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The 5 Biggest Challenges of ADaM

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ABSTRACT

Electronic submission of clinical trial documents and data continues to be a challenge for many companies. Legacy systems and processes, which work well and are efficient, have to be retooled to meet the needs of FDA and ICH requirements. While the implementation of the eCTD is maturing and the implementation of CDISC SDTM is now beginning to mature, the CDISC ADaM standard is still in the adoption stage for many companies. With many pharmaceutical and biotechnology companies making the business decision to wait until ADaM is more widely adopted or have analysis data in company specific standardized legacy formats, service providers and CROs are fully embracing the CDISC ADaM standard as the de facto analysis data standard in lieu of another analysis data standard and because of the seamless use of SDTM as the data source.

The authors of this paper have had years of experience both implementing standards within companies, submitting standardized data for many submissions on behalf of numerous clients. Through their experience, many different challenges have surfaced which they would like to share as more companies adopt the ADaM standard and with the FDA moving closer to requiring analysis being in that form. This paper will discuss the five biggest challenges to implementing CDISC ADaM and offer opportunities for organizations to make that transition a great success.

INTRODUCTION

The authors of this paper have overseen the execution of CDISC SDTM implementations and legacy data conversions by programming teams that have generated close to 5000 SDTM domains for nearly 300 studies, developing 29 submission packages for 23 distinct indications across 11 distinct therapeutic areas, from Oncology and Anti-Viral therapies to treatments for metabolic disorders and cardiac conditions. In addition, they have overseen the programming, including the development of analysis datasets and the production of tables, figures and listings for an even longer period of time, and have, in the past 2 years, moved to a CDISC ADaM based approach for this work, producing more than 250 study level and 35 pooled analysis datasets that have been included in multiple regulatory submissions for multiple indications to the Metabolic and Endocrinology review division at the FDA. The material for this paper is derived from the learning opportunities and experiences gained performing this work.

It is important to note the versions of the CDISC standards that should be currently considered appropriate when reading this paper. For SDTM the focus will be on Version 1.1 of the SDTM data model [1] and Version 3.1.1 of the SDTM Implementation Guide [2] as finalized by the CDISC SDS team in April 2005. Version 1.2 of the Study Data Tabulation Model [3] and Version 3.1.2 of the Implementation Guide [4] for this version of the model were finalized in November 2008 and released to the public via the CDISC website in late Q1 2009. The FDA formally acknowledged these versions of the model and guide in November 2009 via the Study Data Specifications appendix to FDA's eCTD guidance [5], which was tweaked / updated / republished in January 2010 [6]. This document articulated the acceptance of submissions in Versions 1.1 and 1.2 of the SDTM guided by Versions 3.1.1 and 3.1.2 of the SDTM Implementation Guide and deprecating Versions 1.0 and 3.1 of the model and implementation guide effective March 31st, 2010. While this version of the standard has been made available for public consumption, it should be utilized with caution; the FDA has recommended that you consult with your review division prior to submitting materials based on versions 1.2 and 3.1.2 of the model and implementation guide respectively and has indicated that internal systems and processes, such as the JANUS data warehouse, WebSDM checks and patient profiling tools are still evolving to accommodate this new versions of the model and implementation guide.

For ADaM, the reference will be Version 1.0 of the Implementation Guide (ADaMIG) [7] and Version 2.1 of the analysis data model (ADaM) [8], both of which have been available via the CDISC web site since December 2009. Key characteristics of this version as compared in the draft version include the removal of some previously defined variables and the addition of many other variables to support a range of analytical reporting needs.

CHALLENGE 1 – SDTM VS. SOURCE CRF DATA

The first challenge facing organizations contemplating the use of the CDISC ADaM standard, "where do I begin?" What is the basis for my analysis dataset implementation?

