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Structured and Standardized Study Definition drives early study setup for added business benefits

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ABSTRACT

We are all too familiar with the challenges of the Clinical Protocol translation into an accurate and compliant study definition that can easily be understood and implement by clinical downstream processes such as: EDC, Data Management, Data Analysis and Reporting and e-submission.

The challenges primarily arise due to the fact that resources with different background and focus are taking the primary role in the Clinical Protocol planning and design process, to those that are focused on capturing the trial data into the regulatory compliant study setup reflecting the planned trial. In addition, a document representation of the Clinical Protocol, as necessary as it is from the regulatory perspective, is not the optimal framework to translate the study definition into implementable instructions for downstream processes. We demonstrate how Structured Study Definition (SSD) is able to provide protocol definitions and standards much earlier than before and front-load all downstream activities required for study setup.

INTRODUCTION

At present the industry is still very much document driven, especially in the early phases of Clinical Development, clinical trial planning and design. This document driven approach is adapted pragmatically as the regulatory agencies require for example Clinical Protocol document in order to review the proposed clinical trial and the document format is an appropriate format for communicating the clinical trial details to investigators. However, is the document format the right format to communicate all the trial aspects internally to the Clinical Development Operations (CDO) organization?

CDO would be much better served by the provision of the structured and precise information of the trial data required for a particular CDO downstream process, with a level of detail which is required by the process. If we try to achieve that level of details in the clinical protocol documents we risk to inflate such documents with information not needed for the real purpose – communication to the authorities and investigators.
Today, we kind of apply a workaround by interpreting the protocol document for execution of the trial in the CDO organization, instead of having the executable protocol information in the right structured format and sharable with all interested CDO organization parts.

Not only that such protocol information can be provided in a structured and sharable format, it should also be in a dedicated stability to front-load CDO downstream activities, reminiscent of the just-in-time production strategy, thereby reducing the drug development timelines and improving the quality. The same information can be provided to the Medical Writing organization for the finalization of the required Clinical Protocol representation of the structured protocol information.

To implement such a content/data driven approach to clinical project planning and trial design, one needs an appropriate structured format for the protocol information, which we call Structured Study Definition (SSD).
With an SSD approach in Clinical Development, the CDO downstream processes would be receiving stable, qualified, structured, precise and relevant information to complete their part of the clinical trial execution. This approach will become a necessity as the future Clinical Trials are becoming more complex and difficult, if not impossible to manage precisely, using a document centric approach.

In the later section we would apply the SSD principles to the Study Setup downstream process and discuss the benefits in terms of transparency and level of detail required for the process but not needed for the Clinical Protocol itself.

STRUCTURED STUDY DEFINITION

Looking at the structured data in the Clinical Development landscape (Figure 1), it is quite evident that the early stages of the clinical development like study planning and design are still dominated by the unstructured data as these processes are document based (e.g. Clinical Protocol). Later stages, namely Data Collection, Data Management and Analysis and Reporting are much more structured and benefit from the data-driven approach in those processes.

To benefit from the data-driven processes in the Study Planning and Design stage, one need to introduce the structured approach to the planning and design of the Clinical Trials. The structuring process needs to take into account all of the downstream requirements for the protocol information, like Study Feasibility, Clinical Supply Management, Study Setup, etc. On the other hand, the structured model needs to be workable for the Clinical Leaders, Medical Experts and Study Teams in order to effectively capture the structured information, which then can be shared with related downstream processes and also to be presented in the regulatory required documents such as a Clinical Protocol.

The industry trend of creating value/knowledge from existing data using the Artificial Intelligence (AI) techniques, could also benefit from the structured form as opposed to the unstructured data that would need to be mined. In fact, the structuring of the study planning and design as data is an essential first step in employing and profiting from the AI in this stage of the clinical trial.

