When Medical Devices unleash SDTM power
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ABSTRACT

As per CDISC SDTMIG-MD, 7 additional SDTM domains have been created specifically for studies using medical devices. Based on the existing publications, most of the cases where these domains are implemented are drug studies in which a medical device is used. The medical devices either deliver the investigational drug (e.g. Insulin pumps) or assess/measure the impact/effect of the drug (e.g. diagnostic devices such as implanted glucometer). But how to use them in medical device studies where no drugs are involved? Where the main objective is the assessment of the safety and/or the efficacy of the device itself. Even though it is not mandatory to deliver a CDSIC SDTM compliant database for FDA or PMDA submissions yet, some Medical Device companies have started designing the database of their new studies based on the CDISC standards. LivaNova and Terumo are two examples of global leader device companies who took this initiative. By combining experiences, 2 real business cases can be presented: one from LivaNova with a study on implantable heart valves, and a second from Terumo with a study on an implantable a cardiac/peripheral stent. The presentation will focus on the challenges faced and the decisions taken during the mapping and implementation of the CDISC standards. This will hopefully broaden the scope of these 7 additional SDTM domains and bring to light the possibilities they hold.

INTRODUCTION

We all expect medical devices to be safe and to incorporate the latest progress in science and manufacturing technology. The EU's rules on the safety and performance of medical devices were laid down in the late 1990s, and many discrepancies in their interpretation have been found across Europe. Issues have also arisen in some categories of medical devices, for instance breast implants and metal-on-metal hip implants.

To reflect the evolution over the last 20 years, the EU has therefore revised the legal framework. Two new regulations – one on medical devices and the other on in vitro diagnostic medical devices – were adopted by the Council and the Parliament in May 2017. The new rules will only fully apply after a transitional period. That period is of 3 years after for the regulation on medical devices (i.e. May 2020), and of 5 years for the regulation on in vitro diagnostic medical devices (i.e. May 2022). The new regulations contain a series of extremely important improvements to modernize the current system. Among them are :

- improved transparency through a comprehensive EU database on medical devices and a device traceability system based on unique device identification
- reinforced rules on clinical evidence, including an EU-wide coordinated procedure for authorizing multi-center clinical investigations

Before joining Medical Device companies, both authors gathered working experience with CDISC standards in CRO/Pharma companies where clinical trials have standard structures, mandatory use of CDISC, and clear roles of biostatisticians and statistical programmers in the full process. On the other side, medical device companies do not have standardized database structures and CDISC standards are not mandatory but only optional. However, standardization is clearly needed. By using previous CDISC knowledge, internal processes can be enhanced, especially when related to database structures and statistical analyses. The purpose of this paper is to provide two business cases of CDISC implementation in medical device companies, to give evidence of the advantages that all stakeholders could have when adopting CDISC standards.

CDISC AND MEDICAL DEVICES DOMAINS

Among CDISC guidelines there is a SDTMIG for Medical Device (SDTMIG-MD): this covers 7 additional Medical Device SDTM-based domains.

For certain aspects their implementation is not far from subject's data SDTM domains, but their peculiarity is the identifier they describe: the Sponsor Device Identifier (SPDEVID). The Unique Subject Identifier (USUBJID) is even required only in two medical device domains (DR and DX). DR relationship domain links each subject to the associated devices, with one-to-one or one-to-many or many-to-one relationships.

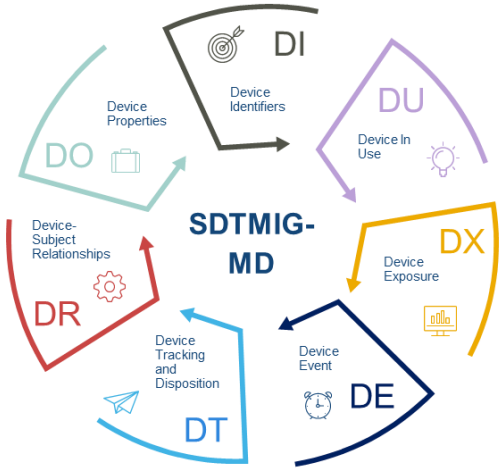

Figure 1. 7 additional SDTM domains for Medical Devices

Here below is a short description and examples of each Medical Device SDTM domain.
The data are referring to two patients enrolled in a Heart Valve clinical study having the following scenarios:
a) Subject ITA1001 has not been implanted with the first valve originally assigned due to sizing issues. It has been implanted with a PERCEVAL ® valve having a different size.
b) Subject USA6001 has been implanted and then explanted few months later, because of a device deficiency.

