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Using a Waiver Process as a Change-Control Tool for ADaM Standards Governance

Karin LaPann, Shire, Lexington, MA, USA

ABSTRACT

Adoption of end-to-end standards is now a reality for most Pharmaceutical (Sponsor) Companies and Clinical Research Organizations (CROs). The Sponsor Company develops clearly defined preferences for versions of CDASHIG, SDTMIG and ADaMIG to be used for study work. The challenge is ensuring that study teams will adhere to these standards. They need to understand when and how to implement standards over the lifecycle of a clinical program. Our Governance team has developed detailed templates and work instructions around ADaM dataset specifications in order to enforce the Sponsor interpretations of CDISC standards. A "Waiver Process" is available when the study team needs to follow previous standards or add non-standard fields, or other unusual data collection items occur in a study. The governance team reviews each instance when the Study team proposes to follow legacy standards, previous versions of sponsor standards or add non-standard fields. Given strong rationale for the departure from existing standards, usually a waiver will be granted. Periodic review of the waivers helps to determine if adjustments need to be made to existing standards. In this paper we describe the steps to ensure compliance, and tools developed to check that the standards are being followed for ADaM.

INTRODUCTION

The CDISC standards are at a mature place, with end to end implementations available. The CDISC metadata is available to all members, first in printed form and also in electronic metadata form through the SHARE initiative. However, even with all this information it remains a challenge to ensure that study teams are motivated to follow the latest available standards for their study work. It is therefore tasked to Sponsors to put in place tools to ensure compliance internally. The rewards of this effort are smooth and timely submissions and getting drugs to market.

Over the past 18+ years, the CDISC data standards initiative has taken hold and widely adopted by Pharmaceutical companies (Sponsors) and by regulatory agencies. These CDISC standards have been developed by hundreds of volunteers working in the drug-development industry, to allow collaboration and ease the submission process. The FDA has also embraced the standards development effort and sends volunteers to the teams as well. Other groups have added to the wealth of documentation and thought pool, through groups such as PhUSE (European computational sciences user group) creating a strong network of buy-in for Sponsor companies. Finding great value in the use of the standards, The FDA has made electronic data submissions to CDER required as of Dec. 17, 2016 and for CBER Dec.17 2017 [2]. Dates for the individual standards requirements are available in the FDA Data Standards Catalog [2], which is updated at least bi-annually. Studies starting after Dec. 17, 2016 must use these standards, according to the FDA website [3]. The European Medical Association (EMA) also accepts these standards. They are not yet required in Europe as there are different submission requirements; however there is avid interest and active membership of European countries in both CDISC and PhUSE organizations. Japan is the newest addition to CDISC compliance, mandating data in CDISC format by April 1 2020. Documents are being translated into Japanese and the Japanese CDISC group is called the Japan CDISC Coordinating Committee (J3C).

Why are data standards important to all these different regulatory agencies and Sponsor companies? First and foremost, researchers in the industry have an altruistic wish to share data and results for the common human good. This motivation is tempered by the reality that Pharmaceuticals are in the business of drug development in a highly competitive world. The thought leaders have found common ground in establishing data standards across the industry as a first step. Regulatory agencies find that reviewing these data in common formats greatly enhances and speeds up the review process. Following standards for Sponsor companies leads to business efficiency across entire clinical development life cycle, enables automation, reduces cycle time, ensures information consistency, facilitates knowledge sharing and generates cost savings.

The FDA has been involved in the CDISC standards development since their inception as one of the 10 original sponsors. At that time, the FDA was not able to be members as there was not the right structure to join. Eventually in the late 1990's they were able to join as part of c-path (Critical Path Institute). The FDA began acting as reviewers for the various deliverables. They initially entered into collaboration with the DIA in a Computational Sciences Symposium (CSS). When that did not lead to the expected outputs, they searched around and found PhUSE. In 2012 PhUSE held its first FDA/PhUSE Annual Computational Sciences Symposium with FDA collaboration, and many new working groups were formed. At around the same time, the FDA created the CDER Computational

Science Center to handle data standards, and to develop tools to assist in review. In 2013 this became the Office of the Computational Sciences. This office is a super-office as it includes other departments such as Pharmacology and Computational Sciences. [4]

CURRENT SITUATION

Our company has been an early adopter of standards (over 9 years). As such, we are ahead of the curve as there is a culture and expectation for following CDISC standards, preferably end-to-end. This means adoption of collection standards (CDASH) and transformation to submission-ready SDTM, which are then used to develop analysis datasets (ADaM) and standardized tables, listings and figures (TFL). Of the four standards, only TFLs are not based on CDISC. However they have a close relationship with ADaM and are annotated with expected ADaM variables. Figure 1 below shows end-to-end standards. The Protocol is in white as the CDISC Protocol Representation Model (PRM) is in the process of being developed, ensuring that it contains the necessary/appropriate control terminology. At Shire, the template has been updated to contain as much information as possible, necessary to populate the Trial Summary (TS) domain; an FDA requirement for SDTM.

