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Practical Lessons Learned from Recent NDA and BLA Submissions to the FDA

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ABSTRACT

This paper describes lessons learned from two different FDA filings. The first is a late implementation of strategies to reduce Pinnacle 21 errors and warnings in a large pivotal drug trial. The focus will be on action items used to address specific issues as well as sponsor and Clinical Research Organization (CRO) collaboration. Additional discussion will be given regarding the use of sponsor subject matter experts. Future considerations will be given on how to avoid implementation issues. Successful eSubmission was achieved with the right plan, persistent adherence to the plan, and a positive collaboration between sponsor and CRO. The second filing is a biologics application with SDTM and ADaM data for individual studies that had divergent implementation methods that required remediation for pooling. Lessons learned will focus on communicating sponsor specific implementation strategies to CROs during development of SDTM and ADaM.

INTRODUCTION

AUTHORS' BACKGROUND

Carey has 35 years of experience using SAS software. He spent his first 14 years in academia as an epidemiologist and has spent the past 21 years in biotech, medical devices (*in-vitro* diagnostics) and pharmaceutical work. He has been involved in the approval / clearance of more than 20 products submitted to the FDA – including NDA, BLA, PMA and 510(k) submissions. His areas of therapeutic experience include: thrombosis, *in-vitro* diagnostic screening and monitoring assays, companion diagnostic assays, vaccines, and Alzheimer's disease.

Lisa has worked in drug and vaccine development for over 20 years and began consulting in 2007. She is a statistical programmer by trade, project manager by nature, and standards expert by careful study. Her consulting focuses on supporting small pharmaceutical and biotech companies in their CDISC data submissions for licensing applications. She has been involved strategically and logistically in 10 New Drug and 2 Biologics License Applications.

INDUSTRY BEST PRACTICES

Pharmaceutical and biotech companies currently have all the necessary means to comply with the FDA requirement for submitting data that conforms to Clinical Data Interchange Standards Consortium (CDISC) standards such as Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) (Smoak 2017). However, getting studies ready to submit to the FDA is challenging even in the best of circumstances. But what if you are hired by a pharmaceutical or biotech company after studies have been started and decisions have been made that were not in line with industry best practices?

What are best practices for submitting data to the FDA? Sirichenko and Kanevsky (2015) have identified the most common data issues in FDA submissions:

- Metadata Issues
- Annotated CRF Issues
- Reviewer's Guide Issues
- Non-Compliance with FDA Business Rules
- Programming and Mapping Errors
- Controlled Terminology Issues

Based on this list, sponsor companies have a lot of pitfalls to avoid in submitting data to the FDA. With the new requirement by the FDA to follow CDISC standards for studies starting on or after 17Dec2016 (see FDA Data Standards Catalog at https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm#Catalog), the

bar for submitting data to the FDA has been set even higher. The challenge increases as many companies contract work out to one or multiple CROs. Thus, sponsor companies need to follow good practices to avoid the common data issues mentioned above.

What are the best practices for managing multiple CROs? There are many best practices, but Nataraj and LaPann (2017) provide some valuable insights with respect to data standards, including:

- Create a Standards Roadmap with long and short-term goals
    - Discuss and provide CDISC standards interpretation
    - Implement Sponsor Standards Library and release after UAT
    - Share in the evaluation and implementation of CRO Processes and Tools

Ahrweiler, Mathur and Ignacio (2015) also realize the importance of a sponsor defining SDTM and ADaM implementation for CROs. Mabe (2011) has developed a method for developing a company standard for SDTM implementation. One of the benefits that Mabe (2011) mentions for developing a company standard is to facilitate traceability for integrated analyses, such as ISS/ISE.

NDA

Prior to the authors' engagement at a mid-size pharmaceutical company, a large CRO was selected for biometric services in support of a very large and long running pivotal trial. When we became engaged in the project our main objective was to ensure that the electronic data was compliant with standards developed by CDISC and eSubmission ready for a New Drug Application (NDA). Up until our involvement, almost no guidance had been given to the CRO on implementation of SDTM or ADaM. Furthermore, the landscape of clinical data standards had developed immensely since the study started. Consequently, the first time that we ran Pinnacle 21, there were hundreds of thousands of errors and millions of warnings. We needed to develop and implement a strategy to address the numerous errors and warnings and institute a system to track progress.

