

PINNACLE²¹ BY CERTARA

THE FUTURE CLINICAL DATA SUBMISSION STANDARDS: CDISC OR ???

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DISCLAIMER

The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of Pinnacle 21 or IBM Consulting.



AGENDA

Introduction

Background

Submission Challenges

Environmental Scan

CDISC, FHIR, or OMOP?

Recommendations

Conclusions



INTRODUCTION

INTRODUCTION

More health-related data from a variety of study designs now available

Can provide more evidence about the benefits/risks of a medical project

Sharp increase in NDAs/BLAs that include non-RCT study designs

- RWD
- Registry and observational studies

CDISC standards developed over 20 years ago

- Developed to support marketing applications
- Developed and optimized to primarily support RCT study designs

SAS V5 Transport format required for study data since 1999

CDISC standards developed to accommodate limitations of SAS V5 transport

Submissions of non-RCT studies has presented challenges to FDA/sponsors

INTRODUCTION

Can our current submission standard (CDISC) support diverse study designs?

Is CDISC evolving to support diverse study designs?

Can a single standard support all study designs

Is there another standard that may be a better fit

Is a hybrid approach (multiple standards) a better option?

Presentation goals

- Reframe the discussion around future submission standards
- Current State: How do we fit RCT, RWD, and other non-interventional designs into CDISC standards?
- Should data from all study designs be submitted using CDISC standards
- Should we choose a different standard to support regulatory submissions
- Should we consider a hybrid approach

CLINICAL TRIAL VS OBSERVATIONAL STUDY

- ▶ “Interventional study (also referred to as a clinical trial) is a study in which participants, either healthy volunteers or volunteers with the condition or disease being studied, are assigned to one or more interventions, according to a study protocol to evaluate the effects of those interventions on subsequent health-related outcomes”
- ▶ “Non-interventional study (also referred to as an observational study) is a type of study in which patients received the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol”

NON INTERVENTIONAL STUDY DATA SOURCES



Electronic health records (EHRs) / medical records



Medical claims and billing data



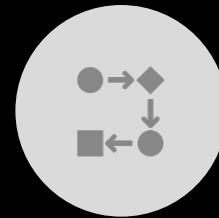
Product, disease, and population-based registries



Cohort study



Case-control study



Other non-interventional designs

WHY RWE? RWE TRENDS

- ▶ 95% of approved NDAs and BLAs in 2021 included an RWE study
- ▶ 75% in 2019
- ▶ 58% of approvals in 2021 used RWE to support safety and/or efficacy

