CDISC Standards End-to-End: Transitional Hurdles

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ABSTRACT

"Plus", "-like", "-ish" – We have all heard it in some variation: SDTM…plus, ADaM…ish, CDISC…like. It is evident there are still some things preventing us from accepting pure CDISC. Many companies find the transition to CDISC difficult for a variety of reasons. They enjoy a "CDISC+" philosophy and believe it is "compliant enough" to work. The types of changes to the standards might be adding or ignoring controlled terminology, changing the definitions of CDISC specific variables, adding non-CDISC compliant variables, and only using CDISC standards for some datasets in a study, but not for all datasets. This presentation discusses common challenges encountered while a company transitions onto CDISC. The pitfalls of the "CDISC+" design will be discussed in depth. Conversely, the pros of what having a fully CDISC – and CDASH – compliant database will also be covered. By using CDISC from end-to-end, meaning from Protocol and CRFs through TLGs, many efficiencies can be gained for project team members at every level. Finally, once a decision for compliance has been made, how can pharmaceutical companies effectively learn CDISC standards so that they feel comfortable using, reviewing, and understanding CDISC compliant studies? The different options available for training through CDISC along with examples of teaching methods which have a positive impact on user knowledge will be presented.

INTRODUCTION

CDISC standards have been around for a number of years. There are CDISC standards now from protocol through analysis data. To name a few we have: Protocol Representation Model (PRM), Clinical Data Acquisition Standards Harmonization (CDASH), Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM). As new versions are released, they are expanded to cover additional concepts, therapeutic areas and agency requirements. Therapeutic area user guides have been created for some areas and are planned and in progress to grow this library for other areas. Compliance rules have been developed and compliance checkers have come into the picture. The FDA and other agencies have shown their support for CDISC standards. With all of this progress and support, it appears CDISC standards are going to stick around for a while. However, there is still some reluctance to fully embrace them.

Many companies have taken a stepwise approach to implementation.

Step 1 – SDTM:

Due in part to both the length of time that SDTM has been around as well as the well-defined rigidity of the structures, SDTM seems to be the most widely used and easier to transition of the standards.

Steps 2 and 3: CDASH and ADaM:

Feeding out in both directions from SDTM comes the implementation of the next likely steps of CDASH (prior) and ADaM (following).

But even taking it one step at a time, compliance to that particular standard is not achieved and the end result is some hybrid that is not quite standard: SDTM-plus, ADaM-like. The intent to use CDISC is there, just not yet the ability or maybe knowledge to commit to 100% compliance. As we move from agency acceptance of the standards to agency requirement, we need to take a closer look at these transitional hurdles. Step one on the path is deciding to run the race and embrace CDISC. But what are these hurdles, why should you do this, how will you be rewarded, and how do you put together a training regimen that allows you and your organization to most effectively gain the knowledge and experience to get over them?

CDISC STANDARDS IN USE

Though CDISC standards run from protocol through analysis, let us target hurdles with SDTM and ADaM first. We now have SDTM Model through version 1.4 and SDTM Implementation Guide (IG) version 3.2 with FDA acceptance as well as SDTM IG v3.1.2, v3.1.2 + Amendment 1, and v3.1.3 as shown in Table 1. In addition to below,

implementation guides are available on topics of Medical Devices and Associated Persons.

SDTM Version	SDTM IG Version
1.4	3.2
1.3	3.1.3
1.2	Version 3.1.2 Amendment 1
1.2	3.1.2

Table 1. SDTM versions listed in the FDA Data Standards Catalog

ADaM v2.1 with ADaM IG 1.0 has FDA acceptance as noted in Table 2. Additionally, ADaM structures for Adverse Events Analysis, Time to Event, and Occurrence Data are available and ADaM IG 1.1 has recently been released.

ADaM Version	ADaM IG Version
2.1	1.0

Table 2. ADaM version listed in the FDA Data Standards Catalog

VARIATIONS OF THE STANDARDS

It is not unheard of to be a little apprehensive about taking the leap to CDISC. Those model documents and implementation guides are quite long and packed with all sorts of nuggets of information. Aside from intimidation, you may have something you like to use and might be resistant to changing what works currently. You may:

- Think it is more convenient to store supplemental data in the same datasets as the related values

- Have existing utilities which do not use the standards

- Not believe current ADaM standards are sufficient for the study needs

- Prefer horizontal datasets for ease of analysis rather than vertical datasets

- Not understand purpose of standard structure

Some of the more common hurdles observed are around Supplemental Qualifiers, nonstandard fields, controlled terminology usage, and analysis hybrid structures.

