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A Tale of Two CDISC Support Groups – Supporting CDISC Standards is Anything but Standard

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ABSTRACT

It was the cleanest compliance report. It was the worst of compliance reports.
It was the team of subject matter experts. It was the team mapping their first SDTM study.
It was the project with well tested standard process used for years, it was the project without any developed standards.

Any standards support team has likely been faced with supporting many of these. Their overall goal is the same: to support teams in the implementation of CDISC standards such as SDTM and ADaM in order to produce a high-quality compliant product following CDISC standards for submission. However, the challenges, structures and approaches to support can differ greatly between companies. As a result, CDISC standards support teams come in many different shapes and sizes with different processes and methods of support. This is the tale of two CDISC support groups, one Sponsor and one CRO, navigating these challenges with converging paths to one common goal.

INTRODUCTION

This is the story of two data standards support teams. The first team is made up of individuals who work solely supporting the data standards needs for one pharmaceutical company, or sponsor. The second team is made up of individuals who work for a contract research organization (CRO). The CRO will support several different sponsors and depending on the situation, might utilize their own data standards library or might use the sponsor's data standards for providing support. In some ways, the teams are very much alike while at the same time being very different.

Whether coming from a Sponsor or a CRO, both support teams start out with the same common goal of delivering good, compliant SDTM and ADaM. Sounds pretty basic, right? Same goal, same path forward to get there. Not so fast! The reality is that all pharmaceutical companies differ in some way. Thus expecting that every company can employ the same support structure and process is not realistic. Differences from company to company and even from team to team within the same company will affect how the SDTM and ADaM are created. These differences can often be found in easily identified components like the format of the raw data, Statistical Analysis Plans (SAPs), and Lists of Analysis (LOA) requirements for the needed tables, figures, and listings (TFLs). But differences also exist in less tangibles like company culture and study team synergy.

So given these differences, how do support teams from both a Sponsor and a CRO achieve their goals? What challenges will they face? How are these challenges met? How is the experience different for the study teams they support? This paper will take a look into the existing factors that impact the differing needs in the structure, approach, and practices of the two data standards support teams.

COMMON GROUND: CDISC SUPPORT TEAM OVERALL GOALS

Not surprisingly, the Sponsor and Contract Research Organization (CRO) CDISC support teams both start with common goals. The primary objective for both support teams is to facilitate the creation of a product that is compliant to the CDISC standards which will facilitate agency review. This involves understanding and implementing the standards (CDASH, SDTM, ADaM and define-XML) while following the requirements of the agency to whom the data is submitted. This includes agency-specific guidance such as the Food and Drug Administration (FDA) Technical Conformance Guide (TCG) and the PMDA rejection criteria. To ensure standards compliance, both teams must utilize tools like Pinnacle 21 Enterprise as well as running their own internal checks.

The CDISC support teams also ensure consistency and compliance by creating and maintaining templates and process documents, developing and providing training, and educating study teams on common issues and pitfalls to avoid. Both support teams provide expertise when novel analysis approaches or ad-hoc support is needed anywhere along the process from data collection to submission. Through each of these interactions, our ears are listening to the needs of the project teams while our eyes remain on the model documents and implementation guides. When the two do not align, it is our job to push back and offer proposals and actions that agree with the established standards.

Another goal that the teams share is clarity. If we were to consider compliance our primary goal, clarity would follow closely as the second. Clarity comes into play in several aspects of the support. One is in helping teams understand and interpret the requirements, specification templates, model documents, and implementation guides. When useful, we provide explanations or examples to avoid confusion or misinterpretation. Another place where clarity is important is in the study team's documentation of actions taken for the study. For submissions to an agency and for internal usage, having clear documentation, explanations, and traceability from raw through analysis is key. This includes specification wording, annotated case report form (aCRF) annotation, define.xml wording, Analysis Data Reviewer's Guide (ADRG), Clinical Study Data Reviewer's Guide (CSDRG) descriptions and explanations of compliance check messages.

