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CDISC in Phase I/II Studies: Approaches to adopting standards for CSR deliverables

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ABSTRACT

Implementation of CDISC standards for CSR deliverables can be complex and costly for Phase I/II studies. The decisions of if and when to implement standards are based on a number of factors including breadth of the development program, potential partnerships, and unknown asset viability. We will discuss the ideal CDISC-compliant process flow – engineered from the final statistical deliverables backwards to the initial planning for data collection. Alternate approaches can be taken to balance time, scope, and effort depending on where in the process CDISC standards are adopted. Case studies illustrate considerations and strategies based on lessons learned from implementing CDISC compliance at different time points.

INTRODUCTION

The FDA Data Standards Catalog[1] requires standardized study data submitted to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for studies that started after December 17, 2016. The Clinical Data Interchange Standards Consortium[2] (CDISC) has developed standards to streamline clinical research from study design to data collection through analysis. Implementation of these standards can be costly and time consuming. This process requires careful consideration at each stage of the development process and a deep understanding of the standards themselves. Smaller, early phase drug development programs can be understandably concerned about the time and costs associated with implementing these standards from the beginning of a trial, especially if they are not yet confident in the efficacy or marketability of their drug or device, or if their main business goal is simply to sell their product to a larger company for further development. Unlike larger companies, they often do not yet have an established process flow from CRF design and raw data to TLFs and may not have the developed infrastructure of a larger pharmaceutical company available to support these activities in-house. Additionally, these smaller companies may not have in house experts regarding submission standards and rely solely on the expertise of a contract research organization (CRO). Thus, smaller drug development programs often must make more complex decisions regarding if and when to adopt CDISC standards.

The key components of CDISC foundational standards are:

- CDASH (Clinical Data Acquisition Standards Harmonization) – describes standards for data collection through eCRF design
- SDTM (Study Data Tabulation Model) – describes standards for organizing and formatting data
- ADaM (Analysis Data Model) – describes standards for creating analysis datasets focusing on traceability and efficient generation of summaries

CDISC collaborates with the National Cancer Institute's Enterprise Vocabulary Services (EVS) to define controlled terminology for data for the SDTM and ADaM foundational standards. The key component of CDISC data exchange standards is define.xml which displays the metadata that describes all SDTM and ADaM datasets.

The ideal CDISC implementation scenario is to first define the TLFs and then back-engineer the components through ADaM to SDTM to eCRF design. This process builds compliance from the eCRFs onward, ensures that all parameters necessary for the final analysis are included, and describes the key deliverables in detail. The CDISC ideal process flow and components will first be discussed. Reasons will then be presented as to why sponsors of Phase I/II trials may choose to implement standards at different time points within the drug development program. As a data management and biostatistics CRO, we have had the opportunity to craft several approaches to this process. Several case studies illustrate different

time points for adoption CDISC standards, the impact of these decisions, and how compliance can be supported with retrofits.

CDISC PROCESS FLOW

COMPONENTS

In order to discuss the impact of adopting CDISC standards at different points in the process of developing a clinical study report (CSR), it is important to understand what the deliverables are from the end product to the first supporting information.

Tables, Listings, and Figures

For the purpose of our discussion, the tables, listings, and figures (TLFs) comprise the “end” of the CDISC-compliant process. The TLFs support in-text summaries and appendices to the CSR. Using the pre-defined mock elements, TLFs are programmed to include the analyses specified in the statistical analysis plan (SAP) and content required by ICH E3 Guidance: Structure and Content of Clinical Study Reports.[3] Organization of the content within each element is influenced by the structure of the supporting ADaM dataset or, in the case of some listings, SDTM domain.

