REAL-WORLD EVIDENCE ALLIANCE

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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; Establishment of a Public Docket; Request for Comments

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to respond to the Request for Comments titled "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 "Request for Comments").[1] We are a coalition of real-world data ("RWD") and analytics organizations with a common interest in harnessing the power of real-world evidence ("RWE") to inform regulatory decision making to improve the lives of patients. Our members have deep knowledge and experience working with healthcare data across disease areas and patient populations, and we aim to bring these collective insights to bear in support of RWE policies.[2]

The RWE Alliance envisions a future in which data from electronic health records, administrative claims and billing records, product and disease registries, personal devices, wearables, and health applications will be used to generate evidence to support regulatory decision making related to medical product safety and effectiveness. To achieve these goals, the RWE Alliance advocates for policies that will (1) advance FDA's RWE Framework, (2) encourage the use of RWE to better understand treatment effects in underrepresented populations, (3) enhance opportunities for RWE

[1] 90 Fed. Reg. 17067 (Apr. 23, 2025).

[2] For information about our members, please see our website, https://rwealliance.org/who-we-are/.

organizations to consult with FDA, (4) increase communication on the generation and use of RWE, and (5) recognize the unique aspects of and opportunities for RWD/E.[3]

We commend FDA for seeking input on a potential new standardized data format for the submission of real-world study data. The use of HL7 FHIR ("FHIR") for RWD submissions has the potential to streamline and simplify the process of submitting RWD as study data to FDA, while simultaneously improving the utility of such data to inform regulatory decision making. While there are many benefits to using FHIR for RWD submissions, FDA should maintain a flexible approach by adopting multiple data standards that permit sponsors and data providers to submit RWD using the data standard best suited for the specific data source and use case. Each type of data standard is built for different purposes and has different benefits. A more flexible approach that permits the use of multiple data standards will allow industry to maximize those benefits and use various standards that are appropriate in different circumstances (e.g., depending on the data source or study design) for the generation, curation, transformation, analysis, and submission of RWD to FDA. This flexibility will allow researchers to more efficiently obtain, harmonize, and standardize RWD, which will help facilitate greater availability of RWD for evidence generation and ultimately to inform regulatory decision making.

FDA's consideration of FHIR-based data standards is a positive step forward and we encourage FDA to consider adopting additional data standards for regulatory submissions as the field evolves. Increasing the options available for submitting study data to FDA will have a deregulatory effect, in that it will reduce regulatory barriers and streamline compliance with FDA's data submission requirements.[4]

For ease of reference, our comments respond to each question posed by FDA in the Agency's *Federal Register* notice.

In Response to 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?"

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[3] Additional information about what we believe is available on our website, https://rwealliance.org/what-we-believe/.

[4] *See* Executive Order 14192, Unleashing Prosperity Through Deregulation (Jan. 31, 2025), https://www.federalregister.gov/documents/2025/02/06/2025-02345/unleashing-prosperity-through-deregulation; Office of Management and Budget, Memorandum M-25-20 (Mar. 26, 2025), https://www.whitehouse.gov/wp-content/uploads/2025/02/M-25-20-Guidance-Implementing-Section-3-of-Executive-Order-14192-Titled-Unleashing-Prosperity-Through-Deregulation.pdf.

FDA's current approach to the submission of clinical study data collected from RWD sources—articulated in its Data Standards Guidance[5]—does not meaningfully facilitate the submission of RWD from various types of data sources, each of which has unique standards associated with the compilation, standardization, and exchange of data for research purposes. FDA recognizes that there are challenges involved in standardizing study data derived from RWD sources, including the variety of sources, the potential use of multiple RWD sources in one study, differences in source data capture and access, lack of standardization at the point of care, and differences in methods and algorithms to create aggregated datasets.[6] These differences preclude a one-size-fits-all approach for ensuring that RWD submitted to the Agency can be supported. Yet FDA requires that sponsors submitting clinical and nonclinical RWD use formats described in the Study Data Guidance and the supported study data standards listed in the Agency's Data Standards Catalog. FDA's currently supported data standards in the Data Standards Catalog were designed to organize clinical trial data and have significant limitations when used with RWD.

This lack of alignment can create challenges in converting RWD to a currently supported data format. For instance, granularity in source data may be lost when mapping the data to a currently supported format[7] or certain RWD sources may be excluded from use altogether because of the lack of alignment. As a result, current FDA required data standards can impose unnecessary constraints on the internal validity and/or external validity (i.e., generalizability) for submitted studies. The linkage of data across multiple RWD sources can raise further considerations because each source may diverge from FDA's currently supported data standards in different ways. Further, each new transformation constitutes an opportunity to introduce bias into an RWE study or to lose the rich detail captured in the original data.