Education is also very important. The standards created by CDISC are ever evolving, so keeping up with the latest requirements is important to be able to support it. So, first we need to educate ourselves. Being aware of new published documents, attending webinars and conferences, and being a part of the development of the standards are all ways that we do that. That new information then needs to be brought back to educate our teams through updates to our standards and templates or trainings and information sharing. Even the process of answering questions or giving feedback and explanations of why something may need to be done differently are ways to help the teams grow. Sharing information so that the project teams can become stronger in their understanding of standards implementation paves the way for a cleaner and more compliant data product.

THE PATHS DIVERGE

So far so good. Having some common goals is a nice start. But when we start to look at the details of how these goals are accomplished and all of the parties and standards involved, differences emerge. We start to see some differences between the Sponsor and CRO support teams in terms of:

- Who and What is being supported
- Who does the supporting and how it is provided
- Standards defined and supported
- Documentation and training
- Handling the unexpected

WHO AND WHAT IS BEING SUPPORTED?

Both support groups have multiple groups of customers as well as a variety of standards to support. We provide support to study teams and individuals both within and outside of our companies.

SPONSOR

Who is the Sponsor Group Supporting?

The Sponsor standards support team interacts with multiple functions (e.g. CRF creation, Electronic Clinical Outcome Assessment (eCOA), Pharmacokinetics (PK)) that require periodic interaction and support. But our most visual partnership is generally with the study teams. This is generally a close relationship with each side having a high-level knowledge of how the other side functions and requires frequent communication and interaction. Because of this familiarity, the intangibles like company culture and product team tribal knowledge are generally addressed without the need to specifically call them out.

When it comes to providing support to CROs or external consults that are working with the Sponsor, the Sponsor CDISC support team generally does not have much interaction. The study team provides support unless issues arise that require escalation.

What is the Sponsor Group Supporting?

While all study teams use CDISC standards, the implementation of the standards can vary across each different therapeutic area (TA). This often results in multiple levels of standards being defined for an individual domain or data set in order to meet the TA unique requirements.

The Sponsor support team adheres to strict standards governance that has evolved over time to best fit the organization. The current governance model has greatly increased consistency, speed, and reuse of programming code in all our clinical trials. It has also increased compliance to regulatory rules which reduces the amount of issue resolution and rework on the back end. Implementation of this approach is to start with an overall global standard. This standard is expected to be used unless a strong scientific or business case exists as to why an alternative standard is needed. When that occurs, the CDISC support team should determine if the alternative standard is needed for all studies in that therapeutic area or is limited to a compound in that TA, or just for one or a few studies. Maintenance and governance of standards at multiple levels can be complex and adding standards at the TA or compound level should only be done with discretion. While all of this is performed in a timely fashion, study teams are often looking for quick implementation. Thus the standards governance process for new or modified requests needs to be built into their study build timelines.

CRO

Who is the CRO Group Supporting?

The CRO CDISC support team must similarly support the company internal project teams with standards implementation, though the standards themselves may differ, as we will see below. The CRO project teams may be working to provide a set of SDTM or ADaM data sets to a Sponsor who does not wish to have much involvement in the process. In that case, we provide support to that project team in terms of answering questions that may arise and providing guidance and feedback on specifications, data sets and documentation. In other cases, our project team may be working with a Sponsor that has standards in place or a standards team involved. In that case, we are sometimes involved in communication between the Sponsor and our project teams. At times we also support Sponsor groups directly. It may be in terms of giving input to a unique situation that has come up or to work towards building a Sponsor standard.

What is the CRO Group Supporting?

Like the Sponsor group, the CRO team has a set of standards and specification templates. These templates provide a starting point for the CRO project teams in a standard familiar structure. However, we support a variety of Sponsors, some with their own well established standards. Where the Sponsor group may have some TA specific standards, the CRO variety in standards comes in having Sponsor specific standards. In the case when a client may not have their own specifications or are more interested in a final product and not as concerned with the appearance of details such as a specification template, the CRO standard support group would be supporting a study team that is using our internal specifications and processes. In cases like these, the internal specifications would be familiar across study teams and the support group. However, many Sponsors have their own established specification templates and interpretations. So while there is a commonality in the ADaM standard for example, the specifications, processes and handling of non-standard variables may differ between Sponsors so multiple flavors of ADaM across these teams needs to be supported by the CRO standards support team for each Sponsor. A particular handling for one project team may not be the same for another project team. One example of an SDTM difference is multiple enrollments. While CDISC teams work to provide guidance around this occurrence and the FDA TCG statements, we have clients following different processes to handle this type of data. Some have their own established standards. Others are using our recommendations for this data. And for some, a combined solution based on our internal process and the Sponsor's historical

handling is used. In supporting each customer's standard, the CRO support team needs to be able to guide the team with the customer specific preferences in mind.

