Paper DS03

Structured Clinical Development – Using a Digitized Study Design and Planning to Drive Process Automation

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ABSTRACT

Innovative Clinical Development Organizations (CDO) take advantage of standards at the earliest point in the development process, during the planning stage. Standardization of protocol elements, introduction of an end-to-end process for clinical development standards and the utilization of TransCelerate's Common Protocol Template (CTP), coupled with the right technology, provide a platform for planning and executing trials more efficiently with a goal of getting products to market sooner.

For successful Clinical Study Protocol digitization, it is essential that core aspects of the protocol development process are incorporated in the solution: alignment of trials within the Clinical development Project (CDP) and Target Product Profile (TPP), structured protocol authoring, and structured development of the schedule of protocol activities (procedures). To adequately cover these core aspects, the digitization solution must cater for the needs and take input from wider user communities like, Clinical Program Leads, Clinical Project Management, Medical Writing, and Clinical Standards; thereby integrating the knowledge and information silos within the CDO.

To support the cross-silos integration and knowledge exchange within the CDO, we see the Meta-Data Repository (MDR) as an essential technology in standards-driven design and planning approach. The digitized study design and planning philosophy puts connected metadata front and center. Standardized Protocol Elements, and the structured CTP are connected to downstream standards to maximize process automation, increase data integrity and ensure consistency. Study design standards also drive other clinical operations processes such as the clinical trial supply chain, study feasibility, and study risk management, thereby having a much greater impact on operational efficiencies and cost.

In this presentation we discuss the benefits of structured clinical development, and how it drives the automation of the downstream processes effectively.

INTRODUCTION

A first question that presents itself of course is 'What is a Structured Clinical Development process?'. A simple view on it, would be that it is a structured process through which Clinical Development Projects are consistently planned and executed with a full traceability from TPP, via CDP into all clinical studies. All structured data in the process is linked and standardized to the maximum extent possible. As simple as it seems, in reality of course, the situation is quite different. The structured information lives in disparate systems or documents and there is very little of active traceability possible not to mention the gaps in standardization along the whole process.

Standardization is an important aspect of managing a clinical trial as organizations must ensure the submission data package meets stringent conformance requirements. A majority of clinical trials standardization revolves around the CDISC data standards as they are required for the submission of data to regulatory bodies. Many research organizations focus strongly on developing processes to manage the implementation of standards on a study level End-to-End (E2E). The process typically starts from data collection (CDASH), to tabulation (SDTM) and analysis (ADaM), and perhaps through to Tables, Figures and Listings (TFLs). That is the most common scope of the E2E implementation in organizations today. However, that scope misses the standardization of the clinical protocol elements, standardizations of the clinical trials within the same project and standardization of the CDO processes which execute the trials.

TODAY'S CHALLENGES

One of the main challenges affecting the clinical development organizations today is difficulty in processing and managing the clinical project information within disparate and disconnected systems and documents. That challenge impedes the separation of operational information to execute trials efficiently and guidance / background information justifying the need for the trials. In such an environment, structuring and standardization of the operational information presents a considerable challenge.

To overcome the information silos and formats, organizations adopt solutions that ease the burden of structuring and standardizing information. Many organizations have adopted an MDR as a solution for managing data standards, usually after a period of managing standards using Microsoft Excel. Excel is a very good place to start, you can define and get some control of standards at the study level, but it is not a scalable solution. With an MDR you have a central repository for standards management that provides versioning and governance capabilities, and a solution to ensure reuse of standards across studies. When managing relationships, in the form of mappings and transformation logic, between the standards, for each stage of the clinical data lifecycle (e.g. CDASH, SDTM, ADaM), the MDR becomes the single source of truth for data specifications.

An MDR will provide mechanisms for integrating with other systems, either directly via API for a robust option, or by other means such as an export/import paradigm or creation of database views. An MDR can expose mappings and transformations to the processes and software solutions used to create study data artefacts, such as SDTM domain datasets.

