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Working Together: The Evolving Relationship of Biostatistics & Regulatory for Support of Study Data Standardization Plans and BIMO Reviewer's Guides

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ABSTRACT

The Study Data Standardization Plan (SDSP) and Bioresearch Monitoring (BIMO) Reviewer's Guide have largely been the domain of Biostatistics since their inception. Historically these documents have been written in retrospect, but now that the use of regulatory-endorsed data standards occurs from the beginning of clinical and non-clinical execution, regulators see these documents much earlier than the full regulatory filing. As corporate regulatory organizations understand more about the key roles these documents play, they have in many cases taken ownership of the authoring and maintenance of these assets. This paper/presentation will explore the challenges and opportunities this new working relationship will have upon the support of these artifacts during their development and delivery to regulatory agencies.

INTRODUCTION

This paper will start with a brief history on what motivated the US FDA to define these documents and assets, what efforts actually led to specific tools and processes for creating these items, the challenges faced by Statistics, Programming and Data Management when producing deliverables, how Sponsor Regulatory Affairs and Operations shifted from passive consumption to active participation and ultimately how this has benefitted organizations as a whole with an eye on even more improvements in the future.

STUDY DATA STANDARDIZATION PLAN AND BIMO PACKAGES – A BRIEF HISTORY

The Study Data Standardization Plan is a document that describes a Sponsor's intended use of data standards. This document puts the impetus on the Sponsor to articulate how they intended to meet the US FDA's expectation of utilizing endorsed data standards [3] or provide justification for where they feel they can't.

The US FDA entered into a Comprehensive Research and Development Agreement (CRADA) with Octagon Research Solutions (now part of Accenture) in late 2011 to convert proprietary format source and analysis data to assets based on CDISC standards to ostensibly support some desired meta-analyses they had planned but to also experience what Sponsors were going through to prepare CDISC based deliverables from data not collected based on these CDISC standards. The pain the US FDA experienced in this process influenced them to articulate the expectation that a Study Data Standardization Plan be created and provided to the agency during asset development [4]. From there, the PHUSE working group Optimizing the Use of Data Standards took up the task of developing the template, completion guidelines and examples available via the PHUSE Global web site [1].

The BIMO package, consisting of a number of study characteristics in tabular format, line listings of specific subject information organized by site, and a clinical summary level dataset organized by site within each target study, was born out of the Office of Scientific Investigations Bioresearch Monitoring capability desiring to reduce the timeline and effort associated with gathering information needed to identify study sites that should be inspected during the review of an NDA/BLA. They were faced with an increasing number of sites per clinical trial and foreign clinical trial sites which complicated their efforts to efficiently make these determinations [5].

The BIMO package was first requested via Type C meetings and/or issued as information requests to Sponsors in 2010. The first draft guidance [6] was introduced in 2012 but superseded by a 2nd draft guidance [7] in 2018. It is accompanied by a finalized technical conformance guide [8], updated most recently in August of 2022. The PHUSE working group Optimizing the Use of Data Standards published a template, completion guidelines and a set of examples [2] for the BIMO Reviewer's Guide in 2022 as well.

SDSP AND BIMO – AN ORIGIN STORY

Both the Study Data Standardization Plan and the BIMO deliverables were born out of specific US FDA use case experiences trying to efficiently work with machine readable data to accomplish a task but met with frustration. As a result, the parties associated with executing these use cases drove the creation of requirements for providing these assets. The need for these assets were initially communicated via FDA draft guidance and reinforced via meeting

topics at various FDA/PHUSE Computation Sciences Symposium (CSS) annual meetings, resulting in the PHUSE working group Optimizing the Use of Data Standards taking up the challenge of designing and deploying useful tools to support their use.

The fact that PHUSE working group efforts defined these tools and processes that were niche deliverables meeting the needs of specific groups at the US FDA led them to fly under the radar of most Regulatory Affairs and Operations professionals as Sponsor organizations. Frequently members of Sponsor Statistics, Programming & Data Management work groups were educating their Regulatory colleagues on the existence of these requirements, notifying them that these assets would be coming their way for a regulatory filing and requesting the be added to the Submission Content Plan. Consequently, Regulatory professionals viewed these assets as the domain of Statistics, Programming & Data Management – put them together as you see fit, help us determine where they should be filed in the eCTD, and send them to us when they are ready, we will drop them in.

SHIFT IN REGULATORY INTEREST

So, what changed? In the months and years that followed formal guidance, draft or otherwise, once the agency became accustomed to receiving the Study Data Standardization Plan and BIMO data and related assets, they started to ensure they received them. The Study Data Technical Conformance Guide [4] suggest that the Study Data Standardization Plan first be provided as part of the briefing document supporting the PreIND meeting and updated at periodic, meaningful intervals, with a formal presentation in support of the PreNDA/BLA meeting and inclusion with the actual regulatory filing. The US FDA would frequently initiate the conversation seeking drafts of the SDSP at the End of Phase 2 (EoP2) meeting if they had not seen it before.

