PharmaSUG 2018 – Paper DS-14

Core and Extension Studies – Challenges and Solutions Towards SDTM Submission

Murali Marneni, PPD, LLC, Morrisville, NC

ABSTRACT

It is becoming common practice in clinical trials to assess the safety, tolerability and efficacy of drugs using Core and Extension studies. Most of the time, subjects that were enrolled and completed the main study will be enrolled into the Extension studies with subject consent. Data for these studies are often collected in the same EDC system with just one eCRF and have two protocols for both studies but the client asks us to treat them as different trials. This often causes some confusion and challenges in creating the SDTM mapping for these two studies. The intention of this paper to produce high quality SDTM data for Core and Extension studies that are submitted as two separate studies. The goal is to explain the key points to consider when reviewing the protocol, CRF, and talks about challenges and solutions that arise while preparing the SDTM domains especially when defining Demographics (DM), Adverse Events (AE), Concomitant medications (CM), Medical history (MH) and baseline related domains for Extension studies while maintaining traceability.

INTRODUCTION

Core and Extension studies are sometimes referred to as main study and open label Extension studies. Most of the time main studies follow double blind procedures to randomize subjects and subjects can get either Placebo or study drug based on randomization. Subjects allowed to enroll into the study typically follows enrollment into a randomized, blinded, well-controlled main study. All subjects are usually informed at the time they are recruited into the main study that they may elect to enroll in an Extension study after completing the main trial. Subjects who withdrew consent or died during the main study would not be eligible for enrollment in the Extension study. Extension studies help to assess the long-term safety, efficacy and tolerability of drugs which take main study data into account as well. This helps sponsor to understand the long-term result of drug and gives more hope and confidence of success in terms of safety of the drug.

WHY EXTENSION STUDIES

These studies take place on subjects that are exposed to study drug for longer periods. This helps to understand and gain confidence in its safety profile and plays a crucial role in drug development and therapeutics.

Core and Extension studies also provide many advantages to sponsors such as allowing a subject from main study to Extension study can save the cost of site maintenance, site training, subject recruitment etc. Although the same sites participate in an extension study, it is still a new study and a start-up process must be initiated. Another advantage about these type of studies is they provide longer patient data which always helpful when seeking regulatory approval, as always better to have more data.

However, a negative aspect of open-label Extension studies revolves around their use as a marketing tool to the sponsors, as it builds a market for the drug and generates pressure for subsidized access to the drug from consumers and their physicians.

PURPOSE OF PAPER

Core and Extension studies often collect data in two separate databases or sometimes in one database for both studies. Both approaches have their own advantages and disadvantages.

The biggest advantage of having both Core and Extension study in same database is just having one eCRF for both studies. This is much easier to use for the sites and monitors and saves lot of time and budget. At the same time, this can cause lot of issues and special care needs to be taken for smooth deliverables with quality.

This paper will go through SDTM challenges and provide ways that help to overcome the challenges that are faced especially when processing Extension study where both Core and Extension studies captured under one database and later split by SAS® programming to separate the studies for submission purpose.

Since every study has its own data structure, objectives and differences in client requests, this paper will present on what you need to concentrate and what questions you need to ask. The solutions for the questions completely depend on discussions with site, monitors, database design, data collection, Data Managers, client and analysis that are involved in study.

This paper is based on the subjects that successfully completed the Core study and who wish to participate in Extension study. It also covers when both studies are captured in same database. The Challenges and Solutions section can help you in case the studies were collected in different databases, or in case the study allows rollover subjects along with new subjects.

CHALLENGES AND SOLUTIONS

From a programming perspective, Core and Extension studies often bring some complications and challenges towards the study submissions. Since these studies run for longer periods, it is important to know the SDTM challenges ahead which can save a lot of budget and hours. This paper explains some of the scenarios and solutions that when applied will resolve the issues, but there are likely other ways to resolve the issues that do not cause any problems with regards to the FDA guidance and SDTM validation rules.

Reviewing CRF:

The crucial stage for these type of studies starts with reviewing the CRF. It is important to have clear differentiation in CRF forms between the studies, like data collection for both studies should have independent visits and form names that helps to differentiate both studies. This will make it easy for programmers to split the data between studies to create SDTM datasets and Analysis datasets for each individual study.