ADaM Datasets, define.xml, and ADRG

ADaM datasets are created from SDTM domains as described in the ADaM Implementation Guide (ADaMIG) to serve as analysis datasets and facilitate the production of TLFs. They serve two key purposes: 1) traceability of data points from SDTM to analysis data and results, and 2) facilitate efficient analyses in the TLFs. Documentation of traceability is accomplished with a set of variables in the ADaM domains themselves and with detailed derivations presented in the define.xml. The Analysis Dataset Reviewer’s Guide (ADRG) serves as a complete introduction and explanation of the ADaM datasets presented, discusses general analysis conventions, describes relationships between datasets, and documents conformance findings. When viewed together, the ADaM datasets, define.xml, and ADRG provide a complete picture of the data presented in the ADaM datasets.

SDTM Domains, define.xml, and SDRG

SDTM domains are created by reformatting and organizing raw clinical data by topic in a standard well-defined manner as described in the SDTM Implementation Guide (SDTMIG). Depending on the use of SDTM controlled terminology and CDASH standards for data collection, as well as the underlying database structure, the complexity of both specifying and programming SDTM can vary substantially between studies. SDTM generation should be used as an opportunity to think forward towards downstream TLF content and ADaM generation. For example, it should be carefully considered whether populating permissible variables (variables that can be added to the domain when appropriate as collected or derived) per the SDTMIG at this point may facilitate ADaM development. As with ADaM, a define.xml file is created to document data derivations from raw data to SDTM. The Clinical Study Data Reviewer’s Guide (SDRG) details the SDTM domains included in a package, lists supplemental qualifiers, and documents conformance findings.

Annotated Case Report Form

The searchable Annotated Case Report Form (aCRF) provides the raw dataset and variable names for each question included on the eCRF in one layer of annotations as captured within the EDC. A second layer of annotations is added for variables mapped directly from the eCRF to SDTM.

Raw Clinical Data

The raw clinical data are collected per the initial eCRF design which may use CRFs in a non-standardized format or CDASH collection standards, or a combination of both. The collection database is designed to reflect the structure and content of the CRF. Companies may choose to use non-standardized CRFs in order to generate data that are structured similarly to those collected in previous studies because it may be a savings in time and effort upfront. However, if SDTM is later required, non-standardized CRFs can

make the mapping much more difficult and sometimes impossible. In addition, if integrated analyses are performed in the future, the generation of SDTM will likely be required for all studies. Using CDASH collection standards and controlled terminology from the beginning might result in more work upfront, but may reduce the complexity of SDTM generation downstream and provide a time savings later.

CDISC IDEAL PROCESS FLOW

As discussed when detailing the components, decisions made for one item impact other items. Figure 1 shows the relationships between the deliverables and the functional groups often responsible for generating each item from the perspective of a CRO.

