

Submitting RWD: Where We Are and Where We Are Going

**Insights from Docket No. FDA–2025–N–0287
Request for Comments:**

**Exploration of Health Level Seven Fast Healthcare Interoperability
Resources for Use in Study Data Created From Real-World Data
Sources for Submission to the Food and Drug Administration**

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Current State for Submitting Study Data Created From Real-World Data* to FDA

- CDISC is required for study data submitted from both randomized clinical trials and from Real World Data sources
 - FDA acknowledges the current catalog of standards may not reflect data derived from real-world sources
 - FDA has initiated projects as far back 2019 to address updating the standards and look at mapping RWD sources to CDISC
 - Sponsors have also noted challenges to submitting RWD in CDISC format
- CDISC was founded in to standardize the data submitted to support marketing applications when NDAs and BLAs were primarily a collection of randomized controlled trials (RCTs)
- FDA has approved drugs using RWD in the past, however due to the increased availability and use of RWD, FDA is interested in a RWD data standard that will reduce the burden on both reviewers and industry

* FDA defines **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; and **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.

Federal Register Docket No. FDA–2025–N–0287

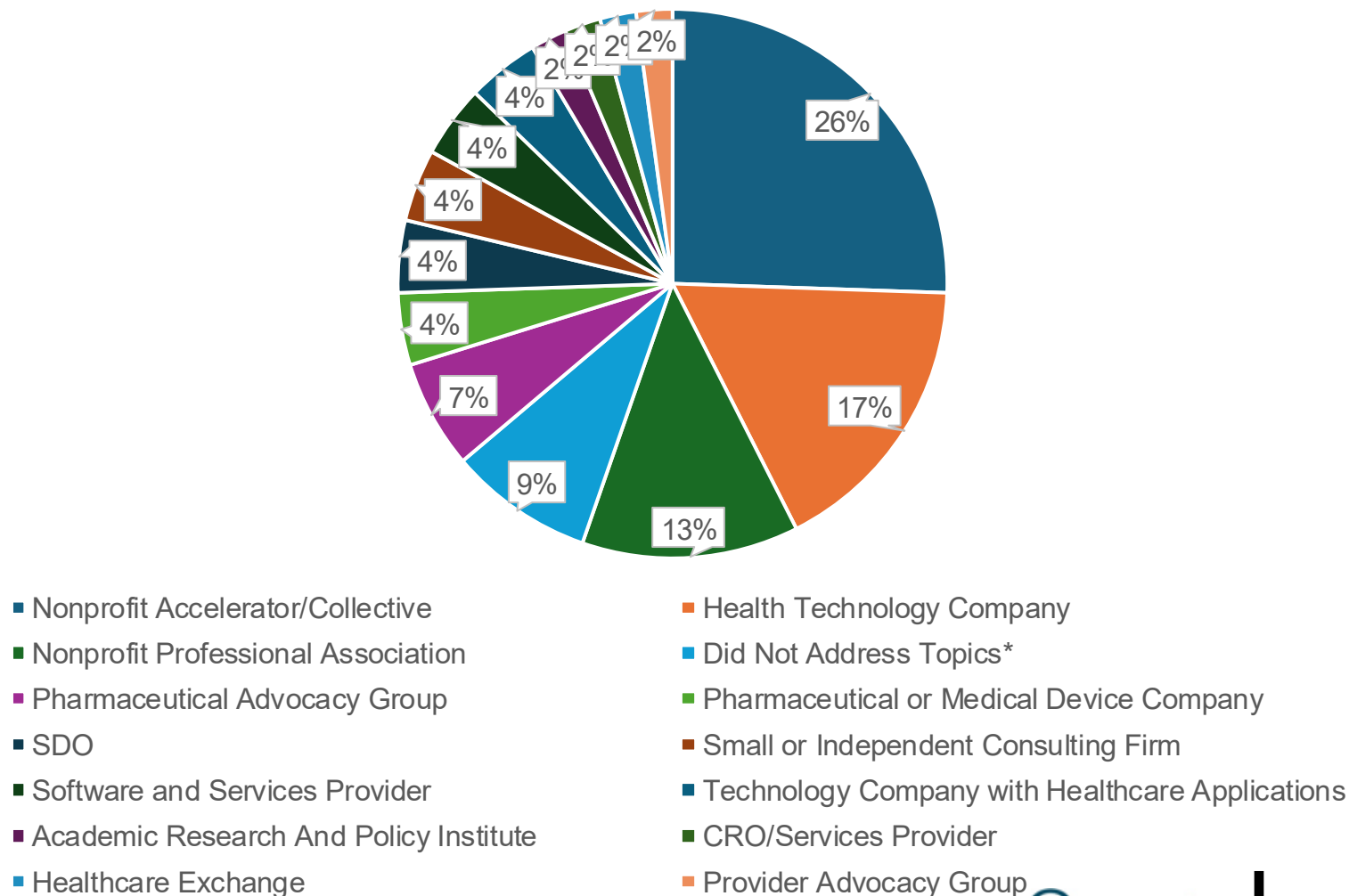
On April 23, 2025, Federal Register Docket No. FDA–2025–N–0287 was posted requesting public comments “Exploration of Health Level Seven Fast Healthcare Interoperability Resources for Use in Study Data Created From Real-World Data Sources for Submission to the Food and Drug Administration”. The comment period lasted the standard 90 days and ended on June 23, 2025. Questions posed included:

1. What challenges do you see for the pharmaceutical industry regarding the current state of submitting clinical study data collected from RWD sources to FDA?
2. What opportunities and/or challenges do you see for the pharmaceutical industry on reaching a future state of clinical study data submissions collected from RWD sources using HL7 FHIR (e.g., business processes, technical considerations)?
3. What are your suggestions on how, from a data standards perspective, FDA might reach a future state of clinical study data submissions collected from RWD sources that aligns with ASTP/ ONC health IT goals for HL7 FHIR-based exchange?
4. Does USCDI version 3 provide enough information for collecting RWD for research purposes? Is there information that USCDI version 3 does not sufficiently address?
5. Under TEFCa, a variety of “Exchange Purposes” are authorized. If “Research” was added as an “Exchange Purpose,” what role could TEFCa play with using RWD for clinical research? How could TEFCa support more efficient collection and exchange of RWD for clinical research purposes? What challenges might exist with this approach?*

Note: Question 5 responses are not included in this presentation.

47 Comments Received, Responses to Questions 1-4 Reviewed

Count of Responses by Category



*Responses that did not address the topics were not included in our review.

Question 1: What challenges do you see for the pharmaceutical industry regarding the current state of submitting clinical study data collected from RWD sources to FDA?

- RWD must be submitted using CDISC standards
- CDISC designed for RCTs conducted under a protocol
- CDISC lacks domains/data elements to adequately represent RWD
- RWD must be mapped to CDISC
 - Loss and misinterpretation of information
 - Many mappings are subjective > Need for a single source of truth
 - Timely and costly
- Interoperability of RWD with existing CDISC standards
 - RWD terminology and coding differ from RCT and inconsistent across RWD sources
 - Possible loss of granularity or meaning

Question 1: What challenges do you see for the pharmaceutical industry regarding the current state of submitting clinical study data collected from RWD sources to FDA? (cont.)

- Lack of ready-made audit trails or methods to understand how and why transformation decisions were made
 - Difficult to ensure end-to-end traceability
 - Limits FDA ability to assess reliability and reproducibility
- Most challenges not due to current submission standards
 - Business purpose of RWD differs RCT data
 - Good amount of RWD is unstructured and not classified in a standard way
 - RWD is typically incomplete, containing lots of missing data
 - Much of the missing data is relevant for research purposes, but does not meet business needs for patient care
 - RWD, by definition, lacks a defined visit schedule

Question 2: What opportunities and/or challenges do you see for the pharmaceutical industry on reaching a future state of clinical study data submissions collected from RWD sources using HL7 FHIR

Opportunities

- **Alignment with U.S. EHR ecosystem:** HL7 FHIR is mandated under the 21st Century Cures Act and widely adopted for health data exchange, positioning it as a logical source format for EHR-derived RWD.
- **Richer contextual data:** FHIR supports patient-, provider-, and site-level context (e.g., location, provenance) that is difficult to capture in traditional clinical trial datasets.
- **Long-term modernization potential:** Over time, FHIR could help streamline evidence generation directly from EHRs into regulatory review workflows, especially as tooling matures.

