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Process Planning for Real World Evidence (RWE) Trials

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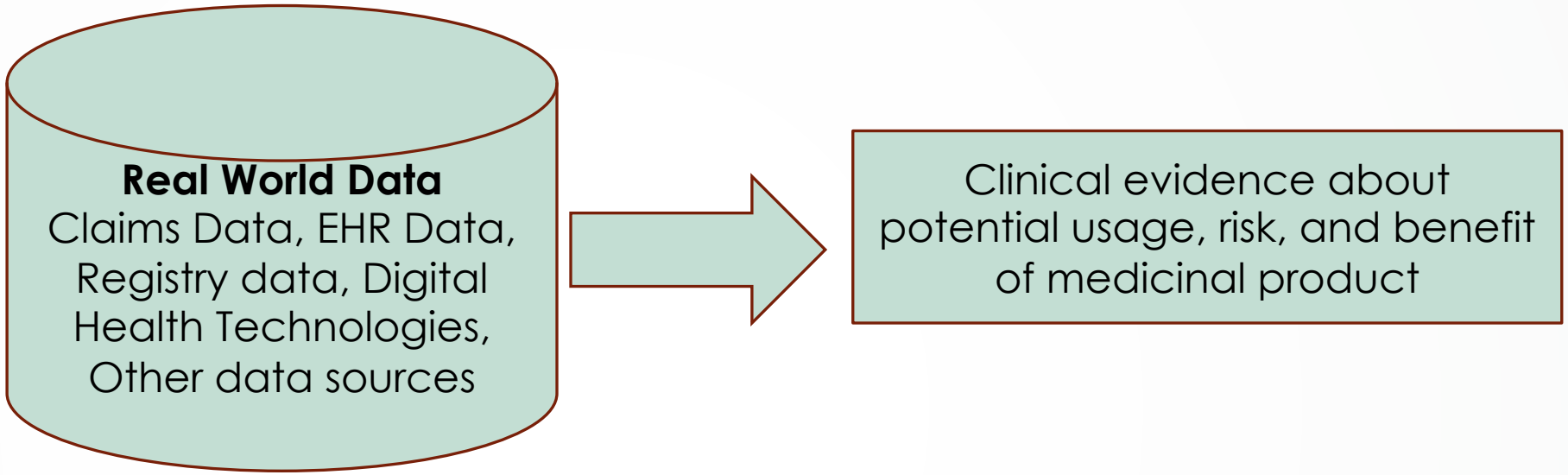
Real World Evidence (RWE) Trials -Quick Overview



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”

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Is the trial you are working on, a RWE?

Trial -A: It's a randomized clinical trial. It uses traditional database. There is one clinical outcomes related to efficacy. This clinical outcome assessment is done from the independent data source from disease registry.

Trial –B: It's a randomized clinical trial. It uses traditional database. There is some real world data used to generate hypothesis required for planning of clinical trial.

Trial –C: It's a clinical trial designed to only to validate the exploratory end point. Such validation of exploratory end point uses the real world data.

Trial –D: Its a single arm clinical trial using real world data for an extended arm.

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Step-1: Recognize if you are working on RWE Trial!

Reference- "Submitting Documents using Real World Data and RWE to FDA for Drug and Biologic Products- Guidance for Industry"- Sep 2022, Following trials are considered as RWE trials!

Randomized Trials using RWD to capture clinical outcomes for safety/efficacy

Single arm trials using RWD as an extended arm.

Observational studies that generate RWD to support efficacy supplement

RWD studies to fulfil post marketing requirements

If you are working on trial-A and trial-D, as described in previous slide, you ARE working on RWE trial!