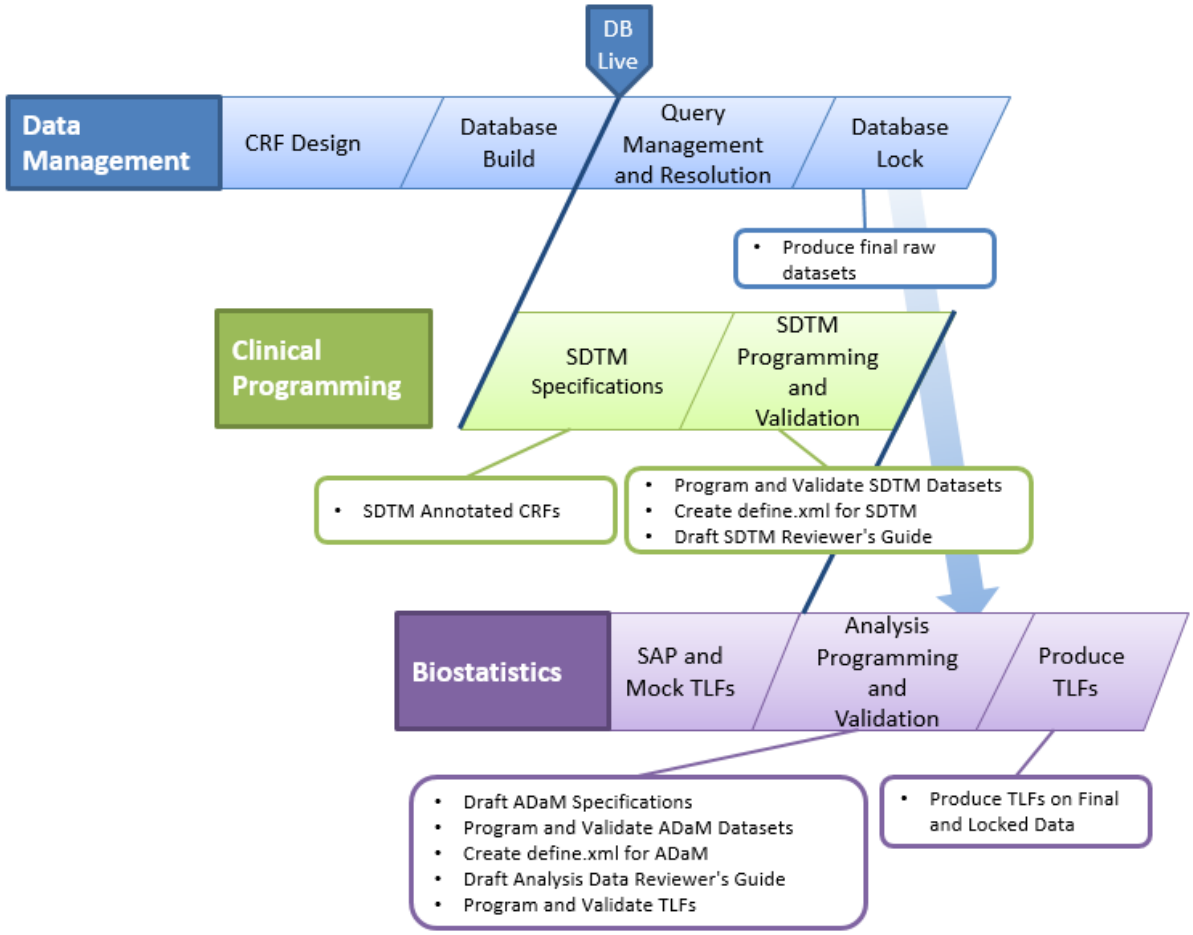

Figure 1. CDISC deliverable process flow

The process flow spans three functional groups: data management, clinical programming, and biostatistics. Close collaboration and communication between the three groups is essential for creating compliant deliverables and incorporating any deviations from a fully compliant process. Depending on resource flexibility and training, it can be beneficial to follow a model where the same programmer completes related SDTM, ADaM, and the associated TLFs to ensure consistency across these items.

NOT ADOPTING ALL STANDARDS FROM THE START

Having described the key deliverables for CDISC compliance and how those deliverables relate to one another, consequences of not adopting standards from the start can be evaluated. Given the relatedness of each step, a substantial amount of planning is required for smooth, seamless execution. Standards are

often implemented with an eye towards a submission. However, they should still be considered even when planning for Phase I or Phase II study. Considering the pros and cons of adopting or not adopting each step in the process should occur early on at the start to avoid substantial time-consuming retrofitting later on. Phase I and II trials are often smaller and more dynamic than their future Phase III counterparts. The situations below illustrate why a sponsor may not want to adopt CDISC from the start when conducting these studies.

BREADTH OF DEVELOPMENT PROGRAM

A sponsor that is smaller or has only a small, early-stage development program, may be looking to only collect a minimal amount of data. Thus, they may have little internal utility or funding for the production of standardized, fully-compliant SDTM data and data mapping files such as define.xml.

UNKNOWN ASSET VIABILITY

With a limited amount of study data to indicate efficacy, sponsors may be looking to economize wherever possible. In this case, a small set of analysis datasets to support TLFs can be a more economical option provided no retrofitting for CDISC is required. Often, sponsors complete one proof of concept study and then consider CDISC deliverables for future studies if the first study was efficacious. At that point, increased funding will likely be available to retrofit the first study as needed.