Key Challenges

- **EHR-to-FHIR variability:** EHR data are rarely stored natively in FHIR; transformations are unregulated and may differ across vendors and sites, creating inconsistency and risk.
- **Flexibility vs. consistency:** Multiple valid FHIR implementations and mapping choices can undermine comparability and increase downstream validation burden.
- **Coding and semantic variability:** Inconsistent vocabulary use (e.g., SNOMED, ICD-10, local codes) and differing levels of specificity can erode data fitness-for-purpose and reviewer confidence.
- **Not analysis-ready:** FHIR functions as an ingestion/exchange layer (like SDTM), not an analytic standard; no HL7 equivalent to ADaM currently exists for FHIR.
- **Stakeholder readiness:** Significant training, infrastructure investment, and workflow adaptation would be required across sponsors, CROs, and regulators.

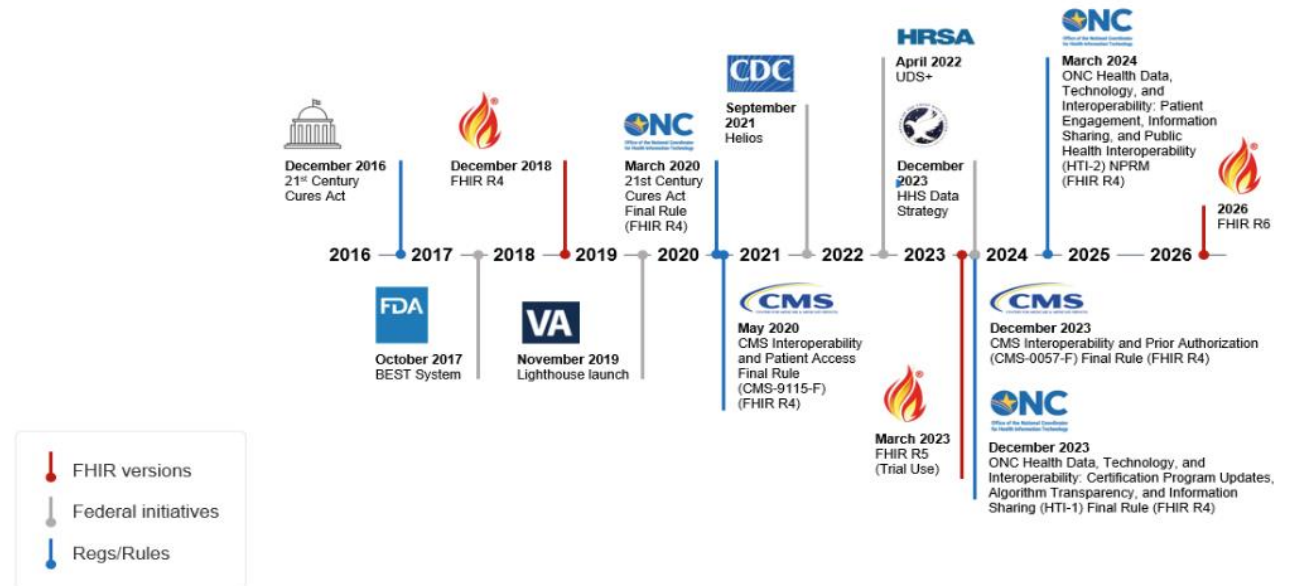
Question 2: What opportunities and/or challenges do you see for the pharmaceutical industry on reaching a future state of clinical study data submissions collected from RWD sources using HL7 FHIR (cont.)

