Poster
OP8

Framework for Real-World Data Used in Regulatory Submissions

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Background and Rationale

- The use of real-world evidence (RWE) for regulatory bodies and health technology assessment (HTA) decision-making has grown over the past decade.
- Numerous guidelines have been put forth by regulators and payors on the use of RWE in such submissions.
- While best practice recommendations for RWE exist, there remains a lack of a clear, operational framework to guide the preparation and transformation of real-world data (RWD) for regulatory use.

Objective: to present a structured framework for the use of RWD in regulatory decision-making.

Methods

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- We conducted a review of FDA guidance documents on RWD/RWE to date, focusing on guidance documents on RWD.
- We conducted a targeted literature review of regulatory feedback on drug approvals containing RWE as supportive or substantial evidence in MAAs from January 2021 - present.
- **Regulatory focus**: Food and Drug Administration (FDA) [US], was selected due to their significant roles in the regulatory landscape.

Case Study Selection

- We selected **seven medicines** for analysis based on RWE included in their MAA submissions:
  - Idecabtagene vicleucel (ide-cel)
  - Omburtamab
  - Sotorasib
  - Alpelisib
  - Palovarotene
  - Tacrolimus
  - Omaveloxolone
- These were chosen to represent a range of therapeutic areas and evidence types.

Analysis

- We collected publicly available regulatory reports from the FDA.
- Two independent reviewers extracted information on the use and evaluation of RWE.
- We analyzed Sponsor practices in the submissions and reviewed feedback from regulators regarding the RWD.
- A framework was developed that synthesized guidance documents and prior regulatory practice.

Key Findings

What did the Literature Review of the Marketing Applications containing RWE Show?

- In multiple submissions, RWD from prior studies was evaluated by the regulators to support revised primary analyses and/or additional sensitivity analyses.
- Raw and source data should be available for regulatory audits, to the extent possible.

What are the Regulatory Requirements for Data (including RWD) in Submissions?

- Regulatory requirements apply to data submitted for Investigational New Drugs, New Drug Applications, and Biologics License Application.
- Data should be submitted in electronic format.
- Data should comply with formats supported by the FDA Data Standards Catalog, including SDTM and ADaM.

What are Good Practices for RWD in Regulatory Submissions?

- Sponsors should generate RWD in a manner that promotes transparency and reproducibility, to enable regulators to analyze source and analytic datasets.
- In addition to transforming the datasets, Sponsors should generate supporting documentation such as data dictionaries, Define XML files, and Reviewers Guides.

Limitations

- This framework offers recommendations and should not be interpreted as mandatory or prescriptive.
- This framework is intended for RWD used in regulatory submissions, although this may also be used as good practice for RWD/RWE used for other non-interventional observational studies.

Why is this Research Important

- This work offers a practical roadmap for aligning RWD with regulatory expectations - supporting transparency, reproducibility, and regulatory readiness.
- This framework provides a structured approach in delivering RWD that bolsters transparency and reproducibility.
- Implementing these practices also enables regulators to analyze sponsor-submitted data.

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Results

Table 1. Approved Data Standards Used in Clinical Studies

	Raw Data	Source Data	Analysis Data
CDISC Data Standard	CDASH	SDTM	ADaM
Purpose	Used for collecting clinical raw data such as from electronic case report forms (eCRFs)	Used for creating source datasets from the raw data. SDTM datasets contain standardized metadata (e.g., variable names, labels, formats). Raw data from the eCRF or CDASH is mapped to SDTM using the SDTM Implementation Guide (SDTMIG).	Used for creating analysis datasets from SDTM datasets. ADaM datasets contain derived variables for analysis and reporting of study results. Source data, such as SDTM datasets, are extracted and transformed to create analytic datasets using the ADaM Implementation Guide (ADaMIG).
Mapping	Blank eCRF are annotated to create the aCRF (annotated CRF), which contains mapped CDASH variable names.		
Example Datasets	○ CRF forms	○ DM: Demographics ○ AE: Adverse Events	○ ADSL: subject-level analysis dataset ○ ADAE: adverse events analysis dataset