POTENTIAL PARTNERNSHIPS

Strategic position can be an important consideration for selecting CDISC compliant deliverables. If a number of small studies are to be conducted with simple endpoints, sponsors may choose to create SDTM data for each study to facilitate basic analysis and data pooling. Based on the results and future strategic partnerships, they can expand their requests for compliant ADaM data.

COMPATIBILITY WITH PRIOR PRECEDENT

If similar studies have been conducted using non-standardized eCRFs to support legacy analysis datasets, sponsors may want to continue in this manner to reduce turnaround time after database lock. Good planning limits the time necessary to run and validate SDTM after database lock, and adequate time must be budgeted given the importance of ensuring correct results.

CASE STUDIES

Having described key CDISC-compliant deliverables, usual standards work flow, and introduced reasons why a sponsor may want to deviate from this work flow, two case studies are presented here. These case studies illustrate the impact of adopting CDISC standards at different points in the workflow, how these decisions deviated from the ideal process, and the solutions for standards compliance.

CASE STUDY #1: CDISC FROM SDTM ONWARD

In this first scenario, the sponsor wanted to use legacy CRFs consistent with prior studies. The development program was initiated well before the FDA's requirement for submission of study data in standard formats. Paper CRFs were used for a study with a double-blind period and an open label extension phase. All data were collected in a single database. The CRFs were not designed with CDASH standards in mind and did not use SDTM controlled terminology. Additionally, the database format was not compatible with all of the SDTM structures. The development program increased in size over the course of several years. CDISC-compliant deliverables from SDTM onward were eventually requested by the client to support a submission.

Resulting Difficulties in SDTM

Example: Determining Visit Numbers and EPOCH

SDTM visit numbering conventions were not considered when building the study database. In the database, visit numbers were recycled from the double-blind period to the open label extension phase. For instance, visit number 0.2 was used for the baseline visit in the double-blind period and the baseline

visit in the open label extension phase. Additionally, all unscheduled visits were assigned visit number 99 regardless of the phase or how many unscheduled visits occurred per subject. Reusing forms in this manner was done to reduce client costs wherever possible at a time when the study was not intended for submission. In order to create SDTM suitable for submission, there needs to be a one to one mapping between visit and visit number. Thus, each unique visit requires a unique and meaningful name including multiple unscheduled visits.

There were two deviations from the ideal process in this example:

1. The CRFs were not set up to allow for multiple unscheduled visits per subject and to collect those visits in the order in which they happened. Visit number and page report variables were collected and could provide direction for a mapping, but they did not guarantee the correct calendar time sequence. With paper CRFs, there can be enormous delays in data entry which would have required constantly revisiting a mapping scheme where correct calendar time could not be guaranteed.
2. Separate CRFs were not used for the double-blind and open label phases to easily derive EPOCH.

In order to assign visits and corresponding visit numbers, all visits were wrangled in the Subject Visits (SV) domain by date. Unique visit names and visit numbers as well as EPOCH were assigned. The SV domain was then used in programming the findings domains to determine visit name, visit number, and EPOCH. Determining EPOCH for event domains required additional programming effort. For example, in the Adverse Events (AE) domain, we needed to determine whether each adverse event occurred during screening, blinded treatment in the double-blind period, or open label treatment during the open label extension phase as illustrated in Figure 2.