ADAM DATA SOURCE

The age-old adage states, “A journey of 1 or 1000 miles both begin with a single step”. The challenge here is, from where do you begin that journey? Depending on the point in the developmental timeline you are contemplating creating CDISC ADaM based deliverables you might a have a number of potential source data repositories on-hand to support their creation. You most likely still have the data as it was collected on behalf of the study, known as “CRF” or “raw” or “Source” data. For consistency throughout the paper, this data will be referred to as “Source” data. You may have already created analysis datasets to a corporate or Service Company provided standard. You might have SDTM domains that were provided directly by a service provider or were converted from a legacy platform to SDTM. And, complicating matters, external data that fall into one or more of the three previous categories, from external source data such as laboratory and ECG information, over read data from clinical professionals and the results of a subsequent pharmacokinetic, pharmacogenomic or immunogenicity analysis might also be available for your consideration. Where do you begin?

The likely scenario is that all of these items play a role in the development of your compound to date and you will need to consider all of them in some capacity in order to assemble a coherent submission. The challenge is that the more sources of data that were created at different time points adds to the complexity of preparing CDISC ADaM components.

ADaM analysis datasets currently allow for multiple sources of data, including SDTM domains, legacy analysis datasets, CRF data, and external data. The more hybrid sources of data, the more complex and complicated the documentation contained within the data definition table (DDT, a.k.a. define.xml or define.pdf) document becomes. The use of SDTM and legacy analysis study data have clear folders in the eCTD; however, the used of CRF or external data may not have a folder in the eCTD.

SOURCE DATA IN THE ECTD

The key to successful agency review from a data perspective is traceability. You need to provide data and supporting documentation that establish a clear path from data collection through to analysis. In order to do this you need to consider where in the eCTD structure you have the opportunity to place the items that offer this transparent view. SDTM domains and study-level analysis data have clear placeholders in the eCTD structure. The challenge is, if you have developed your study-level analysis data from source data rather than SDTM domains and you intend, as guidance suggests, to present your case report tabulation, or CRT data as SDTM domains in your submission, you have lost your opportunity to provide the desired level of traceability. Furthermore the programs used to produce your analysis datasets, which also have a placeholder in the eCTD, will refer to data other than you what you have provided in your submission; while a statistical reviewer will be able to deduce a general model or methodology from your programs, they will likely request that source data also be provided during the review cycle in order for them to reproduce key results.

NON-SDTM SOURCES FOR ADAM

The CDISC ADaM model contains a number of variables that come directly from a CDISC SDTM implementation. If you choose to source your analysis datasets from something other than CDISC SDTM, but intend on submitting SDTM domains as your CRT data, one solution is to develop a bridging document. This document can be provided as part of your data definition table for your analysis datasets, either as an appendix or as a companion item. It would contain a number of instructions and explanations on how data elements appearing in the analysis datasets were derived from source data and how that source data was transformed when producing SDTM domains, explaining ultimately how to connect the two. Again, the goal here is to provide as much traceability and transparency as possible.

In summary, if you have made the investment in CDISC SDTM domain development and intend to include these domains in your submission, the implementation of CDISC ADaM based analysis deliverables can effectively leverage this investment and provide the clear path from source to analysis. If you do not have that opportunity, you need to assess your current situation in terms of assets, available resources and a timeline for submission related activities and subsequently plan accordingly to provide meaningful deliverables to the agency that they can utilize efficiently during the review of your application.

CHALLENGE 2 – PROCESSES FOR CDISC ADAM

Challenge 2 for many organizations is around the processes that currently exist and how an organization should consider if the CDISC ADaM Analysis Dataset standard might require rethinking of existing processes. For organizations that have existing standards and processes this change may require a hard look at existing processes

and roles. For smaller organizations, creating a standard analysis platform using ADaM can be an easy win if current processes and roles do not exist. In fact, companies outside the US, with no intention of submitting to FDA are adopting CDISC SDTM and ADaM standards simply because of the benefits of standards.