WHO DOES THE SUPPORTING AND HOW IS IT PROVIDED?

SPONSOR

Sponsors have the luxury of choosing the structure or hierarchy that works best for their individual situation. Our Sponsor approach is to have a support team of several individuals who together provide governance and maintenance of the standards but are also each individually aligned to support a different therapeutic area. The ideal situation is for each member to support both SDTM and ADaM for their individual teams but sometimes two or more members can work together to provide that support. In these cases, communication and well-established best practices are necessary to ensure uniform consistency in the domains and data sets. In addition, each member is a Subject Matter Expert on one or more topic or tool (e.g. Pinnacle 21E, aCRFs, lab tables, etc.). This approach provides the functions and study teams the appropriate support-team member to contact for any situation. The structure also results in quicker support and issue resolution.

Initial support for the study teams should go to the support team member(s) assigned to their area. This again is to promote consistency since therapeutic areas might have slight differences in the way they apply the standards. But since global standards make up most of every study across all TAs, it is easy for any team member to fill in and/or provide backup to another therapeutic area when necessary. This creates a seamless experience for the study teams who can develop that close support relationship with their support team representative(s). The support team representatives are knowledgeable about the compounds, studies, history, and past decisions when helping develop solutions for their teams.

Occasionally an issue, request, or question arises within a therapeutic area that does not have a clear response. When this occurs, the support team member escalates it to the whole CDISC support team for discussion.

CRO

Since our CRO support team may need to adjust to supporting a different number of clients, projects and indications, the team structure and allocation of supporters must be more fluid. Where the Sponsor team knows that they have a set number of indications and will need an SDTM and ADaM subject matter expert (SME) for each, this will not be constant for the CRO group. We may have more oncology studies in need of support one quarter and more autoimmune the next. We may have a large group of SDTM only conversion studies at one time without an analysis component. Since the more substantial difference in the standards used by the CRO groups tends to be based on which Sponsor more so than TA, it is more effective to have an individual to be familiar with and support a particular Sponsor's projects rather than TA. By doing this, that SME or group becomes familiar with the nuances that make that Sponsor standard unique and can also help to ensure consistency between studies.

Our support team is made up of SMEs and experienced supporters. This is not a stand-alone group team that works only on the maintenance of standards, but a team composed of individuals with hands on active study involvement as well. This helps to have individuals directly in projects to be able to identify any pain points or areas where there may be some clarification or update that needs to be provided. The standard supporter for the team both serves as a question resource for the project team as they are working on development and can also review specifications, data sets, or findings to help identify and correct issues before final product. The aim is to provide adequate templates, training, and resources for the project teams to be able to learn and be confident and for the support team to be approachable for any questions that arise along the way. By encouraging this dialog from the beginning, the uncertainties can be addressed earlier in the process. For example, it would be preferred to have an open exchange and resolution about an unusual CRF page while creating specifications rather than finding a mapping issue in a review after creation or when a compliance check was performed.

Along with directly supporting project teams with mappings and understanding of the models, Implementation Guides (IGs) and Sponsor standards, this CRO team also works on training development and process improvements. Project teams can also contact this group centrally for any general questions

so that the individual with the particular area of expertise can be reached efficiently and a prompt response can be provided. Having the whole CRO standard support group able to see questions and responses also provides the ability to make sure that there is not disagreement in the response and additionally to help to educate team members to strengthen their knowledge in an area or indication that they may not have had as much experience.

Decision making regarding internal standards is done by committee within this group. However, not all decisions are ours to make. When working with a client standard with a possible update needed, the CRO standard support person working with the project team would help that team to present their recommendation for action to be taken to the Sponsor, but ultimately, any change to Sponsor standard would be with that Sponsor.

