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Three Unique Case Studies - On the Trail of the Holy Grail of SDTM Implementation

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ABSTRACT

While it's clear that a critical mass has been reached with a high percentage of pharmaceutical companies engaged in the implementation of SDTM standards into their organizations, what is not so clear is the best path to follow to get there.

From my standards experience on both sides of the pharmaceutical industry - pharmaceutical companies and contract research organizations - it is apparent that there is no "golden egg" or "magic bullet" that ensures a successful SDTM implementation. But it is my objective here to share that experience and insight into 3 situations that have been productive.

Included here are 3 unique case studies of individual companies working hard to implement SDTM, described briefly at a strategic level and then in more depth at an operational level. Not only the mapping result will be shown here, but also the decision-making process that ultimately determined the right mapping for that organization.

INTRODUCTION

The implementation of SDTM into a company's clinical organization demands the internal presence of both strategic thinking and operational expertise to determine the most appropriate decisions for their company, because multiple factors (size, systems, processes, etc.) vary from company to company making each situation different. The common thread running between each of these 3 case studies is the commitment of the people to be accurate in their SDTM mapping while doing what is best for their company.

ROLE OF STANDARDS GOVERNANCE

Although the focus of this presentation is to provide practical situations of SDTM implementation, the subject of standards governance cannot be overlooked – even though it often is. In particular, the consolidation of SDTM implementation practices and preferences within a sponsor company as a facet of standards governance is important in ensuring the consistent application of SDTM across the entire clinical organization.

Effective standards governance might not be the match that sets the standards initiative on fire at a company, but it is the necessary furnace that provides structure, guidance, and constraints on the efficient use of the standards combustion. Without this vital component of standards implementation, the standards quickly devolve into customized versions of the original framework, essentially no standards at all. Their use by clinical and data operations becomes irregular, non-compliant, and eventually non-existent.

Looking across the industry, the most effective manner for effective standards governance is a modifiable framework with multiple components. There is no one-size-fits-all answer for all companies. Company size, available resources, and existing systems are among the variables that determine the best model of standards governance for a company. So while the standards governance framework will vary in size and scope, it should have four major components necessary for successful standards implementation.

- **People**
- **Standards**
- **Processes**
- **Technical Solutions**

People form the foundation for this framework. Securing the services of the appropriate people within the data, statistical, and clinical sides to the business is an important first step. They will form the leadership, the content decision-makers, the developers, and the data stewards within the project teams. One often overlooked human

component is the importance of a high-level, visible, management directive that lays the groundwork for buy-in across the entire organization.

The actual **standards** themselves are the engine that powers the standards governance framework. Whether they are tool-specific constructs for use at an operational level or the standard metadata that define databases and reporting programs, the standards are the reusable parts that allow for efficient and consistent execution of clinical trials. CDISC Standards will bring inherent challenges for implementation, considering their focus and structure are sometimes very different from existing industry practices. If time is not allowed for well-thought out decisions about these challenges prior to implementation, there is a real risk for wasteful re-work and delays.

It is crucial that **processes** be put in place before the CDISC standards are in use. These necessary processes are not limited to just the application of standards within operational tools (e.g.: eCRFs), but they also span processes that address approval of requests, define the scope of standards governance, and dictate standards maintenance and development. This enables consistent, reproducible application of standards, timely turnaround for new requests, and thus breeds a measure of trust by the clinical organization regarding the use of standards.

Technical solutions such as a metadata repository, document version control, and a request/issue tracking system enable the people and processes to work efficiently. Decisions on these solutions are often placed at the tail end of the whole CDISC implementation process, but they are as important to deriving maximum benefit from standards as anything else. A request tracking system, be it minimal or robust, enable the standards governance team to be quickly responsive to the requests of clinical teams, while a metadata repository allows the standards to be maintained at an elemental level and also to be exported to drive the clinical systems all along the clinical data lifecycle (e.g.: EDC database set-up).

It is crucial that as much of this standards governance framework be in place as possible before the implementation of CDISC and other data standards to best ensure the following: compliance, maintenance, integration, accountability, and consistent application of the standards. The framework needs to define and control all of the associated work processes necessary for successful implementation and maintenance.