- Device Identifiers (DI) - Contains information that identifies a specific device unit.

DOMAIN	SPDEVID	DIPARMCD	DIPARM	DIVAL
DI	ABC1234	DEVTYPE	Device Type	Valve
DI	ABC1234	MANUF	Manufacturer	LivaNova PLC
DI	ABC1234	MODEL	Model Identifier	Perceval
DI	ABC1234	SERIAL	Serial Number	ABC1234
DI	ABC1234	VALVENUM	Valve Number	2
DI	ABC1234	MANSITE	Manufacturer Site	Vancouver

- Device Exposure (DX) - Records the details of a subject's exposure to a medical device under study.

DOMAIN	USUBJID	SPDEVID	DXTRT	DXMETHOD	DXSTDTC	DXENDTC
DX	ITA1001	ABC1234	VALVE	SURGICAL	2018-09-27	
DX	USA6001	DEF5678	VALVE	SURGICAL	2018-03-16	2018-10-16

- Device Events (DE) - Contains information about various kinds of device-related events, such as device malfunctions.

DOMAIN	USUBJID	SPDEVID	DETERM	DECAT	DEACNDEV	DESTDTC
DE	ITA1001	XYZ9999	Sizing, positioning or deployment difficulties	VALVE NOT IMPLANTED	Another Valve Used	2018-09-27
DE	USA6001	DEF5678	Material Deformation	DEFICIENCY	Explant	2018-10-16

- Device Tracking and Disposition (DT) - Records of events tracking for a given device (e.g., initial shipment, deployment, return, destruction).

DOMAIN	SPDEVID	DTTERM	DTPARTY	DTPRTYID	DTSTDTC
DT	XYZ9999	NOT IMPLANTED	SITE	ITA1	2018-09-27
DT	ABC1234	IMPLANTED	SUBJECT	ITA1001	2018-09-27
DT	DEF5678	IMPLANTED	SUBJECT	USA6001	2018-03-16
DT	DEF5678	EXPLANTED	SPONSOR	LIVANOVA	2018-10-16

- Device-Subject Relationship (DR) - Links each subject to devices to which they have been exposed.

DOMAIN	USUBJID	SPDEVID
DR	ITA1001	XYZ9999
DR	ITA1001	ABC1234
DR	USA6001	DEF5678

- Device Properties (DO) - Reports characteristics of the device that are important to include in the submission.

DOMAIN	SPDEVID	DOTESTCD	DOTEST	DOORRES
DO	XYZ9999	LVLVSIZE	Labeled Valve Size	S (21 mm)
DO	ABC1234	LVLVSIZE	Labeled Valve Size	M (23 mm)
DO	DEF5678	LVLVSIZE	Labeled Valve Size	L (25 mm)

- Device-In-Use (DU) - Contains the values of measurements and settings that are intentionally set on a device when it is used.

TERUMO BUSINESS CASE - A first CDISC initiative

Terumo Corporation was founded in 1921 by several scientists and doctors, including Dr. Shibasaburo Kitasato, to produce clinical thermometers in Japan. Since then Terumo developed more than 100 different medical devices in order to contribute to society by providing valued products and services in the healthcare market and by responding to the needs of patients and healthcare professionals. Terumo is active in multiple fields, but the recent focus in clinical research is mostly in the fields of Interventional Cardiology, Interventional Oncology, Peripheral Interventions and Cardiovascular Surgery.