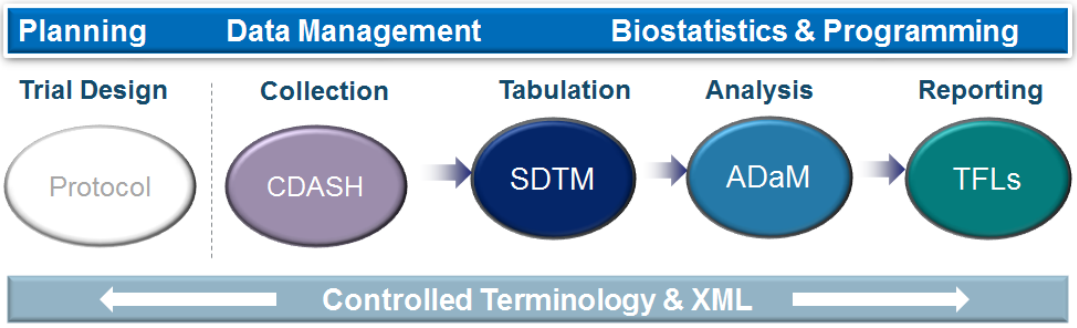

Fig. 1 End to End standards

Although the documentation on the CDISC website for these standards is very detailed, there is still some grey area which allows room for interpretation. It is this grey area that requires interpretation and guidance for our study teams. In addition, specialty drugs require variations of these standards, which may occur in the form of additional variables, detailed criteria flags, and more custom datasets for analysis. The early adoption of standards also enables us to efficiently take on new drugs whether developed in-house or through acquisitions. We have clear expectations of our CRO partners and other vendors, and hold everyone to the same high standard and quality of data.

The standards are delivered to the study teams via a SharePoint site. The site is maintained by the Standards Teams. Major updates occur annually for all standards, while minor additions may occur throughout the year. The major updates are closely coordinated between the standards. They also incorporate any individual updates such as new CDASH forms, additional SDTM domains and ADaM dataset specifications, more table mocks, or Control Terminology. Therefore the annual updates allow for a polished product. Training and notification around releases is also provided.

WHAT IS A WAIVER

A waiver is generally a way to track situations where a team wishes to not follow the recommended business rules or standard. The term is borrowed from the FDA which also requires 'waivers' for submissions that are not as expected. It is a way to track what are the standards being followed by each program, and as a deterrent for the study teams to disregard standards. This situation might be due to a tight timeline, an acquired study, or a long-going study that did not initially follow these standards. The ADAMIG 1.0 has been available since 2009, but there are always situations where a team may have inherited a study which was not up to the standards requirements. In this paper I concentrate on the ADaM standards although these waivers are applicable to all the standards end to end as shown in the next section.

Below is a sample waiver form. Filing a waiver to the Standards board only occurs after exhausting all other options, including a conversation with the Standards Team Subject Matter Experts (SMEs). In our case we have a dedicated team, although other companies might have SMEs spread around in programming, data management or regulatory. The conversation is initiated with a query to the standards team. This might take the shape of a question posed to our internal standards website, an email or call from a colleague in programming, or questions generated by the various training events which the standards team holds for programmers, data managers and clinical programs. In the form, all the end-to-end standards are listed. This is for internal use of the Standards Team, as we assess which standard requires the waiver and whether there is upstream or downstream effect to other standards.

Standards LT Assessment	Recommendataions/Rationale from Standards LT.
CDASH	☐
SDTM	☐
ADaM	☐
TFL	☐
CT	☐
Standards Decision Date	Date at which Standards has made a decision to either reject or submit to the board.

Fig. 1 Sample Waiver form

QUESTIONS TO THE STANDARDS TEAM

As discussed previously the process begins with questions to the Standards team. This starts a conversation with standards SME and the study team, with suggestions provided for resolution. Of all the questions posed to the Standards team only around 5% actually results in waivers. Below are some charts showing question activity for each standard.