Since we need to submit two different studies that is two datasets should be created for statistical needs out of data from one raw database. So, we should check the CRF design such that all raw datasets can be able to split with respect to the study. We should report to Data Management if any of the raw datasets do not have a way to split the datasets between the two studies. Generally, there are three kinds of dataset structures that result in datasets

- Form level splitting, e.g. Adverse Events, Concomitant medications, Medical History etc. See figure 1 as example.
- Visit level splitting, e.g. Vitals, Labs, Questionnaires etc. See figure 2 as example.
- Dataset without form level or visit level, e.g. Demographics, make sure all other raw datasets contain either visit information or form names that will help to differentiate the data between the studies.

eCRF page name	Folder name
Adverse Events	Adverse Events
Adverse Events	AE EXT

Figure 1. Screenshot from Raw AE dataset that shows clear differentiation on records from Core and Extension studies.

eCRF page name	Visit name
Vital Signs 2	Baseline/Visit2
Vital Signs 2	Visit 3
Vital Signs 2	Visit 4
Vital Signs 2	Visit 5
Vital Signs 2	Visit 6
Vital Signs 2	Early Term
Vital Signs 2	Premature Discontinuation of Study Drug for Core Study
Vital Signs 2	Unsch Visit
Vital Signs 2	Visit 1b
Vital Signs 2	TV2
Vital Signs 2	TV3
Vital Signs 2	TV4
Vital Signs 2	TV5
Vital Signs 2	TV6
Vital Signs 2	TV7
Vital Signs 2	TV8
Vital Signs 2	TV9
Vital Signs 2	TV10
Vital Signs 2	TV11
Vital Signs 2	TV12
Vital Signs 2	TV13
Vital Signs 2	EOT TV14
Vital Signs 2	Washout FU EXT
Vital Signs 2	OV2
Vital Signs 2	OV3
Vital Signs 2	OV4
Vital Signs 2	Unscheduled EXT
Vital Signs 2	Early Term EXT

Figure 2. Screenshot from Raw Vital signs dataset that shows clear differentiation on visit level from Core and Extension studies.

Demographics:

When Core and Extension data are collected in one database, the demographics form will be filled in once at the start of Core study. This information will be use in both the Core study submission and Extension study submission.

- USUBJID in Extension studies should be same as USUBJID values that are used in Core study. Since both studies are in the same database, USUBJID origin will be assigned as 'Derived'. If Core and Extension studies are collected in different databases then USUBJID origin should be 'eDT' for Extension study database since we pull the values from Core study which is outside of Extension study. So, whenever we rely on information that not collected in database should show as origin as eDT and this should be documented in Define.xml.
- How is informed consent captured between Core and Extension studies? Is it both studies have separate consent pages? Or is it same consent date for both studies? It is recommended to have separate inform consent pages for both studies as this makes mapping easy and easy to pull data metrics reports about patient participation.
- Some of the question mapping derivations may be different in SDTM.DM for Extension study based on data collection. If informed consent page collected for Extension study then age will be calculated based on date of birth and Extension study informed consent date. If informed consent filled for both studies at starting of Core study then age calculation should be discussed with statistician and client based on analysis requirements of study.
- Does analysis in Extension study require Core study treatment information? If yes, then map the Core study information to SuppDM.
- What is reference start date in Extension studies?

Adverse Events:

It is necessary to understand how Adverse Events (AEs) are collected between studies, as we do not see any issue for Core studies as subject first enters into this study. Since Extension studies are meant to assess long term safety as one of the key objective, it is important to know how we define the handling of AEs which will be very crucial for the analysis.

The important questions to answer are:

- Do we have separate Adverse Events pages in CRF that accommodate the Adverse events for Core study and Extension study like FORMNAME = 'Adverse Events' and FORMNAME = 'Adverse Events EXT' respectively?
- Check how study is capturing AEs between the Core and Extension study?
- What determines an AE is for the Extension study? Does it occur during Extension study? Or does it carry over from the core study if ongoing?
- Handling of duplicate records (events starting in a Core study and continuing to its Extension) need careful consideration of how study is handling the unresolved AEs at end of Core study. Do they capture unresolved AEs again in Extension study with an Extension study start date as AE start date? So, based on the study structure, reconciliation steps need to be performed to catch the data issues.
- Determine clarifications around Treatment Emergent AEs consideration for both Core and Extension study.

Concomitant Medications:

In every trial, Concomitant Medications (con-meds) is required as these con-meds may interact with the study medication, thus leading to faulty conclusions regarding safety and efficacy. Good Clinical Practice (GCP) regulations mandate that investigators pay attention to con-meds used by study participants. So, analysis of con-meds is important to assess safety of study drug, and they are going to be of interest when mapping subjects' data between studies. It is important to check protocol on how con-meds are collected in Core and Extension study. The most common collection method is to provide the con-meds in Core study and transcribe the same information in Extension study along with any new con-meds that are reported by the subject. So, in this case the important things that need to check is to setup reconciliation steps. For example: Subject: 0001 reported "GLUCOPHAGE SR" on Aug 2011 during Core study and same subject reported the "GLUCOPHAGE SR" on Aug 2015 during Extension study. This should be queried and ask data manager to issue a query to the site to get this data point corrected.

