

SDTMs in a Medical Device Trial – A First Attempt

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ABSTRACT

While clinical trial data of pharmaceutical and medical devices have a lot in common, the differences can be difficult to deal with in SDTMs. This paper acknowledges the similarities, highlights the differences and serves as a case-study of how the Transcatheter Heart Valve (THV) Statistical Programming group of Edwards Lifesciences has decided to map their raw data into Study Data Tabulation Model (SDTM) domains. This is not intended to be the definitive guide of how to map medical device trial data to SDTM standards but to serve as the opening statement of a conversation.

INTRODUCTION

Clinical Data Interchange Standards Consortium (CDISC) standards are required for pharmaceutical clinical trials starting after 17th December 2016 but no date has yet been set whereby medical device trials are subject to the same requirements. This is partly because it is more challenging for device trials to conform given the variety and uniqueness of some of the data collected which the current standards do not adequately deal with. However, The Center for Devices and Radiological Health (CDRH) accepts clinical trial data in any format, including CDISC format, and it is anticipated that it will be mandatory sometime in the near to medium term. Consequently, those involved in the programming of medical device trial data are starting to develop strategies for mapping their raw data. This paper demonstrates the first attempt to map the data of a medical device trial by the Statistical Programming group at Edwards Lifesciences.

WHAT ARE MEDICAL DEVICES

According to the FDA, "A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."¹

FDA classifies medical devices based on the risks associated with the device. Devices are classified into one of three categories—Class I, Class II, and Class III.

Class I devices are deemed to be low risk and are therefore subject to the least regulatory controls. For example, dental floss is classified as a Class I device.

Class II devices are higher risk devices than Class I and require greater regulatory controls to provide reasonable assurance of the device's safety and effectiveness. For example, condoms are classified as Class II devices.

Class III devices are generally the highest risk devices and are therefore subject to the highest level of regulatory control. Class III devices must typically be approved by FDA before they are marketed. For example, replacement heart valves are classified as Class III devices.²

The THV Statistical Programming group at Edwards Lifesciences analyzes data from studies involving Transcatheter Aortic Valve Replacement (TAVR) where an artificial heart valve is implanted using a minimally-invasive technique using a catheter instead of open-heart surgery.

SIMILARITIES BETWEEN PHARMACEUTICAL AND MEDICAL DEVICE DATA

In a medical device trial, a lot of the data collected is similar to that of a pharmaceutical trial, such as Adverse Events, Demographics, Vital Signs and Quality of Life. Below is a full list of the domains that are being used by the THV group at Edwards in accordance with the CDISC SDTM Implementation Guide (V3.2).³ In a couple of cases, we decided to use domains that are proposed for Version 3.3 in an effort to be consistent with future studies.

AE (Adverse Events)

CM (Concomitant and Prior Medications)

DD (Death Details)

DM (Demographics)

DS (Disposition)

DV (Protocol Deviations)

EG (ECG Results)

FT (Functional Test – Proposed for V3.3)⁵

IE (Inclusion / Exclusion Criteria Not Met)

HO (Healthcare Encounters)

LB (Laboratory Test Results)

MH (Medical History)

MO (Morphology)

QS (Questionnaires)

RS (Disease Response – currently only for oncology studies in V3.2 but being expanded for all indications in V3.3)⁶

SV (Subject Visits)

VS (Vital Signs)

Additionally, we created the Trial Design domains. These are designed for pharmaceutical clinical trials so not all fields may be relevant.

Trial Design Domains

TA (Trial Arms)

TE (Trial Elements)

TV (Trial Visits)

TD (Trial Disease Assessments)

TS (Trial Summary Information)

TI (Trial Inclusion/Exclusion Criteria)

DEVICE SPECIFIC DOMAINS

In 2012, the Study Data Tabulation Model Implementation Guide for Medical Devices (SDTMIG-MD)⁴ was produced. It contains seven SDTM domains designed specifically for medical device data. As with other domains, you only use those which are applicable to your study. In the Edwards study, only DI, DX, DE and DT were used.

The following seven new SDTM-based domains are included in the Implementation Guide:

1. **Study Device Identifiers (DI):** This is a special-purpose domain designed for the submission of information that identifies a specific device unit. The primary purpose of this domain is to provide a consistent sponsor-defined variable (SPDEVID) for linking data across Device domains, independent of the level of granularity by which a device might be identified by a sponsor in a study. The information included in Study DI depends upon what is needed to identify the device uniquely within a submission and to meet analysis and regulatory requirements. The domain is not intended to contain information about characteristics that can change without affecting the identification of the device, such as supplier details or dial settings (e.g., imaging devices). Device Identifiers exist independently from subjects and therefore the Study DI domain does not contain USUBJID.
2. **Device In-Use (DU):** Device In-Use is a Findings domain that contains the values of measurements and settings that are intentionally set on a device when it is used, and may vary from subject to subject or other target. These are characteristics that exist for the device, and have a specific setting for a use instance. DU is distinct from Device Properties, which describes static characteristics of the device. For example: Device Properties would capture that an MRI machine's field strength has a range from 0.2 to 3 Tesla, whereas the Device In-Use domain would capture that the field strength for the MRI scan for Subject 123 was 0.5 T.
3. **Device Exposure (DX):** Device Exposure is an Interventions domain that records the details of a subject's exposure to a medical device under study. This device is prospectively defined as a test article within a study and may be used by the subject, on the subject, or be implanted into the subject. Examples include but are not limited to stents, drug delivery systems, and any other item under study that is defined as a device in the applicable regulations.
4. **Device Events (DE):** DE is an Events domain that contains information about various kinds of device-related events, such as device malfunctions. A device event may or may not be associated with a subject or a visit. If a device event, such as a malfunction, results in an adverse event, then the AE-related information should be recorded in the Adverse Events (AE) domain (see SDTMIG, AE domain). The relationship between the AE and a device malfunction in DE can be recorded using RELREC (see SDTMIG section "Relating Datasets") and appropriate identifying variables such as DESPID and AESPID.
5. **Device Tracking and Disposition (DT):** The Device Tracking and Disposition domain is an Events domain that represents a record of tracking events for a given device. This could include initial shipment, deployment, return, destruction, etc. Different events would be relevant to different types of devices. The last record represents the device disposition at the time of submission. The sponsor decides upon the level of granularity that is appropriate for this domain based on the type of device and agreements with the regulatory agencies.
6. **Device-Subject Relationships (DR):** The Device-Subject Relationships domain is a special-purpose domain that links each subject to devices to which they may have been exposed. Information in this table may have been initially collected and submitted in other domains (e.g., Device Exposure, Device Tracking and Disposition, Device Events). This domain, however, provides a single, consistent location to find the relationship between a subject and a device, regardless of the device or the domain in which subject-related data may have been collected or submitted.
7. **Device Properties (DO):** The Device Properties Findings domain is used to report characteristics of the device that are important to include in the submission, do not vary over the course of the study but are not used to identify the device. Examples include expiration date or shelf life. Device Properties exist independently from subjects and therefore the DO domain does not contain USUBJID.

DIFFERENCES OF MEDICAL DEVICE TRIALS

Now that the similarities in the data of drug and device trials has been discussed, what are the main differences?

PROCEDURE DATA

A medical device, by its nature, has to be placed on or in a patient in order to give the effect to the patient (refer back to the examples earlier of dental floss, condoms or replacement hearts valves). This involves some kind of procedure. In the case of an Edwards Lifesciences randomized trial involving Transcatheter Aortic Valve Replacement (TAVR)

versus Surgical Aortic Valve Replacement (SAVR), approximately 120 variables were collected regarding the procedure used to deliver the device including

Procedure Start Time

Procedure End Time

Type of Anesthesia Used

Size of the Valve

Implant Access Route.

While some of these may fit into the device-specific domains, many do not. There is a PR domain in the SDTM Implementation Guide but can this be used for the procedure which delivers a heart valve? Even if it can, it would only account for Procedure Start Time and Procedure End Time in the list above leading to the remaining 118 variables to be placed in a supplemental domain, SUPPPR. Because of these reasons, we decided to put all the procedure data in a custom domain called YP.

ADJUDICATED DATA

It's not unique to medical device trials to have a committee to adjudicate Adverse Events but it's much more common than in drug trials. In the example of the Edward's trial, the Clinical Events Committee (CEC), adjudicates certain adverse events triggered from the site-reported forms. It was determined that we would use the CE (Clinical Events) domain for this data.

USE OF DAY 0

It is standard practice to consider the day on which a drug is first administered as Day 1. However, in medical device trials, the day on which the device is first used or implanted, is commonly referred to as Day 0. This contravenes the SDTM Implementation Guide and would result in an error from Pinnacle 21.

FUTURE WORK

As was stated earlier, there is currently no regulatory requirement (as of 2017) for medical device trials to conform to CDISC standards and there is work to be done before it is feasible to do so. On a general point, it would be useful for there to be a new domain created specifically for the data associated with the initial procedure where the device is attached, inserted or implanted. A suggestion would be to add another device-specific domain, DP (Device Procedure). Alternatively, clarification could be made to the existing PR domain so that it's explicitly stated that this is to be used for medical devices and additional variables added to make it more relevant.

It must be noted that creating SDTMs does not make a submission CDISC compliant. Your CRFs must also follow the CDASH conventions. It's important to work with your Data Management group to ensure this. It will also make the mapping process much simpler. For a first attempt, instead of spending time renaming laboratory parameters or splitting variables so that nothing has a length in excess of 200 characters, spend the time working with others to make the CRF compliant. Then, at your second attempt, you will conform to these conventions without additional programming.

CONCLUSION

To map data from a medical device trial to SDTM, there are four steps.

1. Review the Implementation Guides
2. Map to the pharmaceutical domains where appropriate
3. Use the device-specific domains

4. Use custom domains for everything else

Following these steps, mapping medical device clinical trial data is not as daunting as it first appears and not so very different to mapping pharmaceutical data. Additionally, it's important to discuss the mapping approach with your own reviewer ahead of submission. This will confirm you're on the right path and avoid issues at submission time.

REFERENCES

¹ <https://www.fda.gov/AboutFDA/Transparency/Basics/ucm211822.htm>

² <https://www.fda.gov/aboutfda/transparency/basics/ucm194438.htm>

³ CDISC Study Data Tabulation Model Implementation Guide (SDTM IG): Human Clinical Trials Version 3.2

⁴ Study Data Tabulation Model Implementation Guide for Medical Devices (SDTMIG-MD): Version 1.0

⁵ What to Expect in SDTMIG v3.3, Fred Wood, Accenture Accelerated R&D Services, Berwyn, PA, PharmaSUG2015 - Paper DS14 - <http://www.pharmasug.org/proceedings/2015/DS/PharmaSUG-2015-DS14.pdf>

⁶ <https://www.cdisc.org/foundational/grs>

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CONTACT INFORMATION

As the title of this paper stated, this is a first attempt. You may have different ideas and the author would value and encourage your comments, questions and opinions. Contact the author at:

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