Terumo's first study where CDISC standards were implemented is the e-Ultimaster Trial, which is one of the largest, prospective worldwide registries. Main characteristics:

- Clinical Field: Cardiovascular Intervention
- Product: Coronary Stent (Drug Eluting Stent)
- Study Design: Observational study (Registry), single arm, open label, 5 majors timepoints : Screening, Baseline, Procedure, 3 Months Follow-up, and 1 Year Follow-up.
- Primary endpoint: Validate Efficacy and Safety: Composite Endpoint of different Serious Adverse Event up to 1 year after procedure (i.e. Cardiac Death, Target Vessel Revascularization related to Myocardial Infarction and Clinically Driven -Target Lesion Revascularization).
- Secondary endpoint: exploratory analysis
- Status: First-Patient-In in 2015, Last-Patient-Out in Sep 2019, Database-Lock in Dec 2019, N = 37.198, 378 sites, 50 countries.

eUltimaster's legacy data was captured through an electronic Data Capture system (EDC) and extracted in SAS readable format. Over the years, all interim analyses were made on CDISC non-standardized data. However, before producing the final analysis for the clinical study report, it has been internally decided that an additional effort should be made in order to improve the traceability of the data and the transparency of the analysis results.

When starting to map the raw data into SDTM, three main observations were made:

- some domains were easily mapped as the data collected was similar to pharmaceutical clinical trial, and especially DM, MH, CM, AE, EG, LB.
- all medical device's data could fit the MD-specific domain, and especially DU, DI, DE.

- crucial information that could have a direct/indirect impact on the outcome cannot be easily mapped, such as :
    - the **lesions description** data: Segment description, lesion location and complexity, lesion type, vessel lumen, etc.
    - the **procedure** data: Arterial access site, side, guided by use of additional imaging, action taken based on imaging results, etc.

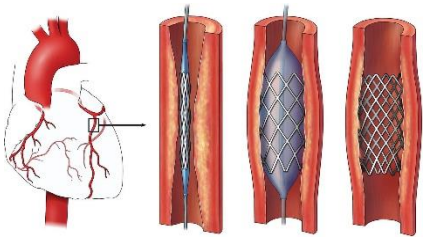

Figure 2. Deployment of a coronary stent.

These important variables cannot find their place in the current SDTM model and should be mapped into supplemental qualifiers' domains or findings about domains while they might play a major role in the primary endpoint of the study.

Furthermore, the complexity of the disease and its treatment increase even more the incompatibility of the SDTM model to the needs of the project. This is mainly due to the multitude of levels of collected information and how they interfere with each other. In fact, in reality, one patient can have multiple procedures (index vs stage procedures) and during the same procedure, multiple lesions can be treated in different ways by placing one or multiple stents with or without overlap.

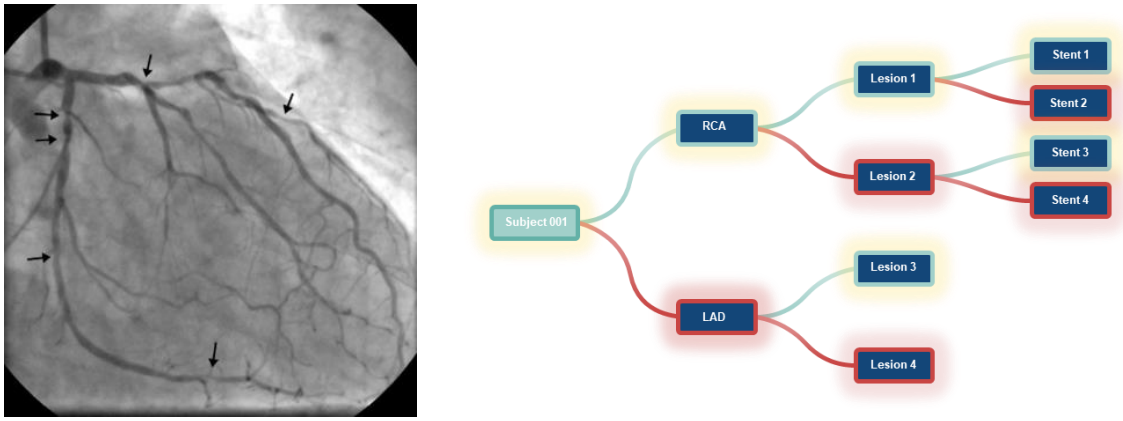

Figure 3. Multi vessel disease image and representation of the different levels of collected information