Figure 1 Structured Data in Clinical Development

The Structured Study Definition (SSD) is one model to manage the structured study information. The essence of the SSD model is that it captures the complete set of executable information, which is normally scattered throughout the Clinical Protocol. In addition, it also contains enough details regarding executable information to ensure that information can be used without further interpretation. This reliance on the information precision is of great importance as it removes the need for re-interpretation of the protocol text which can result in a potential misinterpretation.
To fully embrace the data-driven approach, one needs to:

1) Have the right structured data model based on downstream requirements
2) Rely on and trust the data that is delivered at agreed milestones
3) Share the data in the optimal format for the downstream process needs

SSD MODEL

The SSD model, contains all of the protocol elements and fully describes the Clinical Trial in question. It fulfils the downstream process requirements for data content and precision.
The SSD model, also, forms the basis for the automated protocol document generation. Thus, generated document only needs to be refined by providing the scientific background information, justification for the need of the clinical trial and similar.

Having the structured model, is just the first step in the data-driven direction.
The SSD model, serves to capture and store the data by the Study Team, which is fully executable by the downstream processes. The actual physical modeling of the study definition can be implemented in any of the

available technologies, relation databases, NoSQL databases, graph databases, as well as in simple tools like that offered by the Office 365.

DATA RELIABILITY

Relying and trusting the data, while the protocol is under development, is a little bit more challenging in the current document-based study planning and design. This is due to the fact that no protocol relevant information is provided early. In a typical case, one would wait until the protocol is finalized before any information is shared. Waiting on the protocol finalization, misses the opportunities to front load the downstream processes tasks as much as possible. In our view, the reliance and the trust in the early delivered protocol data is one of the largest change management tasks in the organizations that are adopting the structured approach.
To facilitate the study definition and design data reliability, we introduce several milestones in the form of SSD data stability levels (aka Protocol Quality Gates), at which data is exchanged (Figure 2).
At each SSD stability level an agreed set of data element is released, which front-loads and starts the downstream activities.

For example, at the 'Design' stability level, we would be releasing the data elements required for the start of the study setup. Such early exchange of the relevant design data facilitates timely discussion and clarifications of any outstanding or unclear design aspects that would otherwise be discussed a way later in the process and could even lead to a protocol amendment in some cases.

This case is presented in more details in a later section, showing how this early exchange of the information facilitates the clarifications within the study setup process.