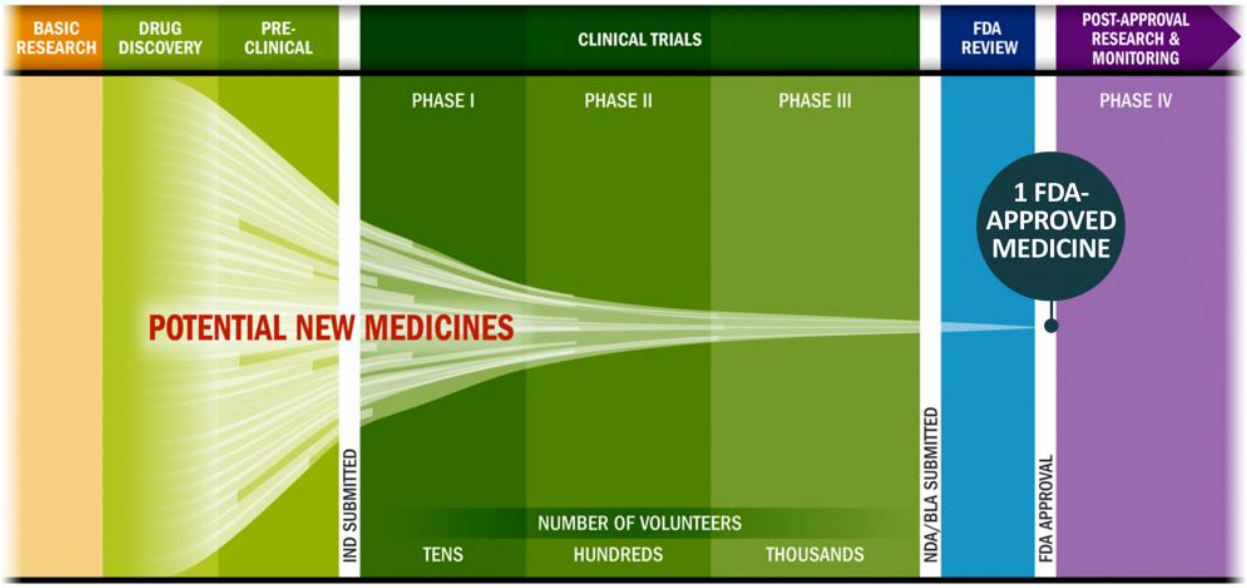
Most organizations are managing end-to-end standards in some form or another, and for the majority standardization starts at the data collection stage with EDC specifications, but that is not the starting point for the definition of study data requirements. The protocol first defines study data requirements, and any discrepancy between the data described and defined in the protocol and the data collection specifications in the MDR, becomes the first point for deviation from standards. Any discrepancy found at this point can be addressed by updating the protocol, if still in the authoring stage, or adapting the data standards to accommodate the discrepancy. Both approaches have cost, resource, and timeline implications and may have additional downstream consequences.

The Gartner CDISC Business Case[(1)] states that 80% of the benefits derived from standards occur in the study startup phase, so standardization must really start in the study planning stages. If standardization doesn't start at the protocol, the percentage efficiency benefits start to quickly erode. It is important for CDOs to recognize that study data standards alone won't help them see anticipated efficiency benefits. This is often because data standards are just layered on top of existing processes. A holistic innovation approach that adopts a digitized protocol and process redesign might be disruptive but is required to maximize the value of standardization and realize significant cost and efficiency pay-offs.

METRICS AND DRIVERS

The clinical development process is complex, long and costly. Due to the laws of nature and the way our compounds act and affect our bodies, there is always an expected attrition of the drug candidates along the R&D path. This type of attrition is hard to predict and can hardly be affected. However, any other type of attrition that involves the process complexity or the choices and decisions that we make along the R&D process can be affected and are made more transparent through the structured, linked and digitized information.

The Biopharmaceutical Research & Development Process diagram (figure 1) shows the attrition rate is significant in the discovery, pre-clinical, and phase I stages of development. Beyond phase I the outlook for success improves. Attrition does still occur in this stage, as efficacy assessments don't generally begin until Phase II after the definition of a safety profile. Standardization of study and clinical development plan design can contribute to more predictable outcomes and higher success rates. High quality design, supported by standards, can help to reduce protocol amendments or even unnecessary attrition.



* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars). Including the cost of the many potential medicines that do not make it through to FDA approval.

Figure 1:The Biopharmaceutical Research & Development Process[2]

Delays at any point in the process can significantly affect the clinical development timeline. Study delays occur for many reasons, but if the delay is caused by bad planning that is a very costly mistake. It is estimated that 85% of all clinical trials will experience delays, with 94% being delayed over a month[3]. The financial impact of those delays can be massive, costing between $600,000 - $8M every day[4].

Contributing factors to unnecessary delay in the clinical development timeline include, but are not limited to:

1. Disconnected and manual processes in clinical operations
2. Development of protocols as standalone documents not explicitly connected to downstream processes
3. Fragmented information and disconnected workflows
4. Lack of a centralized knowledgebase for key design decisions within a program

DIGITIZED PROTOCOL AND STANDARDS

The release of the TransCelerate Common Protocol Template, and its rapid uptake, provides opportunity for digitizing the protocol development process and tying it in to downstream standards. Once modelled in an MDR the CPT can connect to downstream data standards, for example, making a connection between a schedule of activities (SOA) table and the metadata for an EDC build. Assuming the MDR holds operational metadata for the EDC system, the EDC build could be driven directly from the SOA table, in a digitized protocol solution.