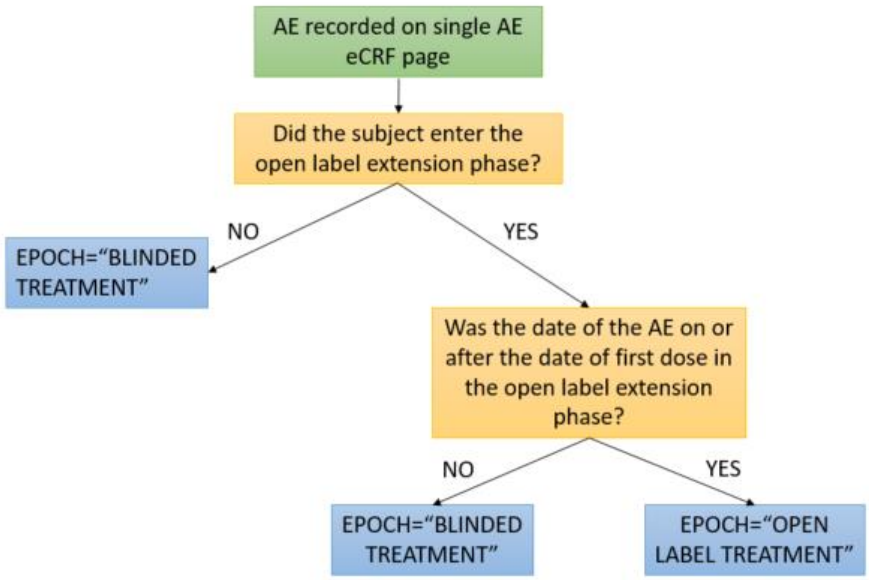

Figure 2. Deriving EPOCH in the AE domain using a single AE eCRF for a study with two treatment periods

We first checked whether a subject entered the open label extension phase and when the first dose of open label extension drug was administered. If a subject did not enter the open label extension phase, then the records were associated with the double-blind period. If a subject entered the open label extension phase, AEs were considered to be in the open label extension phase only if they occurred on or after the first dose of study drug in the extension phase. Similar logic can be applied to determine if the adverse event occurred in the screening period.

Alternatively, two eCRFs could have been used – one for the double-blind period, and one for the open label extension phase. In this case, assigning EPOCH would be facilitated by using the eCRF page name as shown in Figure 3.

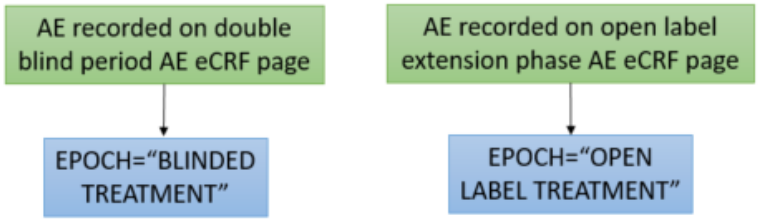

Figure 3. Deriving EPOCH for an AE domain where two eCRFs were used – one for each treatment period.

While this drastically reduces programming effort, there is still a tradeoff to consider. Specifically, EDC entry guidelines would need to be developed for how to handle events that are ongoing at the end of blinded treatment and date imputation procedures specified in the statistical analysis plan (SAP) should also take into account this eCRF design.

The influence of this deviation from the ideal process was generally controlled at the SDTM level and did not impact ADaM development.

Example: Laboratory Data

The CRFs for laboratory data were structured to maximize ease of site entry. Due to the small size of the study, local laboratories were used. Four separate, but similar, forms were used to collect laboratory results. Result units were not collected per SDTM controlled terminology. Finally, reference ranges were not consistent within or across subjects due to the use of local laboratories.

There were several deviations from the ideal process in this example:

1. Laboratory results were collected with multiple forms that did not provide sufficient value for the effort of using multiple forms.
2. Lab units and tests (absolute versus percent) were not consistent within subjects across visits.
3. Data was not collected using controlled terminology for units and tests.
4. Reference ranges were not consistently collected.

