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- 50% at FDA > RWE and Analysis Projects
- CDISC ADAM Team 15+ years
- CDISC Analysis Results Team
- CDISC E-2C Team
- PhUSE Real World Evidence Team
- Vulcav/PhUSE Research on FHIR Team

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PINNACLE 21 BY CERTARA

SUBMISSION STANDARDS FOR RWD: GAPS, LIMITATIONS AND RECOMMENDATIONS

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PharmaSUG NORTH CAROLINA • OCT. 21, 2022

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AGENDA

- Introduction
- Environmental Scan of Existing Standards for RWD
- Current submission standard / regulatory landscape
- Gaps/limitations in current standards
- Recommendation for submitting RWD

INTRODUCTION

RWD/RWE DEFINED

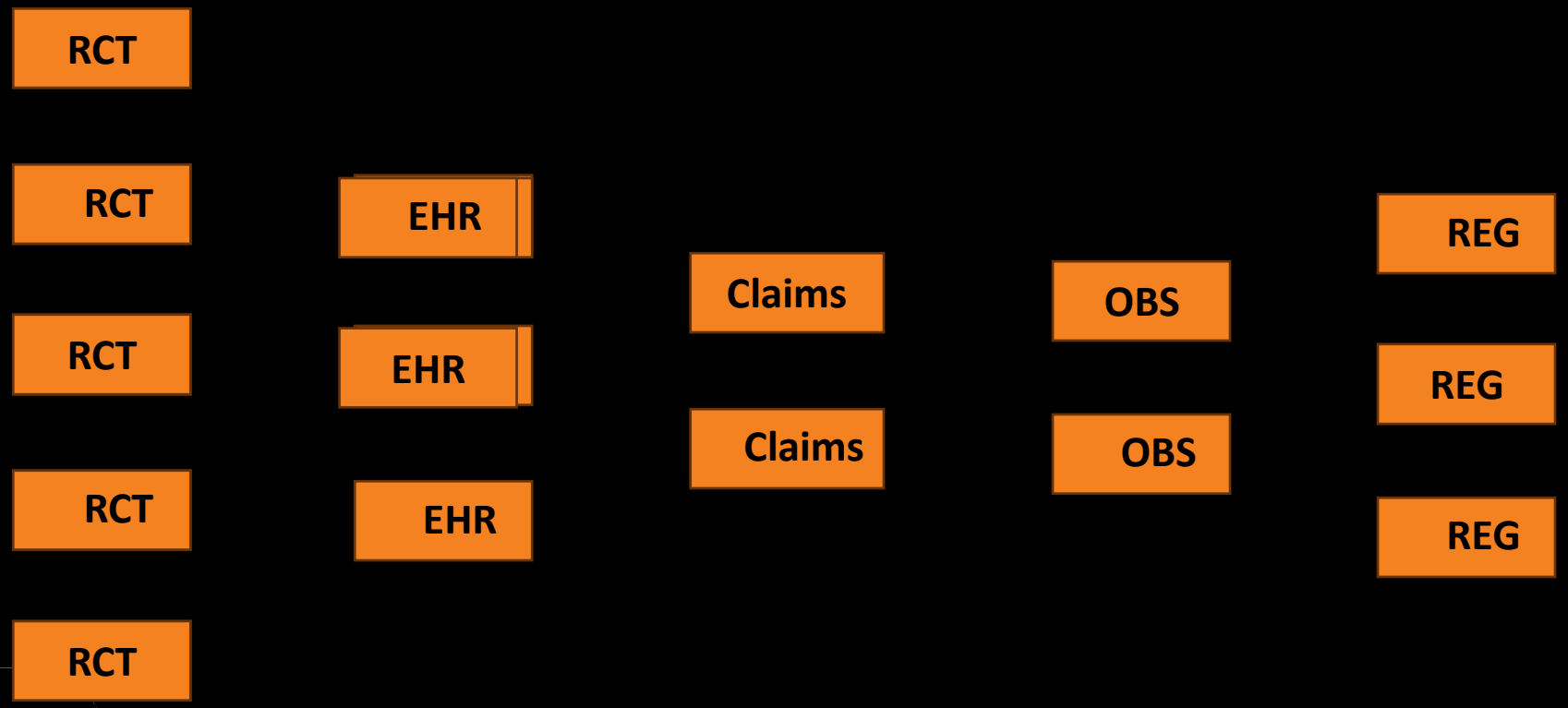
- Section 505F(b) of the FD&C Act defines RWE as "**data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials**" (21 U.S.C. 355g(b)).5 In developing its RWE program, FDA believes it is helpful to distinguish between the sources of RWD and the evidence derived from that data. Evaluating RWE in the context of regulatory decision-making depends not only on the evaluation of the methodologies used to generate the evidence but also on the reliability and relevance of the underlying RWD; these constructs may raise different types of considerations. For the purposes of this framework, FDA defines RWD and RWE as follows:
- Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- Real-World Evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD
- **Clinical data not collected under a protocol**