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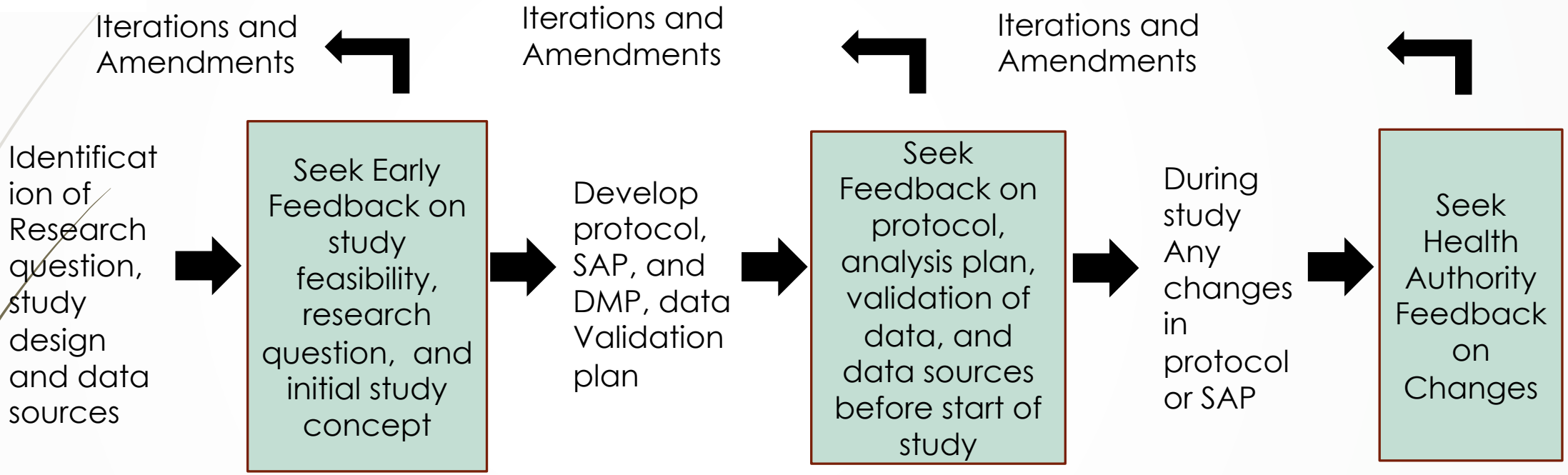
Step-2: Understand the Time points for communication with Health Authorities

Source: Emerging Trends and Future CONSIDERATIONS (transceleratebiopharmainc.com)



*** Understand the data sources to be used.**
*** Early and Frequent Communication with Health Authority**

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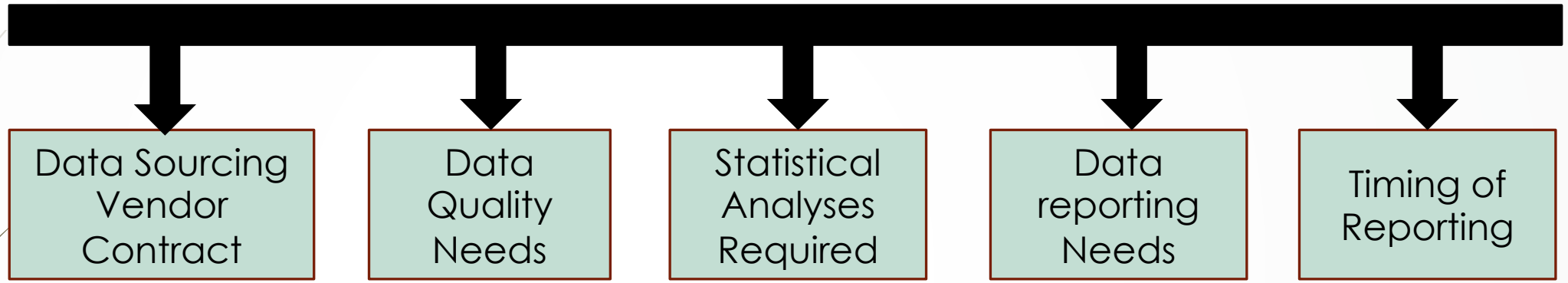
Step-3: Stakeholder Engagement

Why Need Early Engagement with Stakeholders?



Who are the stakeholders?

Internal Stakeholders

- Regulatory Affairs
- Biostatistics
- Data Management
- Statistical Programming
- Real World Evidence Group
- Data Standards Group
- * Portfolio Management
- * Project Management

External Stakeholders

- Regulatory Bodies
- Database vendor
- Real World Data Vendors
- CROs/Contract staff providers
- Technology vendors

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Stakeholder Engagement- Case Analysis

Background: Leading pharmaceutical company conducted pediatric study on Crohn's disease by using Real World Data

Cause of Challenge: Lack of stakeholder Engagement in timely manner.

Issue:
The sponsor had a contract with RWD vendor to get the data in ADaM format. Not knowing what is ADaM and thinking of it as just another data format, the healthcare data provider signed the contract. Statistical programming was not involved in contract finalization with RWD vendor.
The data was delivered in proprietary healthcare format during the trial progression.