SDTM PREFERRED SOURCE FOR ADAM

Since SDTM domains are the preferred source for ADaM analysis datasets, are the SDTM roles and processes established within your organization. The CDISC ADaM team continues to recommend the use of SDTM as the source for ADaM datasets. Most examples and discussions in the ADaM Implementation Guide or what is frequently referred to as the ADaMIG, refer to SDTM data as the preferred source. However, others sources are allowed as of the writing of this paper. SDTM is a critical part of implementing ADaM, therefore the organization should consider these challenges for SDTM implementation in addition to others that will be presented.

Some questions to ask yourself:

- Do you have SDTM expertise in house?
- Is your staff trained in the use of SDTM? *Not just read the manual*
- Have you considered over arching standards governance? *Governance group may include SDTM, ADaM, but also CRF Design, TFL Shells, SAPs*
- Has the organization created an SDTM interpretation? *SDTM has some grey areas.*

ADOPTING ADAM AS STANDARD

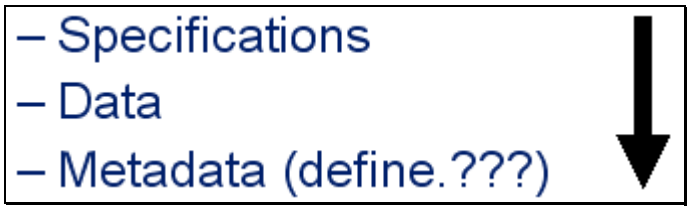
Like just described for SDTM, your organization should have well defined roles and processes around ADaM implementation. Standards governance was already mentioned as something that is clearly needed, but have you also considered how you will manage enhancements to your internal interpretation of ADaM? Some organizations have a metadata repository to store and use these important decisions. What about new and existing roles in your organization? A hybrid role has emerged within our organization that bridges the role of the traditional statistician with that of an experienced programmer.

Some questions to ask yourself:

- Do you have ADaM expertise in house?
- Is your staff trained in the use of ADaM? *Not just read the manual*
- Who is authoring your ADaM Specifications?
- Has the organization created an ADaM interpretation? *ADaM has more grey areas than SDTM*

THE CHICKEN OR THE EGG

"Which came first, the chicken or the egg?“ Cultural references to the chicken and egg intend to point out the futility of identifying the first case of a circular cause and consequence.



The arrow on the figure above references a normal workflow. ADaM specifications are created, ADaM datasets are programmed and validated, and the metadata is documented through a Define file for FDA. The arrow indicates a linear flow but the process does cycle as data specifications are executed requiring updates. Some organizations simply start with creating data and documenting it, no specifications. This approach seems risky. Some organizations start with defining the metadata document then the data. This approach seems restrictive. The point here is to

establish a disciplined, repeatable approach to creating ADaM datasets in the organization. This might be called Active Metadata Management (AiMM).

IMPLEMENTATION STRATEGIES: SDTM AND ADAM

Susan Kenny and Michael Litzsinger wrote a PharmaSUG paper in 2005 titled "Strategies for Implementing SDTM and ADaM Standards". [9] The paper is a really quick read. Review it to determine how to describe your current process and what is the optimal process going forward.

The paper simply defines the advantages and disadvantages of different strategies for implementation.

- Parallel Method: development of ADaM and SDTM are independent
- Retrospective Method: use analysis datasets to create SDTM at time of submission
- Linear Method: create SDTM first then ADaM
- Hybrid Method: draft SDTM to ADaM to final SDTM
- *Multiple Sources Method <NEW>:* create SDTM at time of submission combine with Legacy Analysis data

The authors added a new method, which is commonly seen in practice from organizations, it is the Multiple Sources method. The Multiple Sources method involves creating SDTM for the eCTD then creating a SDTM integrated pool. This SDTM integrated pool with the addition of legacy analysis data becomes the integrated ADaM analysis datasets for the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS).