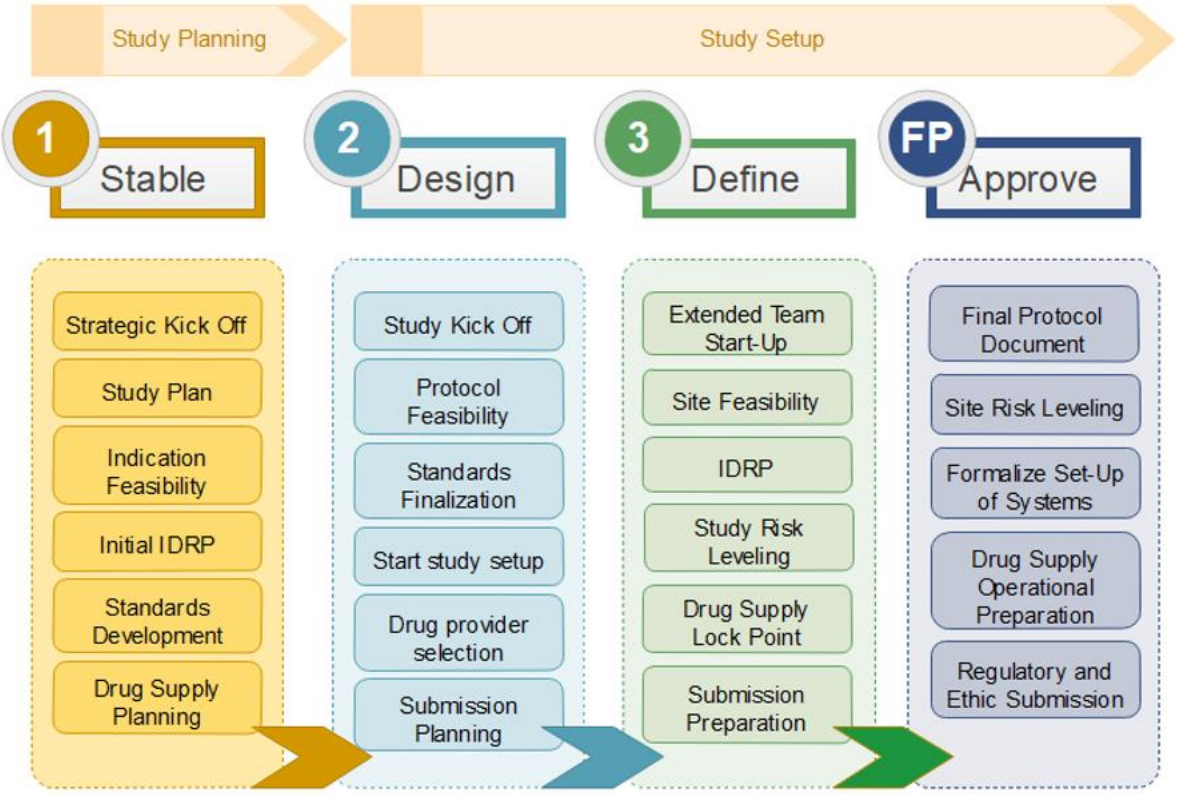


Figure 2 Study Planning with SSD Stability Levels

DATA SHARING

Having the data in the structured form enables us to present that data in many forms, depending on the best way for the downstream consumers to process that information. For example, processing data for the EDC Study Build, one would consider an appropriate electronic readable format like ODM xml, while for the Clinical Supply Management

planning a document representation in human readable form might be the most appropriate.

The protocol translation into trial design will be discussed in more details in the concrete example, in the following sections of the paper, where we look at the titration to target dose study. In this case, we provide the protocol information to the study setup process in the CDISC Trial Design form (consisting of CDISC T-domains, Schedule of Activities and Trial Design Graphics showing the CDISC Trial Design features). Such combined format enables the import of the CDISC T-domains into other systems, outlines the Visit Schedule and CRFs that would be executed at each visit and a human readable graphics for the design alignment.

If we look at the regulatory required documentation, the Clinical Study Protocol document is an example of that and is, in essence, another downstream consumer of the SSD information. In this case, the information is automatically transferred into the appropriate protocol template (e.g. Common Protocol Template) and the Medical Writing team can finalize the document for the communication with regulatory agencies. In case if any of the structured data elements change at a later stability level, that information can be automatically updated with impact and changes made visible.

The study planning, and design transparency offered by the SSD combined with the stability of its contents delivered at agreed milestones:

- Improves protocol quality and avoids amendments
- Focuses on essential trial execution information
- Facilitates protocol standards
- Reduces ambiguities in interpretation
- Enables timely and process required information sharing in agreed formats

PROTOCOL STANDARDIZATION

Structuring Protocol information also facilitates the protocol standardization. In this context, we can differentiate the protocol standardization in 2 dimensions: protocol standards for a given trial and protocol standards for a given clinical project (alignment among other protocols within the same project).

CLINICAL PROJECT STANDARDS

Standardizing Clinical protocol on the Clinical Project level ensures the alignment of the study designs with the project standards (compound standards and therapeutic area standards) and the data alignment of the meta-analysis. Furthermore, the standardization on the project level ensures the alignment with the Target Product Profile (TPP) claims and their adequate coverage in the planned clinical trials.

The SSD model makes the alignment of the design for a given trial to other trials in the project visible and comparable. At a glance, one can evaluate the fit of the trial with other trials already planned and executed. Having such visibility and comparability, we can facilitate the standardization on the project level and avoid expressing the protocol information that has the same meaning in many different forms – making it essentially a language exercise without an apparent benefit and with a risk of potential misunderstanding when implemented and executed in the clinical trial.

Alignment of the trials on the clinical project level, ensures that the trials are executed in the same way and that data is gathered, managed and analyzed in the same way, for trials that share the same standard.

