Duke | Robert J. Margolis, MD Center for Health Policy

Advancing the Development and Implementation of Analysis Data Standards: Key Challenges and Opportunities

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Workshop Summary

Introduction and Background

Across the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), the U.S. Food and Drug Administration (FDA) receives more than 150,000 submissions per year for marketing approval. These submissions amount to millions of data points the FDA must review to make a regulatory decision. Ensuring these data are submitted in a standardized format will support a more efficient review process and greater collaboration between the FDA, sponsors, and stakeholder groups. Uniform study data also enables new research opportunities through the aggregation of data from multiple studies to gain new insights on diseases and better assess key public health trends.

To encourage use of these standards, CDER, in partnership with CBER, established the CDER Data Standards Program.[1] This program identifies key data standards needs and priorities for the Agency, as well as those of external stakeholders, to support more efficient medical product reviews. Through these efforts, the FDA has developed the Data Standards Catalog, which specifies the list of standards currently supported or required per binding guidance[2] to submit data in an electronic format. These supported standards address the lifecycle of clinical research including protocol development, data collection, organization, analysis, and submission.

Analysis data standards (ADS) primarily used by the FDA are developed by the Clinical Data Interchange Standards Consortium (CDISC) and play a critically important role in the clinical trial process by facilitating consistency of data formats and reproducibility of study analyses. The FDA Data Standards Catalog recognizes the CDISC Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) standards, including corresponding Controlled Terminology, which specify the data structure, data domains, variables, and clinical terminology needed to tabulate and analyze study data. These study data become datasets evaluated by the FDA as part of the submission and regulatory review process.

Supported ADS have streamlined and improved the efficiency of regulatory review, but implementation challenges remain. There are acknowledged inconsistencies due to the varied interpretation of these standards, multiple versions that are in use, and potential misalignment between data formats specified in submission governance documents, and data structure requirements in published standards.

On June 12, 2019, under cooperative agreement with the FDA, the Duke-Robert J. Margolis, MD, Center for Health Policy at Duke University and Critical Path Institute convened a public workshop to solicit feedback from stakeholders on how to advance implementation of ADS. Goals included identifying and exploring implementation and submission challenges with ADS and opportunities to improve the

[1] https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/cder-data-standards-program
[2] https://www.fda.gov/media/85137/download

implementation of ADS to improve the predictability and quality of data submissions sent to the FDA. This feedback will inform FDA's strategic planning to improve the efficiency of regulatory review, and advance development of the Agency's efforts to support and enable standardized study data for electronic submissions.

Stakeholder Perspectives on Key Challenges Implementing Analysis Data Standards

Stakeholders representing a number of key perspectives provided input on their experience implementing analysis data standards. Many challenges identified during the discussion resulted from the variability in how stakeholders interpret implementation requirements. The discussion primarily focused on challenges related to industry-led medical product submissions, but also included related viewpoints from non-industry stakeholders such as academic and non-profit organizations.

Industry Challenges

Key themes that emerged from the sessions focused on pharmaceutical industry applications and the underlying drivers of standards implementation variability, as well as complexity of submission analysis and review.

Standards implementation variability

Noted implementation differences can arise from the following sources of variation:

- Inconsistent ADS implementation practices observed in regulatory submissions to FDA, combined with submissions that do not meet requirements posted by review divisions,
- Variability in review and interpretation of datasets across review divisions,
- Differences in dataset requirements specified in published standards that may be inconsistent with posted submission requirements,
- Submission requirement differences across regulatory agencies and with research organizations,
- Provisions for implementation flexibility provided for in published standards,
- Need to support multiple versions of standards at any one time.

Presenters and panel members discussed sources of variability of ADS implementation practices observed in submissions to regulatory agencies, and submissions which at times do not meet all aspects of published requirements. Industry stakeholders noted potential discrepancies in how different review divisions interpret and review data that utilize ADS. Additional variability can arise from differences in deliverable requirements between organizations that specify requirements for research, and differences in requirements across global regulatory bodies. These sources of variability can impact how analysis datasets are structured and analyzed.

Stakeholders also commented on limited international alignment regarding submission nomenclature and data standards requirements. Divergence has been observed between standards supported by FDA and global regulatory agencies. While there are efforts underway, facilitated by standards development organizations, more work is needed to harmonize differences in country-specific regulatory requirements. Special focus will also be needed to understand how new data privacy regulations such as the European Union's (EU) General Data Protection Regulation (GDPR) can affect data mapping, analysis, and transmission of submission data. Country-specific data privacy laws may require additional changes to ensure compliance with both EU and country-specific data privacy regulations.