IMPLEMENTATION STRATEGIES: TRACEABILITY

Each strategy listed above has its own set of challenges. For the Parallel method, a bridging document creates a documentation bridge between the two standards that helps when questions arise from the agency. It will also ensure conclusions made from the SDTM data are supported and concur with the conclusion made by the ADaM datasets. For the Retrospective method, as Kenny and Litzsinger's paper describes and the authors would agree, the disadvantages outweigh any advantages. The Hybrid method, an organization would first draft SDTM then create ADaM to then create final SDTM. This method has clear traceability. The Linear method creates fully compliant SDTM then ADaM analysis datasets. This method also has clear traceability. The CDISC SDTM/ADaM Pilot Project report states this clearly; " the most pragmatic approach to creating analysis datasets was to use the SDTM domains as input. This ensured that the reviewers would be able to trace the creation of derived variables contained in the analysis datasets back to their source in the SDTM datasets and ensured that the analysis dataset creation programs would be of value if requested by the review team." [11] What is seen a lot during the adoption of the CDISC standards by industry is a Multiple Sources method. Again the challenge is blending the two or more heterogeneous structures together with the specifications, with the programming logic, and in the Define documentation. The risk here is if this will save or increase the timelines at a critical point in the submission. So plan carefully. Below find some highlighted challenges and opportunities of each method.

- Parallel Method
    - Challenge: FDA doesn't have the original source data
    - Challenge: No traceability unless a bridging document is provided to connect ADaM to SDTM data
- Retrospective Method
    - Challenge: FDA doesn't have the original source data
    - Challenge: All source variables would need to be present in the analysis datasets "as-is"
    - Challenge: Validation of SDTM back to source data is necessary
- Hybrid Method
    - Opportunity: Complete traceability from ADaM back to SDTM and source
    - Have not seen this used in practice
    - Tendency towards Linear Method with defined iterations
- Linear Method (Recommended)

    - Opportunity: Logical flow of the software development life cycle
    - Opportunity: Complete traceability from ADaM back to SDTM and source
- Multiple Sources Method
    - This is reality during the adoption of CDISC standards with years of completed clinical trial data
    - Challenge: Combining heterogeneous sources together
        - SDTM + Legacy Analysis Data
    - Opportunity: All source data is contained in eCTD

CHALLENGE 3 – ROLES NEEDED TO EXECUTE CDISC ADAM SUCCESSFULLY

For many organizations the challenge is defining the roles needed to execute CDISC ADaM successfully. As stated earlier, the organization should take a hard look at existing roles and ensure they are adequate for successful execution. Maybe it is time to rethink the roles in your organization?

ADAM SPECIFICATIONS

As mentioned before, are qualified individuals with appropriate ADaM and SDTM training and industry experience writing your ADaM specifications? A clinical programmer would be a logical choice but these individuals may not have enough experience writing specifications. A statistician is the logical choice if they are not resistant to adopting the new ADaM standard. Think about a new role in the organization that is a hybrid role between clinical programming and statistics. Does one of your clinical programmers have a statistics degree that is going unused? The opportunity for the organization is a potential new career path for experienced programmers.

ROLES FOR ADAM AND DEFINE.???

Today define.pdf can still be used as the documentation method for ADaM data to the FDA. Existing processes internally or with your vendor of choice are still relevant. Make sure to discuss the documentation type with FDA before any submission. The CDISC SDTM/ADaM Pilot project used define.xml as the documentation method. [11] For STDM data, define.xml can be used however at the writing of this paper define.xml is still being fleshed out by the CDISC ADaM and ODM teams. A challenge facing the organization is the need for an XML/ODM expert. Do you have the technical expertise and appropriate role within the organization to create define.xml? In some organizations, learning XML and the CDISC standard ODM is precariously assigned to one of the SAS® programmers in the group. Is this really the right fit? Is it time to create a new role? Maybe a validated tool or a partnering with a vendor makes sense in the short term.

What current staff or groups create the define document in the organization for your submissions to FDA?