CASE STUDY #1

BACKGROUND

Company Alpha was nudged into action to implement CDISC standards by having to navigate the unpleasant task of responding to regulatory submission questions, realizing the large volume of work that it took to do data mining through unstandardized databases. Data mining under these circumstances can be laborious at best, but can quickly unravel into a highly pressurized scramble for answers while on the clock with the FDA.

STANDARDS GOVERNANCE LEVEL

Senior management subsequently authorized the clinical systems support group to determine the implementation of CDISC standards, particularly CDASH and SDTM, to avoid having to do this type of ill-defined data mining again. There was no accompanying authorization for a standards governance organization, which might likely jeopardize the effectiveness of and compliance to CDASH and SDTM in the long run at Company Alpha.

In the absence of any standards governance at all, Company Alpha incorporated viewpoints from EDC builders, SAS programmers, and Biostatisticians. These resources were sequestered together in a standards development workshop to hammer out CDASH and SDTM implementations simultaneously for their most common 12 domains. The SAS programmers and the Biostatisticians are the typical functional areas with relevant expertise to contribute to CDISC standards development, but the inclusion here of the EDC builders in this process was crucial in facilitating an unusually quick and effective entrenchment of CDASH/SDTM concepts directly into the front-end of collection. Downstream activities in the clinical data lifecycle will surely reap the benefits of this decision.

MAPPING DILEMMA

The EDC panel which collected Signs and Symptoms proved to be one of the more challenging mappings they faced. After the application of a trans-dermal delivery of investigative drug, data was collected for the existence of Signs and Symptoms that occurred within 24 hours (the threshold line for reporting it as an adverse event in this protocol). Within this single EDC panel, data fields existed for severity of rash and the associated diameter.

It was a classic mixture of events and findings that were collected together, leading to not only the classic debate over whether Signs and Symptoms are Events or Findings, but also multiple proposals on how the SDTM domain for this data should look considering it's uses for analysis and reporting.

PROPOSAL 1

- **Domain**: CE
- **Class**: Events
- **Reasoning**: Even though Rash is typically collected an adverse event, it is not reportable as an adverse event until 24 hours according to this protocol. Thus, the CE domain would be used to capture this as a clinical event. The Event class of SDTM domains seems appropriate in this case as it structures nearly all of the data in the classic Events format.
- **Details**: Rash would be captured as an Event, complete with Start Date, Severity, and a flag for Occurrence (CEOCCUR) all within one observation. Since the Rash diameter data field is a finding associated with the event, it would be stored within the supplemental qualifier domain SUPPCE.

PROPOSAL 2

- **Domain**: X1
- **Class**: Findings
- **Reasoning**: This Signs and Symptoms data is collected together in a single EDC panel, so it needs to be submitted together in a single SDTM domain to maintain the clinical intention for the data. Even though there is a mixture of Events and Findings in this panel, a custom Findings domain designated as X1 could be used in a manner that captures the event as an Occurrence. All of the data would be accessible to the statistician in one format, thereby removing the need to handle supplemental qualifier datasets to construct analysis datasets.
- **Details**: The event Rash would be captured as part of the value-level metadata for the X1TEST data field (e.g.: X1TEST="OCCURRENCE OF RASH"), along with the Y/N indication for X1OCCUR and the Date of Collection. The Severity and the Rash Diameter would each be stored in the X1ORRES variable on additional observations separate from the OCCURRENCE OF RASH. The units of measurement for the Rash diameter would be stored in X1ORRESU.

PROPOSAL 3

- **Domain**: FA
- **Class**: Findings
- **Reasoning**: Another variation of a Findings class domain for this data was suggested to be the FA domain (Findings About). Again, this Signs and Symptoms data would be submitted together in a single SDTM domain to maintain the clinical intention for the data, while also obviating the need for using supplemental qualifiers.
- **Details**: The main difference between FA and X1 is in the storage of the Rash event. In FA, Rash is removed from the value-level metadata for the FATEST data field and placed instead into FAOBJ, the data field that describes the object or focal point of the findings observation that is represented by FATEST. One distinct advantage of this proposal is that the use of the FAOBJ variable facilitates the connection of this data to any corresponding data in another SDTM domain.