Another complex case to map is when considering not only the location of the lesion but also its characteristics. One example is multiple coronary lesions at a bifurcation site.
Important parameters to consider are not only the lesion location (proximal vs distal) and the lesion's characteristics but also the vessel diameter (main/side branch), the lesion length, the number of stents used, the presence of stent overlap, etc.

As it is the case for most studies where the primary endpoint depends on a complex endpoint (i.e. combination of different AEs), all AEs were collected in the EDC system, out of which AEs of Specific Interest were reviewed by two independent Clinical Event Committee (CEC) members for adjudication. However, no clear guidelines exist on how to handle and to store the adjudicated data. In the eUltimaster study, it has been decided that all AEs collected in the EDC would be stored in the AE domain while the Adjudication decisions would be stored in the FA domain.

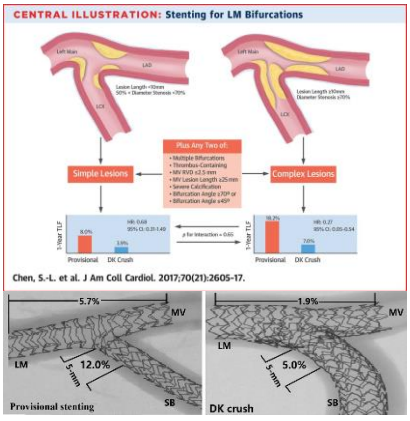

Figure 4. Stenting at Bifurcation site

The remaining questions were :

- Should the FA domain only contain the reconciliated records or both the collected records with the reconciliated one?
- How to justify and trace any data change: start date of event, type of AE, relationship, severity, etc.?
- Where to store the additional information than the CDISC standard AE domain data that has been collected and need to be considered for the analysis (e.g. Relationship to device and relationship to procedure)?
- Where to store the decision rationale for the adjudication of the AE with missing source documentation (e.g. worst-case scenario)?

In addition to the previous challenges, further question arose :

- Most devices do not contain any drugs, but EX domain is mandatory.
- A number of devices contain drugs (e.g. Drug Eluting Stent), even if classified as medical device only (one exposure, only local effect) should it still be recorded in EX?
- In the CRF, all AEs and CM of specific interest are listed, but are not recoded using a standard methodology (MedDRA and WHO Drug Dictionary)

As of today, MD domains are probably designed to fit pharmacological study where a device is used to deliver the study drug but is not yet ready to answer all needs of Device only studies.

LIVANOVA BUSINESS CASE – POOLED DATABASE PROJECT

LivaNova is a global medical technology company built on decades of experience and a relentless commitment to improve the lives of patients around the world. Worldwide leader in cardiovascular solutions with heart-lung machines and cardiopulmonary bypass, heart valves, aortic valve replacement; and neuromodulation solutions: pioneers of the VNS (Vagus Nerve Stimulation) Therapy® System for people affected by drug-resistant epilepsy and difficult-to-treat depression.

As a medical device company, LivaNova needs to abide to European Commission Medical Device Report (MDR) requirements and to submit by May 2020 an MDR for each product which describes the general safety and performance.
Some reflections were internally done about all *regulatory* needs: besides the close and mandatory MDR, each product needs a CE certification which is the result of conformity assessment from a notify body, once received the CE certification, the company can submit to country regulatory agencies for medical device the documentation for the commercialization in that country.

Then just for regulatory purpose, at least 3 analyses for each product must be produced. Then also analyses to plan future trials (*exploratory* purpose) or to produce peer review publications (*confirmatory* purpose) will be required.
The solution in order to satisfy these 3 purposes and the several analyses is the creation of a *pooled CDISC database*. The usage of CDISC standards is a key aspect of this project.
Some months ago, an internal project was set focused on one product, Perceval suture-less AVR, with the usage of all available Perceval Data from 9 studies.