STANDARDS DEFINED AND SUPPORTED

Part of supporting standards is to design and develop the internal processes and templates that will need to be followed by the project teams. This can include specification templates, standard mappings, interpretation guides, job aids and working practice guidelines that a study team will need to effectively produce SDTM and ADaM data sets.

SPONSOR

As a Sponsor, we are equally concerned on how our defined standards impact not only the study teams in the creation of output data but also how easily the output data will be used in data review by the various regulatory agencies. Relationships within or between the domains/data sets need to be clearly defined and easy to identify.

Our data and analysis standards library actualize these goals. The Sponsor starting point for any standard are the CDISC Implementation Guides, Therapeutic Area User Guides (TAUGs), and other published CDISC foundational standards as well as regulatory agency technical conformance requirements. The process starts with data collection templates that define by form (aCRF, eCOA or Electronic Patient Reported Outcome (ePRO) form, etc.) the data variables to be collected. Each variable definition contains the SDTM mapping as well as metadata and any applicable code lists and/or relationships to other variables. The SDTM domain templates define how to convert the collected data forms into SDTM. The ADaM data set templates similarly define ADaM using the defined SDTM variables as input. Ultimately, TFL shells are created using the defined ADaM and SDTM templates as input. This process is designed to start with the end in mind and is essential to eliminating ambiguities, redundancies, duplicate observations, etc. from final data sets/domains.

All study teams are required to use the same data specification template to define programming specifications for both SDTM and ADaM. A completed specification document will contain all the domains (SDTM) or data sets (ADaM) for the study as well as the trial design domains and time points. All trial design definitions, variables, business algorithms, code lists, methods, and metadata are needed for the specification document. It is vital to our processes to have as much of the static information as possible included in the data standards template definitions. It is also important to have clearly identified all inputs to the specification process that are protocol specific, as well as any inputs that have the flexibility to be changed to meet a study team's needs. All of these practices help the study teams quickly provide complete and accurate data specifications.

CRO

Where the Sponsor team is able to design a good part of their company standards that will follow a consistent path from standard CRFs, to SDTM, to ADaM, to standard tables with some derivations and assignments locked down, the CRO group needs to take a different approach. While we have a set of company CRFs and common table shells, that is not always what will be used by a project team. We may have external CRFs and raw data, so domains may not always come from the same CRF pages and source data set structures. The same –TEST/--TESTCD or –QNAM/--QLABEL will not always be present. We may also have a different set of display shells and analysis derivations for various Sponsors, so the CRO cannot mandate that a particular standard derivation is always used on all studies for a variable. Because of this, we need to design a standard that is intentionally flexible. Our CRO ADaM specification

template for example, is built to support our standard tables. However, if changes or additions are needed for another structure of analysis that is required, they are able to be modified within the ADaM rules in order to support the analysis.

DOCUMENTATION AND TRAINING

SPONSOR

Overall, all clinical trials that use the Sponsor's standards are going to be conducted the same across the board. Even in the situations that have been previously mentioned where a therapeutic area, compound, or study might use a slightly different version of a standard, the process is in implementing that standard is the same.

This makes the training process straightforward and easy. Now that CDISC standards have been a requirement for several years, the need to train entire areas at the same time is largely eliminated. Training materials can be provided to new employees as part of the onboarding process and still be available as a reference to the more experienced employees.

Major changes to standards are broadly communicated and all reference materials (e.g. training, examples, readme documents) are updated before the changes go into effect.

A company could still choose to do periodic live training for onboarding or as a periodic refresher. This can be particularly useful after an SDTM or ADaM up version since many of the changes are not readily obvious and can be missed in a communication message.

CRO

As noted, the CRO group will support multiple project teams that may or may not be using the same standard, specification templates and processes. So how can we document and train on these differences effectively? The same general topics of tasks need to be completed on a study, but the processes and tools used for each task may differ. For example, each team creating SDTM will need to use some sort of specification template to create Trial Design Model (TDM) data sets and SDTM and to document the derivations and sources for those data sets. But project teams using the CRO internal standard for Client 1 will use our internal template and process. A team for Client 2 uses Client 2's template and process. A team for Client 3 uses Client 3's template, but our internal process. Because of this variety, our internal trainings may not apply to all project teams. Additionally, some teams may need some Sponsor specific training information. The teams supporting Client 2 and Client 3 will need some supplemental training or documentation for their work requirements.