HURDLE 1: AVERSION TO SUPPLEMENTAL QUALIFIERS (SUPPS)

There are a few flavors of changes to the standard that have been observed around SUPPs. These can come up for a number of reasons. It may be that the goal is to create a warehouse with standalone domains that do not require merging to supplemental qualifiers or concern for the end users ability to understand and attach supplemental qualifiers back to the parent domain. The elimination of SUPPs may result in the forcing of values into non-ideal fields or domains. This could be problematic as there may not be a logical link to the location of the additional value if placed in another domain or if non-ideal fields are used, the meaning of the information may become unclear. Adding non-standard variables to the parent domain to hold the values is another way that eliminating SUPPs is sometimes handled. This is not only a problem because it breaks compliance, but also that the end result is a structure that is no longer standardized.

HURDLE 2: EXPANSION OF SDTM STRUCTURE WITH ADDITIONAL FIELDS

For various reasons, at times the SDTM structures might be expanded to contain additional fields. This might be done with the goal of eliminating the SUPPs as discussed previously, keeping system or other values which may not be necessary in the SDTM, or adding analysis variables to SDTM instead of creating ADaM. This addition of analysis variables to SDTM or the "SDTM-plus" approach is sometimes considered in the stepwise process to CDISC usage. In this approach, variables needed for analysis such as a treatment emergent flag may be added directly to the SDTM on top of what started as a compliant SDTM domain. This concept of a treatment emergent flag in SDTM is a debated topic in general. There is a convention for this to be placed in SUPPAE and at one point this flag was noted

in agency documentation and also appears now in compliance checkers, reminding us that this field should be created. However, this field is highly derived and it can be argued that SDTM is not the appropriate place for this type of field. Also, more recent agency documentation has not listed this as a requirement. This field, continues to be a hurdle, though for compliance sake, we can place it in SUPPAE instead of the parent AE domain.

HURDLE 3: CONTROLLED TERMINOLOGY

Some non-compliant uses of controlled terminology include extending non-extensible terminology lists or unnecessarily extending extensible lists. One example is creating company specific terminology that does not comply with CDISC CT. Another issue that may arise that is more common in legacy data is mapping to standardized values when CRFs are not CDASH compliant. This would include the infamous example of having an AE action taken with study drug of 'dose changed' recorded on the CRF which cannot map directly to values such as 'DOSE INCREASED' or 'DOSE REDUCED' in the non-extensible terminology list. Another common issue observed is the abuse of extensible terminology lists. There is sometimes an attitude that "extensible" means that variables that have values that are "messier" or less frequently used for analysis, such as dose frequencies in concomitant medication data do not need to be mapped wherever possible to the extensible frequency terminology list. If free text frequency values were not mapped to CT, we could end up with DAILY, ONCE PER DAY, EACH DAY, EVERY DAY, ONE TIME PER DAY, EACH MORNING, EACH EVENING, EVERY 24 HOURS, 1/DAY, 1XDAY and numerous other phrases that could simply be listed as "QD". The value list essentially becomes a free text field that is no longer standardized as xxFREQ is designed to be.

HURDLE 4: HYBRIDS FOR ANALYSIS

There may also be an attachment to non-ADaM Analysis. Some non-compliant changes observed in this case may be changing the purpose of standard ADaM variables, changing vertical vs horizontal structure, eliminating required and/or expected variables in the ADaM structure.

SOLUTIONS

It is important to note that in all of the mentioned potential hurdles and reasons why there might be hesitation to adopt compliant CDISC standards, there is a solution available. While it does require some change, training and effort, none of the mentioned issues are insurmountable. Here are some quick options.

- Since the SUPP structure is standard, it is a prime candidate for a standard program or utility to attach the SUPP back to the parent domain.

- Additional fields can be avoided with proper use of SUPPs, possibly RELREC and also the use of ADaM standards for analysis.

- Controlled terminology issues can be lessened by thinking about CDISC earlier on. Adopting CDASH principles can help to ease this type of concern by the time it reaches SDTM stage.

- And finally, the ADaM structures are somewhat flexible and have options to handle most situations through existing structures or, unlike SDTM, with added variables when needed and appropriate.

WHY USE CDISC?

Aside from agency support and upcoming requirements, there are other benefits to complying with CDISC standards. The rewards of using CDISC are extensive thanks to the important collaborative efforts made by industry leaders to improve the quality, efficiency and cost effectiveness of the clinical research process from the protocol through analysis and reporting. We are able to provide the FDA with values they expect and have requested in specific standard; to name a few, we can use SDTM to provide first and last dose dates, EPOCH, and study days in a clear and consistent way. SDTM also provides structures that allow all data points collected during the study to be maintained. Even if it does not fit in a standard SDTM variable, we have SUPP or other structures and can use RELREC for linking to another location. CDISC has also allowed for a more collaborative presence within the clinical trials community where individuals from a wide variety of companies have a voice in determining the structures developed. But secondary to the requirements, the biggest benefit in many eyes may be the potential efficiencies.

EFFICIENCIES!