As we state above, the Agency should adopt a flexible approach that permits sponsors to use various data standards and should not require the standardization of analytic datasets to conform to a specific format in order to be submitted. Expanding the Data Standards Catalog to include FHIR and other data formats that are more consistent with RWD sources, including when data from multiple sources are linked, would help address some of the limitations presented by currently supported data standards.

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[5] FDA, Guidance for Industry: Data Standards for Drug and Biological Product Submissions Containing Real-World Data (2023), https://www.fda.gov/media/153341/download.

[6] *Id.* at 3-4.

[7] As an example, in one RWE study, conversion to CDISC SDTM not only resulted in additional investigator burden when mapping but also reduced the amount of information available in the data. *See* Garza, M., Del Fiol, G., Tenenbaum, J., Walden, A., & Zozus, M. N. (2016). Evaluating common data models for use with a longitudinal community registry. Journal of biomedical informatics, 64, 333–341. https://doi.org/10.1016/j.jbi.2016.10.016.

In Response to 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 (*e.g.,* business processes, technical considerations)?"

A. The use of RWD in regulatory decision making has important and unique technical considerations, which should be reflected in FDA data standards.

FDA's assessment of RWD that is used to generate evidence of safety and effectiveness involves unique technical considerations, including the evaluation of data quality and reliability. FDA should use these technical considerations to inform the Agency's exploration of FHIR data standards to achieve a future state that has the potential to facilitate regulatory submissions for RWD sources. For instance, FDA expects sponsors to demonstrate data reliability for RWD sources, which involves not only using precise data definitions but also tracing the provenance of study data elements and understanding the transformations applied along the data journey to create the analytic data sets. Metadata, including data quality attributes, from the original health care provider organization could be retained to facilitate this demonstration of reliability when data is used for the secondary purpose of clinical research. By reflecting these technical considerations and aligning the kinds of documentation needed to demonstrate reliability of RWD with FDA's data standards, FDA could encourage the further use of RWD in FDA regulatory decision making. We urge FDA to help embed the needs of the clinical research community in evolving data standards and in health data exchange standards promulgated by ASTP/ONC.

B. Challenges for the RWE ecosystem regarding clinical study RWD submissions using FHIR.

We describe several potential challenges associated with the submission of RWD using FHIR below.

- Currently, health care systems use FHIR primarily for health data exchange. FHIR was constructed for interoperability of healthcare operations and was not built for research purposes. FHIR is not designed to work in a research capacity or structured to store data long term efficiently. There may be limitations with FHIR's ability to provide adequate capture of disparate data sources that are linked and limitations associated with integrating certain RWD elements and endpoints with the FHIR format.
- FHIR APIs often abstract away information about data source systems. FHIR APIs are designed to standardize access, but this can obscure the underlying system or user that created the data. For example, a FHIR Observation might not indicate whether it came from a lab system, a clinician note, or a patient-reported app. In multi-system environments (e.g., EHR plus oncology EMR plus lab system), the same clinical concept (e.g., cancer stage) might appear in

multiple places. Without data provenance, it could be difficult to determine which version is authoritative or most recent.

- FHIR typically represents raw data without the transformations, normalizations, and other adjustments typically applied when data is ingested and combined from various sources for research purposes. FDA should work with the RWD research community to ensure that tools are available to preserve this information when converting data into FHIR.
- Each organization currently translates data from various standard inputs (e.g., FHIR) to create their own native data structures. Methods for back translation will need to be developed to ensure data consistency and efficiency.
- Each company may implement FHIR differently, which raises concerns about standardization. Researchers will need to have access to each organization's mapping to FHIR, similar to how Observational Medical Outcomes Partnership ("OMOP") mappings for various datasets are publicly available.
- There are challenges with large-scale data collection in FHIR, which could result in performance and scalability issues. FHIR is optimized for real-time, patient-centric data exchange (e.g., retrieving a single patient's medications or allergies). FHIR is not optimized for bulk data extraction or analytics workflows that require querying and aggregating data across large populations. Querying millions of patients through FHIR APIs can be slow and resource-intensive. Many FHIR servers rate-limit requests or throttle performance to protect operational systems. HL7 introduced the FHIR Bulk Data Access (Flat FHIR / export) specification to address this, but not all systems support it. The specification often requires custom configuration and authorization workflows and may still be limited in terms of data types and query flexibility.
- There may be difficulty with accounting for aggregated or relicensed data elements, as not all data providers own the rights to each component of their licensed datasets. In addition, appropriate methods for de-identification should be considered when developing FHIR-based standards.
- The costs of labor involved in converting native data files to FHIR format may be significant.

In Response to 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?"