Additional Challenges

- **ETL burden likely remains:** Automation gains from FHIR may be offset by the need to manage semantic alignment, provenance, and mapping consistency at scale.
- **Infrastructure investment required:** Legacy systems are not optimized for flexible FHIR structures; storage, transformation, and validation capabilities must evolve.
- **Lessons from CDISC transition apply:** Adoption will require phased implementation, tooling, and shared best practices to avoid repeating early CDISC growing pains.
- **Fitness-for-purpose must be explicit:** Sponsors will need to assess data depth, provenance, and coding practices relative to specific safety or efficacy endpoints.
- **Tooling gap is an opportunity:** FDA and industry could co-develop validation and analysis tools for FHIR-based submissions, similar to early SDTM tooling evolution.
- **Semantic governance from FDA is critical:** Without stronger constraints, unconstrained FHIR risks recreating today's bespoke mapping challenges under a new standard.

Question 3: What are your suggestions on how, from a data standards perspective, FDA might reach a future state of clinical study data submissions collected from RWD sources that aligns with ASTP/ ONC health IT goals for HL7 FHIR-based exchange?

The 2024 Draft Federal FHIR® Action Plan, released by the Assistant Secretary for Technology Policy/Office of the National Coordinator for Health Information Technology (ASTP/ONC), guides federal agency investment and adoption of HL7® FHIR®, aiming for progress by 2026 in many HHS agencies.



Question 3: What are your suggestions on how, from a data standards perspective, FDA might reach a future state of clinical study data submissions collected from RWD sources that aligns with ASTP/ ONC health IT goals for HL7 FHIR-based exchange? (cont.)

- Encourage SDOs, including CDISC and HL7, to establish comprehensive and harmonized standards for RWD and work underway in clinical research (e.g. HL7 Vulcan projects) should be leveraged
- Develop of a “RWD-Core” FHIR Implementation Guide (IG) defining a core set of required data elements and controlled terminologies for regulatory-grade RWD submissions.
- Clarify provenance requirements, including specifying minimum access, auditability, and lineage standards across the transformation pathway from source data to the submitted RWD
- adopt a fit-for-purpose approach to data quality, provenance, and required standards, adjusted for the intended regulatory use
- Create definitive guidance and tooling to map FHIR resources to research-ready formats.
- Convene a multi-stakeholder effort to endorse or develop a framework for FHIR-to-CDISC transformations
- consider adopting a hybrid model supporting multiple data standards that are suited to different data sources and purposes during the transition period.
- Certification criteria for technologies that bridge FHIR-based health data and research-ready formats
- Establishing a regulatory sandbox to test innovative approaches, including privacy-preserving technologies
- Continued active participation in and sponsorship of community efforts such as FHIR Connectathon and early adopter programs.

Question 4: Does USCDI v3 provide enough information for collecting RWD for research purposes? Is there information that USCDI v 3 does not sufficiently address?

Overall Assessment

- **Broad consensus: USCDI v3 is insufficient** for collecting regulatory-grade RWD for research.
- Useful for core clinical exchange, but too high-level for advanced research and regulatory decision-making.

Key Gaps Identified

- **Insufficient clinical granularity and scope**
 - Missing disease-specific details (e.g., oncology staging, histology, tumor response, line of therapy).
 - Limited therapy, outcome, medication administration, and pharmacovigilance detail.
- **Laboratory limitations**
 - Lack of unique device and test kit identifiers needed for validation, integration, and deduplication.
- **Temporal and longitudinal gaps**
 - Inconsistent capture of dates, timing relationships, enrollment, follow-up, and observability.
- **Semantic and structural issues**
 - Ambiguous or non-intuitive classes (e.g., “Goals,” “Problems”) that do not reflect research-relevant clinical meaning.
 - No terminology/value set layer (by design), with reliance on downstream implementation guides.
- **Implementation variability**
 - Different “flavors” of USCDI implementation across sites undermine consistency when aggregating data.
- **Limited scope**
 - Focused on structured EHR data with uncertain relevance to claims, registries, and other RWD sources.

Question 4: Does USCDI v3 provide enough information for collecting RWD for research purposes? Is there information that USCDI v3 does not sufficiently address? (cont.)