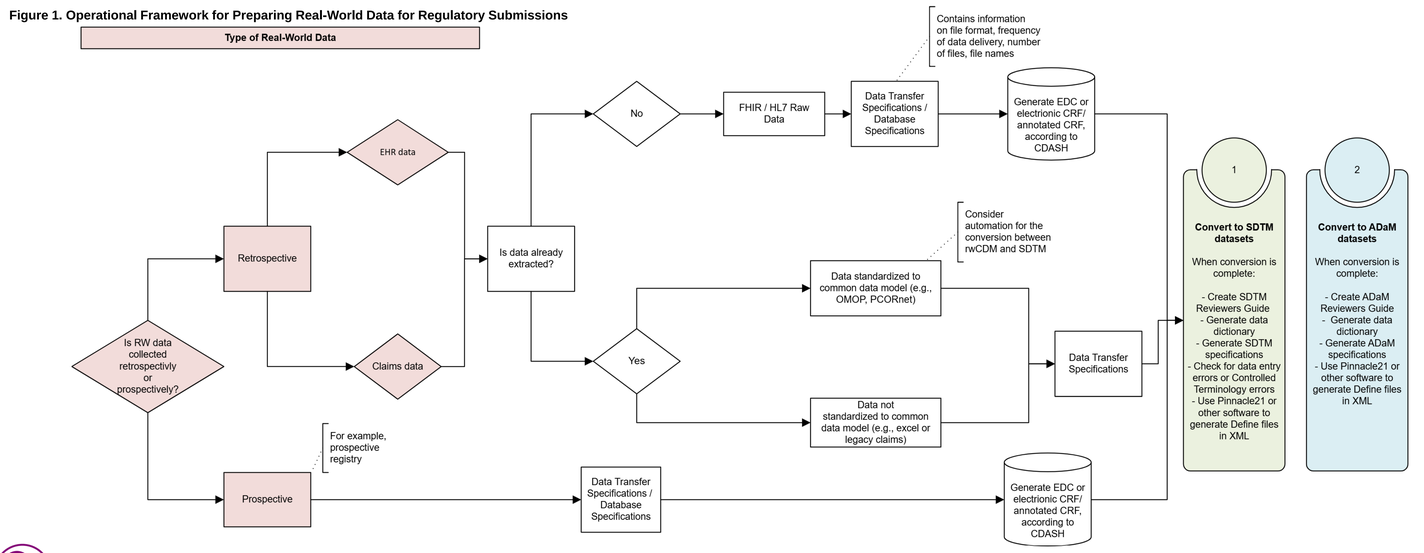
ADaM = Analysis Data Model, CRF = case report form, eCRF = electronic CRF, aCRF = annotated CRF, SDTM = Study Data Tabulation Model.

Table 2. Elements of Data Submissions

Data Standard	Define Files	Data dictionary / Dataset specifications	Reviewer's Guide
Supported data standard	Specifications that describe metadata for datasets, including variables, possible values, and controlled terminologies and codes	Data dictionary / dataset specifications that describe programming definitions for derived variables (i.e. logic).	Comprehensive documentation on study/analysis tables, conformance findings, and other helpful details for FDA review.
SDTM standardized source datasets		Data dictionary: - Variables names and labels - Formats - Variable definitions - Controlled terminology	Reviewer's Guide (SDRG/ADRG): - Mapping information - Study objectives - Summary of datasets - Hardcodes implemented - Special data considerations - Summary of conformance findings
ADaM standardized analytic datasets	A define.xml file that contains metadata for each SDTM and ADaM dataset	Dataset specifications: - Dataset overview - Dataset structure - Variable derivations - Flags	

ADaM = Analysis Data Model, SDTM = Study Data Tabulation Model, XPT = SAS Transport File, a file format used to support data transfers, XML = Extensible Markup Language.

Figure 1. Operational Framework for Preparing Real-World Data for Regulatory Submissions



Reviewer's Guide: A Brief Primer

- A *single summary document* that serves as a reference guide for the FDA reviewer, the RG should describe:
  - Available datasets (e.g., tabulation or analytic), special considerations or directions, conformance issues identified, hardcodes, and any other items that may facilitate the reviewer's use of the submitted data.
- The Reviewer's Guide also assists the reviewer in understanding the relationships between the study report and the data.
- Sponsors may use templates to complete the SDRG and ADRG.

ADRG = ADaM Reviewer's Guide, SDRG = SDTM Reviewer's Guide.

Figure 2. Hierarchy of Required Supporting Documentation for RWE Submissions

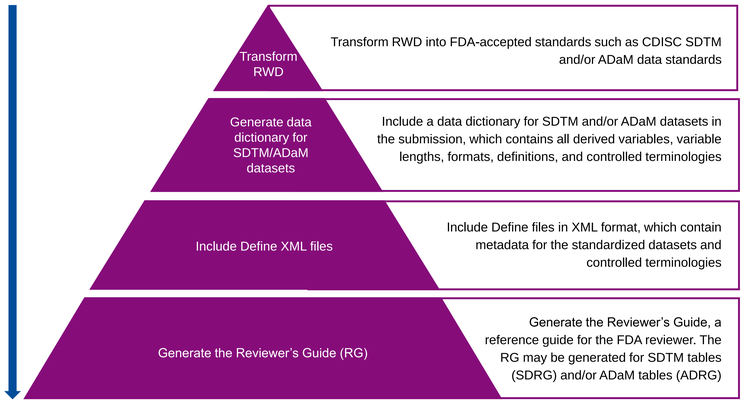
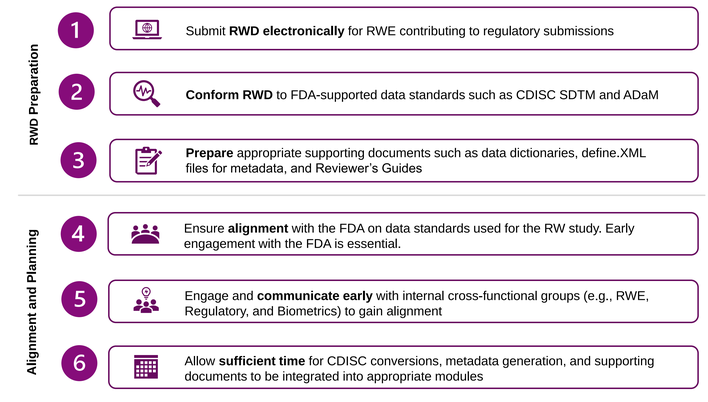


Figure 3. Key Steps and Best Practices for Submitting RWD in Regulatory Applications



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References
References are available upon request to the corresponding author: Shivani@landmarkscience.com

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Disclosures
SA, BS, RT, and DG are employees of or are contracted to Landmark Science, Inc.