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Challenges in Implementing Device Related ADaM and SDTM Standards in a Drug-Device Study

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ABSTRACT

In this case study, a Medical Device was used to deliver an investigational study drug. The analysis needed to monitor the device functionality at the subject level. Of interest were the following events and outcomes: the occurrence of any device malfunctions, whether or not they were resolved and whether a device was removed or another intervention occurred. In order to accurately represent the device life cycle during the study, we implemented the seven published SDTM device domains in addition to the foundational SDTM for the creation of the analysis datasets (ADaM).

The challenge occurred when it was difficult to paint a picture of the device lifecycle with existing SDTM data. The derivations in ADaM were becoming more and more complex. Several data issues were identified, and when traced to the source, we found better ways of collecting the data, simplifying the ADaM process.

This paper summarizes ways to overcome the challenges faced in creating the ADaM datasets by tracing back from SDTM to the Case Report Form (CRF) data collection. We identified areas where collection was not appropriate for certain events (i.e., malfunction vs. failure). Additional issues occurred when sites interpreted forms differently and needed guidance. By working closely with cross-functional groups we were able to enhance CDASH forms and update the SDTM datasets using an iterative process. We learned the importance of: 1) letting the data speak, 2) understanding the relationship in each SDTM domain and how they link and interact 3) working closely with cross-functional groups. The lessons learned were then applied to the entire program using standardized CDISC datasets.

INTRODUCTION

The clinical trial uses a surgically implanted drug delivery device (IDDD) in a drug study. The analysis of the device implantation, device function, and device longevity are part of the study safety assessment. A subject can have more than one device during the study period and one device can have multiple device events (for example, initial implant, malfunction/failure, device adjustment, explant etc.). A malfunction can happen on different parts of the device and the outcome of the malfunction can be ongoing, resolved or device failure. The surgical procedure intervention can change the device status. Many device events are highly related to surgical .

Specific Device Case Report Forms (CRF) were designed to collect device related information, including but not limited to device traceability form, device surgical procedure form, and malfunction/failure form. We overcame the challenge of mapping all device related information to the seven SDTMIG-MD device domains and foundational SDTM PR, AE domains, and then created ADaM datasets to fulfill the analysis needs. At the beginning of the study, everything seemed to work out pretty well; however, we started to encounter data issues when running the analysis as more subjects were enrolled. In order to deal with the special cases, the ADaM logic had to be modified frequently. Data in different domains started to tell contradicting stories. In this paper, we will summarize the ways to map the device domains, the data issues experienced and will provide some solutions to deal with those issues.

MAPPING DEVICE-RELATED CLINICAL DATA

The implantable device was used as a drug delivery system in the clinical trial. As part of the safety assessment, we needed to monitor the device's whole life cycle, starting from device initial implant. The Surgical Procedure CRF form collected a wealth of data pertaining to procedures and device related

information. Collected in the CRF were the time of the procedure, reason and type of procedure, the surgical procedure details (including the application location, and device component used during the procedure) and surgical procedure difficulties. It is challenging to map all of this information in SDTMIG domain. The published seven SDTM device domains meet the requirement to store those additional device data. Therefore, we mapped part of the procedure data to PR domain, and part of the procedure detail information and device component to DU domain and surgical procedure difficulties to DE domain.

BACKGROUND OF SDTM

Device Domains follow the same classification as SDTMIG; the special characteristic for the device domain is that some of them are highly related. As shown in the below schema, intervention class domain, Device Exposure (DX), event class domain Device Events (DE) and Device Tracking and Disposition (DT), data in certain fields such as device event dates need to reconcile across domains.

Figure 1 below is an example of SDTM mapping for our study. This example shows the interaction between the seven SDTMIG-MD device domains with the foundational SDTM PR domain. Other domains such as AE/EX also contain device related information; however, for the scope of this paper, only the PR domain will be discussed.

