Paper DS04

Standardisation in a fast growing environment; MDR, EDC and other abbreviations.

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ABSTRACT

With a fast growing portfolio, the importance and need for standardisation increases. In order to keep up with the growing number of compounds, indications and studies the sponsor Data Standards team implemented a metadata repository (MDR) in 2021. By having a single source of truth for our metadata we aim to spend less time and resources during study set-up phase.

Standardisation however is a dynamic process. New vendors, new guidances and new insights are all in place to improve our processes and data quality, but can be a challenge in standardisation. How many versions do we need and how to best govern different versions? When is something study-specific and when do we decide to standardise? Subsequently, how can we use the metadata repository to further expand standardisation across other processes? What is the impact on upstream and downstream processes?

With standardising our CRFs and Define-XML files we aim to have more standardised raw data. This should enable us to ease the process of creating SDTM datasets. What other actions could we undertake to reduce the time and effort to manage and clean data and to focus on analysing the data not only within, but also across trials, to focus on the bigger picture.

Last year we presented our implementation findings. Now we aim to give a short recap, but to also guide through our current activities, learnings and other projects we are focusing on to standardise more of our processes.

INTRODUCTION

With a fast growing portfolio, the importance and need for standardisation increases. In order to keep up with the growing number of compounds, indications and studies the sponsor Data Standards team implemented a metadata repository (MDR) in October 2021. By having a single source of truth for our metadata we aim to spend less time and resources during study set-up phase.

Standardisation however is a dynamic process. New vendors, new guidances and new insights are all in place to improve our processes and data quality, but can be a challenge in standardisation. What different versions of forms do we need in order to smoothen the process? How should we best implement versioning to keep up with new controlled terminology and new implementation guides? If a study provides us with new insights, do we immediately implement it to our library as well and how does that affect versioning and traceability within the system?

Subsequently, looking forward how can we use the metadata repository to further expand standardisation across other processes? What is the impact on upstream and downstream processes? Can CRF standardisation have an impact on protocol design and reduce protocol amendments? Does it speed up or slow down the process?

With standardising our CRFs and Define-XML files we aim to also have more standardised raw data. This should also enable us to ease the process of creating SDTM datasets. Would it be beneficial to also pull in our source data and to standardise SDTM creation in order to have near real-time insight into our data? Do we also standardise data coming in via other systems, such as data transfer agreements with our lab vendors? What other actions could we undertake to reduce the time and effort to manage and clean data and to focus on analysing the data not only within, but also across trials, to focus on the bigger picture.

Last year we presented our findings of implementing the metadata repository. In this presentation we aim to give a short recap, but to also guide through our current activities in the metadata repository and learnings on using standards for study set-up. Furthermore, we would like to share some insights on projects we are currently focusing on to standardise more and more of our processes.

RE-CAP OF THE MDR IMPLEMENTATION

MDR IMPLEMENTATION FROM START UNTIL NOW

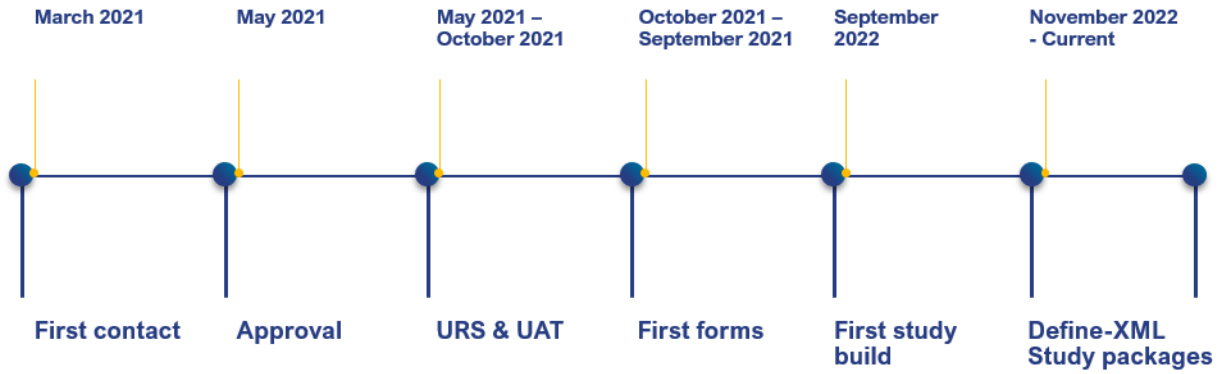

Figure 1. Timeline of MDR implementation

Our process of implementing an MDR started in March 2021. Before the MDR implementation standards had been kept and maintained in a spreadsheet. With only a handful of studies, maintaining this file was workable. However, in a relatively short time the company started to grow and not only the number of studies, but also the number of different compounds, indication and vendors increased. With this growth, the risk of not being able to maintain the spreadsheets had grown and led to the first steps in the implementation of the MDR.