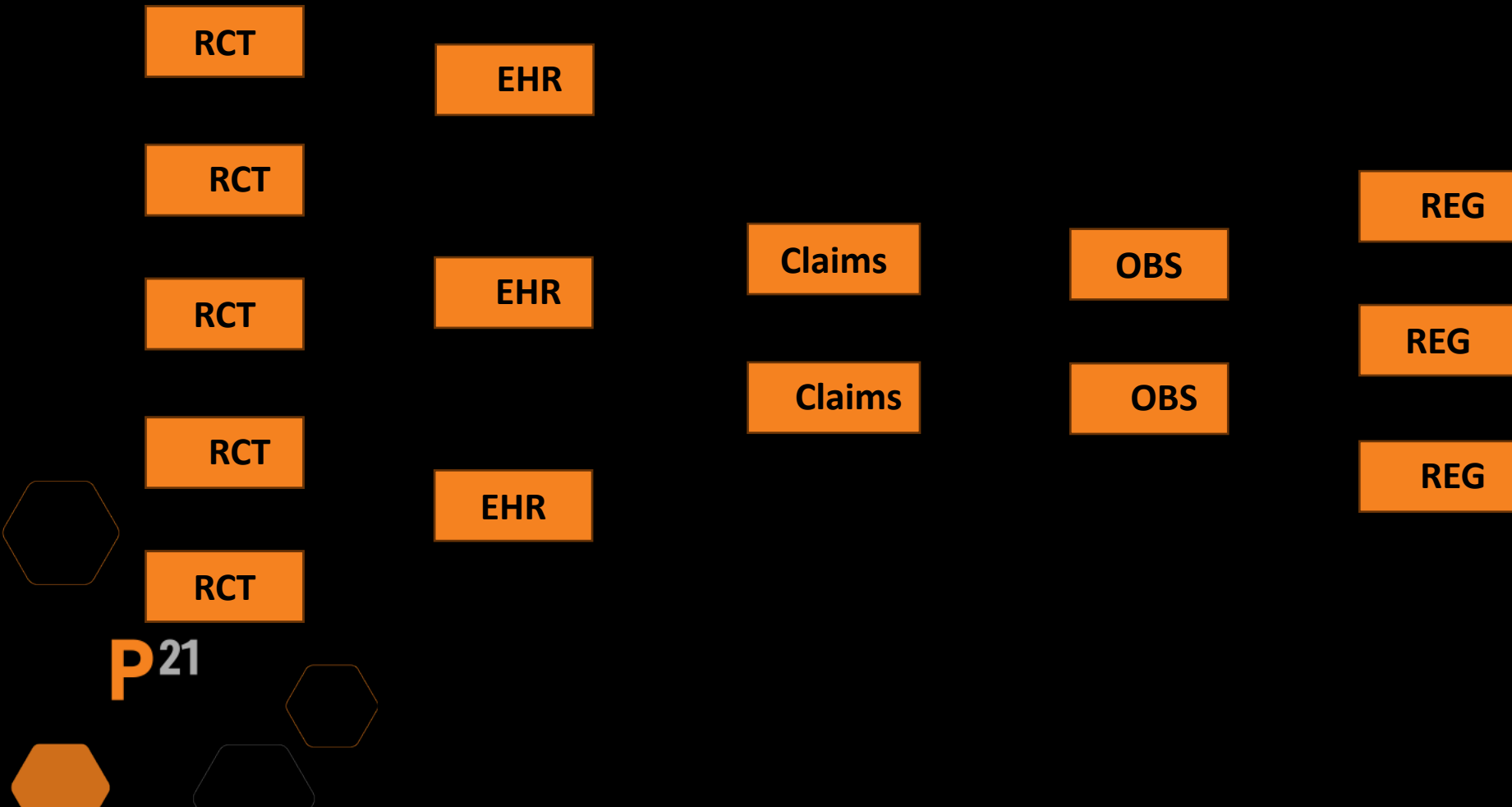
Table 3

Observed intended use of RWE in included NDAs/BLAs, January 2019 to June 2021

Included NDAs and BLAs	2019	2020	2021 through June 30	Total
	<i>n</i> = 51 approvals	<i>n</i> = 59 approvals	<i>n</i> = 26 approvals	<i>n</i> = 136 approvals
Incorporated RWE for any purpose	38 (75%)	53 (90%)	25 (96%)	116 (85%)
Used RWE to provide therapeutic context	25 (49%)	36 (61%)	22 (85%)	83 (61%)
Used RWE to support safety and/or effectiveness	27 (53%)	46 (78%)	15 (58%)	88 (65%)
Safety only	17 (33%)	21 (36%)	5 (19%)	43 (32%)
Effectiveness only	7 (14%)	6 (10%)	2 (8%)	15 (11%)
Safety and effectiveness	3 (6%)	19 (32%)	8 (31%)	30 (22%)

Purpura CA, Garry EM, Honig N, Case A, Rassen JA. The Role of Real-World Evidence in FDA-Approved New Drug and Biologics License Applications. Clin Pharmacol Ther. 2022 Jan;111(1):135-144. doi: 10.1002/cpt.2474. Epub 2021 Nov 22. PMID: 34726771; PMCID: PMC9299054.