- Programmer
    - Challenge: Use SAS or a Tool/System
- Statistician
    - Challenge: Isn't the best use of this resource the review of the documentation?
- Regulatory Staff
    - Opportunity: Use a validated Tool/System or partner with a vendor

There are many other roles that should be considered that might need to be created with the adoption of standards. There will be others as the standards evolve. Here are some examples seen emerging in industry:

- Data Stewardship Manager
- Data Standards Specialist
- Manager of Clinical Data Repository

CHALLENGE 4 – TIME AND RESOURCE CONSIDERATIONS

Some time and resource considerations have already been touched on with the discussion of roles and processes, now let's look a little more specifically at some of the datasets being created from the ADaM standard and review some of the challenges and opportunities that have been uncovered.

FLEXIBILITY OF THE ADAM STANDARD

ADaM does allow for flexibility so that analyses are appropriate. A challenge for your organization is that differences in interpretation can affect timelines. A disciplined approach to standards through governance, metadata management, or simply a working group or standards committee can lessen differences in interpretation. Communication and training of the decisions then becomes important. Get everyone on the same page.

ACTIVE METADATA MANAGEMENT (AIMM)

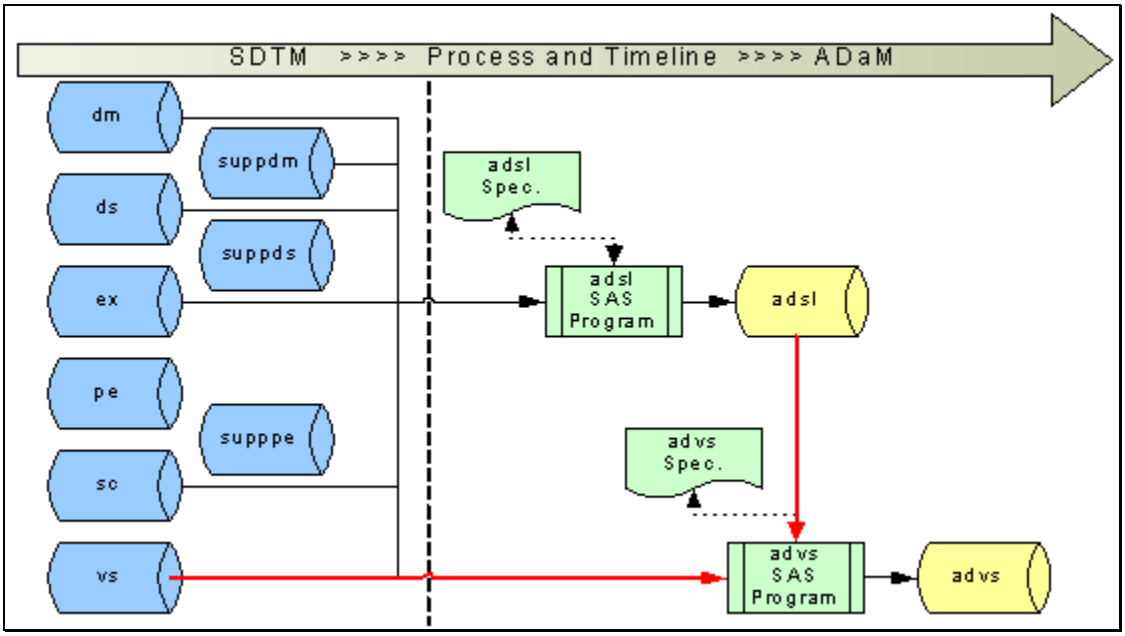
This might seem out of place but it is important to consider all the sections above. Actively managing the metadata within the organization includes looking at your processes, tools, systems, and roles; and how they all interacted together. The opportunity here is a paradigm shift to actively manage the entire ADaM dataset development process through new processes, tools, systems, and roles. The opportunity for the organization is to increase quality and reduce rework by enhancing the entire process from specification through execution then to documentation.