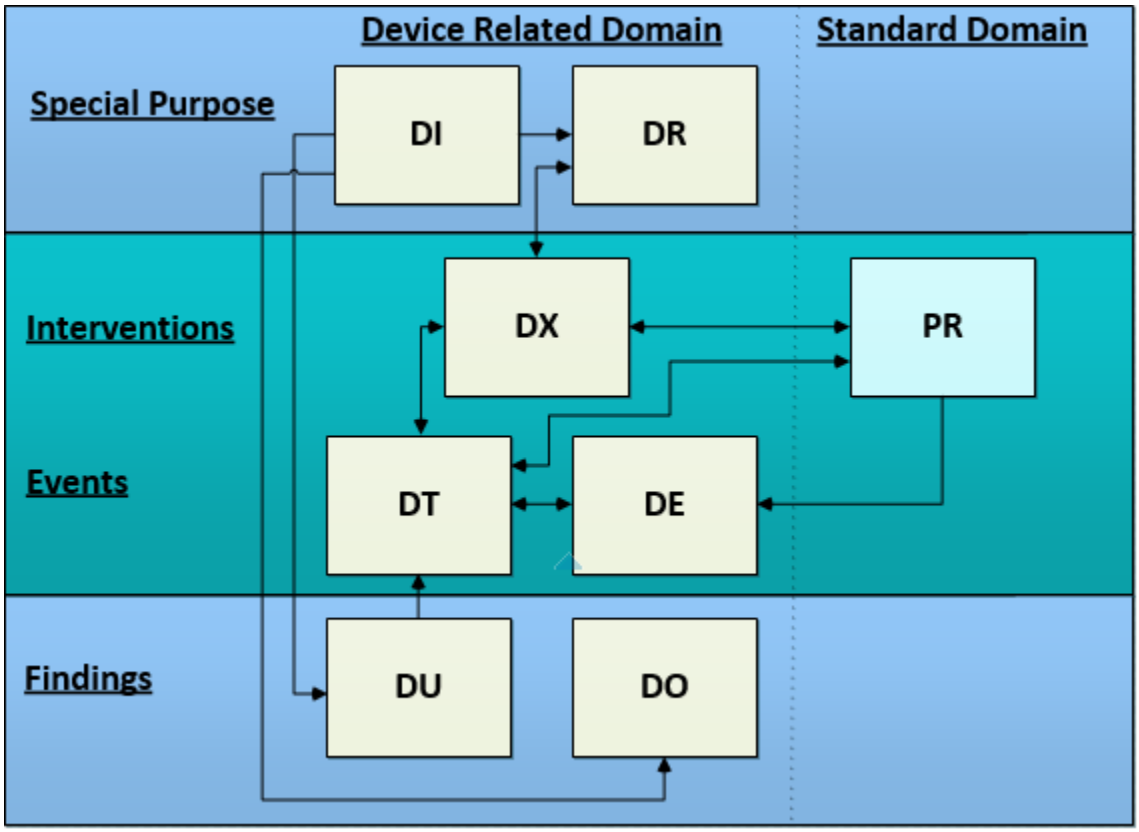

Figure 1 Device SDTM Domains Schema

DEVICE DOMAINS DETAIL MAPPING

It is important to understand the structure of the highly related device domains. It is the key to be able to figure out any data issues that arise and to build the early stage checking system. Figure 2 notes the mapping keys between device domains that are used to link to foundational SDTM domains. The Device-Subject Relationships domain (DR) is a special-purpose domain that links each subject using usubjid to device domains using spdevid.