The first step was to get in contact with vendors and to have demonstrations of the software. After a relatively short period, a vendor was selected in May 2021. In the selection process system requirements and end-user objectives had been set to determine which vendor to select, but after selection the more specific user-requirements had to be specified in order to perform user acceptance testing (UAT). This process of URS specification and design of took from May 2021 until October 2021. After successfully passing the UAT, the metadata repository could be used to make a start with our standards.

Designing the first package of forms ready to be used took around one year. In September 2022 we were ready to use this first package of forms in order to do a pilot study build in the system. This pilot study build served several purposes:
1) see which forms from the standards are used and how many tweaks are needed,
2) identify missing forms that might be added to the standard,
3) investigate how the study build is received within the study teams and last but not least,
4) to see how the study build affected the way we work together with our vendors. After this pilot study build we continued to develop and update our forms where needed, in parallel started to create the metadata, or Define-XML, that goes with the forms and worked on more study builds.

STANDARDISATION PROCESS

When setting-up a study, there are many things to standardise. For our metadata repository we focused first on standardisation of the case report forms (CRF). Rather than taking existing CRFs and tweaking them, we started from scratch. We did use 5 different CRFs of different indications as an example and which each item we encountered we considered: how and where is this item needed, should this item be collected for all studies, is there a way that we can modify this item to make it more user-friendly and how should this item be mapped to our SDTM datasets?

When we encountered differences between studies or indications we verified the following:

- Is this different because the wording is different?
- Is this different because the purpose of collection is different?
- Is this different because it is a different indication or type of study?

Based on the answers on the above-mentioned questions, we then composed the forms and decided whether it could be a general form, used throughout different studies and indications, or if we should multiple versions of the form for different studies or indications.

STUDY BUILD

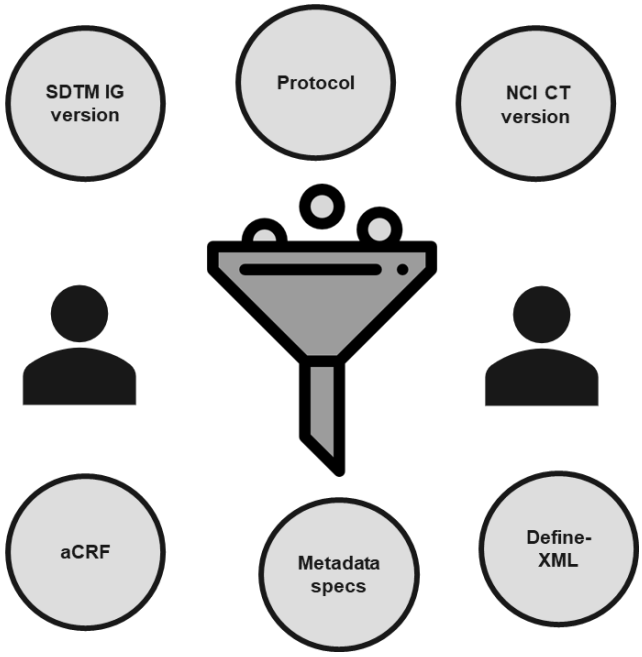

Figure 2. Study build process and requirements

When building a study within the MDR, the clinical data manager collects at least the protocol, the version of the SDTM Implementation Guide, and the version of NCI Controlled Terminology to be used for the study.

Based on this, the data standards team starts building the study-specific aCRF. Together, the clinical data manager and data standards manager identify which forms can be directly imported from the standard and which forms need modifications to adhere to the protocol. The clinical data manager is then responsible for bringing back the CRF casebook to the clinical study team to see if the current design matches the protocol requirements. Once the protocol is finalised and the CRF is updated accordingly, the following documents are planned to be shared with the vendor: the aCRF, the metadata specifications, and the Define-XML. This way of working should support us in creating the CRF in parallel with the protocol in order to align expectations during the study set-up phase, rather than study conduct phase.