ADAM MAY NOT SOLVE OLD PROBLEMS

As with any standard, company, department, or therapeutic area, ADaM does not solve old problems. Even with SDTM, there are even greyer areas of interpretation with ADaM. ADaM allows for structures to continue being highly vertical like SDTM but the standard also allows for highly horizontal structures. As you work on the individual studies that will go into your submission someday, decisions made early may adversely affect later studies. But what squanders time and resources even more are decisions made on later studies that are retrospectively added back to earlier studies for consistency. The challenge for your organization is to strategically decide where to spend time and resources on consistency. The opportunity here is to let individual studies stand on their own and during the integration efforts harmonize the dataset structures for the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS).

ANALYSIS DATASET SUBJECT LEVEL (ADSL)

The subject level analysis dataset (ADSL) is a minimum requirement of having a compliant ADaM submission. The intent of ADSL is well defined, but very study specific. This seemingly simple dataset can be come the biggest bottle neck when implementing ADaM. See below that changes to certain SDTM domains can require updating of ADaM analysis datasets, rerunning of programs, and revalidation of datasets, which wastes valuable time.



As the diagram on the previous page shows, the ADSL dataset requires inputs from many SDTM domains; coordination across groups in the organization can be problematic. As already stated, changes to later studies can increase rework at the wrong time near the time of submission. Management and stakeholders (for example Medical writers, statisticians, sponsors, regulatory) do not understand why this dataset takes so long to create and finalize. Communicate early the scope and the possible increase in timelines. The following sections in the paper will cover ideas you can implement to overcome the ADSL bottleneck and other timeline challenges. The bottleneck is simply stated in the ADaMIG; "… any other fact about the subject that is relevant to analysis or review" add to ADSL. The challenge is to prevent ADSL from being a dumping ground of nice to have variables. The opportunity is to keep the number of variables in ADSL to those absolutely necessary

ANALYSIS DATASET BASELINE (ADBL)

Some team members came up with a novel concept of a baseline analysis dataset that is more flexible for allowing changes in analyses late in the game. Adding additional variables to ADSL can eat into timelines at the wrong time. If variables are added to ADSL, this dataset should be rerun and validated, then all ADaM analysis datasets would also have to be rerun and validated. Because all datasets are rerun all supporting output, tables, figures, and listings would need to be rerun and validated so that the time stamp is chronological. This can really affect timelines at the wrong time.

The new concept of ADBL being created after ADSL is created and all ADaM datasets are created is a simple and an innovative solution. ADBL pulls baseline values from already created ADaM dataset like ADLB and ADVS. The challenge is that ADBL is not "One Proc away" but could be considered "Analysis Ready". The opportunity here is that ADaM currently is more about documentation and traceability so this solution could reduce rework. As new subgroups and analyses are specified the ADBL dataset can be updated and only tables that use this dataset are rerun.

ANALYSIS DATASET LABORATORY (ADLB)

This is not a new problem but ADaM might amplify the magnitude with the merging of ADSL on to each dataset. Merging a huge ADSL on to a huge Laboratory dataset can waste time and resources if an organization does not have powerful servers. But even with powerful servers the size of laboratory datasets could be problematic for the agency to process. Laboratory datasets are generally large in size and after merging ADSL these datasets can become gigantic. The challenge, does the organization have the correct technology so not to waste time and resources?

The opportunity, regardless of your company's technology, is to divide ADLB into three Lab Analysis Datasets:

- ADLBC – Chemistry
- ADLBH – Hematology
- ADLBO – Other, including Urinalysis

Also, here is where having a well-defined ADSL is important. The new ADBL might also help keep these data types or other large data types like Questionnaires (QS) to be a more manageable in size.

TRAINING STAFF AND EDUCATION

Training and education of staff should not be overlooked with up front investments increasing quality and reducing rework. The challenge, there is significant ramp-up and cost to create training programs for SDTM and ADaM with intermittent maintenance. The opportunity here is to have a vendor give instructor led training or look into buying virtual desktop training. This is a classically overlooked cost that has great returns.