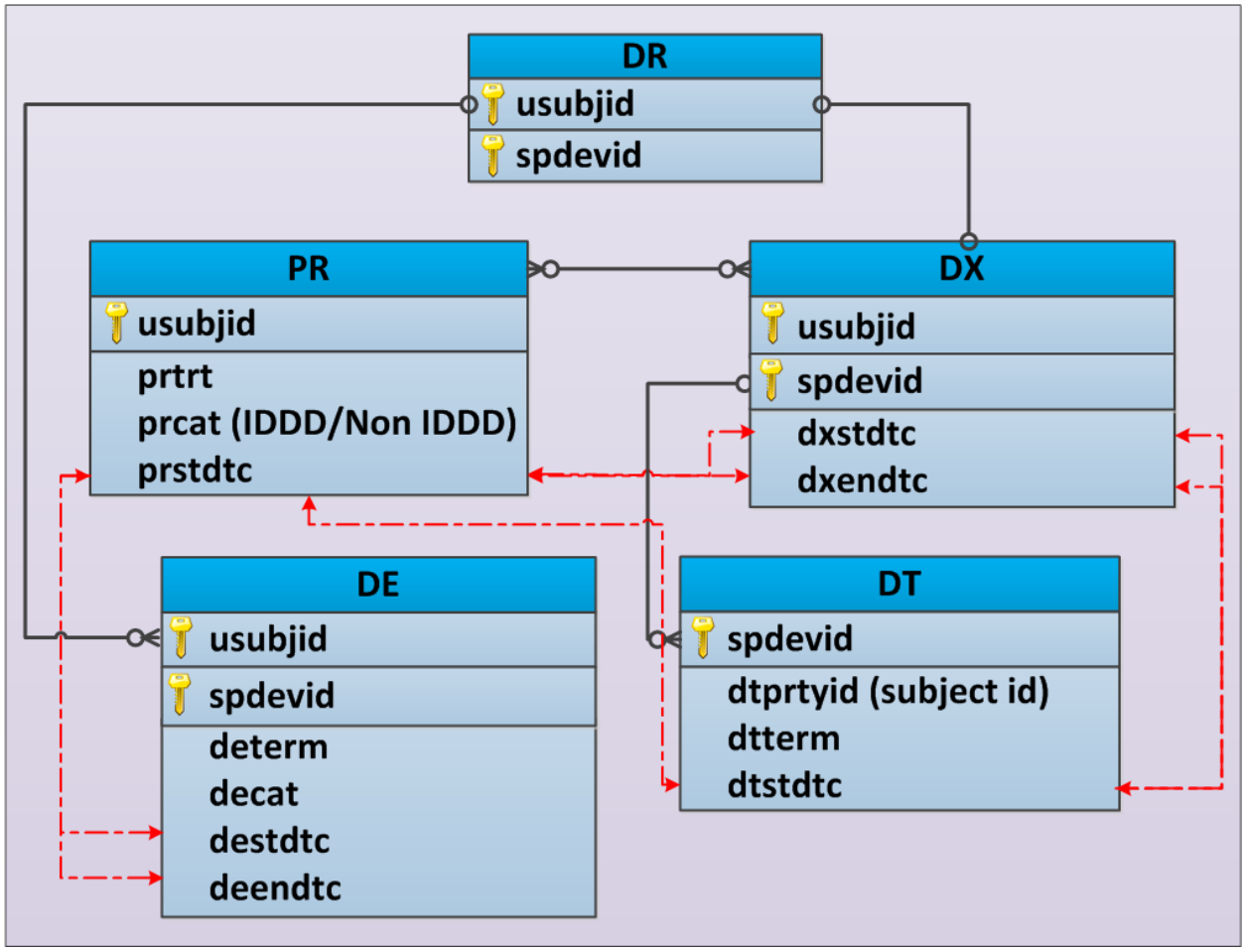

Figure 2 Highly related domains

BACKGROUND OF ADAM

The ADaM device datasets were created using ADaM principles. In addition to ADSL, a device identity dataset (ADIDDD) was created which corresponds to the new ADDL data structure. Also ADDPR dataset in BDS structure was needed for the analysis. This analysis dataset is in standard BDS format and contains parameters for each type of device status or surgical procedure event being analyzed.

Dataset	Label	Structure	Keys	Class
ADDL (ADIDDD)	Device-Level Analysis Dataset	One record per device number, per repeat number, per subject identifier	usubjid, spdevid	DEVICE-LEVEL ANALYSIS DATASET
ADDPR	IDDD-Related Surgeries and Functionality	One record per subject, per parameter	usubjid, paramn, aseq	BASIC DATA STRUCTURE

Figure 3 ADaM

Below is an example of the variables used in ADaM. The datasets have been chosen for the sake of this example. Variable names reflect the new proposed ADAMIG-MD supplement. Variables in blue are not part of the draft standards. The avalc in ADDPR is a character range of weeks, which is then parsed in the program to create a figure of the device timeline for each subject. Aval was not used in order to keep the data consistently in character format.