Another source of ADS implementation variation can result from differences between submission requirement documents issued by regulatory agencies, and data standards published by standards

development organizations. The FDA publishes Technical Specifications, which were established as a process to provide clear statements of submission data requirements in a given therapeutic area. In addition to the SDTM and ADaM foundational data standards, CDISC publishes Therapeutic Area User Guides (TAUGs), which were established as an innovation to build on foundational standards. TAUGs are supplements to the foundational standards that provide for a more detailed representation of data for a specific therapeutic area. Risks noted during the discussion were that an FDA Technical Specification may require the use of data structures for submissions that are not consistent with the data specifications of foundational standards and TAUGs published by CDISC, and that TAUGs may not fully address all aspects of FDA data submission requirements in a given therapeutic area.

As stated in the FDA Technical Conformance Guide, sponsors may use new TAUG extensions of a CDISC standard, but are not required to do so until the extensions have been incorporated into versions of foundational standards supported by FDA, as listed in the FDA Data Standards Catalog.[3] FDA and PMDA are active contributors to the development of ADS and work to coordinate updates of submission requirements such as FDA Technical Specifications with the publication of standards updates and new releases by standards development organizations. Even with coordination of efforts, differences in timing between the incorporation by CDISC of TAUG content into supported foundational standards and the issuance by FDA of Technical Specifications for a given therapeutic area can occur, which can contribute to standards implementation variability.

The CDISC SDTM and ADaM data standards, along with TAUGs, provide a high degree of flexibility for implementation, and user guides can at times be ambiguous, contributing to variability of implementation approaches. Due to the necessary parallel development of updates of these foundational standards and new releases or updates to TAUGs, temporary misalignments across standards can occur. Additionally, differences in interpretation of SDTM during data mapping across organizations can lead to inefficiencies in analysis and regulatory review. At times, conversion of data from legacy systems to SDTM and analysis datasets can also introduce variances, for example, if the analysis datasets are extracted from a sponsor's internal data system instead of directly from SDTM to ADaM.

There are also challenges with the versioning of these standards given multiple versions can be supported and used at the same time (e.g., SDTM Implementation Guide versions 3.1.2, 3.1.3, and 3.2). This adds complexity when a project begins using a specific supported version of a standard, and then that standard is updated or no longer supported. When a version of the standard changes or is no longer supported, the project team then needs to decide whether to continue with the original version or update data mapping to conform to the new standard. If the team decides to continue with an unsupported version of a data standard, the sponsor must submit a waiver request which needs to be approved by FDA.[4]

Complexity of submission analysis and review

Stakeholders noted that some data structures required for submission datasets can result in increased analytic complexity, which is another key driver of variation with standards implementation. Underlying factors contributing to this included the following:

[3] https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

[4] https://www.fda.gov/drugs/forms-submission-requirements/guidelines-requesting-waiver-current-supported-study-data-standard-versions

- Conversions between wide and narrow data structures to meet submission requirements,
- Missing intermediate datasets that hinder reproducibility and traceability of analysis, and
- Varied implementation practices in the use of SDTM custom domains and user defined ADaM datasets.

If the FDA requires datasets that have a wide structure (one record per subject), and a sponsor has performed data analysis using narrow data structures (multiple records per subject), converting the narrow data into wide data may require additional resources and time. In some cases, the type of analysis drives a preference for narrow vs wide data structures. However, early alignment with regulatory requirements might prevent subsequent delays and challenges for the sponsor during later stages of the submission process.

The reproducibility of the analysis is a critical component of medical product review, and barriers beyond dataset structure were identified that could limit the ability to reproduce results. Transformations or interpretations applied to data can introduce variations as data are tabulated and mapped from sources of primary collection (e.g., case report forms) into SDTM and ultimately exported into ADaM analytic structures. Multiple stakeholders at the workshop noted that differences in how organizations interpret SDTM and ADaM requirements can impact how data are mapped. This can affect reproducibility since it can be challenging to trace these transformations and mappings given the large volume of data elements included in analytic data sets.

Another area of complexity is the amount of flexibility allowed in SDTM for customized supplemental qualifier (SUPPQUAL) domains. These domains can accommodate necessary variables or data points not currently structured within the standards. Because the SDTM standard does not allow the addition of new variables to defined domains, a SUPPQUAL domain affords a means to store additional information on a subject or event. This may cause differences in SUPPQUAL customizations which can complicate analysis when datasets from multiple sources or trials need to be analyzed together as part of a submission or regulatory review.