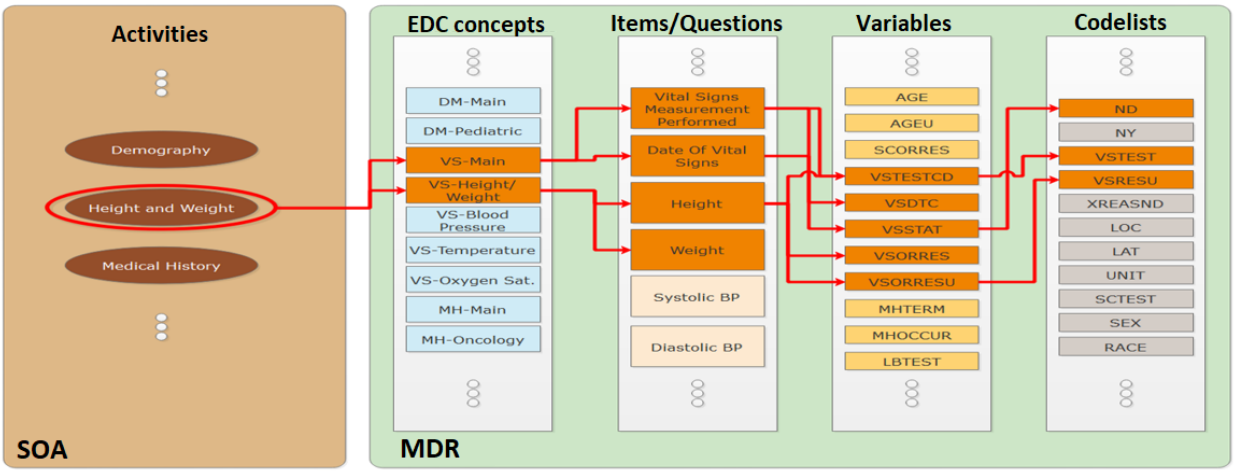


Figure 2: An example of SOA driven study build setup

There are many advantages of a digitized protocol over the current document driven process. One advantage, for example, is the ability to align protocol endpoints directly with data collection specifications to provide transparency between the endpoint and the data supporting it. Unnecessary data collection items can be easily identified and eliminated if necessary. A CDO can use the relationships between standards in the MDR to provide an end-to-end study specification, protocol to clinical study report, driven from a digitized protocol. Once protocol content is digitized it becomes reusable. Other studies from the same clinical development plan, can reuse content stored in a governed and version-controlled repository, taking advantage of best practice and ensuring consistency within the program.

THREE DIMENSIONS OF STANDARDIZATION

To fully utilize the digitized study design and planning information for process automation, we need to consider the three dimensions (3D) of standardization:

- E2E Standards (Protocol to Report)
- Clinical Project Standards
- CDO Process Standards

End-to-end standardization, protocol to CSR, at the study level, is the first dimension of clinical development standardization. This is the type of standardization is the primary focus of many organizations today and is centered around CDISC standards (CDASH, SDTM and ADaM). However, this focus typically does not adequately address the standards for study planning and design. Since that is the area of standardization directly addressed by protocol digitization that would yield most of the benefits[(1)] it would be an imperative to include this early standardization area into the E2E focus.