CURRENT ACTIVITIES

At the moment of writing this paper we have done several study builds consisting of a package with an annotated CRF, metadata specification and Define-XML. Our current activities encompass doing a consistency check between all of our annotated CRFs and Define-XML both within and across the two deliverables.

Moreover, to implement the standards successfully we need to manage expectations of the clinical data manager, study teams and vendors and all other areas that are impacted by the utilization of the standards. We need to agree with the clinical data manager which tasks are taken on by the clinical data manager and which by the data standards data manager. We need to align with the study team and communicate on our expectations what should be reviewed and what could be made study-specific. Finally our vendors also need to know what to expect if we deliver a study build package, but also what expectations are with regards to building the actual study in ryze, for example with regards to implementing edit checks and dynamics.

For our first version of the standards we started with forms that we would expect to be more general and could be used across indications. One of these items not included in this first version were questionnaires, ratings and scales (QRS). Although they are pre-defined and quite some of the QRS supplements are already provided by CDISC, they are often by ePRO systems rather than the CRF. That is why currently we chose to only create metadata, or Define-XML, for these instruments rather than CRF pages.

Our standards are currently not based on the latest controlled terminology, and is still based on Define-XML v2.0. That is why we are currently also in the process of performing impact analysis. On the one hand we need to look at content; how does updating of controlled terminology, or this update from Define-XML 2.0 to Define-XML affect us? On the other hand, how are we going to implement this in the system and how can we ensure traceability and documentation of which versions are used for which study build?

STANDARDISATION BEYOND ACRF DESIGN

Our first focus and aim was to develop standardised aCRFs and thereafter we planned for standardising other deliverables. However, along the way we found that standardisation of case report forms does not come alone. While designing the standardised CRFs we had to consider for example which version of controlled terminology to use. Do we want our standards to keep up with the NCI releases and how to track these changes? Also, where do we store the controlled terminology? Will we create separate controlled terminology on forms than we do for the Define-XML or do we bundle them into one CT library?

With regards to our MDR itself, how do we control versioning? Will we be able to easily see on which version a study was built and how will we keep track of changes between the two? Also, do we use different libraries for different indications or will we use one overarching library and how would that affect versioning?

In addition to decide what items should be on the forms, we have to ask ourselves “where does the data come from”? How will this affect what we need to collect, and how do we make sure we are still able to do proper reconciliation? Also, the data that we collect should it be collected on the CRF or could it be captured in another database? In case of screen failures or rescreened subjects, which data points need to be cleaned and what data need to be included in the SDTM datasets? And when decided which items to display on the forms, how do we annotate them? Do we also want to standardise our annotations and use the metadata submission guidelines v2.0?

While the initial plan was to “just” standardise the annotated case report forms, these were all things that we needed to take into account and that gave us a deeper understanding on how many levels standardisation would affect our day to day work.

LEARNINGS

Being in this MDR project for over two years we have encountered several learnings. First, we found that standardisation can go quite far, but in order to actually deliver, it is all about finding a balance. When do we for example decide to create different variants of a form, and when do we decide to have one form and update it when necessary? Also, for what scenarios can we prepare, or what can we know up front and what do we need to experience after implementation?

Also doing the pilot study build resulted in some learnings we could use to improve the process. First, we found a lot depends on specificity of the protocol. Second, we also needed to provide training on how these standards were created and how we would like to collect feedback. Which items are negotiable and on which ones do we need to give push back?

Third, standardising our CRFs also impacts other processes. For example, log forms at site that need to be filled out, to only later be filled out in the CRF, may be not matching anymore with all items on the new standardised CRFs and thus should be updated. But also our vendor processes are highly affected. When vendors also work with a library for our studies they will over time also have to be updated with the newly standardised forms in our to remain efficient in their processes.

Finally, we experienced a training component was needed in order to get all people involved or affected by the implementation aboard. Our standards are not fully machine-readable yet, which means human interpretation and guidance is needed. By creating a flowchart with responsibilities and actions, providing guidance documents and actively train colleagues on the job we aim to inform and guide all affected by the standards implementation as good as possible.