Implementing standards correctly has many incentives for you, your employees, and your company. The first among these are that, in terms of utilizing CDISC structures, SDTM is the only stage through data displays which will have a varied input structure of source data. Even that can be expedited if CRFs follow CDASH standards! What this means is that if a standard SDTM implementation is used, efficiencies can be gained when moving into analysis datasets in ADaM with a standard structure. Moving forward, with a standard ADaM implementation, efficiencies can be gained in

the process of table, listing, and figure generation. There are great opportunities here for standard programs, automation, and utility development for at least basic safety displays.

With SDTM as a base, ADaM specifications can be started earlier in the process since the location of data in SDTM is known. CT is a helpful addition to this process since even the many specific variable values are known before SDTM datasets exist. Integrations without using CDISC can be lengthy, expensive, and quite a headache depending on the state of the data. However, when all involved studies are already CDISC compliant, you only need to update for consistent versions of SDTM, ADaM, CT, and dictionary versions. Many tools already exist, or can be easily created, to check the compliance and to ensure a high quality data standard when data is formatted consistently to CDISC standards. In this way, industry level experts in standards exist which eliminates the need to teach new employees a company-specific standard. Finally, after everything is submitted, the FDA reviewers are very familiar with SDTM and ADaM datasets. When standardized data is submitted, this accelerates the review process because the reviewer knows exactly where to go to find the information they need, getting your drug to the market faster!

TRAINING OPTIONS

Wonderful, you have decided it is time to transition to compliant CDISC! Now how do you get yourself and your organization up to par? There are numerous options out there for training. Depending on budget, staff skillsets, location and other factors, there is not one training regimen that will work for every group. However, there are many resources available such that each group can find the best combination for their needs. Some of those options include:

- CDISC training courses

- Online standards specific webinars

- CDISC applicable conferences

- Live group trainings

- Recorded/online trainings

- Small group trainings

- Mentorship

- Client/company specific CDISC introduction guides

- Self-study of the vast resources available at www.CDISC.org

Each training resource has its benefit and some best features. Each one will not be good for every level of base knowledge, learning type, size and interaction with groups to be trained. Table 3 Table 3. Benefits and considerations for CDISC training resources.

Training Resource	Best for:	Consideration:
CDISC training courses	• Learn from those developing the standards	• Time • Budget
Online standards specific webinars	• Introduction into a topic and an overview of what is available • Continuing education to keep on top of new things coming out	• Some pre-existing knowledge is a plus

Training Resource	Best for:	Consideration:
CDISC conferences	• View what others in the industry are doing • Emergence of new ideas	• Novice may not take all information • More for ideas than learning the standards
Live group trainings	• Larger groups • Core concepts	• Difficult to assess if everyone is understanding • Time for trainer and large group of trainees
Recorded/online trainings	• Consistent repeatable training • Core concepts • Large number of trainees	• Not able to assess understanding • Ability to ask questions real time
Small group trainings	• Ability to assess if individuals are understanding	• Time to train small groups
Mentorship	• Hands on learning • Continuous feedback	• Availability of a subject matter expert • Most effective for an individual or very small group • Time
Client/company specific CDISC introduction guides	• Company specific interpretation of the standards	• May not be compliant
Self-study of the vast resources available at www.CDISC.org	• Core concepts • Basis for next steps in training	• Theoretical learning only • Scenarios outside given examples • Questions

Table 3. Benefits and considerations for CDISC training resources.

As with anything new, you would not expect to be an expert after a short training session. Regardless of training method(s) selected repetition and usage are key. Practice, practice, practice! Only the rare individual would know every word and spirit of usage of a standard with one training session of a few hours. Learning, reinforcement, putting that standard to use in a real world environment, and keeping current with updates are steps that will make the goal of CDISC compliance achievable.

As you assess what is best for your group, some of the other factors that will impact best training plan will be budget, current and planned staff, and group structure. If budget is tight and group size is large, sending the whole department to conferences and trainings may not be the best option. However, sending a couple to learn first and using a train the trainer approach with these methods may fit. If the need is to bring a department of 50 up from zero previous CDISC knowledge with the use of one experienced CDISC leader, mentorship of one or two people at a time is going to take too long. However, if there is a group of 3 in need of training, the mentorship approach could be wonderfully effective. There is also a need to have balance in the training between theoretical learning and hands on

implementation to be most beneficial. The right combination of training procedures will be different for each group and situation, but there are numerous ways to customize that approach to be most successful.

CONCLUSION

If transitioning to CDISC were simple we would not have posters, papers, presentations and multiple conferences globally each year dedicated to the topic. The move to CDISC compliance comes with its share of challenges. What is important is to identify the applicable hurdles, identify what compliant conventions can be utilized to alleviate concerns and then choose how to train and build individual skillsets to apply the standards. With those challenges also comes the rewards of efficiencies gained. A bit of training and, at times, more than a little bit of creativity can result in the successful implementation of CDISC.

REFERENCES

FDA Data Standards Catalog v4.4
Available at: www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm340684.xlsx

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