ADDL.xpt

Variable	Label	Type	Controlled Terms or Format	Source/Derivation
STUDYID	Study Identifier	Char		ADSL.STUDYID
USUBJID	Unique Subject Identifier	Char		ADSL.USUBJID
SPDEVID	Sponsor Device Identifier	Char		DX.SPDEVID
IDDDN	IDDD Number	Num		Sort by date, count for each SPDEVID
IDDDID	IDDD Identifier	Char		Concatenate SPDEVID||-||IDDDN as '00'
AGEDST	Subject Age at First Exposure to Device	Num		Age of the subject at DEVSDT.
AGEDSTU	Subject Age at First Exposure to Device Unit	Char		Age unit for AGEDST.
DEVSDT	Date of First Exposure to Device	Num	yymmdd10.	Identify date from PR when device was first implanted
DEVEDT	Date of Last Exposure to Device	Num	yymmdd10.	Identify last date from PR where device was removed or turned off
FAILDT	Date of Device Failure	Num	yymmdd10.	Set to date of DE.DESTDTC where SUPPDE.DEOUT='FAIL'
FAILFL	Device Failure Flag	Char	(S_YONLY)	If failure set to 'Y'. Otherwise leave blank

ADDPR.xpt

Variable	Label	Type	Controlled Terms or Format	Source/Derivation
STUDYID	Study Identifier	Char	'ABC-DEVICE'	ADIDDD.STUDYID
USUBJID	Unique Subject Identifier	Char		ADIDDD.USUBJID
_ADSL_SAFVARS_	<additional variables from ADSL>			SITEID, AGE, AGEU, SEX, RACE, ETHNIC, SAFFL
PARAM	Parameter	Char	'Functional' 'Malfunction' 'No Device Implanted' 'Initial Device Implant' 'Device Adjustment' 'Complete Removal and Replacement' 'Complete Device Removal Only' 'Delayed Device Implant'	for PARCAT1='IDDD STATUS' Functional=FUNCT=1 Malfunction=MALFUNCT=2 No Device Implanted=NODEVICE=3 for PARCAT1='SURGICAL PROCEDURE' INITIAL DEVICE IMPLANT=INITIMPL=4 DEVICE ADJUSTMENT=DEVCADJ=5 COMPLETE DEVICE REMOVAL ONLY=REMVONLY=6 COMPLETE REMOVAL AND REPLACEMENT=REMVREPL=7 DELAYED DEVICE IMPLANT =REIMPL=8
PARAMCD	Parameter Code	Char	FUNCT, MALFUNCT, NODEVICE, INITIMPL, DEVCADJ, REMVONLY, REMVREPL, REIMPL	Refer to PARAM
PARAMN	Parameter Code (N)	Num		Refer to PARAM
PARCAT1	Parameter Category 1	Char	'IDDD STATUS' 'SURGICAL PROCEDURE'	Assigned
AVALC	Analysis Value (C)	Char		For parameters where PARCAT1 'IDDD STATUS', range of weeks device is at this status, i.e. '3.1 – 5.0', '6.0 – 15.0'. Round to 10ths. Dates from DE domain where DE.DETERM provides status.

Variable	Label	Type	Controlled Terms or Format	Source/Derivation
				For parameters where PARCAT1 = 'SURGICAL PROCEDURE', set to 'Week n' from the implant date to the procedure date. Dates are from DT domain.