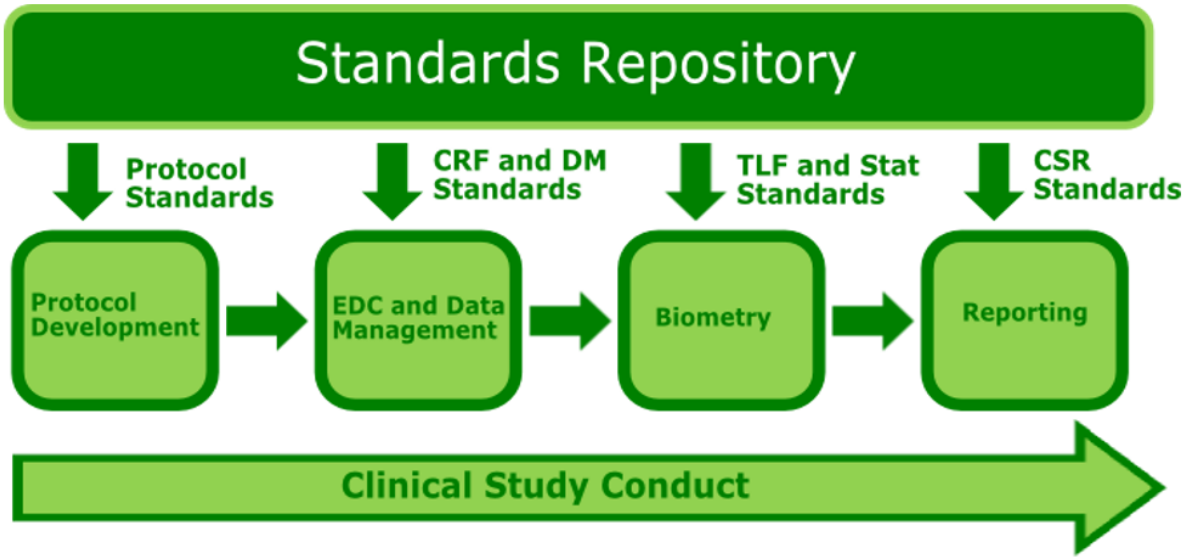


Figure 3 End-to-End Medical Standards Repository

CLINICAL PROTOCOL STANDARDS

When protocol standards are utilized in the SSD, it promotes the alignment of all standards along the Clinical Development landscape – End-to-End (E2E) (**Error! Reference source not found.**).
The entire E2E standards lineage is driven by the protocol standards in the chain that can be described as:

Objectives>Endpoints>Activities>Medical Concepts>Medical Items>Data Standards>Codelists

An example of such E2E standards lineage is given in Figure 4, for the protocol activity Height and Weight measurement (subset of the Vital Signs). By selecting that protocol activity, all of the supporting data structures are selected as well and depending on the MDR capability the large portions of the EDC study build, and metadata structures are likewise predefined.

In order to achieve such standards lineage, in an effective, controlled and transparent fashion, the SSD model requires an MDR integration. However, the same concepts can also be implemented using simple Office 365 tools with manual integration between the two models.