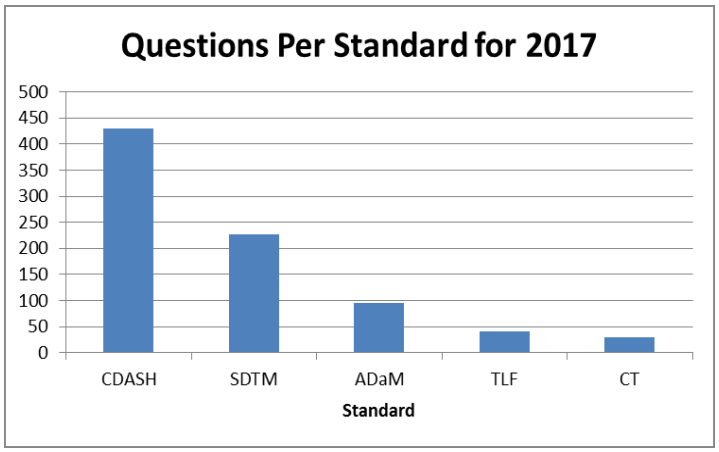

Fig.2 Number of questions to the standards team by standard

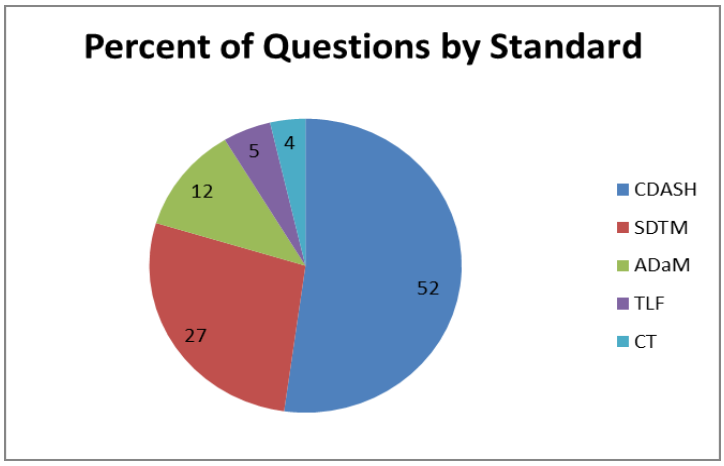

Fig. 3 Percent of questions attributed to each standard

Note that the CDASH team has the most questions (52%), as they are in the forefront of the study. Often CDASH questions are also answered by the SDTM team as they need to assess how changing a standard form would affect them. There are fewer SDTM questions (27%), but SDTM and Controlled Terminology (CT) questions answered during the study build utilizing CDASH are not captured separately.

ADaM standards questions (12%) are at a lower rate. TLF standards and CT follow at 5% and 4% respectively. We anticipate a growth in questions and waivers for ADaM and TLFs as the teams move away from legacy standards studies and the CBER and CDER requirements to follow standards for studies starting December 2016 kick in. Also more questions will be forthcoming as studies transition from ADaMIG 1.0 to ADaMIG 1.1, and the PMDA (in January 2020) adopt the CDISC standards as well. For ADaM, additional changes will be the upcoming release of the new CDISC ADaM Compliance Check v 1.1-R0 (currently under internal review), and the upcoming release of the ADaMIG v1.2, which was out for public review and hopefully will be released Q4 2018.

TOOLS TO CHECK FOR STANDARDS COMPLIANCE

Each standard has its own tools to check for compliance. In the case of CRO oversight by a sponsor, this becomes even more important. We have use cases in the instructions documentation to indicate when a waiver might be needed. Below is a sample of three use cases for ADaM.

Dataset Type	ADaM Business Rule	Use case	ADaM Question Tracker (Y/N)	Waiver Needed (Y/N)	Discussion / Rationale
All ADaM	Sponsor will indicate the minimum requirements for the ADaM-Compliant Datasets (ADaMIG v1.1)	The team wants to exclude a Sponsor-Required Variable.	Y	Y	The Sponsor-required variables are mostly also required by the ADaMIG v1.1, and are indicated by Sponsor Required = 'Yes'. Sponsor-required variables will be mandatory unless the study design clearly does not or cannot support them.
All ADaM	Use of SDTM variables in ADaM datasets must maintain traceability.	Can the team change the name, label or format of an SDTM variable?	N	N	Any variable coming from SDTM **must** be a copy of the SDTM variable, including label, meaning and value. If a change is requested then Sponsor will comment to create a new variable.
All BDS	All ADAM for Sponsor Standards are based on the ADaMIG v1.1.	The team wants to add variables from the ADAMIG 1.1 not in the Sponsor standards.	Y	N	Yes, any variables listed in the ADAMIG 1.1 and accompanying documents listed on page 5 of the ADAMIG 1.1 can be added without a waiver. Please do enter into the question tracker so we can add to the Toolkit in the future.