CLINICAL DATA SUBMISSION TRENDS





BACKGROUND INFORMATION

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CURRENT SUBMISSION STANDARDS (1)

- ▶ October 2021 FDA draft guidance (finalized in 2023)

"Data Standards for Drug and Biological Product Submissions Containing Real-World: Data Guidance for Industry"

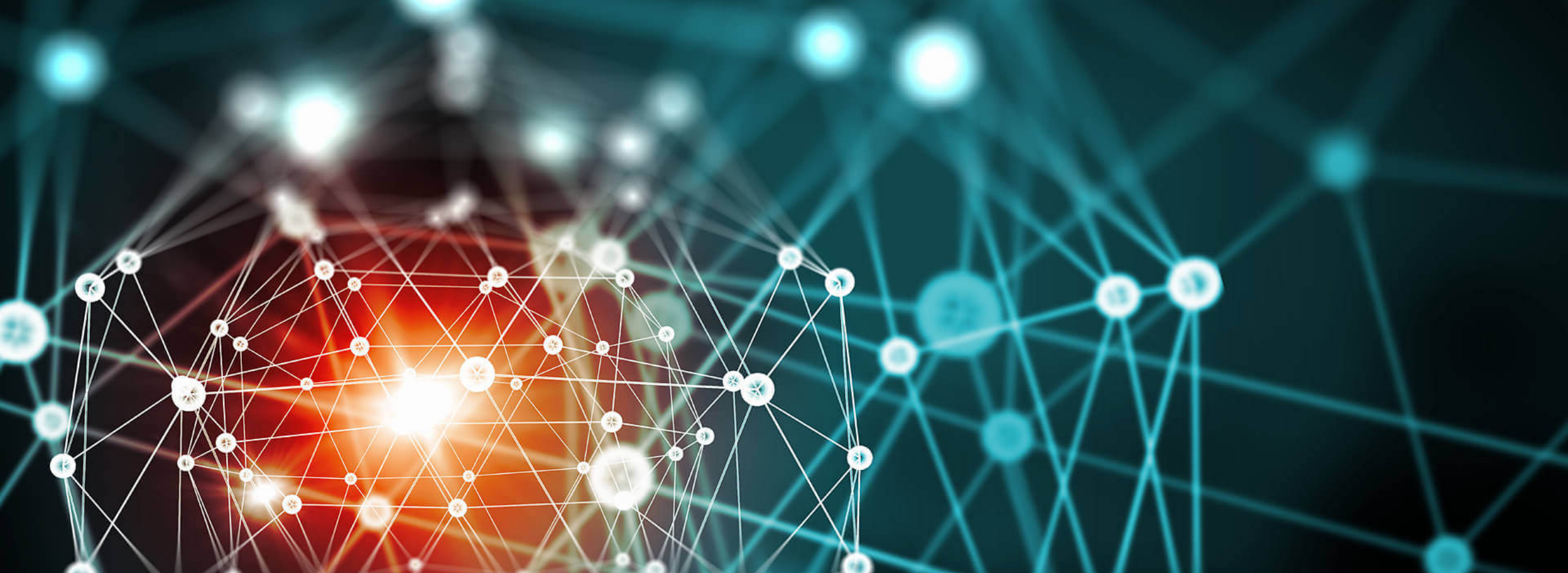
- ▶ Guidance outlined data standards required when submitting RWD (or data from other non-interventional studies) in support of a marketing application

- ▶ **Currently**

- ▶ According to the guidance, RWD must be submitted using the standards documented in the FDA Data Standards Catalog
 - ▶ For now, that means **RWD must be submitted using CDISC standards**

CURRENT SUBMISSION STANDARDS (2)

- ▶ CDISC required for data from all interventional & non-interventional studies
- ▶ Data from non-interventional studies must be converted to CDISC format
- ▶ Agency acknowledges
 - ▶ Current catalog of standards does not necessarily reflect data derived from real-world sources
 - ▶ It is considering updates
- ▶ Presents numerous challenges to sponsors
- ▶ CDISC designed for RCT data



SUBMISSION CHALLENGES

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NON-RCT DATA PRESENTS NEW CHALLENGES

Topic	RCT	NON-RCT
Data Collection	Collected under a protocol	Collected in real world settings
Data Monitoring	Data monitored and cleaned	No monitoring or cleaning
Data Entry	Data collected via CRF	Data entered in EHR(s)
Visits/Encounters	Visits at protocol defined schedule	No defined length between encounters
Treatment Schedule	Pre-defined treatment	As-needed treatment
Data Source	Data designed and collected by sponsor	Curated data acquired by sponsor from vendor
Availability or Source Data	Owned by sponsor	Owned by HCPs / Aggregators
Documentation	Protocol / CRFs / DMP	Aggregators
Sites	Single site	Multiple healthcare systems
Data Uniformity	Uniform data entry across sites	Standards/formats differ by site
Terminologies/Vocabularies	Uniform across sites	May differ by site/type of RWD/region
Data Standards	CDISC	HL7 FHIR, OMOP

