PINNACLE 21

White Paper Series

Preparing a Study Data Standardization Plan for an End-of-Phase 2 Meeting

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Executive Summary

In December 2014, the Food and Drug Administration issued a final guidance titled, "*Providing Regulatory Submissions in Electronic Format — Standardized Study Data Guidance for Industry*". This guidance implements the electronic submission guidance for study data in New Drug Applications (NDAs), Biologic License Applications (BLAs), Abbreviated New Drug Applications (ANDAs) and Investigational New Drug Applications (INDs) being submitted to both the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). It specifies that study data must be submitted in a format that the agency can process, review, and archive. The guidance references the Data Standards Catalog, which lists all of the supported and/or required standards the agency can accept for clinical study data.

All clinical studies with a start date 24 months after the guidance publication date must use the appropriate FDA-supported standards, formats, and terminologies specified in the Catalog.

The FDA Study Data Technical Conformance Guide requests sponsors submit a Study Data Standardization Plan (SDSP) as part of the IND application. Recent industry dialog suggested this would be expected at the End-of-Phase 2 (EOP2) milestone, but the Study Data Technical Conformance Guide requests it sooner. This paper will discuss the changes being driven by the legislation, relevant clinical data standards and how industry timing and practices will be changing as a result.

Details of the Guidance

The binding guidance, "*Providing Regulatory Submissions in Electronic Format — Standardized Study Data Guidance for Industry*", requires all studies starting (first subject enrollment) on/after December 17, 2016 to utilize the most recent FDA acknowledged version of the "standards" available. Waivers will be considered for the standards version, but not whether to use the standards.

> "In theory, theory and practice are the same. In practice, they are not."
> -Anonymous

In theory this sounds rather straightforward. Sponsors can access the Data Standards Catalog to identify the most current versions of standards at study start-up and they can then implement

those standards and disclose them in the SDSP. In practice, however, it is not anywhere near straightforward. Identifying the standards used for a study is complicated because sponsors cannot simply identify the versions for the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and SDTM Implementation Guide for Human Clinical Trials (SDTMIG). They must also identify numerous other standards (e.g., CDISC Analysis Data Model (ADaM), Controlled Terminology (CT) sets, Documentation (Define-XML), validation rule sets, FDA Study Data Technical Conformance Guide.

The guidance also suggests that sponsors use established meetings such as the pre-IND meeting or the EOP2 meeting to bring up any data standardization questions or issues as early as possible. It references the Study Data Technical Conformance Guide, which provides nonbinding specifications, recommendations and general considerations to consider when submitting nonclinical and clinical data. Finally, the guidance encourages sponsors and applicants to reach out to the agency, consider a pre-submission technical review with sample data and continue open dialog as the data strategy evolves.

The Study Data Standardization Plan

The SDSP is an important document that was traditionally compiled as part of submission preparation activities for a New Drug Application, usually shared as part of the pre-NDA and pre-BLA briefing packages. The requirement to begin developing the SDSP at the IND, and present the SDSP at the EOP2 meeting with the agency is forcing sponsors to identify and evaluate its contents earlier in the process, and should give FDA ample opportunity to comment on the standards used with sufficient time for sponsors to improve the package reviewability.

At a high level, the document consists of basic introductory information about the plan, the sponsor and the product, a list of nonclinical and clinical studies and associated standards, documentation of non-conformance to support standards justification, documentation of any FDA standards discussions, and references. The Pharmaceutical Users Software Exchange (PhUSE) has already developed a template for this document. PhUSE works closely with agency and industry participants to develop use cases and documentation supporting the standards that are developed through CDISC and have made other submission documentation templates for the Study Data Reviewer's Guide and Analysis Data Reviewer's Guide publicly available. The template provides a solid starting point for the SDSP, but sponsors will need to

modify it considerably in order to provide the reviewer with a complete inventory of the standards used and the myriad components of those standards.

The requirement to begin developing the SDSP at the IND and present it at the EOP2 meeting also represents an opportunity for sponsors to consider their approach to data standards earlier in the process. The SDSP is a living document that should continue to be updated as the product moves through various phases of development. Evaluation of data standards versions and whether they require updates to current versions is a complex discussion that requires input from Regulatory, Biostatics and Project Management leadership because it impacts the Regulatory strategy. It may be beneficial to the sponsor or the agency to reassess chosen standards versions to facilitate Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) review, but it will have time and cost implications. At a minimum sponsors should run the most current validation rule sets against all data, regardless of how long ago the Clinical Study Report (CSR) was prepared, since the FDA will assess standards compliance and data quality using the most recently available validation rule sets at the time of submission.

Relevant Standards, Implementation Guides and Influencing Initiatives

There are numerous standards that sponsors need to address in the SDSP in detail. In addition, there are many companion standards that should also be included and each brings with it another layer of complexity. Sponsors will want to, and may be required to depending on interpretation of the binding guidance, identify the version(s) of the SDTM, the SDTMIG, the CDISC Analysis Data Model (ADaM), Controlled Terminology (CT) sets used, the Documentation (Define-XML), the validation rule sets initially and subsequently used, and the FDA Study Data Technical Conformance Guide.

Further complicating the version identifications are the relationship of the standards to the FDA Study Data Technical Conformance Guide, the relationships between standards (and their associated user guides), and the myriad components that are not fully described in those standards.

Study Data Tabulation Model and Study Data Tabulation Model Implementation Guide

The SDTM and SDTMIG are versioned separately and any data standard version discussion should reference both independently. It is not as simple as referring to SDTM 1.4. The current correct reflection is SDTM 1.4, SDTMIG 3.2. But adding considerable complexity are the

associated documents (e.g., Associated Persons, Pharmacogenomics, Therapeutic Area User Guides (TAUGs)), as well as CDISC's plan to decouple the one-to-one relationship between an SDTM version and an SDTMIG version, and CDISC's plan to manage versions of some components of the SDTMIG at a more granular level (e.g., standard Domains at the Domain level instead of the SDTMIG level).