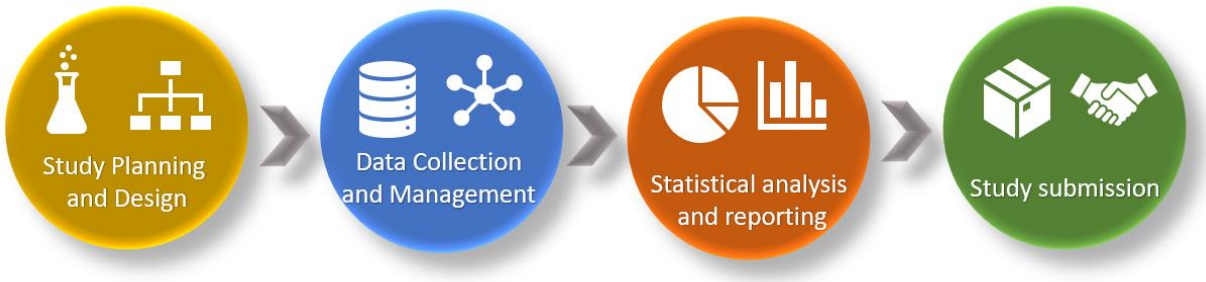


Figure 3: E2E standardization

The second dimension of clinical development standardization is at the program level. We've touched on the value of program level standardization a couple of times in this paper, but, what does that really mean? Essentially, once you have control of study level standardization, starting at a digitized protocol, you can look to standardizing at the Clinical Development Plan (CDP) level. With a model that supports a Clinical Development Plan, a digitized clinical development process can drive standardization across the program, for example reuse of standard inclusion/exclusion criteria. An MDR's workflow can record critical decisions and the reasons for changes within a program. This effectively provides a knowledgebase where decisions can ripple more easily across other studies in a program. It also provides a system of record for changes to the CDP with information that can be easily retrieved at a later point in time, perhaps in response to a regulatory question. In the document-driven processes of today, that kind of information is often lost in comments and track changes in draft versions of Microsoft Word documents.

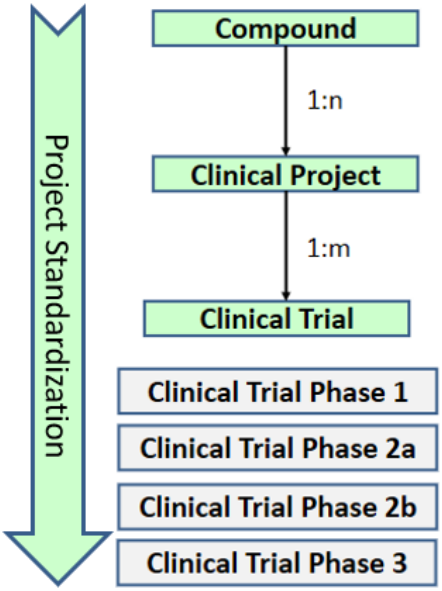


Figure 4: Clinical project standardization

The third dimension of the 3D clinical development process is process level standardization. We've discussed study level standards, starting at the protocol, managed within an MDR, and then rolled up to the Clinical Development Plan level. A digitized solution for the first two dimensions provides a real opportunity for process automation within clinical development operations. Multiple processes can run in parallel when supported by a digitized protocol solution as the protocol authoring task is no longer a linear or serial process. A CDO can develop and lock down some sections of the study protocol while they are still developing other sections. With appropriate business rules in place, workflow capabilities within an MDR can easily manage a non-linear protocol authoring process. No longer dependent on final approved protocol, processes such as Feasibility & Recruitment, or Clinical Supply Chain Management, can be triggered much earlier than is possible in a document-based solution. Some of the processes may remain manual but can be triggered by an automated workflow. Parallelizing the clinical operations processes has the capability of significantly reducing cycle times and cost. At the same time the standards-driven approach will improve overall quality.

Figure 5: Clinical operations processes standardization

CONCLUSION

The industry has a good degree of control of data standards and success instantiating those standards at the study level. We lack a consistent definition of end-to-end standardization, with many organizations limiting standardization to data collection (CDASH), tabulation (SDTM) and analysis (ADaM). The protocol is often not considered as a component in end-to-end standardization, largely because protocol authoring remains a manual and disconnected process. Implementing a digitized solution for protocol authoring in conjunction with an MDR provides a link to all the downstream study specifications for a study, and automation of the process to produce SDTM and ADaM. Once an organization has implemented the digitized solution at the study level, it can realize the second dimension of standardization at the Clinical Development Plan level. The MDR will drive consistency across a program and provide a knowledgebase for decisions with rationale, dates, and any other pertinent information. The third dimension of standardization is at the clinical operations process level, where an MDR can provide a workflow engine to drive parallel processes from a digitized protocol. Not, all clinical development processes will be digitized but this parallelization can only be achieved with a workflow engine that can trigger both digital and manual processes.

At the recent DPharm Disruptive Innovation Conference in Boston Ed Seguine discussed two types of standardization: innovation with a little “i”, and, innovation with a big “I”. Little “i” innovation is incremental and generally project based. Big “I” Innovation is disruptive, and platform based[5]. Both types of innovation are important, and needed, little “i” is small and sustaining whereas big “I” is game changing. Digitization of the Clinical Development Process is a big “I” platform innovation. It is time to think of clinical development standardization in 3D and to embrace the digitization of clinical development processes. We believe that this approach is a valuable enabler to the successful adoption of master protocol methodologies and other clinical trial design innovations to the benefit of patients, researchers, drug developers and regulatory bodies[6].

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