Flexibility in ADaM standards can also introduce complexity. The ADaM standard currently defines multiple classes of ADaM datasets, some with specified wide data structures, some with specified narrow data structures, and some with user-defined data structures. At times, analysis datasets that do not use ADaM are also required to fully represent analysis results, and as a result, submissions in the same therapeutic area from different sponsors may have very different analysis dataset content and structure. It is important to fully document and include in submissions of ADaM and non-ADaM analysis datasets, including intermediate or temporary datasets, metadata, analysis variable metadata, and analysis results metadata.

Challenges Implementing Standards in Academic and Non-Profit Research Settings

Discussion on research and applications outside of industry highlighted a different set of challenges with standards implementation and particularly the acceptance of data standards and funding aspects that can limit resources needed to adopt and implement standards.

Several challenges were highlighted when considering implementation of data standards in academic settings. Often these studies are designed for the exploration of new hypotheses, which can provide several challenges for consistent use of data standards given the uncertainty of whether the research will advance forward. This can be observed especially with unique drug development programs in academic settings that have highly specialized, small research groups where applicable standards may

not be available for studies with new types of subject observations due to the exploratory nature of this research. Example data types discussed during the workshop where there may not be well-defined standards structure for regulatory submissions are genetic data, imaging data, and digital health data.

Academic institutions and non-profits may also have limited experience with data sharing practices that are contributing to the inconsistent use of study standards. In a culture that recognizes novel research, investigators may not prioritize easier sharing of data over pursuing new avenues of research. There are also concerns that data standards may limit the ability of investigators to pursue research or dictate how their research needs to be conducted. Additionally, since this research is often conducted in the clinical setting, data initially collected through an electronic health record is often later re-entered into electronic data capture (EDM) systems. This adds additional steps to processes for data collection and could lead to missing clinical context when imputing observations into EDM systems.

Lastly, key supporters and funders of academic research may not fully understand the benefits of standards, and consequently, grant-based funding mechanisms may not provide adequate resources needed for standards training and implementation. However, during the discussion multiple academic investigators shared interest in transparency and the need for practical ways to implement standards.

Key Opportunities to Improve the Implementation of Analysis Data Standards

Reducing the variability of how standards are applied, addressing the technical complexity of developing analysis datasets, and spurring wider adoption of ADS across the stakeholder community were identified as key priorities to advance ADS implementation.

Reducing variability by aligning stakeholder ADS requirements through greater harmonization, communication, and collaborative partnerships

Non-profit collaborative organizations such as PhUSE and for-profit standards validation tool development organizations are major contributors to efficient and consistent implementation of data standards, and can help with harmonization and integration across SDTM and ADaM. Improved integration is needed starting with define.xml structures and extending to more consistency in the applicable controlled terminology. In general, establishing ADS best practices across industry, standards development organizations, and regulatory agencies could lead to improved consistency and better alignment between SDTM and ADaM technical requirements.

Workshop discussants suggested it would be helpful to have more feedback from FDA reviewers during the regulatory review process to ensure submissions are utilizing standards appropriately to support efficient regulatory review. There was general support for developing a formal process where the Agency provides feedback on application specific issues related to data structure and format, which was coined as a technical “postmortem” during the discussion. Such feedback could address sources of variation that cause review challenges, but are not severe enough to impact the approval of the application. Both the U.S. FDA and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) emphasized importance of discussions with agency review teams when questions arise (Type C meetings). Also, adding representatives from data and standards teams, including data scientists, could help facilitate Agency-sponsored discussions given their role in designing and implementing data systems that employ these standards.

Additionally, stakeholders would like more opportunities to work collaboratively to identify problems and shared solutions to improve the quality of submissions. A recommendation was made to increase the use of real-time-reviews as used today in FDA’s CDER Office of Hematology and Oncology Products,

which involves the submission of data to FDA after the clinical trial database is locked. This facilitates early communication between the Agency and the organization developing the medical product prior to submission, and allows the Agency to start evaluating the pre-submitted data for sufficiency and integrity. By the time the company submits the application, the Agency might have already completed analyses and be familiar with the data. This model may provide a potential best practice for other therapeutic areas.