The sponsor's biometrics team had a good understanding of the requirement for a strong data submission to support the NDA filing. However, it was necessary to educate the sponsor's key stake holders in project management, regulatory and the executive team regarding resources, timing and cost. We learned that the primary concerns were quality and timing for key milestones. In response, we developed a high-level Management Summary Report that provided information on improvements in quality as far as reduction in warnings and errors, achievement of stable domains, and completion of tasks as far as data review and programming.

STRATEGY IMPLEMENTATION FOR NDA

Our first step was to review the Pinnacle 21 report to identify possible sources and causes of the errors and warnings. We prepared a detailed document of SDTM Review Findings to identify common issues and rank complexity. To facilitate review and resolution, these findings were categorized into 2 areas:

- **Mapping Specification Findings**:
    - Time consuming data review
    - Easy to medium programming changes
    - Unit conversion for local labs
- **Open CDISC Validator Findings**
    - Missing domains
    - Duplicate records
    - Date inconsistencies
    - Controlled Terminology messages
    - Data inconsistencies (expected variables missing, i.e., EPOCH)
    - Data attribute errors (incorrect variable names, labels, and types)

Our next step was a face-to-face meeting between the sponsor company and the CRO to discuss the Pinnacle 21 findings. There was initial pushback by the technical team at the CRO. Meeting face-to-face proved invaluable in developing a collegial relationship with the team. We jointly developed action items to deal with the Pinnacle 21 findings. The CRO was given the task of developing a timeline and budget to implement the action items. It was clear that this effort would be on the critical path of the NDA submission timeline. A contract change order was negotiated and executed. Regular teleconferences were set up to keep track of progress on the action items. On the sponsor side, we ran and annotated the Pinnacle 21 validation report upon each data transfer from the CRO to keep track of the resolution of the issues and to identify stable SDTM domains. The high-level Management Summary Report was reviewed and regular meetings by the sponsor's program oversite team to ensure that we were making progress towards the submission deadline.

ACTION ITEM TRACKING

From a careful review of the report's Issue Summary and Details tabs, we categorized each type of issue and placed them in a tracker. Issues were categorized to streamline action items and were grouped into 5 categories:

- Controlled Terminology Error
- Domain Structure Error
- Duplicate Error
- Missing Value Error
- Visit Error

Further issue description included domain, variable, and examples of problematic values. The actions included specific and adjudicated agreement on how to fix errors, who was responsible, and the timing for expected completion.

Actions included:

- Document in SDRG after database lock
- Items that could be implemented immediately (this includes data cleaning and programming changes)
- Items that could be implemented after a dry-run was completed (this includes data cleaning and programming changes)
- Controlled terminology issues that needed to be reviewed and implemented
- No action to take

For the controlled terminology issues, we took the issues from Pinnacle 21 and put them into a spreadsheet. We developed a process of identifying terms that needed to be mapped. We also identified a group of subject matter experts, mainly in Clinical Operations, to provide input on how to map the terms. Input from Subject Matter Experts was documented and delivered to the CRO programming team to implement. Having a dedicated group to provide input to the CRO resulted in more consistent implementation with less iterations.

Review of the Pinnacle 21 report identified issues in data cleaning. The CRO team and the sponsor team worked closely with Data Management to develop database queries, self-evident corrections, and notes to file to document known issues.

Implementation of the action items by the CRO and sponsor lead to an immediate and dramatic 68% reduction in error and warning messages within 6 weeks. The sponsor's annotated Pinnacle 21 report showed that there were three primary reasons for the reduction in errors and warnings by Pinnacle 21. They were controlled terminology (reduced from 1M to 300K), data cleaning (reduced from 24K to 5K) and programming changes (reduced from 13K to 80). We continued to track efforts over a total of 3 months, including 2 face-to-face meetings and multiple Management Summary Reports over an additional two months. At the end of 5 months, there was only an incremental improvement in Pinnacle 21 findings as measured by an overall 69% reduction in errors and warnings. In total, we went from 1.7 million errors to 524,000 errors which were mostly addressed in the first 6 weeks of a targeted and planned effort. In the end, although we had many unresolved issues, we were able to adequately understand and explain each warning and error to the Agency in the clinical study data reviewer's guide.