CHALLENGES FOR SUBMITTING NON-RCT DATA

Challenges are presented in our previous three papers:

Abolafia, J, Ferko, S, & Holt, I. (2022). “Submission Standards for RWD: The Good, the Bad and the Ugly”. Paper presented at the PHUSE Annual Conference 2022, Belfast, United Kingdom.

https://phuse.s3.eu-central-1.amazonaws.com/Archive/2022/Connect/EU/Belfast/PRE_RE09.pdf

Ferko, S., Holt, I., & Abolafia, J., (2023). “Challenges and Considerations for Submitting Real World Data”. Paper presented at the PHUSE US Annual Conference 2023, Orlando, FL.

https://phuse.s3.eu-central-1.amazonaws.com/Archive/2023/Connect/US/Florida/PRE_RE05.pdf

Abolafia, J, Ferko, S, & Holt, I. (2023). “Submission Standards for Real World Data: Gaps, Limitations and Recommendations”. Paper presented at the PHUSE Annual Conference 2023, Birmingham, United Kingdom. [https://phuse.s3.eu-central-](https://phuse.s3.eu-central-1.amazonaws.com/Archive/2023/Connect/EU/Birmingham/PAP_RE03.pdf)

[1.amazonaws.com/Archive/2023/Connect/EU/Birmingham/PAP_RE03.pdf](https://phuse.s3.eu-central-1.amazonaws.com/Archive/2023/Connect/EU/Birmingham/PAP_RE03.pdf)