Associated Documents - Associated Persons and Pharmacogenomics

Associated persons are anyone who you are collecting information on who is not enrolled in the study. These individuals are somehow associated with the subject in a clinical trial (e.g., a child of a mother in a trial, an unborn child of a pregnant woman in a trial, site personnel that may be exposed to the study treatments(s) inadvertently while administering those treatments). The standards for associated persons have developed on a separate path from the SDTM/SDTMIG with their own version numbers.

A set of standards has also emerged for Pharmacogenomics, the study of how a subject's genes affect their response to drugs. The Pharmacogenomics standards are identified by their own versions and are separate from the SDTM/SDTMIG.

Both of these standards are seen as companion standards to the SDTM/SDTMIG. They also both span therapeutic areas. As the sponsor implements these standards, the proper versions of each should be documented in the SDSP.

Therapeutic Area User Guides

The TAUGs are provisional user guides that are being developed under The Coalition for Accelerating Standards and Therapies (CFAST). The TAUGs contain basic material about the disease being studied, the processes required to collect specialized data and guidance on representing that data compliant with multiple standards (e.g., SDTM/SDTMIG, ADaM). They act as a mechanism for sponsors to leverage CDISC standards and help to extend their use in targeted therapeutic areas. CFAST is a collaborative effort among TransCelerate Biopharma, Inc., National Cancer Institute, Critical Path Initiative, FDA, Association of Clinical Research Organizations, Innovative Medicines Initiative, and the National Institute of Health. CFAST activities are governed by the Therapeutic Area Standards Program Steering Committee (TAPSC). Currently, there are over 50 TAUGs published or in development. The increasing number of TAUGs illustrates the need to apply standards in a meaningful way within specific

therapeutic areas. The variations across TAUGs illustrate the constantly expanding opportunities to extend the CDISC standards.

Adding complexity to the situation, within the SDTM, there are standard domains included in the SDTMIG. Standard domains are within the three general-observation-classes (interventions, events, and findings). Any general-observation-class domains used in TAUGs that are not published in an SDTMIG can be submitted as "custom domains". However, some of the current TAUGs propose new Special Purpose and Relationship domains and this has created a conundrum because SDTMIG rules do not allow for the creation of new Special Purpose or Relationship domains and they will fail validation rule sets. The FDA recognizes some TAUGs in their Technical Conformance Guide, but not all, and the Technical Conformance Guide is updated on a separate schedule from all the other relevant standards. Also, the Technical Conformance Guide includes non-binding recommendations, and does not explain how to handle anything new in the TAUGs that would cause validation rule sets to fail.

Adding even more complexity, there may also be new variables available in later versions of the SDTM (possibly added because of TAUG usage) that are not yet represented in an SDTMIG. New variables can be submitted as supplemental qualifiers, but for new special purpose or relationship domains, there is currently no accommodation until the domain is published in an SDTMIG. This further complicates the sponsor's ability to use TAUGs relative to the SDTMIG, and how to represent the appropriate versions of the standards used in the SDSP.

Considerations

The SDSP is a living document that captures the sponsor's data standardization strategy and rationale at a given point in time. It requires updates and modifications as that strategy evolves. The EOP2 meeting is an ideal milestone for the plan to take its final shape, but needs to begin development at the IND. It allows sponsors to be more specific than might have been possible earlier in the development lifecycle, and facilitates communication with regulators earlier in the process allowing sponsors and regulators to jointly plan for an efficient review. It is also a good time to weigh the pros and cons of aligning data standard versions with planned Phase 3 trials and beyond. This discussion is typically driven by two important questions: 1) what is the most cost effective approach to finalizing the supporting data for the ISS and ISE in the marketing application? and 2) what approach facilitates the most efficient review? If different versions of

standards were used that vary significantly in the modeling of key safety or efficacy data, and/or controlled terminologies, it may be cost effective to programmatically upgrade the data for the individual studies to the same data standard versions to support the ISS and/or ISE, which would likely also support reviewability by the regulatory agencies.

There are many factors to consider in this discussion and it is important to understand the implications of the decision for the marketing authorization and any subsequent near-term submissions such as the safety updates and annual reports. Sponsors should also consider any planned post-marketing studies and future supplementary submissions (sNDA or sBLA).

On a practical note, when creating your SDSP you may choose to use the Study Data Standardization Plan template published by the Pharmaceutical Users Software Exchange (PhUSE). It is important to note that this template is a great starting point. However, as described above there are myriad additional details that add nuance to the discussion and should be included as part of the plan. The template does not include this critical level of detail. A sponsor's customization of the template will ensure that essential details like the model versions, relevant implementation guide versions and provisional standards and implementation guides and their versions are documented and easily accessible to the reviewer.

Conclusion

Yogi Berra once said, "In theory there is no difference between theory and practice. In practice there is." As clinical trial sponsors shift their standards discussions earlier in the development process, there will continue to be points of contention and practical challenges that teams must navigate. These challenges and obstacles do not negate the value of implementing the standards, tracking and managing them and reporting them in the SDSP. The opportunity to do this at the EOP2 meeting gives sponsors a moment to take pause, and to adjust their strategy to improve regulatory review processes and future submissions. It may also motivate sponsors to have broader discussions about their clinical data standards programs and best practices for how they are being used across their organization. Over time, these discussions will lead to improvements that will impact both sponsor submission preparation processes and health authority regulatory review processes.