could address

- Handling missing data (imputation of missing dates, etc.)
- Analysis considerations*
- Other topics we discover in scoping

*We do not plan to include ADaM in v1.0, but knowing how analyses may be done in observational research could help upstream SDTM modeling. Also, some imputations may best be handled in ADaM, which was discussed in the PHUSE white paper



What have we done so far?

Identified team members

Sent a survey 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?

Draft Timeline and Progress

<p>31 May 2022</p>	<p><input checked="" type="checkbox"/> Develop Survey (experience trying to use CDISC standards in observational studies, and the issues encountered while doing so)</p>
<p>06 Jun 2022 - 30 Jun 2022</p>	<p><input checked="" type="checkbox"/> Send out a survey to team members - 2 week timeline</p> <p><input type="checkbox"/> Compile results</p> <p><input type="checkbox"/> Schedule kick-off call 3rd week of June</p> <p>Kick-off Call</p> <ol style="list-style-type: none"> 1. Introduce project, scope, timeline 2. Determine meeting time 3. Q&A
<p>Jul - Aug 2022</p>	<p>Scoping - Observational Study (non-interventional studies) Guide v1</p> <ul style="list-style-type: none"> • Study types, study design - prospective • Domains and variables that would not be used • Concept identification • Conformance rules - separate set of rules, add and remove based on study type
<p>Aug - Sep 2022</p>	<p>Identification of Concepts</p>
<p>Oct - Mar 2023</p>	<p>Development - Considerations and Examples for using SDTM for Observational Data/Studies (need to make sure we are clear what we mean i.e., will not include mapping FHIR etc)</p>
<p>Apr - May 2023</p>	<p>Internal Review</p>
<p>Jun - Aug 2023</p>	<p>Public Review</p>
<p>Sep 2023</p>	<p>Publication</p>

← Next Step, date TBD





Thank You!

If you are interested in participating in the observational studies guide document development please contact Alana St Clair or Jon Neville soon!

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jneville@cdisc.org