We commend FDA for its work, to date, on initiatives to advance the development of FHIR for regulatory use cases. Moving forward, we recommend that FDA focus on exchange of and access to data that is suitable for regulatory decision making, with a particular focus on data auditability, to facilitate a future state of regulatory submissions for RWD sources using FHIR that is aligned with ASTP/ONC health IT goals. In a recent article on FDA inspections of submissions including real-world data, Grandinetti

and colleagues noted "inconsistencies in how RWD are collected, recorded, and maintained across different systems, along with gaps in quality control monitoring" complicate the use of RWD in regulatory decision making.[8] To inform the Agency's work in developing standards for the submission of real-world study data sets—and, as we recommend above, related information about data lineage and source records needed to confirm data reliability—we recommend that FDA pursue demonstration projects related to data auditability. For instance, FDA could conduct a series of "mock data audits" in collaboration with industry that are focused on reviewing source records of data collected from a variety of settings (e.g., inpatient, outpatient, ambulatory, laboratory) used across a range of study designs intended to generate evidence of medical product effectiveness and/or safety for regulatory decision making. By examining the findings from these demonstration projects, the RWE ecosystem and the FDA could gain common knowledge to help develop regulatory guidance, data standards, technical manuals (e.g., on inspection procedures), and governance practices for real-world data sets. Doing so will facilitate the exchange and use of RWD, and thus further advance the ASTP/ONC health IT goals.

In Response to Question #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?"

The suitability of USCDI version 3 for the submission of RWD depends on several factors.

- Data Elements: While USCDI has expanded its support for additional data elements over time, USCDI version 3 is still focused on a baseline set of data elements designed to support interoperable health information exchange. These data elements may be sufficient for some research purposes; however, many studies designed to assess the safety and effectiveness of medical products require additional concepts. We encourage FDA to coordinate with ASTP/ONC to explore additional data elements that would further support the collection of RWD for research purposes. For example, FDA and ASTP/ONC should consider adding data elements from the OMOP Common Data Model ("CDM") that are not in USCDI version 3. OMOP CDM is built for research purposes and facilitates standardized analytics, including support for temporal reasoning (e.g., medication start and end date, observation periods); quantitative analysis (e.g., lab result values with units, drug dosages); health economics (e.g., cost data); and population-level studies (e.g., death, provider, location). In addition, elements such as Medication Administration, Adverse Events (specific to Clinical Research) and Genomic Data could support the collection and use of RWD in research. With respect to Adverse Events, FDA should consider leveraging the

[8] Cheryl Grandinetti et al., *Keeping the End in Mind: Reviewing U.S. FDA Inspections of Submissions including Real-World Data*, THER INNOV REGUL SCI. (2025), https://pubmed.ncbi.nlm.nih.gov/40413363/.

FHIR implementation guidelines created by the HL7 Vulcan group. Adding these data elements will help to fill gaps that currently limit researchers' ability to capture accurate data.

- Type of RWD: The adequacy of USCDI version 3 differs depending on the specific type of RWD collected. For example, certain specialized data elements or endpoints, such as those from wearables, may not be fully addressed in USCDI version 3. In addition, the lack of support for non-standardized data from all of the various sources (e.g., lab data) of RWD raises challenges. While USCDI and FHIR can support various types of data sources, some data is available only in unstructured form (e.g., PDF format) that is less supported. Investment in technology supporting the use of unstructured data has progressed, but many of the technological developments focus on converting unstructured to structured data rather than on analyzing the unstructured data directly—though this is a promising area for methods development. We recommend that FDA consider how to account for all forms of RWD to facilitate its use in regulatory decision making.

- Data Integration and Transformation: The integration and transformation of data from multiple sources into a standardized format such as USCDI version 3 can be challenging. Researchers may need additional tools or standards to ensure data fidelity and completeness.

In Response to Question #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?"

There are both opportunities and challenges associated with the potential use of TEFCA to facilitate the use of RWD for clinical research. A research-enabling exchange purpose in TEFCA could streamline RWD collection and exchange by providing a standardized framework for different types of participants in the data ecosystem. Adhering to TEFCA's standards could enhance the quality and consistency of RWD.

However, different organizations may implement TEFCA standards inconsistently, which would affect data exchange and interpretation. Another challenge is that only a subset of patient data is currently available through qualified health information networks, which is typically centered around the data required for the currently mandated exchange purposes. The data elements needed for research may be different from those needed for other purposes, such as treatment, billing, or public health reporting. In addition, implementation of a research-enabling exchange purpose may be a challenge in light of TEFCA's enforcement mechanisms. Finally, to advance the use of TEFCA for research, it will be important for FDA to take concrete steps to address challenges associated with access to source data for regulatory submissions,

including by deploying privacy-sparing solutions for submission, review, and inspection of RWD.

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The RWE Alliance appreciates the Agency's commitment to facilitating the submission of data collected from RWD sources to inform regulatory decision making. Thank you for considering these comments, and please let us know if you have any questions. We welcome the opportunity to discuss further.

Best regards,

The RWE Alliance