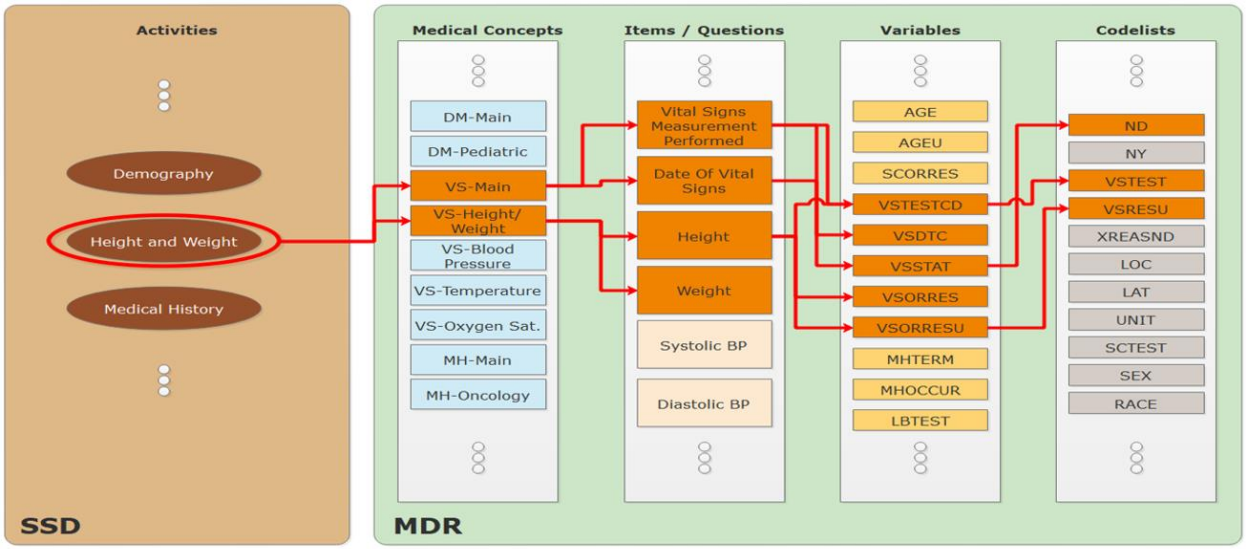


Figure 4 Protocol activities drive the study setup

Once the medical standards are well defined and connected in this fashion, we are not only clear on the study definition and protocol instructions for the regulating agencies and investigators, but we are also very clear on how each aspect of the protocol definition is executed. There is no longer any ambiguity in the study definition and no interpretation is required.

An added intrinsic benefit of such SSD-MDR integration is that the Risk Based Monitoring is built into the system and one is immediately aware of the riskiest aspects of the trial and which data would need to be more closely monitored. That way the risk can be managed by carefully considering the design aspects of a trial.

In our example of the study setup process considerations, below, for the SSD data delivered at early milestones we can evaluate the role of the protocol activity selection on the availability of the required data elements on the CRF forms and data structures, as well as the applied trial design. As a concrete example we will take a look at the titration to target dose study and discuss how the early provision of the structured study definition aids the discussion.

APPLICATION OF PROTOCOL DEFINITION IN TRIAL DESIGN AND IMPACT ON CRF AND DATABASE

INTRODUCTION OF THE EXAMPLE

The study design diagram from the protocol is a common representation of a titration design; It shows the different parts (Screening -> Randomization -> Titration to Target dose -> Follow Up)
and their length. The diagram is depicted in Figure 5.

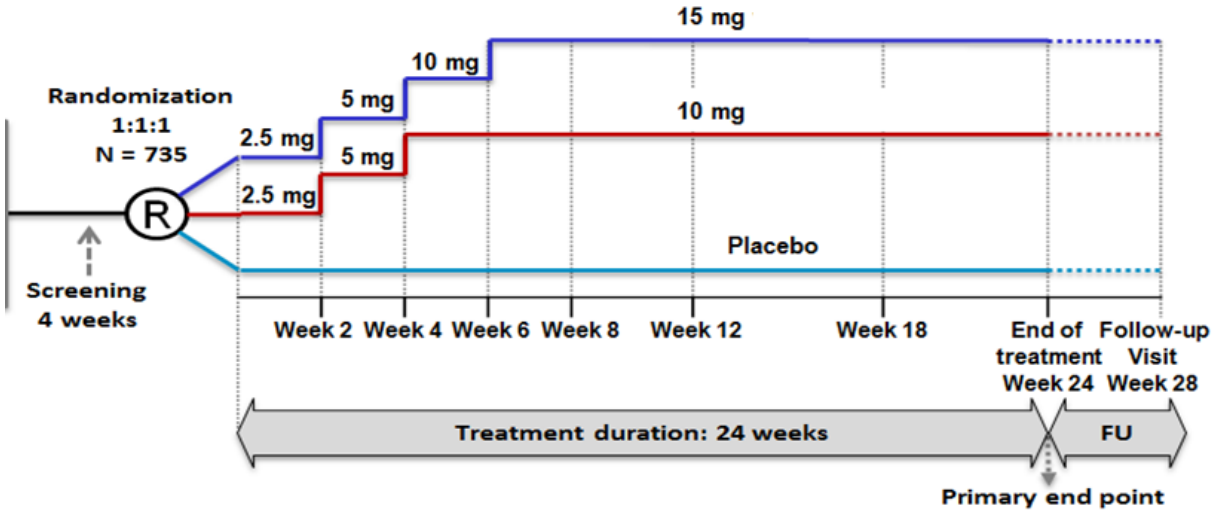


Figure 5 Study Design Diagram

This is also reflected in the assessment schedule table below (Figure 6)