LESSONS LEARNED FROM NDA

The lesson learned here is that sponsor companies need to give early input to CROs on dealing with Pinnacle 21 findings. When I joined the company, database lock for the pivotal Phase III study was about one year away. At that time, the sponsor company had not included resolving Pinnacle 21 issues in the scope of work with the CRO. Once the scope of the work was amended, a lot of effort was put into resolving the Pinnacle 21 findings. Three trips to visit the CRO were made that year to oversee the process. Unfortunately, many sites had closed out, but on the flipside, we were lucky that the database had not locked yet. It would have been much better for the company to properly scope the work by the CRO from the beginning to avoid such a Herculean effort towards the end of the study. This is not unusual in my experience. I have seen other companies put off working on Pinnacle 21 findings as though it was a trivial task which can be done at the end of a study. In my opinion, this is a mistake.

BLA

Prior to the authors' engagement at a mid-size pharmaceutical company, two CROs were chosen for a product that would be submitted to the FDA as a BLA. The company chose to simply ask the two CROs to implement the most recent version of the SDTMIG which at that time was SDTMIG 3.1.2 Amendment 1. The company gave no guidance to the two CROs on implementation of SDTM. As a result, the two CROs made implementations of SDTM that were different. Thus, when it came time to do the ISS/ISE, the SDTM and consequently ADaM datasets

were incompatible for integration. This made it necessary for one of the CRO's SDTM and ADaM datasets to be re-done for the ISS/ISE to proceed.

The decision by the sponsor to not give guidance to the two CROs was costly, as creation of SDTM had to be redone. This oversight caused delays in getting the ISS/ISE done and, consequently, delayed submission of the BLA to the FDA.

LESSONS LEARNED FROM BLA

The lesson learned here is that companies should not simply ask CROs to implement the most recent version of SDTM. Ideally, companies should develop an internal standard of SDTM implementation which can be provided to CROs to implement. Different CROs may still make slightly different implementations, but the sponsor company is more likely to get back compatible SDTM and ADaM when CROs are following the same company standard. Thus, ISS/ISE is likely to be easier when a company standard is followed.

It is important to note that this situation of two different implementations of SDTM is not an issue when using a tool like Pinnacle 21. Each implementation of SDTM may conform to the SDTMIG and not have any significant Pinnacle 21 errors which need to be fixed. Thus, the problem here is that the two implementations (which were ok by themselves) were incompatible for integrated analyses (i.e., ISS/ISE). The way for companies to avoid this incompatibility is to develop a company standard (a standard way of implementing SDTM) and provide the company standard out to CROs. There still may be differences in implementation due to differences in EDC systems, but the sponsor company is much more likely to get compatible SDTM implementations when they push company standards to CROs than when they do not provide a company standard.

I asked a colleague who is a director of statistical programming at a CRO (not one of the CROs used by my company) about this issue of implementation of SDTM. My colleague commented that she would prefer that companies give guidance on implementing SDTM instead of simply asking them to implement the most recent version.

DISCUSSION AND CONCLUSIONS

Under ideal circumstances (when best practices are followed), putting together a quality submission to the FDA is challenging. However, when best practices are not followed then the challenges may become insurmountable. As Poona, Busa and Southwick (2015) have shown, a Herculean effort may be necessary to rescue a project that has fallen behind schedule for submission to the FDA. While a rescue vendor may not be necessary for a project that is in danger of falling behind schedule, the challenges presented in this paper still represent a Herculean effort due to not following best practices.

First, not implementing a company standard for SDTM is not best practice (Nataraj, LaPann 2017; Ahrweiler, Mathur, Ignacio 2015; Mabe 2011). Developing an internal company standard is truly the best way to have consistency in receiving SDTM from different vendors. This also has the benefit of traceability for integrated analyses, such as ISS / ISE.

Second, ignoring fixing Pinnacle 21 findings until the end of a study is costly in terms of time to fix the problems. If a study lasts several years, generating and resolving queries may be difficult if not impossible. Thus, dealing with Pinnacle 21 findings in real-time is preferred over waiting to the end to address the issues.

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