Paper SI06

Let CDISC be!

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ABSTRACT

As per CDISC SDTMIG-MD, 7 additional SDTM domains have been created 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, but how to use them in medical device studies where no drugs are involved? Even though it isn't mandatory to deliver a CDSIC compliant database for FDA/PMDA submissions yet, some Medical Device companies have started to implement it when designing the database of new studies. LivaNova and Terumo are two examples of global leader device companies who took this initiative. By combining experiences, 2 recent real business cases can be presented. The presentation will focus on the challenges faced and the decisions taken during the implementation of the CDISC standards. This will hopefully broaden the scope of these 7 SDTM domains and bring to light the possibilities they hold.

INTRODUCTION

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

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

But implementing CDISC in Medical Device is not limited to the production of these 7 domains, these are just the heart of the SDTM database, also SDTM general domains are needed: trail design domains, subject domains (e.g. CM, MH, EG, CV, PR), supplemental qualifiers, associated persons (if needed), etc.

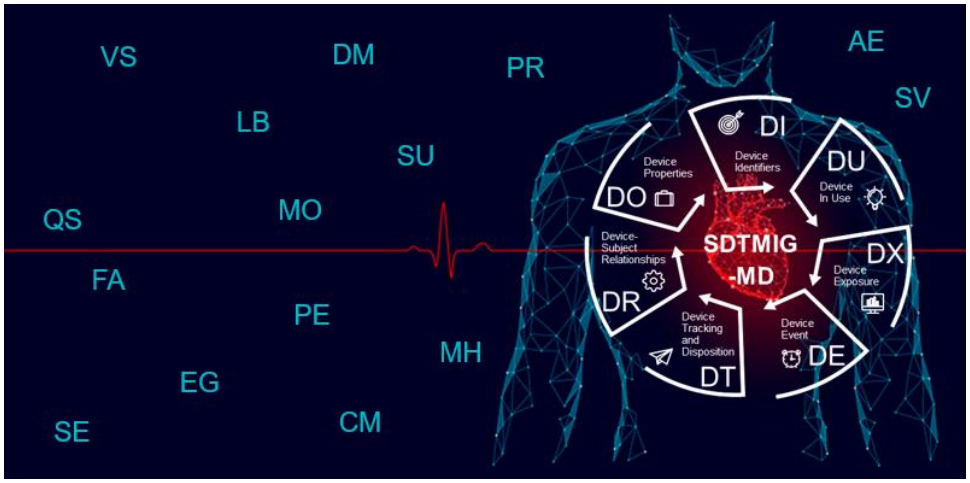


Figure 1. Setting MD domain in the heart of the full SDTM database.

This means that a full SDTM database should be created, and this includes CDISC controlled terminology usage and define-xml documentation. Moreover, also ADaM standards can be useful.

However, about CDISC implementation for Medical Devices some other considerations can be done: even if CDISC standards are not mandatory, the full process and compliance to CDISC are preferable, but specific waivers can be justified.

As follows few examples for each aspect:

- Process waiver, it can be decided not implement part of the process based on internal knowledge, available resources, budget, timelines
    - Due to available resources, define-xml useful if all stakeholders are trained to use it, e.g. created for SDTM but not for ADaM.
- Compliance waiver, due to eDC data limit or sponsor decision
    - In some Perceval studies Core lab data were collected twice at Preoperative visit, one of the two timepoints has collection date equal to Surgery visit date: decided to keep the issue in SDTM and identify the baseline value to be used as per SAP specifications in ADaM. (Note: Core lab data is an external data transfer).

CVTEST	CVORRES	CVORRESU	CVSEV	VISIT	CVDTC	CVTPT
Aortic Height	1.37	cm		PREOPERATIVE	2010-03-11	BASELINE
Aortic Height	1.13	cm		PREOPERATIVE	2010-03-12	PREOPERATIVE
Aortic Height	1.29	cm		SURGERY	2010-03-12	
Calcification	Y		SEVERE	PREOPERATIVE	2010-03-11	BASELINE
Calcification	Y		MODERATE	PREOPERATIVE	2010-03-12	PREOPERATIVE
Calcification	N		NONE	SURGERY	2010-03-12	

    - In CV domain there are one parameter with unit “m/sec” and one parameter with unit “cm/sec”, based on CDISC controlled terminology this second unit should be replaced with “cm/s”, but the label which will be displayed in tables need to have “/sec” for both, then it was decided not to recode in “cm/s” in SDTM.LB.LBORRESU and map back to “cm/sec” in ADaM.ADLB.PARAM.

Code	Codelist Code	Codelist Name	CDISC Submission Value	CDISC Synonym(s)
C102406	C71620	Unit	cm/s	cm/sec
C42571	C71620	Unit	m/sec	Meter Per Second

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 in its field. Its main characteristics were:

- 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 like pharmaceutical clinical trial, and especially DM, MH, CM, AE, EG, LB.
- Most of 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.