The first use case shows an example of a situation where the teams must discuss with the Standards team and possibly file a waiver. In the case of a sponsor-required variable that is not also an ADaMIG required variable, the waiver will be granted. The second use case enforces an important traceability rule from SDTM to ADaM which is being highlighted here as a training opportunity. The situation is not allowed and no waiver is required. The third use case describes where teams wish to add variables that are in published standards, and possibly not part of our ADaM template. In this case we wish to track in the question tracker to enable for future updates to the ADaM Tool.

Additional use cases include scenarios where teams do not wish to follow BDS structure, and might request an ADaM Other. Or they want to digress from an existing recommended dataset, such as sub-dividing the lab dataset for specialized labs. Or they might have questions how to create a custom analysis dataset for efficacy endpoints.

Some additional tools used to ensure compliance are programs that compare the Study team's specifications metadata to Shire's approved metadata. These can be run by the internal study teams or CRO's as needed to prove compliance. The checks are different than those provided by packages such as Pinnacle 21 Community, as they concentrate only on metadata. The intent is to approve the specifications before any programming takes place in order to limit rework at the programming step, thus increasing efficiency.

WAIVER GOVERNANCE PROCESS

The waiver governance process begins with the questions and answer period between the standards and study teams. For CDASH, these conversations mostly involve the data managers. For SDTM data managers may also be involved but primarily the responsibility to follow the standards falls on the team lead in programming and/or biostatistics. For ADaM all the questions also come from programming and biostatistics. The questions are tracked and answered as they come in. This enables the teams to keep a running log of issues and recommendations, much like a 'lessons learned' or 'frequently asked questions' list. If after discussion the teams find that they still wish to follow a legacy standard or even no standard, then they must file a waiver.

The Standards team members discuss the waiver and determine which standards would be impacted by the decision. At this point, the Standards team can either reject the waiver (if a waiver is not needed in this situation) or pass it on to the next step. The waiver then goes to the leadership team which we call the Standards Governance Board. The board is responsible for overseeing the development and adoption of our Clinical Standards throughout our Clinical Development enterprise. It is comprised of 6 cross-functional individuals, so that they can assess the waiver from multiple disciplines. They are provided with a recommendation from the Standards SME and sometimes even a presentation with a recommendation. The entire effort is supported by executive sponsorship from the top.

The waiver must be reviewed and decided upon in a timely manner. The clock starts when an SME accepts the waiver and provides a recommendation. It then needs to go to the board within 5 business days. The board votes and the decisions are considered final.

CONCLUSION

In summary, the waiver process is an important tool to implement compliance to the CDISC standards at a Sponsor company. There must be buy-in from the executive leadership, and a process to allow a study team to digress from a standard in a controlled manner. It is important to have a questions component so that the study teams engage in conversations with the Standards SMEs at their company. The questions should be tracked and answered in a formal manner so that it becomes a reference document for frequently asked questions and lessons learnt for other teams. Issues should be addressed early, and resolved before a waiver event even takes place. An actual waiver is the last resort after all options have been explored. It is intended to start the conversation between Standards and study teams. Once it is shown that there is good justification for a study team to continue using a previous or legacy standard, the waiver provides clear documentation for the decision. This process can be tailored to any organization.

REFERENCES

[1] Submissions in Electronic Format – Standardized Study Data, Guidance for Industry, December 2014 electronic submissions
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf
[2] FDA Data Standards Catalog https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[3]https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm
[4] Stephen Wilson, DrPH, CAPT USPHS (retired), Director FDA/CDER/OTS/OB/DBIII

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RECOMMENDED READING

Analysis Data Model Implementation Guide Version 1.1, February, 2016
Analysis Data Model (ADaM) v2.1, December 2009
The ADaM Basic Data Structure for Time-to-Event Analyses v1.0, May 2012.
ADaM Structure for Occurrence Data (OCCDS) v1.0, February, 2016

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Karin LaPann
Shire HGT
300 Shire Way, Lexington, MA USA
Work Phone: 1-781-266-3968
Karin.lapann@shire.com