Reference: "Framework for FDA's Real-World Evidence Program", December 2018.
https://www.fda.gov/media/120060/download

RWD DATA SOURCES

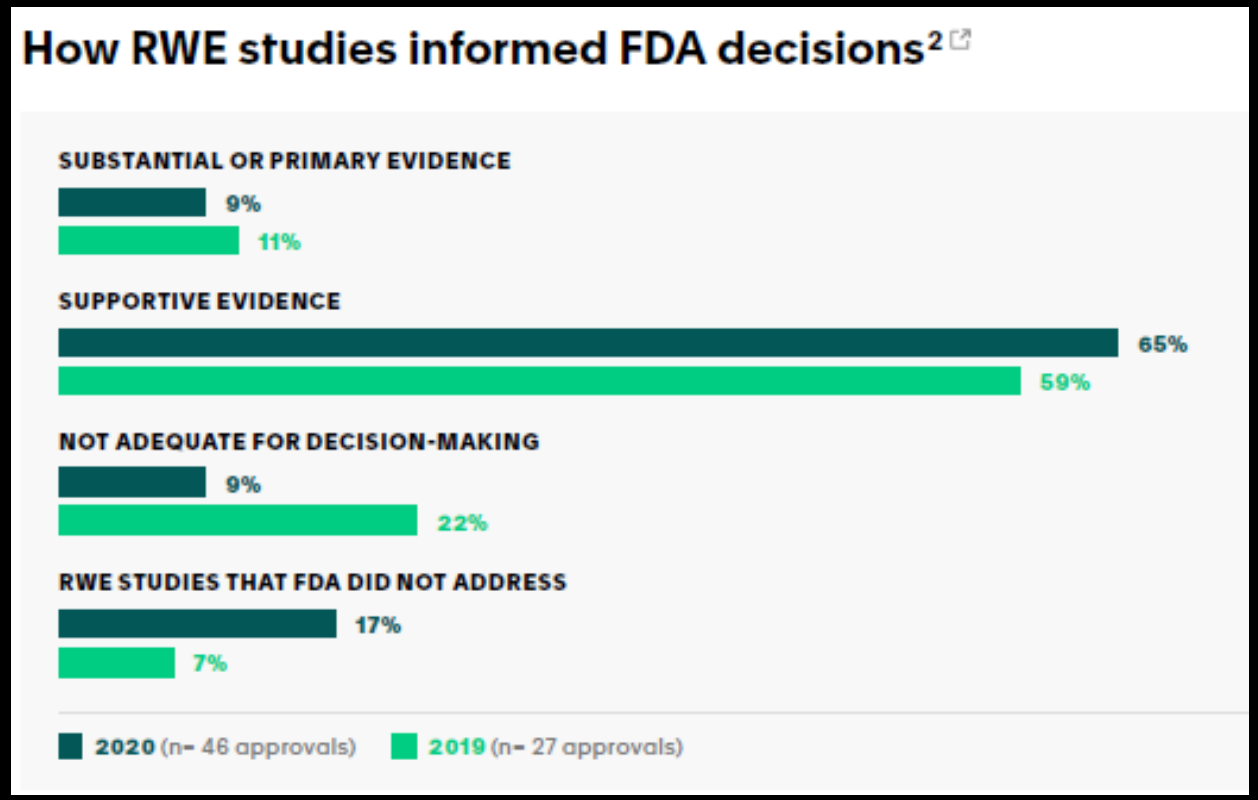
Electronic health records (EHRs) / medical records	Medical claims and billing data	Product, disease, and population-based registries
Mobile devices (wearables)	Social media data	**Focus of this presentation is Electronic health records (EHRs) / medical records**

CLINICAL DATA SUBMISSION TRENDS



WHY RWE? RWE TRENDS

- 78% of approved NDAs and BLAs in 2020 included an RWE study to provide evidence of safety and/or efficacy
- 53% in 2019
- 50% of approval that included RWE studies in 2020 were for oncology
- Primary use is efficacy