The importance of sharing best practices in standards implementation was consistently highlighted throughout the workshop. Regulatory agencies, standards development organizations, sponsors, researchers, and funding institutions all have a role in facilitating the sharing of best practices and communicating the benefits of standards adoption. Stakeholders at the meeting suggested additional collaborations and training led by the CDISC community would be helpful in developing strategies to communicate the value of standards, and formal training within academic programs that train data scientists to improve use of standards. Another collaborative opportunity discussed was supporting more clinician engagement in developing definitions for therapeutic area outcomes, which would also facilitate dialogue with study investigators on capturing high-quality data at the point of entry.

Improving data traceability to reduce analytic complexity

Opportunities to improve data traceability were identified as critical to improving the reproducibility of research and efficient review of submissions by FDA staff. It was suggested that sponsors should submit all datasets to support analysis conclusions including intermediate datasets as well as software scripts/programs used to run the analysis. Since providing this information can be resource-intensive for both sponsors to submit and FDA to review, additional innovations may be needed to streamline this process. Some stakeholders suggested streamlining datasets to an accepted minimum amount of data elements required to execute the analysis and pointed to efforts already underway at the National Institutes of Health (NIH) to define common data elements (CDE) to be collected for studies engaged in a specific therapeutic area. There has been exploratory work to incorporate CDEs into CDISC TAUGs, and this could be a promising area for CDISC to advance moving forward.

A suggestion to strengthen the consistency and traceability of data was to constrain SDTM domain size, enable splitting of domains, and support more standardized approaches for leveraging SUPPQUAL variables. These improvements could result in more standardization of ADaM dataset structures in a manner that does not impact analysis capability. Finally, a comment was made about the benefits of broader adoption and use of the CDASH standard to help standardize how data are collected in clinical trials to improve traceability of data into SDTM.

Supporting tool development and implementation resources to reduce barriers impacting standards adoption

Another area of opportunity lies in the development of tools and automation of standards implementation processes. Tools that could automate data mapping and submission preparation would be helpful given the growing volume of data being captured from increasingly diverse sources of data. Such tools could support greater integration of data into analytical files for submission. Approaches that can make use of new and emerging data science technology such as data visualization and machine learning could also improve or streamline how standards are applied as well as the regulatory evaluation of data, analytical methods, and trial results.

Multiple stakeholders suggested there would also be substantial benefit from the availability of more standards knowledge bases and reference sources as well as stakeholder engagement to reduce

variation and improve standards adoption. The cost of producing standardized datasets for submission can be high, particularly for smaller sponsors and academic groups who may be hesitant to adopt standards in early-phase studies given the costs and uncertainty whether the investigational product will move forward to late-stage studies, and therefore, such groups may especially benefit from the availability of tools and resources needed to help reduce the burden of implementing standards. Making materials more accessible to all stakeholders, including providers, could support more uptake and adoption of these standards.

Emerging Opportunities for Standards Development and Innovation with Real-World Data and Evidence

The workshop demonstrated growing interest in the regulatory uses of emerging sources of data being increasingly used to support medical product submissions such as real-world data (RWD) and resultant real-world evidence (RWE). Today, there are gaps between approved uses for medical products and how health systems and providers use these products for treating patients. Additionally, the increasing costs and resources needed to design and conduct clinical trials are a key challenge for getting new products approved. RWD provides opportunities to both make clinical trials more efficient to implement, and also potentially serve as a data source to generate a broader range of evidence and insights into a patient's functioning compared to traditional trials.

Key regulatory considerations for utilizing RWE as part of a medical product submission were discussed in the context of FDA's ongoing efforts to explore the utility of RWD. There are important regulatory questions that must be addressed for appropriate regulatory review of these data sources and study designs, which must have the sufficient scientific rigor needed to make a regulatory decision. For example, when looking at treatment exposures and outcomes, it may be important to understand the correct sequencing of treatment administration. There could be numerous variables needed to understand this context, including medication order, administration, and confirmation of administration. Study methodologists and standards implementers need to ensure these variables are completely and consistently represented in SDTM datasets, using SUPPQUAL if necessary, with corresponding inclusion in ADaM.

There was general agreement that existing CDISC standards would be crucial to support regulatory submissions to FDA, but additional standards development may also be needed. While CDISC standards are tuned for the regulatory submission use case, they may not be able to fully accommodate the diversity of real-world data sources available as envisioned under the FDA's regulatory framework for RWE.[5] Additionally, there is complexity with the growing number of data environments being used and common data models (CDM) for structuring and describing data (e.g., Sentinel Initiative CDM, Observational Health Data Sciences and Informatics (OHDSI) CDM, National Patient-Centered Clinical Research Network (PCORnet) CDM, and proprietary data models). The Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR) standard was discussed as a potential approach that could serve as an intermediary step to accommodate these different data structures and transform them into CDISC data structures used for submissions.