BIMO discussions have not been as consistent, as their existence is not codified in the Study Data Technical Conformance Guide but requesting documentation of a Sponsor's intentions for BIMO deliverables became part of the boilerplate response to PreNDA/BLA meeting requests. Sponsors were expected to articulate plans for BIMO package implementation in the PreNDA/BLA briefing document for agency consideration, including which studies would be included in a BIMO package and the timing of the BIMO package delivery if it was not coincident with the primary regulatory filing.

Sponsor Regulatory Affairs and Operations representatives were now on notice to prepare for and provide these assets in a timely manner. This has led to a desire for ownership of these documents by Regulatory professionals within Sponsor organization. Once they peeled back the onion layers on these documents, they realized that Statistics, Programming and Data Management professionals were currently tasked with assembling documents with content that was outside of their domain. In the case of the Study Data Standardization Plan, creation of the document involved the provision of information that came from both clinical (typical Phase I through III study support) and non-clinical/pre-clinical professionals. For the BIMO package, you would need input/support from Clinical Operations/Study Execution as well as resources responsible for maintaining the Trial Master File in addition to Stats / Programming / Data Management.

Sponsor organizations put a high priority on sending consistent messages throughout their regulatory interaction for an asset in development. Once Regulatory Affairs examined the content of the Study Data Standardization Plan, they realized that there were sections dedicated to a summary of the product in development as well as a list of relevant Sponsor/US FDA interactions (meetings, written responses, etc.) that affected the deployment of data standards. Similarly, when the content of the BIMO package was reviewed, many content areas – financial payments to sites/site personnel, decisions to outsource aspects of study execution to service providers and lists of site information (primary contact, address, phone number, etc.), among others – needed to be consistent with other places this information would be presented in the submission, primarily the Trial Master File for the study.

EVOLUTION OF THE PROCESS

As expectations and usefulness of these assets in the eye of the US FDA increased, Sponsor Regulatory professionals have taken the lead on managing the creation of these assets. Medical / regulatory authors are now assigned to, literally, write these documents but not on their own. Content providers are defined and content is developed by the subject matter experts for each of their domains. As a result, Statistics / Programming / Data Management can focus on their areas of expertise – what <u>is</u> the standards metadata for a clinical study, what will be in the set of pooled data presented in our submission, producing data listings by site in support of site inspectors – and not have to worry about items outside of their domain.

Members of Statistics, Programming and Data Management still have strategic opportunities to work collaboratively with their peers in other organizations. Cross checks of data, such as confirming the studies presented in the Study Data Standardization Plan are consistent with the set of studies included in the NDA/BLA, are essential to ensure consistent messaging; deploying SMEs from relevant disciplines for confirmation is wise.

In the future, we look forward to taking advantage of advances in Regulatory Information Management platforms. We have a goal of loading the PHUSE templates for the Study Data Standardization Plan and the BIMO Reviewer's Guide into our Regulatory platform, which will facilitate consistent use of the template to produce these assets and support joint, simultaneous "one version of the truth" editing, reviewing, approving and final publishing.

CONCLUSION

The time from the specification of Study Data Standardization Plan and BIMO Package deliverables to the universal expectation of their inclusion in a US FDA submission has driven a sea change for how these items are prepared and incorporated into eCTDs. Statistics, Programming and Data Management have had to cede some of the responsibility and decision making for these assets to other members of their organization; forgoing the opportunity for broad leadership and responsibility can be a challenge but, in this case, makes sense as the right people are filling the right roles to get something done in a timely manner with quality.

REFERENCES

Regulatory Referenced Deliverables available from the PHUSE Global website (https://phuse.global) by selecting "Deliverables" and, once in the search window, using selection criteria "Working Group = Optimizing the Use of Data Standards" and "Deliverable Types = Regulatory Referenced Deliverable":

- [1] Title = Study Data Standardization Plan V1.0 16-01-2018, link = https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/TP-034.zip, accessed 13th Feb 2023
- [2] Title = BDRG, link = https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/TP-034.zip, accessed 13th Feb 2023

[3] *Providing Regulatory Submissions in Electronic Format – Standardized Study Data: Guidance for Industry*, available at https://www.fda.gov/media/82716/download, accessed 13th Feb 2023

[4] *Study Data Technical Conformance Guide - Technical Specifications Document*, available at https://www.fda.gov/media/153632/download, accessed 13th Feb 2023

[5] Paul Okwesili, *Summary Level Information and Data for CDER's Inspection Planning* (FDA Webinar Presentation), https://acrpnet.org/wp-content/uploads/dlm_uploads/2017/04/Summary-Level-Information-and-Data-for-CDERs-Inspection-Planning.pdf, accessed 13th Feb 2023

[6] *Guidance for Industry: Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning*, available at https://www.fdanews.com/ext/resources/files/archives/1/12/12-19-12-ClinicalSiteInspection.pdf, accessed 13th Feb 2023. NOTE: this guidance had been superseded at the time this paper was written and was located in an document archive, not via the FDA Study Data Standards Resources website (https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources).

[7] *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, available at https://www.fda.gov/media/85056/download, accessed 13th Feb 2023

[8] *BIORESEARCH MONITORING TECHNICAL CONFORMANCE GUIDE*, available at https://www.fda.gov/media/85061/download, accessed 13th Feb 2023

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