Impact: Significant impact in terms of getting the trial data curated, transformed, analyzed, and reported to regulatory body as per eCTD requirements and in defined trial timelines

Source: PHUSE US CSS, 2022, Real World Evidence Work Stream Discussion

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Step-4: Data Traceability and Completeness

Component	What it is?	Possible Method to Address it
Missing Data	Key missing information	Establish data linkages
Data Relevance	Data with Lack of fit for purpose	Gather co-variates, and Outcomes data
Data Reliability	Inability of data to get Clinical evidence	Ensure consistencies in Coding such as ICD codes
Data Traceability	Source and quality Of Data during accrual And curation	Full proof data acquisition, And curation processes

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Step-5: Data Consistency and Standards Planning

Why Data Quality Planning is Required?

Real World Data

Hospital Data	HL7/FHIR	Incomplete Data
Registry Data	No standards/NIH Standards	Missing Data
EHR Data	HL7, no standards	Inconsistent Data
Claims Data	HCUP, Insurance Data Standards	Non-traceable Data
Other Sources Data	No or undefined standards	

Clinical Data

Operational Data (Clinical and Operational Database)

Submission Data (SDTM)

Analysis Data (ADaM)

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Step-5: Data Consistency and Standards Planning

What Industry Efforts you Should be Aware of?

EMR –Common Data Model (Observational Health Data Science and Informatics –ODHSI)

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Fast Healthcare Inter-operabilty Resource (FHIR)

VULCAN
HL7 FHIR

HCUP, Insurance Data Standards

Proprietary Efforts

No or undefined standards

Proprietary Efforts

Clinical Data

Operational Data (Clinical and Operational Database)

Submission Data (SDTM)

Analysis Data (ADaM)

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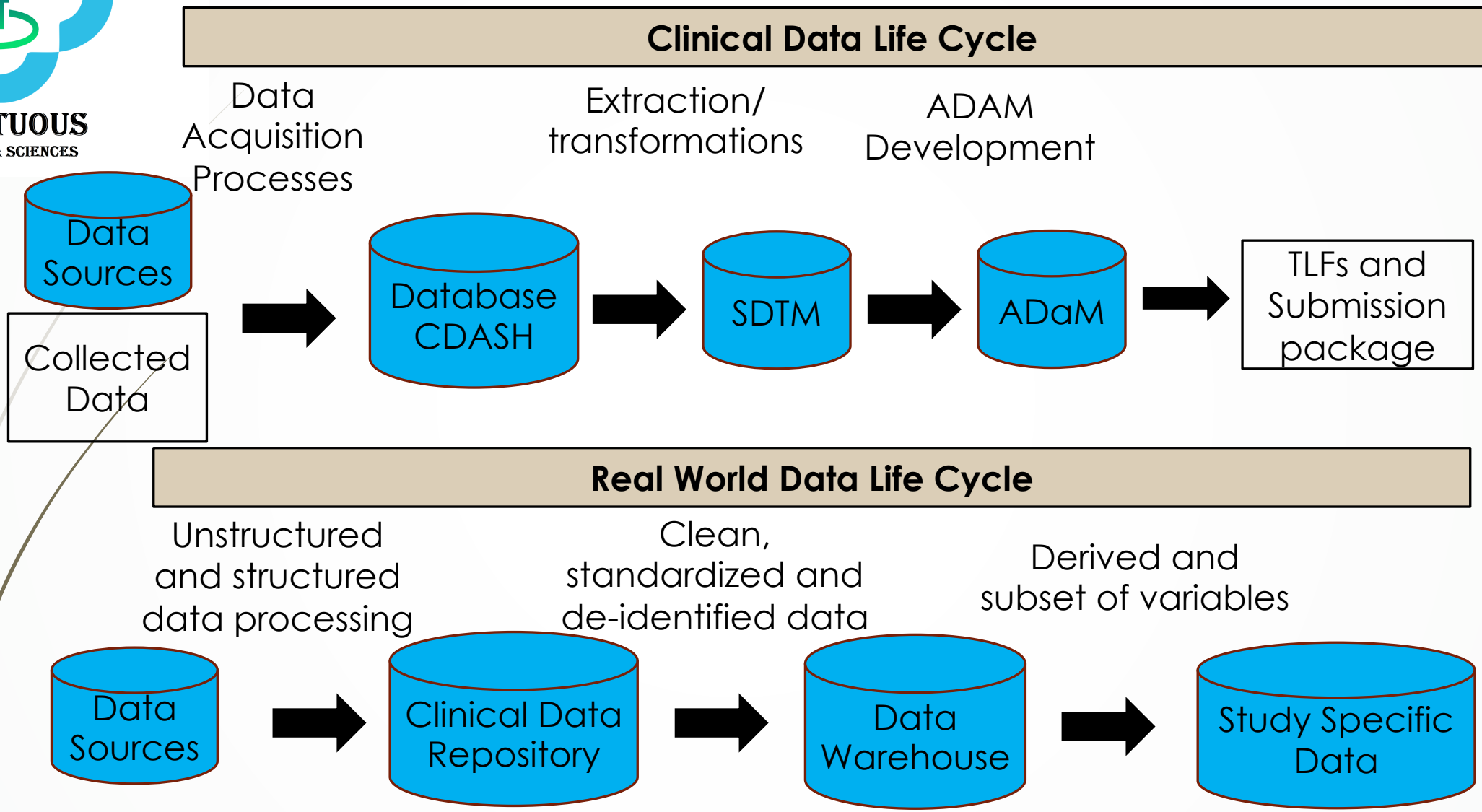
Step-6: Statistical Programming Planning