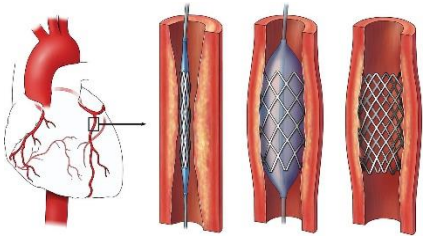


Figure 2. Deployment of a coronary stent.

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, 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.

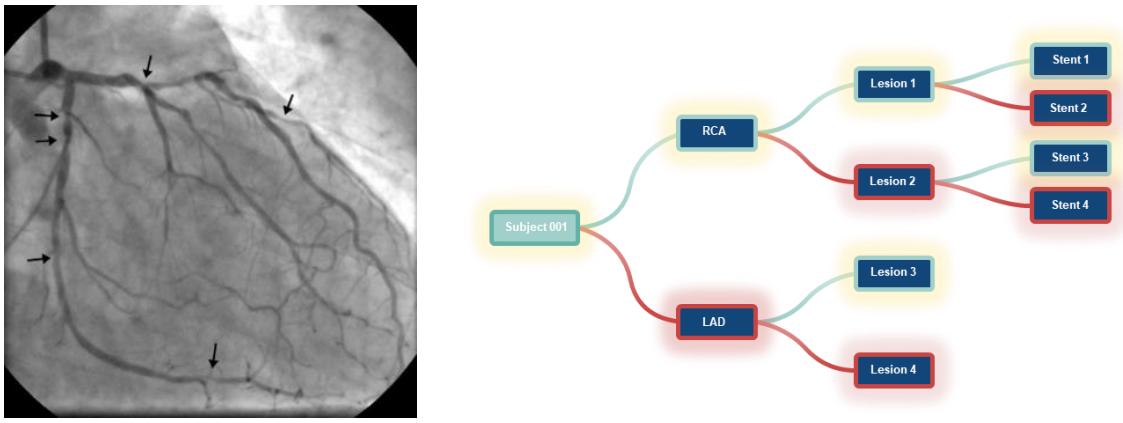


Figure 3. Multi vessel disease image and representation of the different levels of collected information

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 placement technique used, the presence of stent overlap, etc.

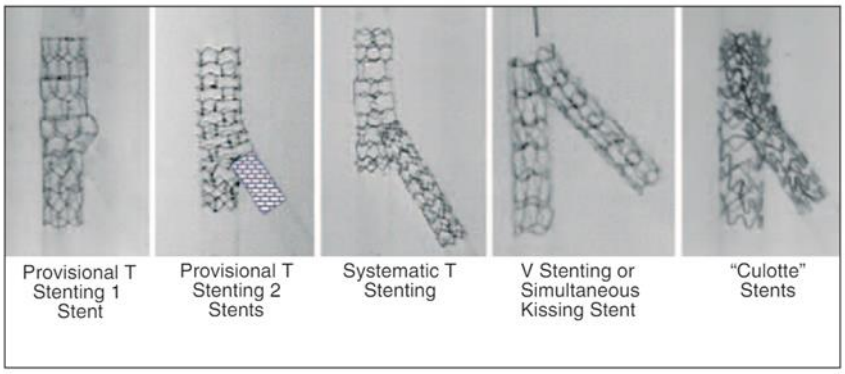


Figure 4. Different Stenting Techniques used at Bifurcation site

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.
The remaining questions were :

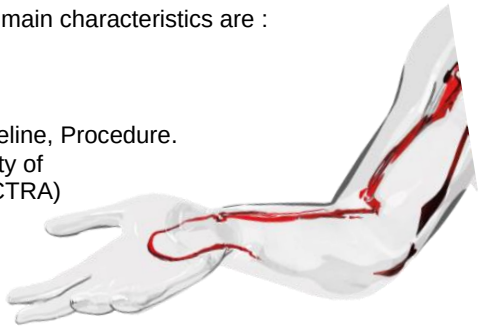
- Should the FA domain only contain the reconciliated records or both the collected records with the reconciliated one?
- How to justify and trace any data change: start date of event, type of AE, relationship, severity, etc.?
- Where to store the additional information than the CDISC standard AE domain 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.
- Several 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)

Another study that worth mentioning is the DISCO RADIAL Study : "*DIStal versus COnventional RADIAL access for coronary angiography and intervention: a randomized multicenter trial*". Its main characteristics are :

- Clinical Field: Peripheral Intervention
- No Investigational Device, Comparison of Access Technique
- Study Design: Interventional study (RCT), 2 arms, open label,
  FU only until discharge (Day 3)3 majors timepoints: Screening, Baseline, Procedure.
- Primary Objective and Primary Endpoint: Demonstrate the superiority of
  Distal Radial Access (DTRA) to Conventional Transradial Access (CTRA)
  regarding forearm Radial Artery Occlusion rate (RAO) at discharge
- Secondary endpoint: safety and efficacy exploratory analysis
- Status: FPI 2019, LPLV 2021, N ± 315/1300 (SEP-2020),
  14 sites, 9 countries.



