June 23, 2025

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2025-N-0287: 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

To Whom It May Concern:

Accumulus Synergy, Inc. ("Accumulus"), on behalf of its member companies, appreciates the opportunity to provide feedback to the Food and Drug Administration ("FDA" or "the Agency") on Health Level Seven (HL7) Fast Healthcare Interoperability Resources (FHIR) for submission data collected from real-world data (RWD) sources. Accumulus is a nonprofit industry trade association working to accelerate global policies and the need for digital transformation to enable efficient and technology-forward data exchange.

Accumulus supports FDA's efforts to explore the potential of FHIR to streamline data exchange, enhance the quality and consistency of RWD submissions, and ultimately accelerate evidence generation for regulatory decision-making. We commend the Agency's proactive approach in engaging stakeholders early in the process and welcome the opportunity to contribute to the development of solutions that promote trust, transparency, and efficiency in the use of RWD for regulatory purposes.

ACCUMULUS RESPONSE TO FDA QUESTIONS

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?***

   Challenges in Mapping RWD to CDISC Standards

   One of the primary challenges the pharmaceutical industry faces in submitting clinical study data collected from RWD sources to the FDA is the significant effort and cost involved in transforming RWD into CDISC-compliant formats. While CDISC standards are well-suited for randomized controlled trials (RCTs), they were not designed with the structure or variability of RWD in mind. Common data models like Observational Medical Outcomes Partnership (OMOP) and Sentinel Common Data Model (SCDM) are optimized for storing and analyzing RWD, but transitioning from these models to CDISC often introduces risks of data loss, inconsistencies, and interpretation variability due to differences in how sponsors approach mapping and

the Extract, Transform, Load (ETL) process. This not only impacts study reproducibility but also makes maintaining traceability more difficult, especially when data has already been transformed once prior to CDISC conversion, leading to issues like unclear sources of exposure records.

Fragmentation and Scale Challenges

RWD is often collected across a variety of healthcare settings, such as emergency rooms, primary care, and telehealth, each of which may use different systems and documentation standards. This lack of standardization can result in fragmented records that can lead to missing or incomplete information about diagnoses or treatments. These gaps complicate data interpretation and regulatory review. Additionally, RWD datasets tend to be much larger than those from traditional trials, and current FDA systems may not be fully equipped to efficiently ingest and process data at that scale.

Lack of Data Ownership and Standardization

Another complication arises from the lack of ownership or control over how RWD is collected and structured. Sponsors often inherit data with inconsistent formats, ambiguous variable definitions, and non-standardized vocabularies, which can result in unnecessary rework and longer timelines. Unlike RCTs, RWD is not collected with research objectives in mind, but rather is structured to support clinical care rather than regulatory submissions. This creates challenges in aligning it with CDISC's predefined domains and variables.

Structural Limitations of SDTM for Analyzing RWD

Even when data is mapped into SDTM, there are structural limitations – such as the inability to easily analyze important contextual information (e.g., treating provider for each visit), which often ends up in supplemental domains that are not well supported by common analysis tools. The lack of controlled vocabulary and standardized variable naming further adds to the burden, requiring customized programming and increasing the time and effort for both sponsors and reviewers.

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 HI7/FHIR (e.g., business processes, technical considerations)?***

Opportunities

The adoption of HL7 FHIR standards presents a significant opportunity to reduce the cost and time required to prepare and submit RWD for regulatory purposes. If widely adopted, FHIR could support a more seamless, interoperable infrastructure for

gathering and organizing RWD across diverse healthcare systems. Implementing FHIR at or near the point of care would ensure data quality and traceability, minimizing the need for data transformation to support research and regulatory use cases. Leveraging HL7 FHIR standards also creates an opportunity to support pragmatic clinical trials, which would be particularly valuable for assessing safety in specific patient subgroups, real-world efficiency and/or effectiveness, as well as detecting rare adverse events, and ultimately contribute to improved pharmacovigilance and post-marketing surveillance.

A future state where a standardized, FHIR-based model exists for organizing source RWD could mirror the current clinical trial data submission structure. This would create a pathway for structuring both structured and unstructured RWD in a consistent manner and make it easier to compare RWD with traditional clinical trial data. Establishing such standards could also enable FDA to provide clearer guidance for how RWD should be tabulated and analyzed.

Additionally, there is an opportunity for FDA and industry to collaborate on developing or adapting existing FDA review tools to support HL7 FHIR-based submissions. Stakeholders could also work together to define and pilot what a CDISC Define.xml equivalent might look like in a FHIR context.

Finally, lessons learned from the development of CDISC standards could be leveraged. Starting with standardized organization (like SDTM), then defining analysis models (like ADaM), and finally establishing collection standards (analogous to CDASH), a phased, iterative approach tailored for RWD would be both logical and impactful.

Challenges

Despite these opportunities, there are challenges that also need to be addressed. A key gap is the lack of an established analytical data model that aligns with HL7 FHIR. While FHIR is strong in data exchange, it is not inherently designed for statistical analysis. The industry would either need to adapt current models like ADaM to map to FHIR or develop a new analytics framework that fits FHIR's structure.