Looking into old projects, in the past few pooled analyses were performed using a linear process where there was no integration of all stakeholders needs.

Figure 5. Linear process – no stakeholders needs integration

The main difference in the process for the present (and future) pooled analyses is to integration, a circular process to apply efficiency to programming steps and to give consistency between analyses.

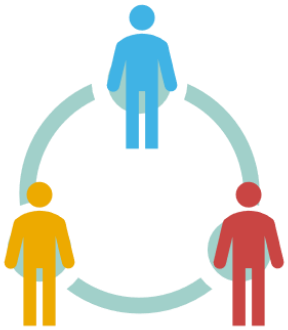

Figure 6. Circular process – stakeholders needs integration

For the new process implementation, training of the clinical team to have a global overview of the upcoming analyses/submissions was needed.
Moreover, starting from pooled databases experiences using SDTM/ADaM datasets, some other considerations for integrating the data must be done about:

- Studies with different designs
- Decision on source data used
- Different dictionary versions
- Maintenance of traceability in iSDTM and iADaM.

POOLED DATABASE PROJECT – STRATEGY

Two possible strategies are usually applied when CDISC databases are integrated (Figure 6), these strategies have as primary source SDTM/ADaM databases.

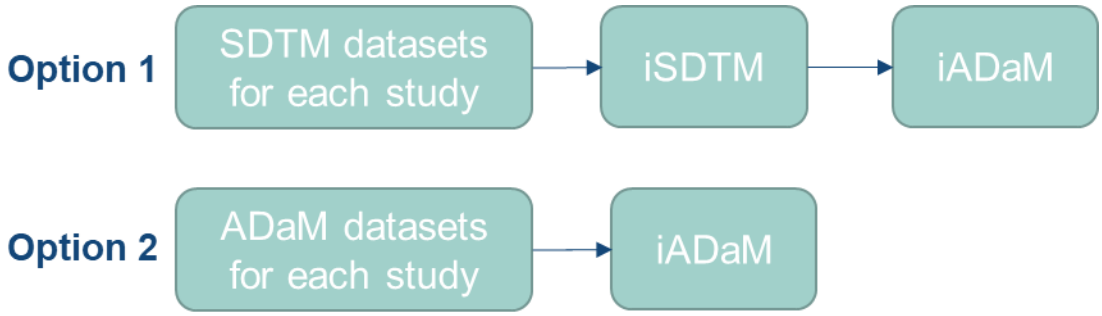

Figure 7. Strategies with SDTM/ADaM datasets source

For Perceval AVR studies SDTM database is available only for 1 study out of 9 studies and no ADaM database is available. Then the two options should be modified as presented in Figure 7.

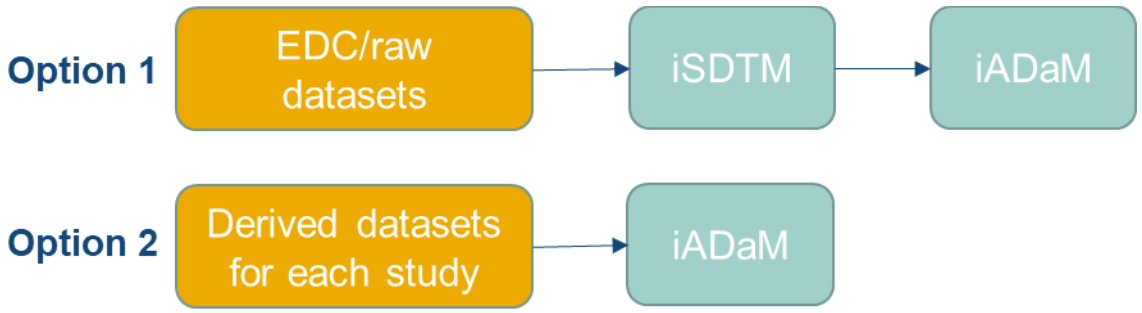

Figure 8. Strategies without SDTM/ADaM datasets source

Then the choice is between having as source EDC/raw datasets or derived datasets. The usage of derived datasets from 9 different studies has two main issues:

- As they cover different requests/analyses, then the pooling would be complex without clear traceability.
- They contain only the info for the required analyses, derived datasets cannot be the unique source.