Recommendations:

Anchor, don't overload

- Use USCDI v3 as a foundation, not a comprehensive research model

Define a regulatory RWD layer

- Develop a constrained, FDA-specific “RWD-Core” FHIR Implementation Guide, aligned with USCDI but tailored to regulatory needs

Leverage existing standards

- Consider use of existing CDISC domains & terminology, rather than creating parallel research-specific USCDI expansions

Consider impact on patient care

- Any updates must avoid negatively impacting patient care or imposing significant new data collection burdens

Learn from CDISC implementation and Proceed incrementally

- Similar to CDISC's evolution, focus first on core domains, with selective expansion over time as tools and workflows mature

Build on Areas where USCDI adds value

- Standardizing common core elements (demographics, diagnoses, drug exposure)
- Mandated inclusion of FHIR Provenance supports traceability and data lineage

Summary of Recommendations for use of FHIR for RWD Submission

- A standard for RWD is needed as CDISC does not appear to be expanding to incorporate RWD elements.
- FHIR is a strong candidate given its flexibility and adoption by other HHS agencies but needs to be constrained by an implementation guide for FDA submission.
- Determine how to submit analysis data for RWD and/or plan for analysis standard creation.
- Address semantic interoperability explicitly for mapping to CDISC
- Clarify expectations for EHR-to-FHIR transformations.
- Pilot analysis pathways rather than assume efficiency gains.
- Invest in tooling, training, and phased adoption.
- Maintain clear separation between near-term and future-state use cases but keep the future state in mind.
- When partnering with ONC/ASTP and providers, prioritize patient care over data collection and look for innovative ways to collect data during routine care, such as using DHTs and other technologies.
- Recommend that ONC/ASTP to invest in ways to improve the reliability and quality of EHR data

Our View of Possible Paths Forward

1. Keep all submissions, RCT and RWD, with CDISC
 - Use of non-standard variables and domains until/unless CDISC develops these for RWD
2. Expand FHIR-to-CDISC Mapping project
 - Have an industry standard for this mapping, so that all FHIR submission will be automatically mapped to CDISC, these may need to vary by therapeutic area and may also require use of non-standard variables and domains but there could be consensus around these
3. Hybrid FHIR & CDISC
 - Use FHIR as a standard for collected RWD and keep CDISC SDTM for collected RCT data
 - Use CDISC ADaM for analysis data, enabling RCT and RWD to be aggregated at the analysis level
4. Everything goes to FHIR
 - Start with FHIR for use with RWD, as FHIR and technology advances, RCTs will be done through EHRs
 - Analysis Standard will need to be determined

Conclusion

- Current state is not sufficient for RWD.
- RWD is difficult to standardize due to high variability across sources and inconsistent data quality
- FHIR is a promising but non-turnkey path for RWD-based submissions.
- This FRN specifically deals with submitted data; however, the use of FHIR, a standard mandated by ONC/ASTP for EHRs, paves the way for a future where there could be near real-time access to clinical data.
 - This can enable adaptive trial designs, earlier safety/efficacy insights, and even an end state where data RWD, collected during the routine care of patients, can be considered regulatory grade without the need for any transformation.
- Recommendations for successful adoption depends on constrained implementation guides limiting some of the flexibility inherent in FHIR.
 - Work should consciously build on (and not replace) the decades of clinical research standards development.
- Explicit semantic alignment with existing standards (e.g., CDISC) that allow for the integration of RCT data and RWD is needed
- Pilot use cases and deliberate investment in FHIR-ready tools and training is needed
- If using AST/ONC levers, care needs to be taken not to add additional burdens to clinical staff caring for patients.
- Consider how research from regulatory use cases can be fed back into an interoperable healthcare system

Thank You & Questions

Thank you!



Ingeborg Holt
Orizaba Solutions
iholt@orizabasolutions.com



Sarah Ferko
IBM Consulting
smferko@us.ibm.com



Jeff Abolafia
Formerly of Certara/Pinnacle21
jabolafia7@gmail.com



Questions