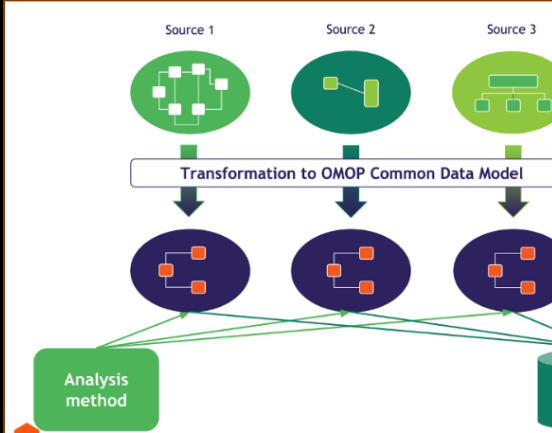
ENVIRONMENTAL SCAN



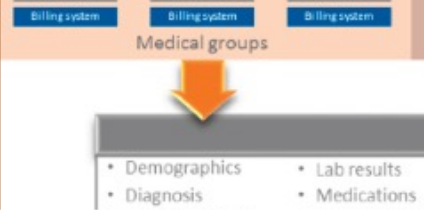
EXISTING DATA MODELS & STANDARDS FOR RWE AND CLINICAL TRIALS



Healthtech /

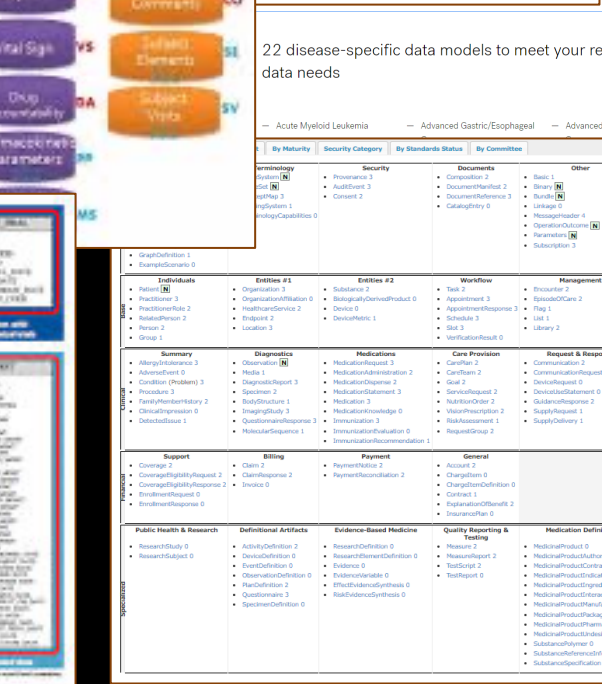
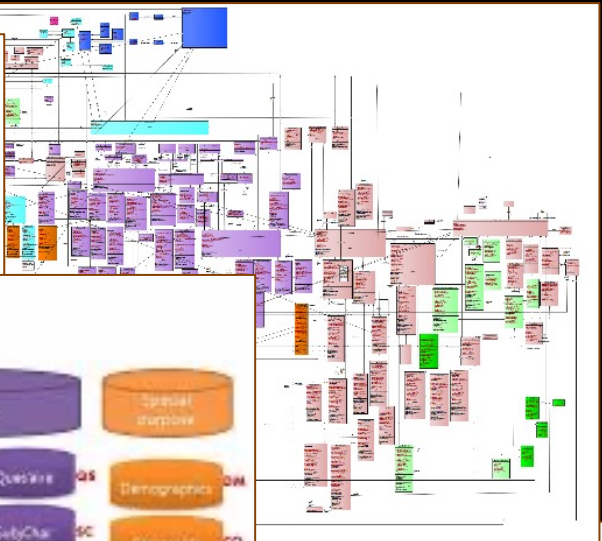
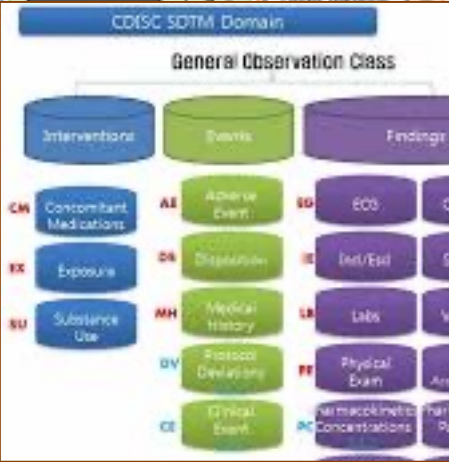
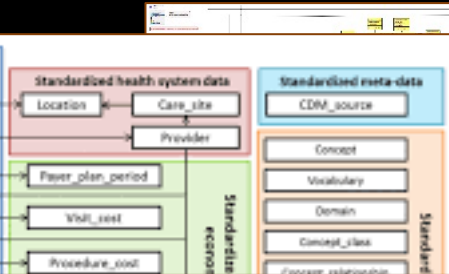
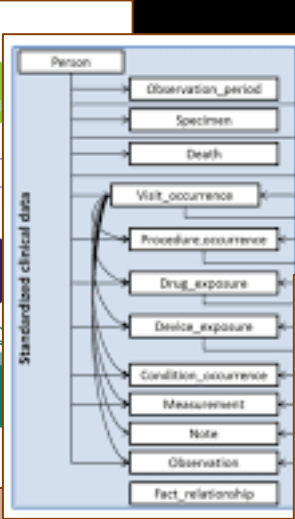


Data standardization, the key to federated analysis



Administrative Data					
Enrollment	Demographic	Dispensing	Encounter	Diagnosis	Procedure
Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID
Enrollment Start & End Dates	Birth Date	Dispensing Date	Service Date(s)	Service Date(s)	Service Date(s)
Drug Coverage	Sex	National Drug Code (NDC)	Encounter ID	Encounter ID	Encounter ID
Medical Coverage	Zip Code	Days Supply	Encounter Type and Provider	Encounter Type and Provider	Encounter Type and Provider
Medical Record Availability	Etc.	Amount Dispensed	Facility	Diagnosis Code & Type	Procedure Code & Type
			Etc.	Principal Discharge Diagnosis	

Registry Data			Inpatient Data	
Death	Cause of Death	State Vaccine	Inpatient Pharmacy	Inpatient Transfusion
Patient ID	Patient ID	Patient ID	Patient ID	Patient ID
Death Date	Cause of Death	Vaccination Date	Administration Date & Time	Administration Start & End Date & Time
Source	Source	Admission Date	Encounter ID	Encounter ID
Confidence	Confidence	Vaccine Code & Type	National Drug Code (NDC)	Transfusion Administration ID
Etc.	Etc.	Provider	Route	Transfusion Product Code
			Dose	Blood Type
			Etc.	Etc.