One way that we have found to support this structure is to modularize our training and process outlines. The general tasks to be done in the process of raw to SDTM to ADaM and documentation follow the same order for the most part. So we can train that tasks are done in a common order. We have a training on our processes and templates, but when we use a Sponsor process or template, that module can be placed into the order where needed. The team then has a reference where to find the training information that would contain the additional project specific details. Any updates to process or documentation can also be referenced in a similar way.

HANDLING THE UNEXPECTED

This is the area where the CDISC support team often shines brightest. The core principles that guide all employees working on clinical trials must not be compromised. These include following good clinical practices, data integrity, strict adherence to policies and procedures and quality.

But sometimes the unexpected just happens. Unexpected or missing data, study design flaws, clinical trial interruptions, or even your once-in-a-century pandemic can lay waste to the best of clinical plans.

SOMETHING NOT COVERED BY CURRENT STANDARDS

Through the course of a study, even with standards, we need to expect the unexpected. It is not uncommon to have something come up that is not covered by current standards. It may be a different

version of a CRF page that contains a new data point, a new CRF page, a new analysis approach, or something that is common, but not yet clearly handled by the standard, such as multiple subject enrollments or integrated data. When this occurs, the CRF page or data point(s) need to be accounted for in the SDTM and/or ADaM. It needs to be determined what that change should be and if this is a change to a standard or a one-time change for a particular study.

Sponsor

The Sponsor's approach to a situation that is not covered in the current standard is to first assess whether the impact is global or limited to a therapeutic area or compound. Depending on the outcome of that assessment, it could triage either to the affected study team or to the entire support team to discuss and create a solution. This solution would then be routed through the standards governance process so that it could ultimately be added to the data and analysis standards library. The considerations that go into finding a solution include whether CDISC has already addressed the situation in a different IG version than is currently being used and what impact the various options will have on current and future studies.

When a Sponsor-defined domain is needed in SDTM, the support team will look at the most recent published and draft IG versions of SDTM to see if an appropriate domain has been created or drafted. If one does exist, we would most often implement it as Sponsor-defined in our current SDTM library over creating a new domain from scratch. This approach has the benefit that future up versioning would be easier since the domain name and variables would stay the same. But the approach also carries risk if the domain is still in draft form since it could still get dropped from the IG or the final version could be different than the draft was at the time we implemented it.

CRO

The CRO standards team approach to adding to a standard differs based on the project type. If this is a project where the project team is using an established Sponsor standard, we would need to approach the Sponsor about potential to update to their standard. To maintain consistency for that Sponsor's studies, we would want to work up a suggested change/addition with reasoning and make sure the Sponsor was aware of the fact that some change or addition was needed.

An addition or change to our internal standard would involve a discussion among the standards group and follow-up to the appropriate team whether this is a specification template change, training change, or process change. However, if there is something that comes up that is not part of the current SDTM or ADaM standard, it does not necessarily mean that it will become a part of our CRO internal standard. Changes or additions to the SDTM or ADaM standard in a new version would necessitate changes to internal specification templates and/or processes. However, a change due to a Sponsor that has a standard way of capturing a field or something that may be handled differently across Sponsors would not. It may mean a difference in how that particular project team maps or stores a value, but it may not be applicable to all other clients/teams, so it would not necessitate a to change our internal standard.

DISAGREEMENT HANDLING

Disagreements can also occur in relation to the incorporation of something new or even in the interpretation and understanding of existing standards. Disagreements occur within teams, within the standards group, or between a Sponsor and team. When this occurs, many times teams will look to the standards support group to find a solution.

Sponsor

Disagreement resolution is one of the most challenging tasks for the standards support team. Practically every situation must be evaluated on a case-by-case basis, even when scenarios are similar to previous situations. That is not to say that knowing the history of previous decisions is not useful. Study teams want consistency and familiarity in their process so whenever possible, the solution will be similar.

Balancing between following CDISC principles and delivering the portfolio, we strive to arrive at the best solution regarding quality and good clinical practices, data integrity, existing data and analysis standards, and the amount of work involved with each option. Ultimately, the final decision for resolution resides with the study team although sometimes it will get escalated up the chain of command. The final solution often

either creates the need for a modified standard or additional explanation in the Reviewer's Guide. When this happens, the standards support team continues to work closely with the study team to ensure clarity and transparency.