Below is a hypothetical example of ADDPR. The avalc is a time point for 'Surgical Procedure' and a character range of weeks for 'IDDD status'

USUBJID	PARAMN	PARAMCD	PARAM	PARCAT1	PARCAT1N	AVALC
sub-abc-111	1	FUNCT	Functional	IDDD STATUS	1	0-52
sub-abc-111	2	MALFUNCT	Malfunction	IDDD STATUS	1	15.0-15.1
sub-abc-111	3	NODEVICE	No Device Implated	IDDD STATUS	1	52-60
sub-abc-111	4	INITIMPL	Initial Device Implant	SURGICAL PROCEDURE	2	Week 0
sub-abc-111	5	DEVCADJ	Device Adjustment	SURGICAL PROCEDURE	2	Week 15
sub-abc-111	6	REMVONLY	Complete Device Removal Only	SURGICAL PROCEDURE	2	Week 52

Figure 4 ADDPR

As noted previously, the IDDD is the drug delivery system. It is important to monitor its functional status for safety assessments. In order to visually represent the device status, the data from ADDPR was graphed to show the event timeline. It consists of two types of parameters which are assigned to parcat1. One type is the IDDD status: functioning, malfunction or period of no device. The second type is the surgical procedure, which can change the IDDD status. We successfully created the figure to visually observe the device functionality at the subject level.

After overcoming the SDTM mapping and ADaM dataset design challenges, we were able to map all the device-related data within SDTM datasets and create ADaM datasets to meet the analysis needs. However, as more subjects were enrolled, we started to face another road block, especially for ADDPR. For example there were some cases where surgical procedure time point did not match to the device event start or end date; one device had two events, one was an ongoing malfunction and the other was a device failure. Both happened at the same time, which indicated a data issue. In some cases, one type of procedure difficulties showed in the Device Events (DE) domain, but was missing a matching surgical procedure in ADDPR. The first step to investigate those types of data issues was to trace back to the SDTM datasets:

The following are hypothetical examples to illustrate the situation:

Row	Domain	USUBJID	SPDEVID	DESEQ	DETERM	DECAT	DEOCCUR	DEOCCUR	DEENDTC
1	DE	sub-abc-2222	DV-SER01	5	Nonfunctional - cause unknown	IDDD FAILURE	Y	2000-02-21	
2	DE	sub-abc-2222	DV-SER01	6	Unable to inject study drug	IDDD MALFUNCTION	Y	2000-02-21	

DEOUT
Ongoing
Ongoing

Row 1 shows an example of device failure that started on Feb 21, 2000 without an end date. The reason for failure is Nonfunctional-cause unknown. The variable deout from SUPPDE shows ongoing.

This record has two issues. If it is a device failure, the outcome in SUPPDE should be device failure. It cannot be ongoing and should have an end date. This means that DE and SUPPDE tell conflicting stories.

Row 5 shows a malfunction that started on Feb 21, 2000 and the outcome is ongoing. This looks fine.

The next step is to check the raw data if the SDTM mapping is correct. For this case, the raw dataset confirmed our SDTM mapping was correct. The site was queried and confirmed that it was an ongoing malfunction.

But, where did that IDDD failure record come from? After pulling all the malfunction/failure records, and looking at the data pattern, finally we understood the reason why some ongoing malfunctions had device failure as an outcome. Malfunction and Failure are captured on the same CRF. The first section is specific

to malfunction and the second section is specific to device failures. There is a form note under the device failure section that reads “Only complete if a failure of the device occurred”. The ‘Nonfunctional-cause unknown’ is the last choice under device failure, and was selected although no failure occurred. After understanding the root cause of the issue, the CRF was enhanced and automatic edit check(s) and skip logic were added to restrict users from entering device failure information when no failure takes place.

For some established clinical trials following standards, we only need a one way process flow which starts with protocol design, TFL shell design, then CRF design, SDTM mapping, followed with ADaM creation, and Table/Figure/Listing (TFL). However, because of the complexity of implantable device involved in the drug studies, sometimes a reverse process flow may be needed to enhance the quality control of the data.

Our experience shows that after correctly mapping all necessary information into the corresponding SDTM domains, and building a strong standards foundation, data will speak for itself if there are any issues that somehow pass Electronic Data Capture (EDC) edit checks. Even at the analysis stage, one is still able to capture them and track back to SDTM or to the CRF. These can then be addressed, either by enhancing the CRF, or updating the SDTM mapping logic to ensure final data quality. By using this iterative process we are able to fine tune our standards for the next study.

Based on this experience, we summarize the reverse logic flow in figure 5 below, to enhance the design, and ensure the final delivery with high quality.