	Subject	FolderName	CMTRT	CMDOSE	CMDOSU	CMROUTE	CMSTDAT_C	CMENDAT_C	CMONGO
1	0001	Concomitant Medications	EBIVOL	2.5	mg	Oral	UN AUG 2011		Yes
2	0001	Concomitant Medications	GLUCOPHAGE SR	750	mg	Oral	UN AUG 2011		Yes
3	0001	Concomitant Medications	LERCAN	20	mg	Oral	UN AUG 2011		Yes
4	0001	Concomitant Medications	MILURIT	300	mg	Oral	UN MAY 2014		Yes
5	0001	Concomitant Medications	VIVACE	10	mg	Oral	UN AUG 2011		Yes
6	0001	CM EXT	ACARD	75	mg	Oral	17 DEC 2015		Yes
7	0001	CM EXT	AUGMENTIN	2	g	Oral	20 DEC 2015	27 DEC 2015	No
8	0001	CM EXT	CLEXANE	40	mg	SC	28 DEC 2015	06 JAN 2016	No
9	0001	CM EXT	CLINDAMYCIN MIP	1200	mg	Oral	28 DEC 2015	09 JAN 2016	No
10	0001	CM EXT	DIURESIN	1,5	mg	Oral	17 DEC 2015	05 SEP 2016	No
11	0001	CM EXT	EBIVOL	2.5	mg	Oral	UN AUG 2011		Yes
12	0001	CM EXT	GLUCOPHAGE SR	750	mg	Oral	UN AUG 2015		Yes
13	0001	CM EXT	LERCAN	20	mg	Oral	UN AUG 2011	26 JUN 2016	No
14	0001	CM EXT	MILURIT	300	mg	Oral	UN MAY 2014		Yes
15	0001	CM EXT	STOPERAN	2	mg	Oral	14 MAY 2016	10 JUN 2016	No
16	0001	CM EXT	VIVACE	10	mg	Oral	UN AUG 2011	25 JUN 2016	No
17	0001	CM EXT	VIVACE	5	mg	Oral	26 JUN 2016		Yes
18	0001	CM EXT	ZAHRON	10	mg	Oral	17 DEC 2015		Yes

Figure 3. Concomitant medications data for subject that have both Core and Extension data.

Medical History:

We need to apply the same reconciliation step to the Medical History pages when study collection shows that Medical History information should be transcribed as well as shown in above Concomitant medications sections. Other important things that need to get confirmation is what if AE has occurred and was resolved in Core study then does Extension study require it to be recorded as Medical History? Does it add any value towards analysis in Extension studies? This needs an answer to decide upon the approach.

Findings Domains:

The main thing to focus on findings domains is creating baseline records, it is important to check the protocol and SAP towards creating baseline records. Most focus and discussion necessary to create baseline records for Extension studies is based on analysis expectation. A common approach to create baseline record is to flag last non-missing record before first study treatment, but this may change for Extension studies as described in protocol. So, study teams should focus on protocol and study design towards deriving baseline for Extension studies. The common cases that we saw based on our experience are:

- Creating baseline in Extension study by using the true baseline records from Core study, ok! But problem is how do we pull the records from other study. So, when you use another study's data, you first need to make sure to map the baseline record visit values to one common value, for example: "Core Baseline" and make sure to keep this visit in SV dataset to avoid Pinnacle 21 issues. Another thing to make sure to have clear documentation for derivation of –BLFL flags in Define.xml and as well as reviewers guide.
- Creating baseline from last visit of subject from Core study and same approach can be followed as discussed above step 1 to pull the data to Extension study
- Last non-missing before first study drug date in Extension study. There are no issues with this and can follow traditional methods for baseline derivation.

Sometimes, we may also need to carry forward some Core study visits data into Extension study for analysis purpose, so careful mapping of this Core visit values in Extension study is necessary to avoid the Pinnacle 21 issues and clear documentation that needs to be specified in derivations to avoid any misperceptions.

CONCLUSION

There may be number of ways to resolve the issues in processing the Core and Extension studies but main idea of this paper is to invoke the leads thinking and can help them to get answers before starting the programming, this approach saves lot of hours and re-work. So, getting this information ahead helps to handle these types of complicate studies much more easily and helps to work efficiently in tight timelines of studies towards drug development.

Since most of the issues are resolved based on discussion with larger study group, it is very important to maintain traceability between SDTM and ADaM. This is achieved by proper documentation in Define.xml, SDRG and ADRG for successful study submission towards study drug approval.

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ACKNOWLEDGMENTS

We would like to thank each one from PPD Phase 2-4 department, RTP for continuous support and especially thanks to Catherine Edwards, Ken Borowiak, Hunter Everton, Ryan Wilkins, Ajay Gupta, Evangela Hager for their inputs, comments. I would like to thank to my family for support.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:
Murali Marneni, M.S
PPD, LLC
3900 North Paramount Parkway
Morrisville, NC 27560
E-mail: Murali.Marneni@ppdi.com, marneni02@gmail.com

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