CRO

Disagreement handling within teams will generally be handled by the standards supporter with documentation of why. When possible, references to documentation in the standards, implementation guides or agency documentation and reasoning to support the decision are helpful. Disagreement within standards group is usually resolved by talking out the options with reasoning within the group. When a clear path forward is not evident, the SME for that topic area will weigh in.

If a CRO study team and Sponsor are having a difference of opinion, standards team may be brought in to investigate the situation and help the study team to understand the reasoning for the difference and if it is something that is required by the standards. If not, we help to provide some alternative approaches if possible or to provide reasoning why an approach does not align with the standard in question. While we can provide recommendations, reasoning and documentation when available, the ultimate decision for something like a non-standard mapping would be with the Sponsor.

UNEXPECTED COMPLIANCE RESULT

Unexpected results from compliance checking software also find their way to the standards group for resolution. In the case of unexpected compliance results, the Sponsor and CRO standard team handling is similar.

Unexpected compliance check messages become evident when our project teams are responding to their compliance output. Either the study team questions a finding or standards group may identify something that does not look quite right. Teams may come across a message with a record level detail that is not clear and will ask about how to resolve. Another way these may be found is in the review of the compliance report with explanations attached. For this type of message, sometimes the tendency for a study team is to write some text as an explanation if they do not really understand what the message means. It is part of our role in standards support to identify if there is a false positive, if the check is actually meaning something other than what the study team is understanding, or at times to help to explain why an issue remains and provide some clear explanation text that is appropriate for a reviewer guide. For example, CRITy and CRITyFL variable labels may cause a message of 'Variable label mismatch between data set and ADaM standard', but it is acceptable within ADaM to add text after the end of the label for this type of variable. A team might think that this needs to be changed because of the compliance check message, but instead it can be explained with clear text in the reviewer guide.

On the other side of this, compliance checking software cannot catch all issues such as mapping problems, variable content, checking data fields with more complex dependency or conditional/permissible existence. Because of this sometimes there is not a compliance message in the report when there is an issue in the data. However, in reviewing a project's data set specifications or looking at data sets or values a CDISC support team member might identify issues in content that are not among the structural or consistency checks that compliance software will recognize. In the review and communication with the project teams, we will give guidance to the project team to update for compliance and not only to the compliance check output. Some teams may argue that if there is not a compliance check message, then the data set is ok. For example, if an SDTM variable is created or altered in ADaM, a check may not catch this, but it is still against ADaM rules and must not be done so a data set update would be needed in this case. As a standard supporter, sometimes the disagreement to handle is explaining to the team that certain mappings or values should be corrected even if there is not a compliance check for it.

CONCLUSION

Our Sponsor and CRO data standards support teams differ in structure and process. Those we support and the variety of standards that we support varies. We train, document, and function in our own ways. Each company's specific needs require a unique solution. Because of these differences, the study team experience will also differ. The Sponsor team provides a close, long-term relationship that includes a

shared knowledge of past experiences, decisions, and solutions. Strict adherence to standards governance helps drive consistency, quick implementation, and programming code reuse across the organization. The CRO support team provides consistent support to the ebb and flow of project teams. While the CRO team history with a particular client standard may not be as long as with the Sponsor team, the CRO team has the benefit of a wide breadth of prior experiences. This varied exposure helps the CRO team to be familiar with a wide range of issues that may arise and be able to quickly come up with a solution tailored to the needs of a project. This particular company comparison shows just some of the unique issues and challenges that a company in the Pharmaceutical industry may face and the working structures and processes put in place to meet those needs. These areas and examples can be a starting place for considerations to build or even examine and optimize an existing standards team. Looking across 10 other companies, we would likely find 10 other novel approaches to support teams tailored to best meet the needs and challenges of that particular group, so this is by no means a finite list of considerations and options. While we all differ in how the support is accomplished, the common thread remains the commitment to provide the best and most compliant SDTM, ADaM, and documentation possible.

RECOMMENDED READING

- *www.cdisc.org*

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

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