Below is how each of these issues was addressed and the impact on compliance and data summarization:

1. In order to document which CRF each data point came from, thorough value-level metadata was included in the define.xml. This expanded the define.xml sections compared to using one CRF form, but provided all information needed for traceability. The impact of this deviation was limited to the SDTM level.
2. To standardize units to facilitate summarization, a laboratory standardization plan was created and sponsor-defined criteria was used for mapping. Results were converted so that each test was represented by one unit. The impact of lack of standard units was addressed at the SDTM level. However, inconsistent collection of percent results versus absolute results impacted ADaM and TLF development. The TLFs were designed to only display summaries of normal and abnormal results as well as shifts by visit.
3. Test names, test codes, and units were mapped to controlled terminology. The impact of this deviation was limited to the SDTM level.
4. Lack of reference ranges significantly reduced the interpretability of the collected data and limited ADaM development. Laboratory results could not be graded per CTCAE criteria.

In these two examples, deviations from CDISC standards have varying impacts. In the example with visit number and EPOCH, strategic programming was able to mitigate the impact of the deviations at the SDTM level. The cost of deviating from standards at the start was an increase in programming effort, but there were no costs to compliance in adopting CDISC standards at the SDTM level. In the case of the laboratory data, the cost of adopting CDISC standards later resulted in multiple queries for units that didn't make sense, the creation and execution of a standardization plan, and limits to ADaM and TLF development. The scope of the effort to handle the laboratory data was much greater than the effort needed to address the visits and visit numbering. On the other hand, it could be argued that some of the deviations in the laboratory example were less than ideal when trying to collect complete and interpretable data, regardless of data standards adoption.

CASE STUDY #2: POTENTIAL RETROFIT FOR CDISC AFTER NON-STANDARDIZED ANALYSIS

In this scenario, the client was interested in generating quick analysis datasets and TLFs. Due to unknown asset viability, they prioritized fewer deliverables, and indicated they may want to retrofit for CDISC compliance based on the results of the study. While acknowledging this approach was not ideal, a plan was devised to meet the client's needs. The eCRFs were designed using CDASH data collection standards.

The primary deviation from the ideal process was the lack of SDTM domain creation. Understanding that the client may want to create SDTM in the future, the use of CDASH data collection standards and an easy to work with database structure will enable SDTM creation.

The analysis datasets were specified to closely resemble the ADaM datasets that would be created from SDTM. The ADaM dataset specifier anticipated the underlying SDTM structures and naming structures. Thus, we can mimic the structure of the anticipated ADaM datasets, but in no way claim compliance. See Figure 4 below for an example using select vital signs collected for one subject at one visit.