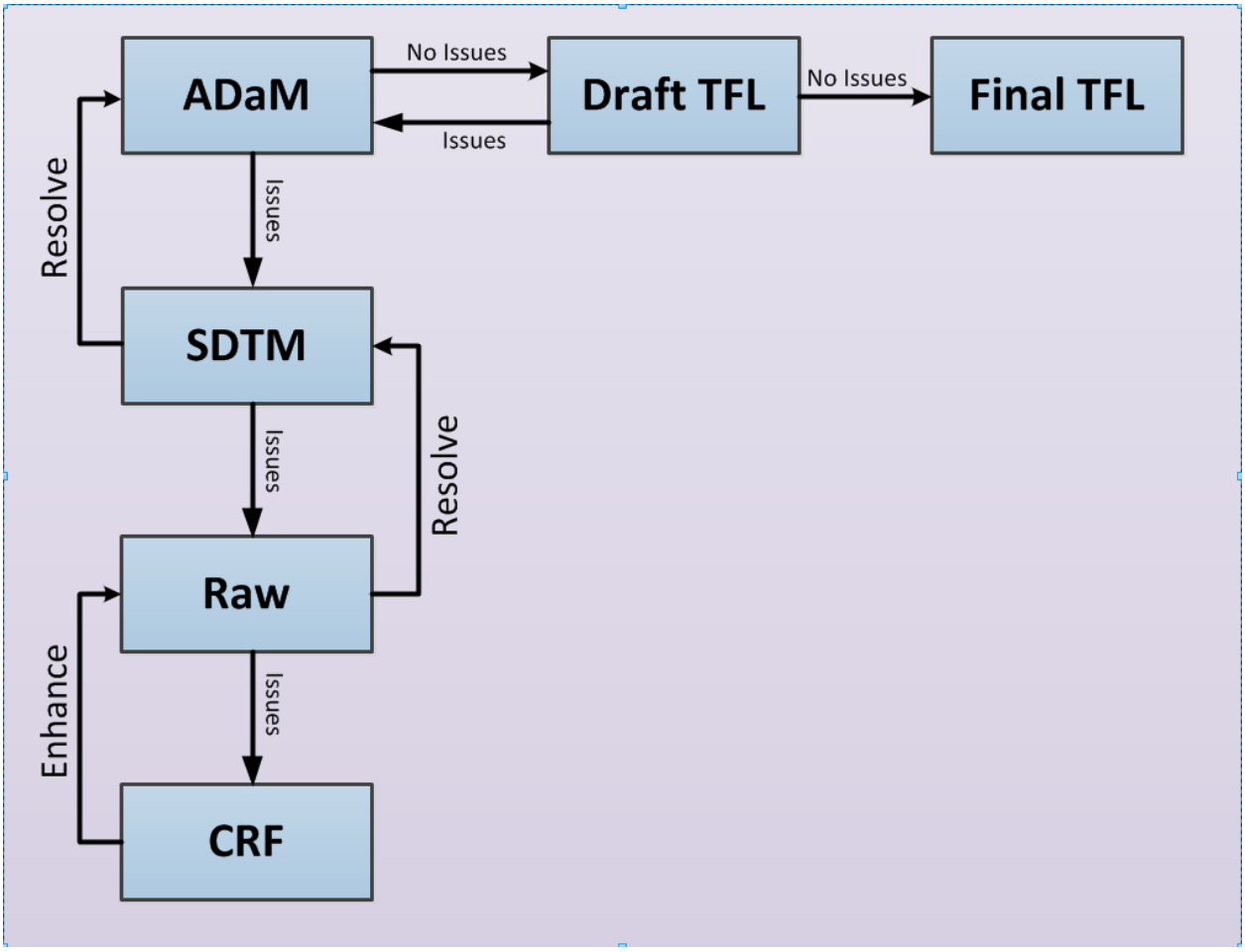

Figure 5 Reverse Process Flow

As shown in the above flow chart, sometimes it is need to go as far back as the original CRF design. The way to figure out if the issue is caused by the CRF is to pull all related raw data, observe the data pattern, and compare it to the original CRF.