Ultimately, solutions will require finding ways to collaborate with the stakeholder community – industry, health systems and providers, payers, patients, etc. – around both collection and analysis of RWD. More education and awareness of RWD mapping initiatives was identified as a critical step towards improving

[5] U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. 2018. Accessed on Oct. 9, 2019 at: https://www.fda.gov/media/120060/download

consistency and reducing variation. Minimizing the number of data elements needed for mapping could also help reduce variation combined with hybrid approaches for data collection. This would involve combining retrospective data from sources such as electronic health records and claims databases with prospective data potentially collected by a registry to ensure the necessary context is available in the submission. As with clinical trial data, opportunities to automate data mapping and certain study data collection processes combined with quality by design principles where human judgement is still needed.

Conclusions and Next Steps to Advance the Development and Implementation of Analysis Data Standards

This conference sought to review current experience with foundational standards STDM and ADaM and identify any challenges that prevent the consistent use of ADS, which impacts FDA's review of evidence submissions. Key takeaways from the conference include the need for greater harmonization, communication, and innovation to reduce sources of variation and improve consistency across stakeholders submitting applications to the FDA.

Harmonization is needed between ADS user requirements and implementation guides, between regulatory agencies, sponsors, researchers, and funders of medical product research and development to improve efficiency and quality of regulatory review. More communication and partnerships are needed to not only support alignment of requirements across stakeholders, but also collaboratively identify challenges, build shared solutions, and disseminate best practices. The stakeholder community should also continue supporting opportunities for innovation with data standards and tools such as data visualization and machine learning to improve efficiency of analysis and reduce costs. This applies not only to traditional clinical trial data, but also standards for emerging data sources such as RWD and RWE. Table 1 below overviews each theme of challenge areas and opportunities to improve the efficiency of standards implementation for the Agency to consider as part of their strategic thinking and continued planning to develop or revise relevant guidance associated with submissions and promote use of standardized datasets for regulatory review as part of the PDUFA VI agreement.

Table. 1 Challenge Areas, Key Gaps, Solutions and Next Steps for ADS Implementation.

Challenge Category	Gaps	Potential Solutions or Next Steps
Harmonization	Misalignment or inconsistencies of ADS user requirements: 1) Between regulatory submission requirements and standards implementation guides, 2) Across regulatory agencies (global regulatory bodies, across FDA centers, and within review divisions) 3) Implementation practices that vary across industry sponsors, and 4) Within academic research, including non-industry funders of medical product research and development.	Harmonization of workgroups across the stakeholder community to align submission requirements with data standards specifications (e.g., data structure, format, variable domains), and drive consensus on common approaches for ADS implementation.
	The flexibility in data structures used by foundational standards resulting in increased complexity of submissions that reduces the efficiency of regulatory review.	Reducing variability in dataset structure for analysis datasets. Potential opportunities include: 1) Identifying required variables and terminology by therapeutic area, 2) Stakeholder engagement with clinicians and data collectors to improve and standardize outcome definitions, 3) Supporting use of CDASH to improve and standardize data collection and mapping into SDTM and ADaM, and 4) Develop a more standardized approach for use of SUPPQUAL domains
Communication	Collaboratively identify challenges, build shared solutions, and disseminate best practices.	More opportunities and forums to support dialogue and engagement throughout the standards development process. Opportunities include: 1) "Postmortem" review audits between FDA and sponsors, 2) Use of "real-time reviews" that have been adopted for new drug applications in oncology, and 3) CDISC-based trainings, tools, and knowledge bases to support particularly non-industry groups in academic settings or non-profits that have larger barriers to standards adoption and implementation.
Innovation	Inconsistencies with data transformations and mappings into and across foundational standards.	New technologies such as data visualization tools and machine learning techniques could be pursued to improve efficiency of analysis. These technologies could automate data mapping processes to reduce potential human judgement error. These technologies could also support more transparent and streamlined regulatory reviews by providing new tools to evaluate data quality.
	Foundational standards are tuned for traditional clinical trials and may not be able to accommodate increasingly diverse sources of real-world data the Agency is exploring as a complementary data source for fit-for-purpose datasets.	Identify opportunities to leverage foundational standards, potentially through updates or extensions, for integration of real-world data along with exploring new data models and standards that could further complement existing standards where gaps might exist.