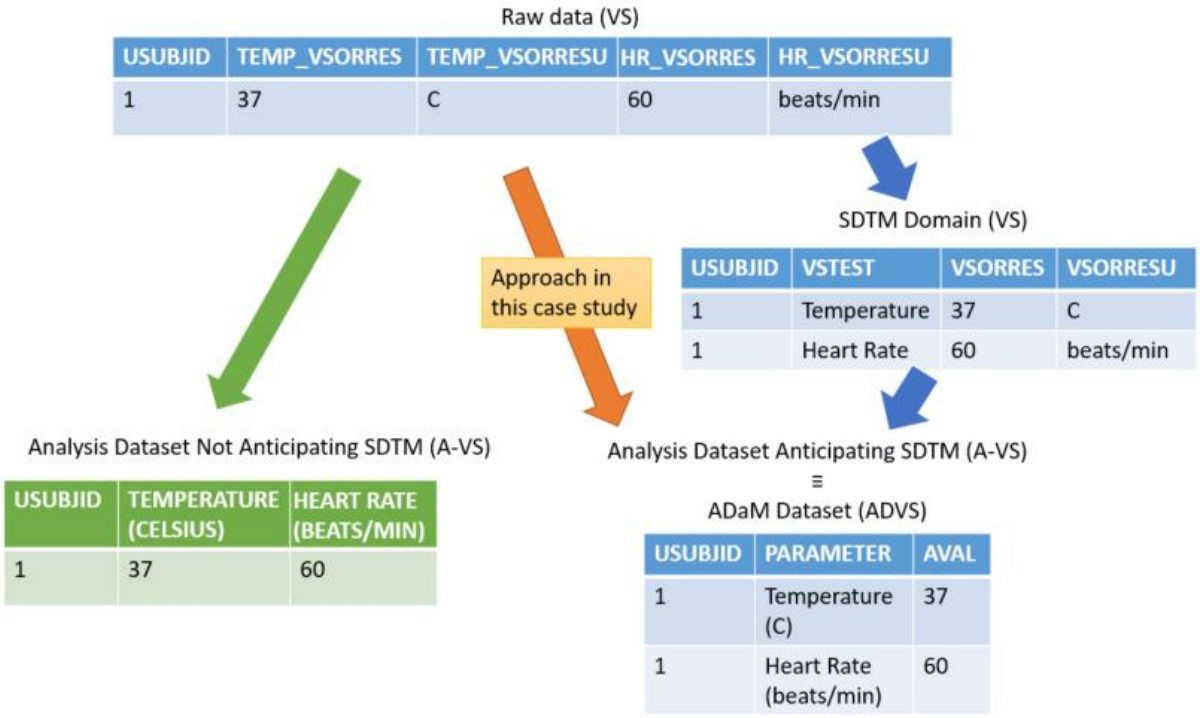

Figure 4. Three approaches for deriving analysis datasets from raw data.

Using this approach, TLFs can be programmed and validated. If SDTM were to be created in the future, the analysis datasets will require reprogramming; however, the TLFs would not likely need any

substantial changes. Standard internal specifications for the analysis datasets were used that are designed to facilitate writing the ADRG and creating the ADaM define.xml.

In this case, the cost to adopting CDISC standards at the end of the project will be the cost to produce the SDTM, re-program the ADaM datasets, and produce the define.xml and reviewer's guides for each set of data. That's a major change in scope and is justified from the client's perspective only after the trial has been shown to be positive. While this approach delays the timeline to create deliverables to support a submission, this approach maximized this client's utility.

CONCLUSION

A firm understanding of CDISC standards in conjunction with regulatory requirements is essential for crafting a plan of if and when to adopt CDISC. The first case study illustrates that if little attention is paid to the possibility of submission and the creation of CDISC compliant deliverables, mitigating earlier decisions can be difficult. While values can be standardized and terms can be mapped to controlled terminology, you cannot make up for the limits imposed by lacking data necessary for interpretability of the data you did collect.

In the second case study, submission and CDISC standards were considered from the start. While their implementation was limited in the initial scope of analysis, the perspective allowed us the opportunity to carefully architect a strategy. Instead of having some changes ripple through the entire process from data collection to TLFs, the changes are contained in SDTM and ADaM. Thoughtful specification of the ADaM datasets means that the analysis datasets look like the ADaM datasets created from SDTM. As noted earlier, these datasets can look like ADaM and facilitate TLF development, but they are not truly ADaM datasets. This is a more cost-effective approach than the first case study as all current and future costs are considered from the start. Additionally, this informed strategy reduces the likelihood of unpleasant surprises when the study is converted.

Prior planning is the key to successfully adopting CDISC standards at different points in the data collection and analysis process, just as it is the key to successfully using data standards from the start. All potential challenges in the process flow should be anticipated, including the use of multiple vendors. Building eCRF pages in such a way that the underlying data structure is reasonable to work with facilitates later SDTM, ADaM, and TLF development regardless of where in the process standards are adopted. Understanding best practices for CDISC submission is essential to considering when CDISC standards can be adopted.

REFERENCES

[1]U.S. Food & Drug Administration. 2018. "Study Data Standards Resources." Accessed July 18, 2018. https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

[2]CDISC. 2018. Accessed July 18, 2018. http://cdisc.org.

[3]International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 1995. "Structure and Content of Clinical Study Reports E3." Accessed July 18, 2018. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

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