Reference: “Aetion_eBook_2021_The role of RWE in FDA Approvals”

WHAT CAN WE LEARN FROM PREVIOUS RWE SUBMISSIONS

- A lot to learn from submitted RWE studies FDA judged as inadequate for regulatory decision making
- Can be used to avoid common errors that may result in an RWE study being rejected or not considered
- Can be used to avoid delays in regulatory review of marketing applications containing RWE

RWD PRESENTS NEW CHALLENGES: RCTS VS RWD

Topic	RCT	RWD
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
Data Uniformity	Uniform data entry across sites	No harmonization across sites
Visits/Encounters	Visits at protocol defined schedule	No defined length between encounters
Treatment Schedule	Pre-defined treatment	As-needed treatment
Follow-up	Defined follow-up	As-needed follow-up
Sites	Single site	Multiple healthcare systems

Note: RCT (Randomized Clinical Trial)

ENVIRONMENTAL SCAN OF EXISTING STANDARDS FOR RWD

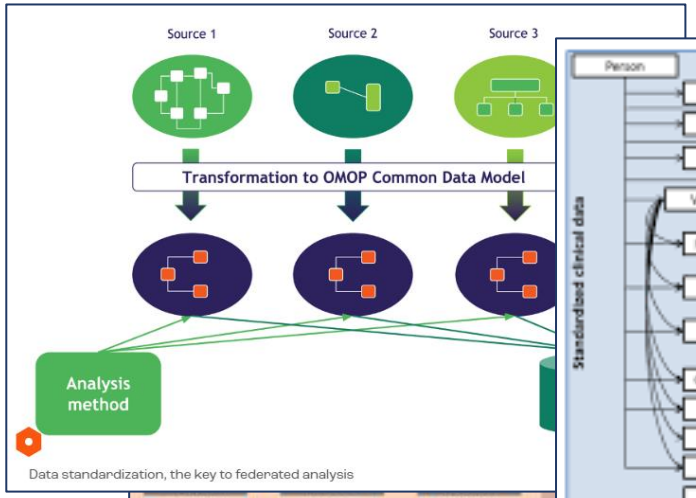
Existing Data Models and Standards for RWE and Clinical Trials