Trial Periods	Screening	Baseline	Titration / Sham titration			Treatment			End of treatment	Safety Follow-Up	Premature Treatment Discontinuation	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Week			2	4	6	8	12	18	24	28		

Figure 6: assessment schedule table

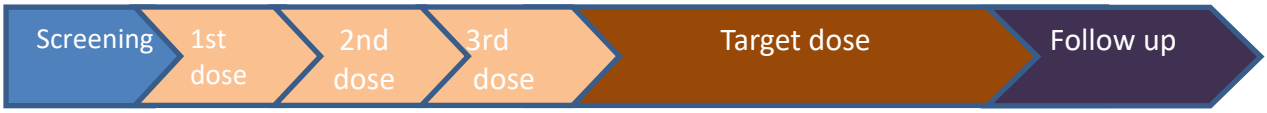
However as indicated before, this information is not sufficient to create the Trial Design (namely Trial Element and Trial Arm domain) and to setup the study.

Questions like
- what does the subject know - since it is a blinded trial?
- How to define the elements and epochs?
- Is a prospective or retrospective representation appropriate?

have to be answered.

WHAT DOES THE SUBJECT KNOW?

From the protocol one knows that after 3 dosing steps one has reached the target dose.



HOW ARE THE EPOCHS DETERMINED?

The study design diagram is not very specific on this question, nor is the assessment schedule. The “Screening” and “Follow-up” periods are obviously EPOCHs. But what about “drug application” period? Is that covered in one or two EPOCHS?

To answer that question, one needs to consider the focus of the trial:
Option 1: Is the titration to the target dose the established/recommended treatment regimen?
Then all elements describing the drug application can be assigned to one EPOCH. In such a case the discussion of the titration part should not be in the focus of the analysis.
Or
Option 2: Is the titration to the target dose still evaluated as a safety and tolerability aspect?
In this case the titration part should be separated from the fix dose / target dose part and therefore represented in two EPOCHs.

However, even with clarity on the two options, one is led to the next question:

WHERE DOES THE “TITRATION” EPOCH END?

Option a: At the last dose increase when the target dose is reached?
Or
Option b: 2 weeks after the last dose increase? (note: titration is every 2 weeks)

The answers to both questions will have an impact on the trial elements, independent of the view of the trial.

A PROSPECTIVE OR RETROSPECTIVE VIEW?

Is the trial design view appropriate? Note: This paper will not give an answer to this question, it should only show the impact on the Elements and Clinical Database.

SELECTED EXAMPLES HOW TO REPRESENT THE SAME STUDY IN THE TRIAL DESIGN (TE/TA)?

Note: different colors represent the different doses, while different intensity indicates different elements for the same dose.

The first example covers the prospective and retrospective view of option 1 (one EPOCH for the treatment period)
In this case there is no separation into a and b since the subject knows when titration ended, and fix dose start.

Table 1: Prospective view after unblinding (Option 1)

EPOCH/ ARM	SCREENING	TREATMENT				FU
15mg	screening	2.5 mg (tit)	5 mg (tit)	10 mg (tit)	15mg (fix)	Follow up
10 mg	screening	2.5mg (tit)	5 mg (tit)	10 mg (tit)	10mg (fix)	Follow up
Placebo	screening	Placebo (tit)	Placebo (tit)	Placebo (tit)	Placebo (fix)	Follow up

Table 2**: Retrospective view** (Option 1)

EPOCH/ ARM	SCREENING	TREATMENT				FU
15mg	screening	2.5 mg (tit)	5 mg (tit)	10 mg (tit)	15mg (fix)	Follow up
10 mg	screening	2.5mg (tit)	5 mg (tit)	10mg (fix)		Follow up
Placebo	screening	Placebo				Follow up

In both views the "sham" titration is not represented in the Elements. The number of Elements (except for Placebo) is identical, but the length (TEDUR) as well as the starting rule for the "10mg fix dose" is different.