It is important to have a well-designed CRF as a starting point. It is a difficult decision to modify the CRF in an ongoing study due to the amount of work involved by all parties. Here are some suggestions for additional considerations in the initial CRF design for device studies:

- Based on the Protocol and the SAP, what concepts related to the device are needed for analysis?
- Other than the technical questions related to device components and surgical procedures, can the site interpret this section differently? Do we need to have additional form notes to provide guidance?
- How do we define the device failure from a device component point of view? Can we create the Device ID based on additional device component identifiers?
- Are there any opportunities to set up additional online edit checks or ways to restrict data entry?

CRF update steps

These are the steps followed in those cases where there was a need to modify the CRF during an ongoing study period:

- The study team(s), along with the device team, Programming/Biostatistician evaluate requests for CRF modifications to determine the significance and to decide how quickly any modifications must be implemented (e.g. FDA request for additional information on a device event vs. adding a form note)
- Data Management revises the CRF with input from the study team and CDASH standards representative. The revisions are then proposed to the Clinical Standards Team and Clinical Standards Governance Board for review and approval.
- Once approved, Study team(s) determine the strategy for implementing the revised standard device CRFs and whether the revisions will be retrospectively enforced or if they will only be expected to be used from that point forward
- Data Management works with the vendors to update the clinical database(s), the case report form completion guidelines, and the edit check(s)
- The clinical group then evaluates the need for site retraining on device case report forms

After ensuring that the sites completed the CRF according to the CRF completion guidelines, we modified the SDTM DE mapping logic, confirmed DE included all device events, malfunction & device failure, and all device surgical events correctly. There were less special cases to deal with at the ADaM level, and we were able to create the figures successfully.

CHALLENGES

Mapping Medical Device information in drug studies is still a new area. The necessary information can be mapped into the seven device domains plus additional SDTMIG domains, but there are some limitations.

1. Uniqueness of spdevid: The variable spdevid is created in SDTM using serial number of the device. When a device is packaged with one serial number for multiple components, then one device might have multiple failures. The device id needs additional information to make it unique in ADaM.
2. Match Key: In PR domain spdevid was not included. But this domain is highly related to device events. We used subject ID and time window as the match key in the analysis, causing some complication in the further analysis. The good news is that spdevid is a model-permissible identifier variable available to all domain classes in the SDTM version 1.4 model document, and so available for use in PR under SDTM 3.2 and later. (For SDTM 3.1.3 and earlier, spdevid would need to be captured in SUPP-- datasets.)
3. Potential data collection issues: one of the causes is the highly related information entered in separate CRF forms by different people. It is possible to have inconsistent data entry between

each form. How to set constraints to prevent inconsistent data at raw data entry level remains a challenge. The lead programmer plays an important role to understand the data and set up additional checking at early stages to avoid those data issues at SDTM level.

4. Cross functional cooperation is essential for device-drug study. Some data issues will need working closely with field experts, and any CRF design updates or SDTM mapping changes need to follow the proper steps.
5. It is challenging to map the device related information into SDTM datasets. Device-Drug study standardization is still in the early stages without enough references. Don't expect to get perfect mapping to SDTM at once. Collecting all the necessary data is essential and will give the opportunity to modify the mapping/logic as needed.
6. Creating the ADaM datasets is a challenge as CDISC device analysis standards are coming soon but not universally available. We developed similar mapping to the ADDL independently as a solution to describe subject-device level data. This standard will be available in the ADAMIG-MD supplement under review.

CONCLUSION

In this paper we discussed methods to map device data in a device-drug study to SDTM domains, and then to create ADaM datasets for the analysis using both SDTM-MD and foundational SDTM datasets. We provided an example using the SDTM PR domain as relates to device domains. We also provided a case study of data challenges. We checked the data using a reverse process flow. The case study showed how by 'letting the data speak' we were able to enhance the CRF design over time. We provided additional guidance in the form of considerations for a good CRF design. The list of challenges describes the primary issues faced during the project. Hopefully these will also provide a starting point for further discussions on device data standards.

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