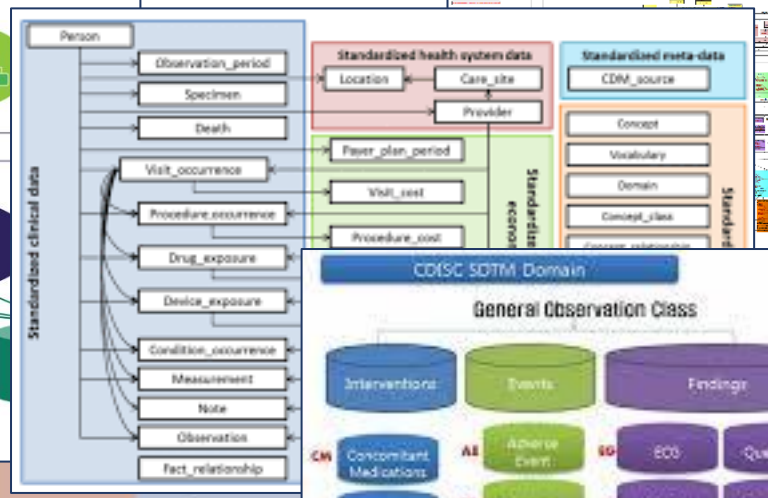
SDOs

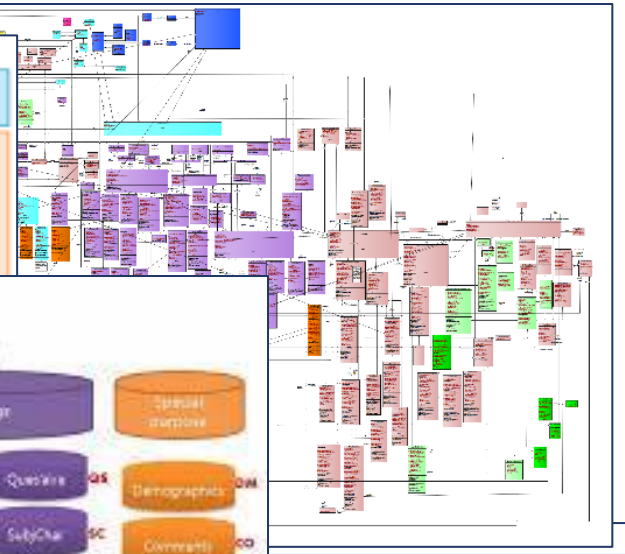
Healthtech / Industry

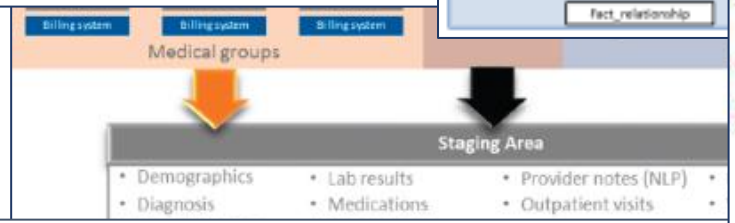
Government

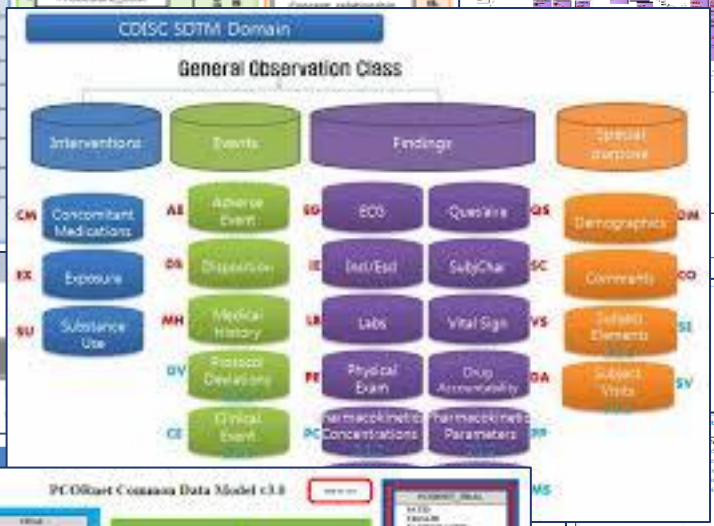
Consortium

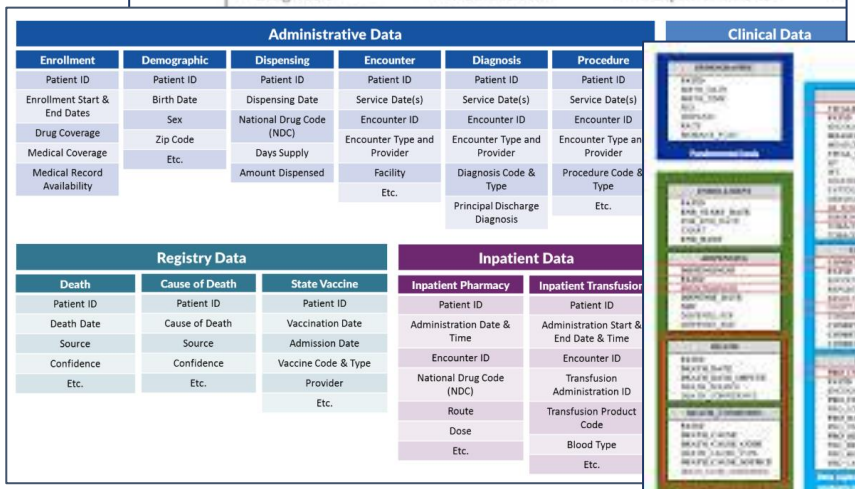












CURRENT SUBMISSION STANDARD / REGULATORY LANDSCAPE

CURRENT SUBMISSION STANDARDS

- October 2021 FDA draft guidance

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

- Guidance outlined data standards required when submitting RWD in support of a marketing application
- At this time
  - 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**

Reference: **https://www.fda.gov/media/153341/download**

GAPS IN CURRENT STANDARDS

Topic	RCT	RWD
Traceability	Annotated CRF /define file	Some type of traceability to source / annotated document describing source? Need to go back to original source
Data Provenance	Sponsor controls data flow	RWD typically acquired from vendor > lack of documentation about source data
Exposure	Protocol determined	Reside in various record types. Need to determine what variables are needed to derive exposure, determine quality and certainty or records.
Trial Summary Dataset	TS	For RWE studies is TS needed? If so, are new parameters related to RWE needed.
Core Variables	CDISC has defined core variables for RCTs	Set of core variables for RWE has not been identified
Terminology	MedDRA / WHODrug	SNOMED / ICD. Need to represent multiple coding systems and their mappings.