22 disease-specific data models to meet your real-world data needs

Acute Myeloid Leukemia		Advanced Gastric/Esoophageal		Advanced Non-small Cell Lung	
By Maturity	Security Category	By Standards Status	By Committee		
Terminology System [N] Ref [N] Entity [N] System [N] Policy/Capabilities [0]	Security • Preserve [1] • Audit/track [1] • Consent [2]	Documents • Compliance [1] • Document/Manifest [2] • Document/Reference [3] • Cataloging [0]	Other • State [1] • Binary [N] • Binary [N] • Linkage [N] • Message/transfer [4] • Operational/Outcome [2] • Parameters [N] • Subscription [3]		
Entity #1 Organization Organization/Definition MedicalDevice Device Location	Entity #2 • Substance • Biopsy/OperationalWorkflow • Device • Document [1] • Location	Workflow • Test • Appointment • Appointment/Referral • Schedule [1] • Slot • Verification/Outcome [1]	Management • Provision [2] • Episode/Care [2] • Flag [1] • List • Library [2]		
Diagnosis Observation [N] Media [1] Media [2] DiagnosticReport [3] Physician/Entity [1] Physician/Ref [1] Questionnaire/Response [1] Questionnaire/Response/Ref [1]	Medications • MedicationRequest [3] • MedicationStatement [1] • MedicationDispense [1] • MedicationStatement [3] • Medication [5] • MedicationKnowledge [0] • Immunization [3] • ImmunizationRequest [1] • ImmunizationRecommendation [1]	Care Provision • CarePlan [2] • CarePlan [2] • CarePlan [1] • ServiceRequest [2] • NutritionOrder [2] • MedicationRequest [1] • RiskAssessment [1] • Requesting [2]	Request & Response • Communication [2] • CommunicationRequest [2] • CommunicationResponse [1] • DeviceStatusStatement [0] • GuidanceResponse [1] • Supply [1] • SupplyDelivery [1]		
Billing Claim [2] Device [2] Item [0]	Payment • PaymentIntake [2] • PaymentTransaction [2]	General • Account [2] • Charge [1] • ChargeDefinition [0] • Contract [1] • ExplanationOfBenefit [2] • Insurance [0]			
Definitional Artifacts					
Evidence-Based Medicine					
Quality Reporting & Testing					
Medication Definition					

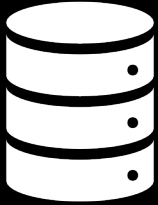
SELECT CLINICAL DATA STANDARDS (1)

	CDISC	HL7	OMOP
Attribute			
Tabulation Standard	Yes (SDTM)	Yes (FHIR)	Yes
How organized	Topic Related Domains in SDTM	Resources	Relational database tables for clinical data, vocabulary, and other healthcare concepts
Typical exchange format	SAS V5 Transport / Metadata ODM XML	JSON	Each organization or user builds their own CDM, tools are provided for assistance with ETL to transform data
Use case(s)	Submission of RCT data to regulatory authorities including FDA and PMDA	Electronic health records, claims data	Enable efficient analyses of observational data
Supported FDA clinical data standard	Yes	No	No

SELECT CLINICAL DATA STANDARDS (2)

	CDISC	HL7	OMOP
Attribute			
Supports Non-rectangular structures	No	Yes	Not directly, but data could be extracted in non-rectangular format defined by user
Record linkage	Implicit (RELREC domain in SDTM)	Explicit (Data elements are linked via the model)	Yes, identifiers are used to link the data as needed.
Non-standard data elements	Supplemental variables	Extensions	No
Analysis standard	Yes (ADaM)	No	No
Typical dictionaries	MedDRA, WHODrug, CDISC Controlled Terminology	SNOMED, LOINC, ICD, RxNorm	Over 100 supported, see https://github.com/OHDSI/Vocabulary-v5.0/wiki/Standardized-Vocabularies
FDA review tools	Yes	No	Not applicable, but tools to support data analyses using the CDM do exist