Due to these issues, the chosen option is the number 1 of Figure 7.

Figure 9. Selected strategy

Applying the selected strategy produces some *advantages*:

- due to the aggregation at SDTM level (iSDTM), which allows *alignment and standardization* of controlled terminology and dictionary versions, *harmonization* of coding strategy, creating a single source for ADaM.
- the creation of integrated ADaM (iADaM) starting from iSDTM allows to *focus on derivations*, alignment of algorithms, *clear traceability* to the predecessor.

There can also be found some disadvantages, but they are acceptable giving the context, e.g.: a more complex traceability for iSDTM and the major number of datasets to create and validate.

POOLED DATABASE PROJECT – WORK IN PROGRESS

Before the statistical programmer can move to CDISC implementation, some preliminary teamwork with the clinical specialist and the biostatistician should be done: this is the concretization of the integration between all internal stakeholders needs.

During the *preliminary teamwork*, the following aspects will impact CDISC implementation:

- Comparison of general info/characteristics of the 9 studies, e.g.: number of enrolled subjects, age and gender, treatment arms, visits schedule, analyzed timepoints, primary and secondary endpoints.
- Comparison of Coding strategies, e.g. prespecified terms vs free-text fields.
- Agreement on some concepts, e.g.: visits schedule, treatment arms.
- Comparison of info collected in the CRFs, e.g.: content overlapping, different terminology, similar content vs different structure.
- Controlled terminology harmonization, e.g.: echocardiography parameters.

With the outcome of this teamwork, CDISC Implementation will go smoother for the statistical programmer: as follow some examples, looking at some details of 4 out of the 9 (Cavalier, SURE-AVR, Perceval IDE, PERSIST-AVR, Perfect, Believe, Perceval Japan) studies about Perceval.
Trial Design Domains harmonization is important as it is the base for a consistent iSDTM mapping.

	CAVALIER	SURE-AVR	PERCEVAL IDE	PERSIST-AVR
# subjects	658	1134	422	914
Arm 1	PERCEVAL	PERCEVAL	PERCEVAL	PERCEVAL
Arm 2	-	STENTED VALVE	-	STENTED VALVE
Age min	65	18	18	18
Age max	INF	INF	INF	INF
Follow-up	5 years	yearly follow-up	1-5 years	5 years

Table 1. Studies characteristics

CAVALIER	SURE-AVR	PERCEVAL IDE	PERSIST-AVR	VISITNUM	VISIT
Preoperative	Preoperative	Preoperative	Preoperative	1	PREOPERATIVE
Operative	Surgery	Surgery	Intraoperative	2	SURGERY
Discharge	Discharge	Discharge	Discharge	3	DISCHARGE
-	-	-	1/3 months	4	3 MONTHS
3/6 months	-	3/6 months	-		
12 months	1 year	12 months	1 year	5	1 YEAR
2 years	2 years	2 years	2 years	6	2 YEARS
3 years	3 years	-	3 years	7	3 YEARS
4 years	4 years	-	4 years	8	4 YEARS
5 years	5 years	-	5 years	9	5 YEARS
-	6 years	-	-	10	6 YEARS
-	7 years	-	-	11	7 YEARS

Table 2. Visits schedules

From the studies characteristics (Table 1) and the visits schedules (Table 2) Trial Summary, Trial Arms and Trial Visits are clearly defined as these tables contain all the information to assign the values correspondent to several TSPARM/TSPARMCD, ARM/ARMCD, VISIT/VISITNUM.

Moving to the subjects data domains, the preliminary information collected can impact on the usage of a codelist from controlled terminology, codelist extension, variables, SDTM structures usage (supplemental qualifier or findings about).
For example, VISIT/VISITNUM codelist came along with the decision to use timepoints variables: the data collected between discharge and Year 1 must be mapped to 3 Months visit, but related timepoints variables must be set in domains (e.g. CVTPT/CVTPTNUM).