RECOMMENDATION FOR SUBMITTING RWD

VERY EARLY COMMUNICATION: FDA AND VENDORS

Challenge

- RWD not collected under a protocol or to address a specific research question
- RWD must be fit for purpose and non-bias
  - Does the RWD appropriately address the study question
  - Is the population selected in the RWD appropriate to address the study question
- Quality/provenance
- Sponsors should be able to submit patient level data for studies used to support a marketing application

- Missing data
  - How much
  - Is missingness random or biased
  - How is missing data distributed among key variables and covariates

VERY EARLY COMMUNICATION: FDA

Recommendation

- Notify FDA well in advance of submission date that RWD will be submitted (Type C meeting)
- Submit Study plans and Statistical Analysis Plans (SAPs)
- Request FDA feedback before starting a study on
  - RWD is fit for use
  - Study design
  - Rationale for choosing data source
  - Can data source address study questions
  - Is the data reviewable

Reference: [Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products]

VERY EARLY COMMUNICATION: VENDORS

Recommendation

- “Make sure you know what you are buying”
- Make sure to vet data before purchasing
- Will patient level data be available for submission
- Sample size after exclusions
- Data for all key variables/covariates available
- Information on data provenance/traceability to source
- Amount of missing data
  - for key variables including covariates
  - Is missing data random

DETERMINING STUDY START DATE IN RWD

Challenge

- A valid study start date is needed to pass FDA's technical rejection criteria and to determine whether a clinical study must comply with CDISC standards as specified in the FDA guidance *Providing Regulatory Submissions in Electronic Format—Standardized Study Data*[1]
- As stated in the FDA Study Data Technical Conformance Guide[2], clinical studies submitted to CDER or CBER started after December 17, 2016 for NDAs, BLAs, and ANDAs must comply with the *Providing Regulatory Submissions in Electronic Format—Standardized Study Data* guidance.
  - Further, the sdTCG specifies that "For clinical studies, study start date is the earliest date of informed consent among any subject that enrolled in the study".
- Within retrospective RWD studies such as in scenarios where a historical control arm is created, the dates associated with a patient's data from the selected RWD source(s) such as EHR, registry, or claims data can occur prior to development of the RWD study protocol. Thus, current sdTCG guidance for study start date is not feasible for certain RWD studies.

Problem

- What value should be represented in Study Start Date within the TS domain for a retrospective RWD study?

[1]June 2021. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

[2]Available at FDA's Study Data Standards Resources web page.

DETERMINING STUDY START DATE IN RWD (CONT'D.)

Recommendation

- Given that the current state for determining study start date as specified in the sdTCG is not feasible in certain RWD clinical studies, consider leveraging an **administrative start date** of the RWD study as determined by the Sponsor and documented within the RWD study protocol.
  - This may include the date that the inclusion/exclusion criteria is finalized or the date that the complete RWD study protocol is finalized.
  - This recommendation aligns with the current guidance for nonclinical studies, where sdTCGv4.9 states: "For nonclinical studies, study start date is the date on which the study protocol or plan is approved (signed) by the Study Director, also known as the study initiation date[1]" which is also reported within the CDISC SENDIG[2].
- This should be discussed with FDA

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[1]Available at FDA's Study Data Standards Resources web page.

[2]Available at http://www.cdisc.org.

PATIENT DEATH DATA

Challenge

- Death data from a RWD source within a RWD clinical study may not be captured for a patient or questions may be present around the accuracy of patient death data, including death date and cause of death. Valid values for date of death and other death data are critical in the evaluation of efficacy and safety for a drug of biologic

Problem

- How can confidence in death data be increased within RWD?

PATIENT DEATH DATA (CONT'D.)

Recommendation

Consider implementing fields similar to the death table specifications (DEATH, DEATH_CAUSE) within the PCORnet Common Data Model Specification Version 6.0

- If patient death data (date and/or cause of death) is missing or questionable, consider aggregating additional death data from sources such as state death records, the National Death Index (NDI) or the Social Security Death Index (SSDI)
  - Source(s) of death information for each patient could be included within the submitted dataset as a supplemental qualifier within SDTM
- Derived 'confidence' variables can be useful to report the level of confidence in the accuracy of the date and/or cause of death.
  - Useful for linking subjects from external sources when probabilistic patient matching strategies are used
  - Values reported within PCORnet include E=Excellent, F=Fair, P=Poor, etc.)