EXCHANGE STANDARDS

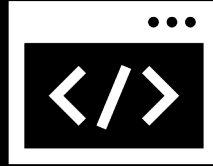


SAS V5 Transport

Openly documented specification developed by SAS in late 1980's

Required format for submitting study data since 1999

Imposes several restrictions on submission datasets



XML (Extensible Markup Language)

“Text” format, where you can define your own tags to meet specific needs

Current standard for the define file

CDISC published Dataset-XML standard in 2014 > can be used to submit data (but not accepted standard)



JSON ((JavaScript Object Notation)

Consists of human-readable text to store and transmit data objects comprised of attribute-value pairs

Used extensively when exchanging data using the FHIR model

De facto standard for data exchange using APIs

Dataset-JSON was adapted from the Dataset-XML specification, but instead uses JSON format for regulatory submission needs

Ongoing project in collaboration with FDA, PHUSE, CDISC to pilot the use of JSON for submitting study data



CDISC, FHIR, OR OMOP?

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CDISC: ADVANTAGES

Supported by the FDA as defined in the Data Standards Catalog

Industry familiarity with the standards across pharma, SDOs, regulatory agencies, and other industry groups

Contains concepts needed to represent clinical research data; currently the only 'submission ready' standard

CDISC defines comprehensive end-to-end standards from data collection through analysis; both nonclinical & clinical

Documentation by SDOs (e.g., IGs, TAUGs, QRS supplements, controlled terminology) and regulatory agencies (e.g., tech specs)

Tools developed and in use by SDOs, pharmaceutical companies, & regulatory agencies that use CDISC

Analysis standard (ADaM) exists and is harmonized with SDTM (unlike FHIR)

Many sponsors have designed end-to-end processes around CDISC standards from collection through analysis

CDISC: DISADVANTAGES

'Siloed' for clinical research; data elements relevant to RCTs

Not optimized for RWD

A lot of work to convert RWD into CDISC format

CDISC SDTM is rigid; hard to add new elements

Cumbersome and burdensome to link data (RELREC)

Rectangular structure

Limitations & constraints with SAS Version 5 transport format

FHIR: ADVANTAGES

FHIR is optimized for RWD (and, for EHR and claims data). Over time, there is a trend for more RWD to be submitted as part of a marketing application.

There is a trend toward collecting data for RCTs and other observational study designs in an EHR.

Most data in EHRs are already exchanged using FHIR, and in the future, it is likely that almost all EHR data will be represented in FHIR.

FHIR is a more “modern” standard, that leverages web standards such as JSON, HTTP, Atom, OAuth and others.

Data exchanged using FHIR is usually represented in JSON and is not limited by the constraints on SAS Version 5 transport format.

Linking to related data w/i a marketing application and external data sources is much easier than in CDISC.

FHIR is already being used at FDA for several submission-related activities.

OMOP: ADVANTAGES

OMOP has been optimized for RWD and its analysis and has a track record for use with epidemiological studies.

OMOP was designed to support interoperability between different terminologies and dictionaries.

OMOP CDM supports large-scale collaborative research efforts and the OHDSI community is actively involved in creating tools and providing user support.

OHDSI offers a wide range of open-source tools designed for use with one or more of the databases of the Common Data Model (CDM).

The OMOP CDM is being used by some major health systems including The University of California Health System.

Designed as a relational database schema facilitates easy manipulation of the data for aggregate or individual patient analysis.

Given the relational structure is similar to that of CDISC SDTM, creating a submission package with data similar to CDISC should be straightforward.

FHIR/OMOP: DISADVANTAGES

Lacks many of the concepts necessary to represent clinical research data

Many non-standard variables and domains must be created

Many validation/business rules do not apply

FDA /sponsors are less familiar with FHIR/OMOP than CDISC

What would a FHIR/OMOP submission package would look like ?

New tools needed to facilitate a FHIR/OMOP submission

FDA would have to update documents/tech specs

No model for analysis data > just a collection/exchange standard

Many sponsors have designed end-to-end processes around CDISC standards

SINGLE OR HYBRID?