The next examples deal with option 2 (two EPOCHs for the treatment period).
Table 3 and 4 show the influence of the "end of treatment Epoch" on the elements for the retrospective view.

Table 3: Retrospective view when the titration ends with the last dosing step (Option 2a)

EPOCH/ ARM	SCREENING	TITRATION			FIX DOSE	FU
15mg	screening	2.5 mg (tit)	5 mg (tit)	10 mg (tit)	15mg (fix)	Follow up
10 mg	screening	2.5mg (tit)	5 mg (tit)	10 mg (tit)	10mg (fix)	Follow up
Placebo	screening	Placebo (tit)			Placebo (fix)	Follow up

Table 4: Retrospective view when titration ends after 2 weeks after the last titration step (Option 2b)

EPOCH/ ARM	SCREENING	TITRATION				FIX DOSE	FU
15mg	screening	2.5 mg (tit)	5 mg (tit)	10 mg (tit)	15mg (tit)	15mg (fix)	
10 mg		2.5mg (tit)	5 mg (tit)	10 mg (tit) 4W		10mg (fix)	Follow up
Placebo		Placebo (tit)				Placebo (fix)	

The retrospective view leads to an unbalanced number of Elements in the non-Placebo Arms. While it will be a balanced number of Elements in the prospective view (see next table).

Table 5: Prospective view when titration ends after 2 weeks after the last titration step (Option 2b)

EPOCH/ARM	SCREENING	TITRATION				FIX DOSE	FU
15mg	screening	2.5 mg (tit)	5 mg (tit)	10 mg (tit)	15mg (tit)	15mg fix	Follow up
10 mg		2.5 mg (tit)	5 mg (tit)	10 mg (tit)	10 mg schem	10mg fix	
Placebo		Placebo (tit)	Placebo (tit)	Placebo (tit)	Placebo(tit)	Placebo fix	

In this case also the “sham” titration becomes visible

SUMMARY

According to the desired view (prospective/retrospective) and the number of Epochs, different (number) of Elements are needed.
These elements (incl. their starting rule) have impact on e.g. the number of records in Exposure, setup of the EC CRF page as well as the disposition event page(s).

Example: Option 2 b (prospective view) requires 3 different elements for the 10 mg dose and therefore (at least) 3 records in Exposure. Ideally these 3 different treatment parts are also collected as 3 separated treatment durations and stored in Exposure as collected (EC), while from the subject’s knowledge perspective 2 entries would be enough. Or the split of the last treatment interval has to be covered when Exposure (EX) is calculation.

As you can see, in some cases decisions on the trial design have deep impact on the operative part and cannot be corrected during the trial. At this point, be reminded that all these different trial designs we are still representing the same study design. If we now, consider 2 studies with the same study design (“sister studies”): depending on the chosen trial design one can emphasize the similarities in the studies or completely disguise the similarities.

Based on this limited example and the discussions one can have within the organization regarding the study design interpretation, it is of great benefit to have the SSD information as early as possible in the study setup process and thereby promote the understanding and alignment within the downstream processes.

CONCLUSION

Structuring the Clinical Study Planning and Design stage of the Clinical Development enables the downstream processes to receive focused, precise and executable protocol information earlier than before. Such timely provision of the structured study data is essential to promote the understanding and alignment of the downstream processes to front-load their activities.

In addition to the obvious advantage of having the SSD information earlier and employing the data-driven study development, the structured data benefits the future applications of the AI and Analytics solutions. Having the protocol data in a structured form is the very first step to smarter clinical trials and trial digitization.

An appropriate SSD model connected to the Medical Standards Repository is not only ensuring the alignment of the trials within the same Clinical Project but is also driving the Clinical Development Operations productivity by re-applying the knowledge through standards.

As we have seen in the concrete example of the titration to target dose study design, having the discussion and alignment on the relevant trial design aspects is essential to expose and evaluate the similarities of the trials with the same study design or completely missing on these similarities by interpreting the trial design differently.

CONTACT INFORMATION

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