RESOLUTION

Since the standards development workshop yielded no single proposal that everyone agreed on, the decision on which proposal to use was delayed to incorporate how the data was intended for analysis and reporting purposes. The answer from the statisticians was for Proposal 1, primarily since that was the structure currently in use for this their analyses, despite the additional effort needed to handle SUPPCE. Secondarily, it was difficult for them to rearrange their mindset to view this data in the vertical structure of the Findings class and project how they would handle it for analysis.

CASE STUDY #2

BACKGROUND

Company Beta had several CDISC advocates in their organization for several years, but the organization's leadership never seriously listened to them until a budget crisis occurred. This budgetary tightening forced them to seek solutions to save money, which for the clinical organization translated into the smarter use of resources and the quicker execution of clinical trials. The internal project that included the implementation of CDISC standards was presented to the clinical organization as a necessary evolution in order to remain competitive and profitable in the current pharma environment.

STANDARDS GOVERNANCE LEVEL

Originally the only standards governance in place when the project began was a small effort in data management charged with the company's proprietary collection standards. So a small separate group of internal resources with SDTM expertise from the data management and SAS programming areas first addressed the mapping of the 15 standardized collection domains to SDTM to lay the preliminary foundation for 2 key SDTM submissions in the near future.

Eventually Company Beta issued a highly-visible, strong statement from a respected senior Vice President to jump-start the standards governance initiative. This effective directive was used by the clinical leadership as an authorization to spend the necessary resources to build a fully-capable standards governance organization which is still functioning efficiently and effectively today.

MAPPING DILEMMA

Within a single therapeutic area (TA), a standard CRF was in use at the patient's screening visit which captured medical history information specific to that TA in both content and structure. The SDTM mappers recognized that the majority of this data fell neatly into the existing MH domain in SDTM as Events data, but faced choices as to how to submit the minority of Findings data that did not.

Also, a debate was opened over how to address both pre-specified questions and how to map findings data that are connected to events data. Since Medical History data is traditionally not analyzed very extensively, the statisticians had no preference on SDTM mapping. The SDTM mappers found themselves needing to resolve these issues within their own group.

PROPOSAL 1

- **Domain**: MH
- **Class**: Events
- **Reasoning**: Medical History data is included in few analyses as part of a clinical study report, so there is little harm in placing the Findings data from that medical history CRF into the supplemental qualifiers data set called SUPPM. Also, there is no need to indicate whether or not these pre-printed events are pre-specified in SDTM.
- **Details**: Medical history events (pre-printed or not) on the CRF would be captured as Events, complete with Start Date, while the additional Findings data would be stored within the supplemental qualifier domain SUPPMH. The Y/N question would be captured in MHOCCUR.

PROPOSAL 2

- **Domain**: MH + FA
- **Class**: Events + Findings
- **Reasoning**: Medical history data is beginning to be used more frequently in analyses across the industry, and there is concern that eventually that will spill over to the FDA reviewer. The structure of SDTM and the accompanying tools for its use will only accelerate this. Using the FA domain to capture the Findings data allows not only for this data to be more easily analyzed, but also to be tied back to its parent event via the use of the FAOBJ variable. By using the MHPRESP data element, it can be highlighted to the FDA reviewer that a medical history event was specifically prompted to the patient. This consideration is gaining traction at the FDA in the evaluation of events.
- **Details**: Again, medical history events (pre-printed or not) on the CRF would be captured as Events, complete with Start Date, while the Y/N question would be captured in MHOCCUR and the MHPRESP field would be Y for all events that were pre-printed. Additional Findings data would be stored in FA within the appropriate FATEST and FAORRES variables. In FA, the FAOBJ the data field would store the name of the associated event, facilitating the connection of this data to the corresponding data in MH or any other SDTM domain.

RESOLUTION

The emerging standards governance organization at Company Beta operated under the directive to be forward-thinking and proactive when it came to use of CDISC. Proposal 2 was chosen because it enabled them to move beyond traditional methods of handling medical history data and to look down the road towards the advantages of submitting this data in a format that allows FDA reviewers to manage it according to their evolving methods.

CASE STUDY #3

BACKGROUND

Company Gamma was attempting to introduce CDISC standardization into their organization to part of a larger project that centered around the implementation of a clinical data repository. The challenge this presented was that 16 of their most frequently used collection domains had to be mapped in a very short time window and with only sparse internal expertise. Conversely, the quality had to be high and the mappings stable to facilitate the subsequent mapping of TA data domains very soon thereafter to meet the demands of an upcoming submission.