Can one of these standards adequately represent all designs?

If not a single standard, would a hybrid approach be better?

Single standard option encompasses choosing either the CDISC SDTM, OMOP or HL7 FHIR standard to represent collected data for all study designs

Hybrid approach

- Collected data is submitted in the standard for which it is optimized
- RCT data are submitted using the SDTM standard
- EHR and claims data are submitted using the FHIR standard
- Data from registry studies and other observational study designs are submitted using OMOP standard
- CDISC ADaM is still the analysis standard (for now)
- May be challenging to harmonize collected data into a single analysis standard



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RECOMMENDATIONS

SHORT TERM CONSIDERATIONS/SOLUTIONS

CDISC currently required

- Transform all collected data to STD
- Use ADaM for analysis > required and FHIR/OMOP do not have an analysis model
- Create non-standard variables/domains
- Document violations of validation rules in reviewer's guides
- See our previous 3 papers (documented above) for short term solutions

Exchange standard >Transition to JSON as soon as possible

- So far, results of pilot look promising
- Overcomes many of the shortcomings of SAS V5 transport
- Can capture RWD more accurately
- Not a large impact on FDA/sponsors

LONG TERM CONSIDERATIONS/SOLUTIONS

**Recommendation:
Re-examine
current
submission
standards (CDISC)**

- Change the conversation
 - From > how to we fit all study designs into CDISC standards
 - To > What should the paradigm be for submitting study data, when considering the increasing diversity of study designs
- Can a single standard accommodate data from all study designs?
- Would a hybrid approach be better?

LONG TERM CONSIDERATIONS/SOLUTIONS

CDISC has developed core data elements for representing data from RCTs needed for regulatory submission. Can industry continue to develop core data elements and terminologies for non-interventional studies needed for regulatory submission and review?

Can CDISC standards be modified to accommodate data from all study designs? Can CDISC develop “profiles” for each type of study design. Profiles would contain core elements and validation rules for a given study design.

- If so, what changes are needed?
- What progress has CDISC made to date to accommodate non-RCT study designs?

Is OMOP or FHIR a more viable future submission standard?

- If so, what changes are needed?
- How have these standards evolved in the past several years?

LONG TERM CONSIDERATIONS/SOLUTIONS

How will changes in technology affect future submission standards?

Will we be able to eliminate the artificial packaging of clinical data and enable real time data steaming?

Can we develop technologies and tools to eliminate the need for analysis datasets?

Can we harmonize CDISC, FHIR, and OMOP, so any of these standards can easily be mapped to the other two standards?

Over time, will more and more data be collected in EHRs?

If so, does it make sense to transform this data from FHIR to another standard?

LONG TERM CONSIDERATIONS/SOLUTIONS



Can industry, regulatory authorities, and standards organizations work together more effectively on pilot projects related to the future of submission standards?



How can mapping, especially dictionary to dictionary, be resolved to ensure issues related to loss of granularity as well as the introduction of granularity that may result in signals (both of safety and efficacy) being diluted?



Can our industry and regulatory authorities move beyond their comfort zone?



Right now, CDISC is familiar to both sponsors and FDA. Sponsors and FDA are much less familiar with other standards such as FHIR and OMOP. Though CDISC standards are currently required, this should not inhibit our industry from considering the best future state and evaluating other alternatives. Collectively, we should continue to monitor how each standard is evolving and how this affects its ability to meet future submission needs.

CONCLUSIONS

Submitting non-RCT
presents a number of new
challenges

There are significant gaps in
the current standards for
submitting non-RCT data

Future is not complex
transformations

Are we asking the right
questions to solve these
challenges?

Is it time to re-evaluate the
use of CDISC as the single
submission standard?

Need for pilot projects
related to the future of
submission standards across
industry and regulatory
agencies to help make these
decisions

Let's collaborate!



THANK YOU ;)

KEEP IN TOUCH!



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A blurred background image of a modern office hallway with large glass walls and a polished floor. Several people are walking through the hallway, their figures blurred to convey a sense of motion and activity.

QUESTIONS?