As there is no investigational device or drug here, this study forces the CDISC programmer to think outside of the box. How to derive standard variable related to the exposure such as the Safety Population Flags, not from the EX or EC domains, neither from the DX domain but from the PR domain where the procedure is recorded. Furthermore, many data in relation with the procedure is collected but no straightforward place is defined to store it in the actual SDTM-IG.

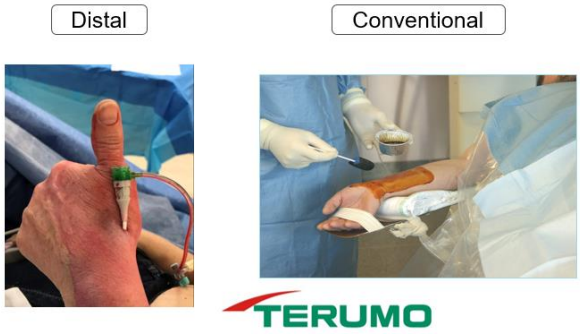


Figure 5. Comparing Distal and Conventional Radial Artery Access

Finally, the use of the investigational medical device can sometimes be influenced by other medical devices used at the same time or just before or just after. For example, in order to place a stent, you need first to make a puncture, then to insert a sheath then to reach the target lesion with a guidewire (assisted or not by some external or intravascular imaging). All these "concomitant devices" can have different shape or size or material and their specifications are often collected in order to evaluate impact on the outcome of the procedure (as per MDR requirement). By putting all these information's in the DX domain, it becomes difficult to make the difference between the real exposure which is the purpose of the study and all the additional ones. Maybe an additional dataset (comparable as CM vs EX for investigational drug) could simplify the understanding of the datasets and its content.

As a general rule, it is preferable to try to avoid developing many user-defined domains, because if we don't, we might end up losing certain advantages of standardization, and among other things the reproducibility between studies of datasets. 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 (DRE) and Difficult-to-Treat Depression (DTD), Obstructive Sleep Apnea (OSA), Treatment-Resistant Bipolar Depression (TRBD).

Some reflections were internally done about all regulatory needs: besides the new Medical Device Report (MDR) requirements, 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.
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. The usage of CDISC standards is a key aspect of this project.

A CIRCULAR PROCESS

In order to avoid a linear process where there was no integration of all stakeholders needs, the selected strategy for the team was a circular process to apply efficiency to programming steps and to give consistency between analyses.

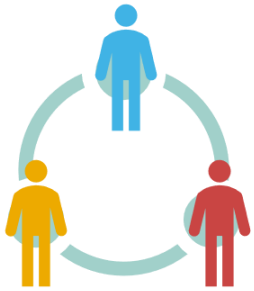


Figure 6. Circular process – stakeholders needs integration

Lesson learned – successful aspects

- Clinical team encouraged to have a global overview of the upcoming analyses/submissions;
- Sharing and clarifying needs and knowledge;
- Parallel review of the 9 CRFs allow to better understand the role of some biomedical concepts.

Lesson learned – unsuccessful aspects

- Some reviewers completed the review of different documents as if they were silos, e.g.: SDTM specifications not checked versus Statistical Analysis Plan (SAP) content.

Lesson learned – points of improvement

- To assign all team roles and to have on board key opinion leaders from the beginning.
- Be timely and together on the project needs.

POOLING STRATEGY

Figure 7. Pooling strategy

The selected pooling strategy has as source EDC/raw datasets, from which integrated SDTM (iSDTM) database has been created, then iSDTM is the source for integrated ADaM database. The advantages and disadvantages foreseen during the planning phase of the project were all confirmed.

Lesson learned – expected and actual advantages

- aggregation at SDTM level (iSDTM) 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.

Lesson learned – expected and actual disadvantages

- a more complex traceability for iSDTM and the major number of datasets to create and validate:
    - the complexity of SDTM specifications document created some messages back and forth between SDTM specification author and SDTM datasets programmers.
    - Due to the different eDC structures, besides SDTM validation by double programming, some additional checks between raw and SDTM datasets were setup in SAS.