Another challenge lies in vocabulary alignment. HL7 FHIR typically uses terminologies like SNOMED, LOINC, ICD, and RxNorm, whereas CDISC-based submissions rely on MedDRA, WHODrug, and CDISC Controlled Terminology. Bridging these vocabularies, or developing robust mapping strategies between them, is essential to ensure consistency in data interpretation and regulatory analysis.

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 align with ASTP/ONC health IT goals for HL7 FHIR-based exchange?***

Develop Clear HL7 FHIR Implementation Guidelines

The FDA should collaborate with stakeholders to create detailed HL7 FHIR implementation guidance specific to regulatory submissions. These guidelines should include practical examples, real-world use cases, and hypothetical scenarios that illustrate how RWD can be structured, exchanged, and analyzed using FHIR. Clear documentation will enable stakeholders to align more easily and reduce ambiguity in how FHIR is applied in the regulatory context.

Support a Phased and Inclusive Transition

To ensure that valuable RWD sources are not prematurely excluded, the FDA should incorporate a transition period that allows for progressive adoption of FHIR-based approaches. This would give stakeholders time to adapt their systems and workflows without disrupting ongoing or planned studies. The transition should also include opportunities for piloting and feedback to refine standards in a real-world context.

Define the Scope of Applicable Study Types

The FDA should clearly communicate the types of studies that may benefit from or be eligible for HL7 FHIR-based submissions, such as observational studies for example. This clarity will help stakeholders prioritize where to invest in FHIR-based data strategies to better align their efforts with regulatory expectations.

Promote a Common Data Model for RWD

Establishing a common data model for RWD from sources such as electronic health records (EHRs), aligned with HL7 FHIR, would allow for consistent data handling throughout the entire lifecycle. Standardizing this model would help bridge the gap between healthcare data collection (designed for clinical care) and regulatory data needs (designed for evidence evaluation), improving data quality and comparability.

Leverage FHIR's Technical Strengths

FHIR is natively compatible with modern technologies such as XML, HTTP, OAuth, and RESTful APIs, making it ideal for scalable, secure, and interoperable data exchange. Additionally, HL7 FHIR has steadily gained traction since 2012 across the healthcare industry and major technology companies, and this strong foundation enhances its reliability for complex healthcare and regulatory needs. By addressing current technical and structural gaps in FHIR for regulatory use, the FDA can help unlock its potential to support high-quality RWD submissions. This would also encourage

broader industry innovation in tools and platforms designed to collect and submit data more efficiently.

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?***

   Limited Coverage of Patient-Reported Outcomes (PROs)

   Depending on the research questions, USCDI v3 offers only limited support for PROs, which are increasingly important in RWD research for capturing outcomes that matter to patients. The absence of implementation guidance and standardization in this area can hinder the integration of PROs into regulatory-grade datasets.

   Insufficient Granularity in Clinical Data Elements

   Many of the existing data classes, such as "Goals" and "Problems," lack clarity and depth. For example, the "Problems" category appears to be shaped by behavioral health intake forms and does not generalize well to other domains, such as oncology. Critical disease-specific elements, such as tumor size, grade, histology, and staging, are notably absent, which limits the utility of USCDI v3 for research in high-impact therapeutic areas.

   Inadequate Date and Temporal Data Capture

   Accurate data and time fields are essential for RWD research, particularly when reconstructing clinical timelines, understanding treatment patterns, and establishing chronological relationships between interventions and outcomes. USCDI v3 does not currently provide robust support for these temporal data points.

   Missing Research-Ready Data Elements

   USCDI v3 includes 80 data elements, which may not be sufficient for collecting RWD that is fit-for-purpose for regulatory submissions. To address this gap, FDA should develop best practices and provide clear guidance on the use of additional data elements not currently included in ESCDI v3.

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?***

   Opportunities and Potential Benefits

   Including "Research" as an Exchange Purpose would allow authorized participants in TEFCA to collect and share RWD more seamlessly across diverse sources such as EHRs,

insurance claims, patient registries, and other clinical systems. This broader access could significantly reduce the time and effort required to gather data for clinical studies, particularly for pragmatic, clinical research.

Challenges and Considerations

Not all healthcare organizations or data holders may be equipped to support standardized data sharing for research. Investments in infrastructure, workforce training, and alignment with research-oriented data standards will be necessary for consistent participation. In addition, data sharing must comply with HIPAA and other patient privacy regulations, which can further complicate efforts to exchange data seamlessly. Even when data exchange is technically feasible, a significant challenge remains in ensuring that the data are research-grade. TEFCA would need to be accompanied by frameworks or best practices that promote high-quality, interpretable, and analyzable data suitable for clinical research and regulatory use.

CONCLUSION

Accumulus appreciates FDA's ongoing leadership in modernizing data standards and advancing the use of RWD in regulatory decision-making. The adoption of HL7 FHIR, refinement of data standards such as USCDI, and consideration of "Research" as a recognized Exchange Purpose under TEFCA are critical components of this transformation.

We encourage FDA to continue fostering collaboration across regulatory authorities, industry stakeholders, and technology partners to align on practical implementation strategies, identify areas where existing standards may fall short, and develop best practices to support the responsible and effective use of RWD. Accumulus remains committed to contributing to this effort and supporting the development of digital solutions that enhance regulatory efficiency and ultimately benefiting patients.

Thank you for the opportunity to provide input on this important initiative.