	CAVALIER	SURE-AVR	PERCEVAL IDE	PERSIST-AVR
Age, Sex, Race, Ethnicity, Country	Age, Sex, Country	Age, Sex, Country	Age, Sex, Race, Ethnicity, Country	Age, Sex, Country
Reference Dates	IC, Surgery, Death	IC, Surgery, Death	IC, Surgery, Death	IC, Surgery Death
Surgical Approach	Median sternotomy	Median sternotomy	Full sternotomy	Full Sternotomy
	Minimal invasive	Mini sternotomy	Partial sternotomy, Minimally Invasive	Mini sternotomy
		Mini thoracotomy	Right thoracotomy	Mini sternotomy

Table 3. Demographics and baseline info

CAVALIER	SURE-AVR	Perceval IDE	PERSIST-AVR	PRTRT
Cross Clamp - min	Cross Clamp - min	Total Cross Clamp Time - min	Cross clamp (start time - end time)	Cross Clamp Time
Implant - min	Pump Time - min	Pump Time - min	Operating room suite (start time - end time)	Pump Time
Pump Time - min		Open to Close - min	Skin-to-skin (start time - end time)	Skin-to-skin Time
		Ventilation Time - min	Extracorporeal circulation (start time - end time)	Implant Time
		Perceval Time - min		Operating room Time
		Total Time patient in OR suite - min		Ventilation Time

Table 4. Surgical Times

About Demographics (DM) domain the following considerations were done (Table 3): controlled terminology must be reviewed and standardized also for those variables collected not in all studies (e.g. DM.RACE, DM.ETHNICITY); another peculiarities of medical device is that, in most of the situations, the start of exposure is considered the surgery date, then this info is mapped into DM.RFXSTDTC.
Other two info to be mapped related to surgery are the surgical approach and surgical times:

- Surgical approach is a variable often used also to produce subgroup analyses, then the choice is about where to map it: SUPPDM or in PRSCAT?
- Surgical times are mapped to PR.PRTRT: for them a standard codelist must be defined (Table 4) and for one of the studies the duration must be derived (SDTM allows for easy derivation) as start datetime and end datetime are available.

These are just few examples about how the preliminary teamwork can make smoother CDISC implementation.

The benefits of the usage of CDISC standards are not just into the initial phases, but overall in the next phases of the first analysis and in all subsequent analyses for the consistency and the efficiency gained.

CONCLUSION

Thanks to the new Medical Device European Regulations, some companies have started to implement the CDISC standards in their studies. We are seeing a global desire to improve transparency through a comprehensive EU database on medical devices and a device traceability system based on unique device identification and to reinforce the rules on clinical evidence, including an EU-wide coordinated procedure for authorising multi-centre clinical investigations. However due to the lack of regulatory requirement and lack of previous industry experience, hesitations and reluctance are often expressed by upper-management representatives.

In order to progressively migrate to the CDISC standards implementation, mandatory action have to be taken such as the training of the teams, the setup of new settings or update of current ones, creation of the domains, redesign of the eCRF, use of dictionary, etc.
Additional CDISC documentations should be developed in order to integrate the needs of the medical device trials (e.g. SDTM-IG enhancement or TAUGs) and validation/conformance rules should be reviewed as they do not fully apply to medical device trials (e.g. no drug exposure to be reported while EX is mandatory and PR domain could contain key information).

Even if this represents many challenges, the effort is worth it because the use of CDISC standards has a lot of benefits, such as:

- reusability of the data and facilitates data pooling
- increase in clarity and accessibility of the data
- transparency and traceability of the data from eDC to CSR
- cross-functional collaboration by sharing information and knowledge, empowering analyses and facilitating decision making
- efficient data manipulation reducing costs and time
- enhanced innovation (e.g. Big Data, Data Visualization Dashboard)

CDISC standards have already proved their value in pharma.
We decided to unleash their power, when will internal/external stakeholders set them free?

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