Source: RWD –Accessing EHR and Medical Claims data to support regulatory decision- making for drug and biologic products- September 2021 (Draft Guidance)

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Step-6) Impact on Statistical Programming

Key Areas of Focus

Adaptability of changes in processes for data processing and submission

Adaption of new technologies and development of new processes for data processing, management, and submission

Training and development for staff for use of data linkages, interoperability, processing, analysis, and reporting.

Develop interoperability models to bridge various data standards

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Step-6) Impact on Statistical Programming

Adaptability of changes in processes for data processing and submission

What Process?	Why it is required?
Frequent sensitivity and specificity analyses during trial progression	To align scientific and operational definition of variables and to reduce/ eliminate bias in data
Code mapping- • ICD code alignment • Lab codes to LOINC • SNOMED to MedDRA	To improve data reliability and relevance
Data Curation Processes	To get the data in correct format and standards

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Step-6) Impact on Statistical Programming

Adaptation of New Technologies

What Technologies?	Where could be the impact?
Real World Data sourcing platforms	Source data verification
Real world data sourcing technologies	Reasonable knowledge of the pros and cons for usage of such technologies
Technologies and platforms used in data acquisition and curation processes	Are results of curated data acceptable for clinical data processing?

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Step-6) Impact on Statistical Programming

Training and development for staff for use of data linkages, interoperability, processing, analysis, and reporting.

What Type of Trainings?	Where could be the impact?
Know the landscape of RWE trials and know the regulatory guidance	Planning of processes and timelines for statistical reporting deliverables
Training on data sourcing platforms and technologies	Ensure that biostatistics and programming is getting the right, clean and usable data
Data Curation processes, and technologies	Ensuring use of CDISC compliant data

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Step-6) Impact on Statistical Programming

Develop interoperability models to bridge various data standards

What Interoperability Models	Where could be the impact?
Data Standards Governance	Multiple data standards or some data sources with no standards
Data Transformation Processes	Development of new data transformation processes
Data Compliance management	How much CDISC compliance can be achieved?

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Step-6) Impact on Statistical Programming

- October 2021 FDA draft guidance

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

According to the guidance, RWD must be submitted using the standards documented in the FDA Data Standards Catalog

- **RWD must be submitted using CDISC standards**

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PHUSE Efforts- RWE Working Group: Please Join for Knowledge Gaining and Sharing!

- **Submitting the Real World Data**
- The scope of the project includes developing collaterals for submission of real-world data through mutual discussion, knowledge and experience sharing by industry colleagues. The collaterals will be developed by undertaking research of existing draft guidance documents on real-world evidence by regulatory bodies, and by analyzing members' lessons learnt from completed case studies. The scope of this project will include submission of real-world data obtained from primary and widely used real-world data sources. These may include key electronic health record sources, patient reported outcomes, widely used and accepted claims data sources, and other commonly used observational data. This project will also touch upon the data curation and ingestion processes pertaining to clinical operational as well as submission data. Since real-world data can come from a wide variety of sources, the scope of this project will consider the widely and most commonly used real-world data sources by industry and member companies.

- Source: Submitting Real World Data - WORKING GROUPS - PHUSE Advance Hub

References

- CDISC and HL7 Jointly Release Mapping Guide to Facilitate the Use of Electronic Health Record Data in Clinical Research | CDISC
- Vulcan | HL7 International
- Overview - FHIR v5.0.0 (hl7.org)
- OHDSI – Observational Health Data Sciences and Informatics

Questions/Comments?

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