STANDARDS GOVERNANCE LEVEL

No formal standards governance existed at the time, so a lightly-supported group of clinicians and statisticians was hastily thrown together to provide centralized decision-making for this mapping effort. As the project ran, the small standards governance group was encountering some major responsibilities that were additionally placed on their plate, such as CRF development, metadata generation according to an unstable metadata model, and the tracking of standards requests for which they had no technical means for doing so.

Lacking both in resources and proper areas of expertise, the standards governance group was nearly paralyzed before long. Without a highly-visible, strong statement from upper management, this group soon became overworked, under-appreciated, and overwhelmed. This set back the development of an effective standards governance mindset at Company Gamma by more than 2 years.

Also, because this standards governance group was very limited in representation, other areas of the clinical organization that were affected by SDTM (e.g.: EDC builders) that did not have a voice in the CDISC standards implementation soon became disenfranchised and aggrieved.

MAPPING DILEMMA

Within a single TA, an important TA-specific collection domain captured at each visit the usage of specific medications that might impact the efficacy evaluations the patient was required to perform at that visit. Because the topic of this data panel included concomitant medications in conjunction with efficacy information, 3 separate directions emerged as to how best to map this data in SDTM.

PROPOSAL 1

- **Domain**: CM
- **Class**: Interventions
- **Reasoning**: All concomitant medications data within the patient's CRF needs to be submitted together in the CM domain in SDTM, despite the fact that in this case, only the medication class, start date and time are the relevant CM data fields. The use of the MHPRESP data element to capture that the medication was pre-printed on the CRF might be valuable to highlight to the FDA reviewer that a concomitant medication was specifically prompted to the patient.
- **Details**: The medication classes listed in the prompted questions are collected as interventions in the CMTRT variable, complete with Start Date and Time. All other data fields would be placed into the supplemental qualifier domain SUPPCM, except for the Y/N question that would be captured in CMOCCUR while the CMPRESP field would be Y for all events that were pre-printed.

PROPOSAL 2

- **Domain**: DV
- **Class**: Events
- **Reasoning**: The purpose of this data is to identify patients with a protocol deviation regarding the use of restricted medications before performing efficacy evaluations. Thereby, this data needs to be collected as an event within the DV domain of SDTM that was designed specifically for collected protocol deviations. Upon tabulation of this data for analysis and reporting needs, the important data fields can be easily accessed.
- **Details**: The pre-printed medication class would be incorporated into the DVTERM variable in a standard manner (e.g.: "PRE-SPIROMETRY BETA 2-AGONIST USAGE DIVERGENT FROM PROTOCOL"), while the Date & Time Taken would be collected in the Start Date field DVSTDTC. The Y/N question would be captured in the supplemental qualifier domain SUPPDV.

PROPOSAL 3

- **Domain**: XC
- **Class**: Findings
- **Reasoning**: In order to properly store all the data in this CRF in a similar manner that can be accessed identically no matter what the purpose, a new custom SDTM domain needs to be created that facilitates this

consistency in handling. There is no need for this data to indicate whether or not the medication class was pre-specified or not.

- **Details**: The medication classes would be captured as part of the value-level metadata for the XCTEST data field (e.g.: XCTEST="BETA @-AGONIST USAGE"), along with the Y/N indication stored in the X1ORRES variable and the Date & Time Taken in XCDTC.

RESOLUTION

Like most pharma companies, Company Gamma had no consolidated method of pulling all the possible sources for protocol deviations into a single dataset (e.g.: clinical monitoring reports, edit check listings, a CRF specific to protocol deviations, etc.), let alone a clear process for making the clinical determination of whether it was a true protocol deviation or not. The SDTM mappers quickly realized the struggles the organization would face if they mapped this to DV.

In lieu of that, Proposal 3 was subsequently chosen primarily to put this data in the most flexible situation that could allow for access and analysis as concomitant medications, protocol deviations, or qualifiers for efficacy data.

CONCLUSION

While there is no single perfect method of SDTM implementation, a successful application of SDTM into clinical organizations can be a reality with the proper forethought in advance, the thorough consideration of multiple functional areas in the data lifecycle, and the empowered standards governance in place.

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