PhUSE 2017

Paper RG05

Extension Studies - CDISC Submission Challenges and Scenarios

Deepak Ananthan, Zifo RnD Solutions, Chennai, India
Sachin Bharadia, Zifo RnD Solutions, Cambridge, UK

ABSTRACT

Ever thought about a piece of data that was not collected but was needed for submission? This might not seem out of place if you have worked on SDTM conversion for a follow-up study or an extension study. To assess the long-term safety, efficacy and tolerability of drugs, sponsors continue studies for an extended duration. These assessments are often conducted as a separate trial, but sometimes with the same subjects from the main study along with new patients. In such cases it is plausible that, for existing subjects, some data like Demographics, Medical History, and Adverse Events etc. can be moved from the main study. In such cases, the following questions arise: 1.How do you represent these in SDTM? 2. How do you integrate data from both the studies for analysis? Through our presentation, we will present important considerations during the CDISC conversion process and study conduct.

INTRODUCTION

Every research could be better with more data. Every researcher feels that with more data I can prove my claims. But research feasibility and budgets act as a constraint in making a bigger investment without any hint of success. In clinical research, luckily, we have extension studies. Sponsors go for extension studies for a variety of reasons but with more hope and confidence of success in terms of safety of the drug. So extension studies play a crucial role in clinical research but they also pose some challenges when it comes to data collection, curation and submission. In this paper, based on our experience, we will focus on the challenges during CDISC conversion for submission.

WHY EXTENSION STUDIES? WHAT ARE THE ADVANTAGES AND DISADVANTAGES?

The number of open label extension studies being performed has increased enormously in recent years. One of the main purposes of these studies is to gather more patient-years of exposure to the new drug to understand its long term safety profile and this can play a huge role in drug development and therapeutics.

It helps to get a new perception of the adverse effects reported during the main study. From a subject perspective these studies give continued access to an effective but otherwise unobtainable drug for those who participated in such a trial.

On the downside there can be some ethical questions about the appropriateness of enrolling patients whose response to previous treatment is uncertain, largely because treatment allocation in the preceding randomized, double-blind, controlled trial has not been revealed at the time of entry into the open-label extension study. Another downside is using this as a marketing tool to build a market for the drug and generate pressure for subsidized access to the drug from consumers and their physicians.

Consumers, institutions where these studies are conducted, and research ethics committees, need to be convinced of the motives, as well as the quality, of the open-label extension study and its execution before supporting such studies.

CHALLENGES FACED

So by its very nature these studies are long running; and they come with their own set of challenges. Right from protocol review, thinking about what to collect; to eCRF design taking into account the need to merge data across 2 studies. The challenges continue during the study as well like the best approach for monitoring in terms of deciding which data belongs where for a particular patient and even identifying adequate data management, right type of analysis to perform, and how to handle subjects who are lost to follow up (which is very common due to the length of these studies).

In this paper we are going to dwell deeper into the specific set of challenges we face with regards to Data Submission and Analysis with specific focus in terms of representing the data in SDTM and how different type of analysis might affect the ADaM structure. As there is no one solution to most of the challenges described in this

paper, the structure of this paper is designed to evoke the questions in everyone's mind when they are involved in the process of CDISC conversion for extension studies. The solutions would mostly depend on many stakeholders like Site staff for data collection, Monitors, Data managers and Sponsors to define the practices they want to follow in their studies and then the Statistical team for how they want to analyze the data.

SDTM CHALLENGES - DEMOGRAPHICS

The extension study is considered as a separate study and it is submitted as a separate study. So the challenge starts from Subject Identifier itself. Most of the times the same subjects are carried forward to the extension study and so as per SDTM and FDA submission requirements the subject identifier for the same subject across studies should be the same. The real problem is in some studies the relationship between the subject in the Main study and the extension study is not clearly established in the eCRF. Which means to establish the relationship the sponsor must get the data from the site again to establish that relationship.

The next possible question could be "What is the ORIGIN for Subject Identifier in Define XML?"

Secondly, "What AGE should be populated in DM for extension study?"

And finally here, "What is the Reference date for the subject in extension study?" Common sense is to use the same reference study as the Main study but "What if the gap between the two studies is significantly high?"

There is no one common solution for all these questions. From what we have seen across multiple cases - each case is always different. At the end of the day it boils down to a sponsor decision. But whatever the decision it must be clearly explained in the submission comments and data reviewers guide.

SDTM CHALLENGES – ADVERSE EVENTS

Since long term safety is one of the main objectives of extension studies, how we define the handling of AEs will be very crucial the analysis. There will be several questions that need to be thought about. Starting from the basic definition of "What is an AE in the extension study?". Is it the ones that start during the extension study or is it also the Adverse events that start in the Main study and continue in the extension study as well?

Should the AEs recorded in the Main study be considered as AEs in the extension study?

What if the AE was Resolved before start of extension study? Again a common sense approach would be to consider those that ended before the study as a Medical History in the extension study. But does it really add value in the Analysis is the question that needs to be answered to decide on the approach.

Another questions can be, "Will the AEs starting between the Main study and extension study be considered as Treatment Emergent AEs?". These are just few questions around an important safety aspect.

SDTM AND ADAM CHALLENGES

Another interesting topic of discussion we usually have in extension studies is the baseline data. A common case is that the last visit of main study would be same as the baseline visit of the extension study. So typically the last visit value of the main study would be considered as the baseline value of the extension study. So far so good, right? But then how do you bring the values collected in Main study into the SDTM of extension study? Because these are not technically collected in the extension study, so should they even be in the SDTM of the extension study or can they be included directly in the ADaM because they are only needed for the analysis? If they are included only in the ADaM, then the SDTM would not have any baseline data. What should be done about this?

It is not just baseline data that might need to be carried forward from the Main study. There are instances where some visit specific data too has to be carried forward. Let's take Vital signs for example. They might have collected vital signs during the injection visits and these needs to be carried forward to ADaM. So we have seen baseline data and visit-wise data being carried forward. Is there any difference between the two?

How are they supposed to be represented in ADaM? Will it be "Derived"? A lot of intriguing details can be argued here. So a careful analysis of the protocol and the SAP is very important to discuss these questions very early in the conversion process to avoid very expensive re-work.

CONCLUSION

So to conclude, I would say all these questions (and more) must be answered during the protocol/SAP review/finalization stage. Most often we see these intricate details are being missed and thus causing delays in submission. If these are discussed and analyzed at the beginning, it becomes a lot of easier for all the stake holders to be on the same page and there are no interpretation differences during study conduct and submission.

Another issue we see is proper documentation of the decisions made. This doesn't always clearly come out in submission and results in delays with approval. Proper traceability is also very important as the authorities must understand the source of some data and this is where the use of Define XML comments and SDRG comes into picture. This will help them get a clear picture of how the data is flowing from EDC to CSR.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Deepak Ananthan
Zifo RnD Solutions
Work Phone:
Email: Deepak.a@zifornd.com
Web: www.zifornd.com