Lesson learned – points of improvement

- SDTM mapping order taken from the order of collection (visit order, form order), while a strategic order based on SAP content would be more efficient:
    - Following form order (Enrollment info, patients risk factors, previous surgical/non-surgical procedures, prior medications, preoperative status, ECG, blood exams, etc.) the order followed for both SDTM specifications and programming was DM, MH, PE, VS, PR, EG, LB, DI, DO, CV, CM, AE, etc.
    - It would have been more efficient to complete as first all SDTM domains involving efficacy and safety endpoints for heart valves: DM, DI, DO, CV, PR, AE. The most derivations to be programmed in ADaM have these domains as source, and these ADaM are the source of the key outputs to be produced.

As follow some other advantages will be discussed.

ADVANTAGES ON TIME

In the table below the distribution of the hours worked for each task is shown.

Task	Items	% hours
iSDTM documentation[1]	-	15%
iSDTM programming	23	50%
iADaM programming	16	10%
1° analysis TF	80	25%

[1] specifications and define-xml.

Looking at the statistical programming time spent on the whole project, iSDTM database creation took the most (65%), but for future project we need to consider that iSDTM will need an update only in 2 situations out of 3 options:

- No ongoing study, no additional study, no need to be updated → no additional work, 0 hours.
- There are two ongoing studies, then when their eDC database will be updated/locked a new run of AE coding, Core lab data transfer, run of SDTM programs, run of SDTM validation, run of additional SAS checks are needed → a rough estimation of these tasks based on the two ongoing studies is given in 80 hours which is around 7% of the time spent for SDTM tasks until now.
- If a new study on Perceval needs to be added into the pooled database, in addition to the above tasks also some additional work on SDTM specifications will be needed → a rough estimation of these tasks is given in 120-160 hours which is around 10-13% of the time spent for SDTM tasks until now.

Moving to iADaM programming and TFL outputs for the first statistical analysis, it is clear that the benefits of the usage of CDISC standards are not just into the initial phases, but overall in the next phases:

- 35% of the statistical programming time was spent on these two tasks;
- For both tasks efficiency gained due to CDISC standard structure of the source;
    - iSDTM datasets source for iADaM datasets;
    - iADaM datasets source for TFL outputs;
- Two weeks before the delivery an amendment to SAP was done, this added two safety endpoints and two additional subgroup variables → CDISC structure allowed a quick update for both ADaM and outputs programs.

For future projects the planned time for iADaM and TFL will also have some saving:

- iADaM new variables, new datasets → +40 hours, around 33% of the time spent for iADaM task until now.
- TFL new outputs / updates needed → +160-200 hours, around 40-50% of the time spent for TFLs task until now.

With the estimation of the hours needed for future projects a comparison of the percentage distribution of programming tasks with the first analysis can be done, into the following table a huge time reduction is foreseen both looking at the best scenario and at the worst scenario.

Task	1° analysis % hours	Next analysis Best scenario % hours	Next analysis Worst scenario % hours
iSDTM	65%-	0%	9%
iADaM	10%	3%	3%
TFL	25%	10%	12.5%
Total	100%	13%	24.5%

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

WHAT'S NEXT?

With all the above evidences LivaNova confirmed CDISC implementation for all new studies and for pooling of legacy data of certain products:

- just right after the delivery of the first analysis on Perceval Pooled Database, 2 new analyses have been required.
- for VNS Therapy ® a new pooling project has started.

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.

From the business cases presented here, we can say that before the CDISC standards implementation we saw challenges and potentialities, after CDISC standards implementation we put power in action achieving 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 added value in pharma. Then LET CDISC BE also in medical device.

REFERENCES

- CDISC Device Team, "Study Data Tabulation Model Implementation Guide for Medical Devices (SDTMIG-MD)" Version 1.1, dated 2018-12-12, www.cdisc.org
- R. Teli, A. Sacco, "Paper PP05 - Medical Device SDTM: A Real Case", Sorin Group Italia srl (LivaNova group), PHUSE EU Connect 2019.
- R. Debrus, S. Faini, "When Medical Devices unleash SDTM power", EU CDISC Interchange 2020.
- Terumo eUltimaster Trial's Presentation, https://www.terumo-europe.com/en-emea/clinicaldata/e-ultimaster-trial
- Terumo DISCO Radial Trial page on ClinicalTrials Governemental's website, https://clinicaltrials.gov/ct2/show/NCT04171570
- Tambaca, Josip & Kosor, Mate & Canic, Suncica & Paniagua, David. (2010). Mathematical Modeling of Vascular Stents. SIAM Journal of Applied Mathematics. 70. 1922-1952. 10.1137/080722618.
- David Sidebotham, Andrew McKee, Michael Gillham, Jerrold Levy, Cardiothoracic Critical Care E-Book, Elsevier Health Sciences, 12 sept. 2007 - 672 pages.
- Lefèvre T. (2005). Lesiones en bifurcación: cuanto más simple, mejor [Bifurcation lesions: the simpler, the better]. Revista espanola de cardiologia, 58(11), 1261–1265.

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