EVALUATION OF STUDY BUILDS

What we see when evaluating our study builds over time is that after the pilot study (compound a- study 01 in figure 3) we have reached a rather high percentage of 65-80% of subsequent study builds being able to directly copy forms over from our standard. At the same time, we see the percentage of studies requiring newly build forms decreasing.

We expect over time that these percentages of forms directly copied might increase slightly when creating more indication-specific forms. However after the indication-specific release, we expect the percentage will stabilize. The numbers we are seeing so far look positive, and we hope to maintain this trend in future studies.

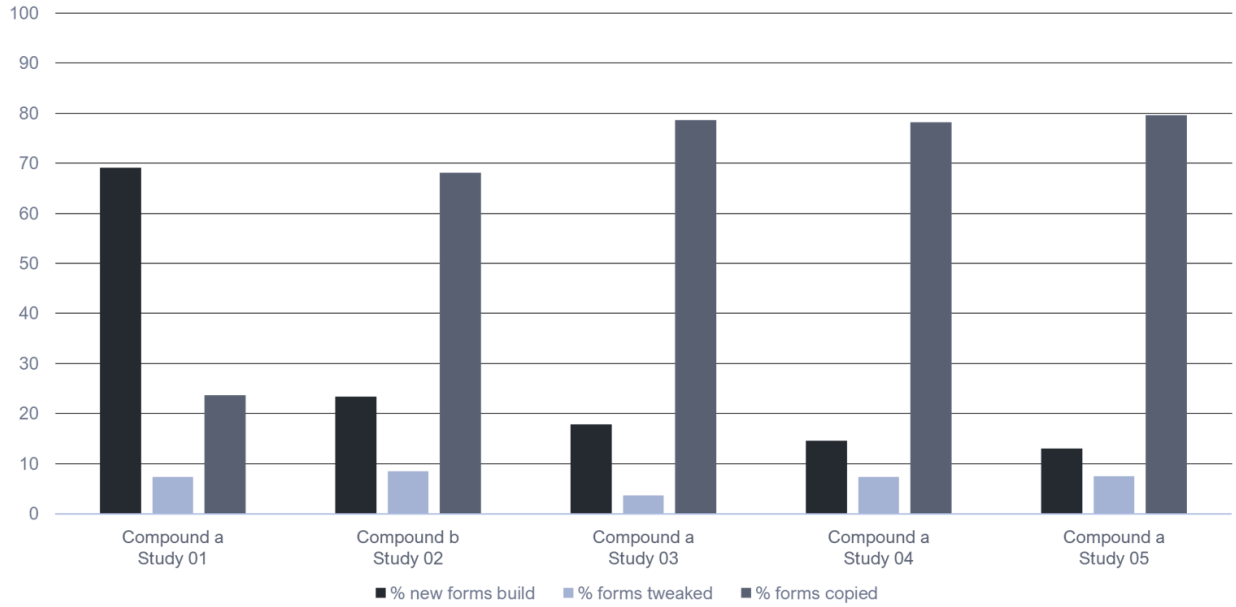

Figure 3. Overview of nr of CRFs newly build, tweaked or copied per study over time

CONCLUSION

Prior to the implementation of an MDR we followed a very traditional set-up path for eDC. All activities were sequential from protocol design to study design to EDC build and integrations, and reiterations after every protocol amendment. As EDC go-live was always on the criticial path, anything that could be postponed to beyond the first participant screened was moved to conduct phase.

Having standardised, and with an MDR in place, we were able to transform the process. Right now, we design the study CRF in parallel with protocol design. This means that the CRF is a visual confirmation of the protocol, and we have an opportunity to derisk and identify potential protocol deviations, together with the clinical trial team, including less technically skilled team members. With this process, we aim to avoid protocol amendments due to human error or lack of understanding how science translates to clinical practice.

Since EDC build is now off the criticial path, full study build is completed prior to first participant screened and the teams are ready for study execution.

Finally, we are in a much better position to oversee the trials and the data and develop continuous insights and knowledge from the data we collect.

ACKNOWLEDGMENTS

First, we would like to thank our client for the opportunity to present about our journey of implementing the MDR and all learnings from the past years. We would also like to acknowledge our colleagues that are involved in the reviewing rounds. Thank you all for sharing your useful feedback, knowledge and the fruitful discussions. Furthermore, we would like to thank the vendors for helping us to take our standards governance to a next level. And especially to our MDR vendor; thank you for patiently answering all our questions and supporting us along the way.

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