UPDATING EXISTING SYSTEMS AND MACROS

Another classic cost to the organization is the updating of your systems and macros to use the ADaM standard. Updating of existing systems and macros to use ADaM should be strategically analyzed. Now that ADaM and the ADaMIG are stable and further updates will be backwards compatible, the opportunity is that it might be a good time to dust off that update plan now. However, if further stability and wider use by the industry is requested by your organization's leadership use the opportunity to partner with a vendor until a more widely excepted release is vetted.

ACCELERATE TABLES, LISTINGS, AND FIGURES (TLFS)

In conclusion of this section, well-designed ADaM datasets can accelerate TLF production when timing is most critical. Has your organization considered all the recommendations in the previous sections?

- Governance
- Interpretation
- Metadata Management
- Specification Development
- Training/Education
- Implementation and Development Strategies
- System Updates

Make sure to consider all of these.

CHALLENGE 5 – MANAGING INDUSTRY AND REGULATORY EXPECTATIONS

The final challenge might have a more pragmatic title might like, “Okay, if I go to all of this trouble, what is in it for me, my work group, my company and, ultimately, the individuals who will use my compound some day as a result of a review of the deliverables provided for review using this standard?”

MOTIVATION FOR CONSIDERING CDISC ADAM STANDARDS

All of you are reading this paper for one reason or another. Each of you represents a unique combination of factors that lead to your interest in this topic. Perhaps you have been directed by company leaders to establish ADaM standards for analysis assets. Maybe you have a personal goal to remain current on industry standards surrounding the presentation of data for statistical review at the agency or you want to remain current and marketable in today’s precarious economy. Others might be motivated by the realization that you could save your company considerable time and resources by leveraging their investment in CDISC SDTM domain development as a springboard for CDISC ADaM standard adoption. All of these are reasonable motivations for considering CDISC ADaM standards, but what are your expected results if you pursue this implementation?

SPONSOR COMPANY MANAGEMENT

In the short term the primary motivation for considering CDISC ADaM would be the opportunity to leverage your existing CDISC SDTM investment. The Linear implementation and inclusion of CDISC SDTM and ADaM assets in your submission provide a clear, sponsor independent standards based implementation that will, hopefully, lead to a transparent, efficient and accurate regulatory review. This assessment of CDISC ADaM might lead to the realization that completing a retrospective legacy SDTM implementation is prudent in order to secure a successful product review, which will also support an ADaM implementation.

There are a number of probing questions your can ask of yourself and your organization as you are contemplating CDISC ADaM implementation, specifically addressing when you would be attempting this implementation. While the ADaM standard is truly an application of a nomenclature and organizational structure to a process that organizations currently execute, the learning curve with these items can be steep, particularly if CDISC SDTM standards have only recently been added to the mix. If you are leveraging that high-profile, well-funded project in order to make the implementation of ADaM happen, make sure you have the necessary bandwidth in terms of people to truly understand the standard, its relationship with CDISC SDTM and nuances of its use to represent the analysis assets for a submission.

SPONSOR COMPANY STAFF AND SERVICE PROVIDERS

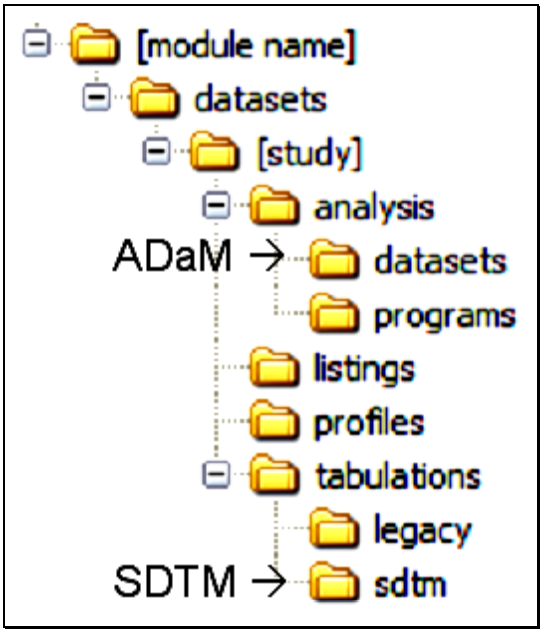
On the other side of the coin, if you are working with CDISC SDTM to build your analysis datasets to a standard other then CDISC ADaM, you need to ask yourself why you are spending considerable time undoing the inherent

efficiencies of standardization offered by CDISC as a whole.