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[1]Available at https://pcornet.org/wp-content/uploads/2022/01/PCORnet-Common-Data-Model-v60-2020_10_221.pdf

TERMINOLOGY DIFFERENCES

Challenge

- Clinical research and Healthcare terminology lack harmonization
- Many concepts have different names/meaning and controlled terminology
- Coding systems differ in clinical research and health care
- EHRs use SNOMED, ICD
- Clinical research uses MedDRa and WHO Drug coding
- Source data verification is challenging

TERMINOLOGY DIFFERENCES

Recommendation

- Create new supplemental variables in SDTM to capture
  - Source coding system (i.e., SNOMED)
  - Source verbatim term
  - Source code
- Provide an explanation of the process to convert the source terminology to submission compliant terminology/coding systems
- For example > Converting SNOMED or ICD to MedDRA

EXPOSURE EXPOSED

Challenge

- In RCTs exposure data collected under a protocol
  - Treatments/dosage pre-defined in protocol
  - Data monitored / cleaned / collected in structured CRF
- In RWD exposure data resides in a variety of places (record types)
  - Medication request > medication ordered
  - Medication dispensed > prescription filled
  - Medication administration > medication administered at clinical care site
  - Medication statement > medication usage provide by patient or significant other
- EHR may (or may not) contain data from 1 or more source
- Difficult to accurately construct exposure to a given treatment from above sources

EXPOSURE EXPOSED

Challenge

- Missing or conflicting exposure data
- Data typically not available for all relevant record types > may have medication request data but not dispensed data
- Accuracy of medication statement data
- Different record types may contain conflicting information
- Likely data from other health care systems not recorded in EHR

EXPOSURE EXPOSED

Recommendation

- SDTM
  - "As SDTM as possible"
  - Submit data from as many sources as possible
  - Create custom domains and supplementary variables as needed
  - Document source of each record type > Include a source variable for each record
- ADaM
  - Construct exposure dataset from all available sources
  - When possible, verify from an alternative source (e.g., multiple record types, claims data)
  - Provide detailed traceability to source data in define.xml and ADRG
- Derived 'confidence' variables can be useful to report the level of confidence in the accuracy of exposure data

CDISC STANDARDS OPTIMIZED FOR RCTS

Challenge: Current submission standards inadequate to represent RWD

- CDISC standards designed for Randomized Clinical Trials (RCTs) or intervention studies
- Built on older technologies (SAS transport)
- Lack many concepts related to RWD
- Core variables not identified for RWD
- Validation rules apply to RCTs
- RWD must be repackaged and transformed to meet regulatory submission guidelines
- Data linking solutions are cumbersome and outdated

CDISC STANDARDS OPTIMIZED FOR RCTS

Recommendation: Re-examine current submission standards (CDISC)

- Can CDISC standards adequately represent RCTs + RWD + Observational Studies
- Should we have a hybrid approach for collected data?
  - Hybrid approach
  - Each data type represented in the standard for which it is optimized
  - RCTs > CDISC
  - EHR/claims > FHIR
  - Observational studies > OMOP
- Should we use a more “modern” standard like FHIR?
  - Trend toward more RWD submitted to support marketing applications
  - Most RWD will be represented in FHIR in the future
  - Will most RCT data be collected via an EHR?

MISSING DATA

Challenge

Due to the nature of RWD, information commonly collected for a RCT may be missing, for example a score for used to assess cancer stage may not be collected as structured data

Problem: If key data is not available, the FDA cannot assess the data to ensure the safety and/or efficacy of the drug

Recommendation

The sponsor should provide a clear explanation of missing data and how it will be handled, ideally before the data is submitted and again in the reviewer guides

1. The data domains holding RWD should make clear when data needed to assess inclusion, exclusion or key safety and efficacy measures is not available, so reviewers don't waste time requesting information that is not available

CONCLUSIONS

- Submitting RWD presents a number of new challenges
- There are significant gaps in the current standards for submitting RWD
- The bar/standard for assessing RWD is the same as for data from RCTs
- We can learn a lot about submitting RWD from previous submissions
- Document, Document, and Document
- We should re-evaluate the use of CDISC as the single submission standard?
- **COMMUNICATE WITH FDA EARLY AND OFTEN**

THANK YOU ;)

KEEP IN TOUCH!

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QUESTIONS?