The implementation of a standard independent of any particular sponsor company or service provider will allow for a number of efficiencies over time. Many of the tools, such as data and metadata validators for SDTM domains can be modified to address the requirements of ADaM based assets. The use of this independent nomenclature will provide a common language that can be used to effectively communicate requirements and results. And the knowledge, skills and abilities of the analysis or statistical programmer, for so many years regarded as one of those mystery sciences that you just had to "do" in order to be regarded and respected as a capable individual, will become more transparent and transferable from one organization to another.

REGULATORY AUTHORITIES

From a standards perspective, the FDA's eCTD guidance currently sets a very low bar. This guidance [6] dictates that you provide your analysis datasets and also gives you a location to provide programs used to produce the analysis datasets and table, figures and listings generated from the analysis datasets (see figure below). Tables, figures and listings have a place within the eCTD structure, primarily as components to the associated Clinical Study Report and Summaries of Clinical Safety and Efficacy. Only recently has this document been updated to suggest a possible standard (ADaM) and they only indicate it is a divisional review question, not a mandate. Industry largely still follows the "99" or "traditional" guidance for these analysis datasets but, beyond that, the ultimate structure and content are left largely to the sponsor's discretion. And once these items end up in the hands of the statistical reviewer, they have a number of powerful tools, such as SAS, SAS*JMP and iReview to perform their review functions but without any significant enhancement beyond what is available "out of the box".



If the statistical reviewer has not received all of these items they will typically request them, and then take on the responsibility of learning all about what has been presented to them in order for them to complete their review of efficacy claims made by the sponsor. You can see the role of an analysis dataset standard could play a part in making the role of the statistical reviewer that much more efficient.

The FDA is moving in a direction of setting higher expectations for analysis datasets and related documentation as part of a regulatory submission. In the recent version of the Study Data Specifications [6], the agency suggests on Page 5 that, "Prior to submission, sponsors should contact the appropriate center's reviewing division to determine the division's analysis dataset needs. CDISC/ADaM standards for analysis datasets (http://www.cdisc.org/adam) may be used if acceptable to the review division." As the agency sees more and more CDISC ADaM based submissions of analysis data and related metadata, they will likely start to request it as part of the pre-NDA process or during the review cycle. Indications are that the FDA's expectations will become even clearer as 2010 progresses; Per the FDA web site [10], CDER plans to issue a guidance document in 2010 entitled "Providing Regulatory Submissions in Electronic Format – Analysis Datasets and Documentation". It is starting to look like the agency adoption of CDISC

ADaM standards will occur much quicker than the 3 years it took for CDISC SDTM to become a part of regulatory guidance.

CONCLUSION

How fast FDA will adopt ADaM officially is still an unknown. Adoption, however, seems to be accelerating rapidly based on documents recently published by FDA and requests for ADaM datasets being made from sponsors and clients of the authors. As discussed, the use of SDTM as the source for ADaM is essential. Establishment of robust processes and strategies for metadata management and traceability can increase success at the time of submission. With new standards and processes come the creation of new important roles and the rethinking of existing roles. Being new to many organizations, the ADaM standard will be interpreted differently by individuals and groups in your organization. Communication, training, and interpretation, therefore, are essential to get everyone on the same page. Finally, set everyone's expectations realistically and early. During the first implementation having multiple changes at once generally takes more time but improvements will be seen over time in reduced execution times of clinical trial programs and decreased review times by FDA. Remember, the ultimate goal is better, safer treatments making their way to market to improve patient lives through the use of standards.

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