Successful US Submission of Medical Device Clinical Trial using CDISC

Phil Hall, Edwards Lifesciences, Irvine, CA

ABSTRACT

It is not yet mandatory for medical device trial data to be submitted using CDISC but The Center for Devices and Radiological Health (CDRH) accepts clinical trial data in any format, including CDISC. This paper serves as a case-study of the successful FDA submission of the Edwards Lifesciences' PARTNER 3 trial which utilized SDTMs and ADaMs. There will be a review of the SDTM domains used for medical device-specific data and a general discussion of the submission approach.

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. This paper details how Edwards Lifesciences received approval of the SAPIEN 3 Transcatheter Heart Valve for low risk patients in the PARTNER 3 Trial using analyses performed utilizing SDTMs and ADaMs.

THE PARTNER 3 TRIAL

The PARTNER 3 trial is a multicenter, randomized trial in which transcatheter heart valve replacement with transfemoral placement of a third-generation balloon-expandable valve compared with standard surgical aortic-valve replacement in patients with severe aortic stenosis and a low risk of death with surgery. The objective of the study is to establish the safety and effectiveness of the Edwards SAPIEN 3 Transcatheter Heart Valve (THV) in patients with severe, calcific aortic stenosis who are at low operative risk for surgical aortic valve replacement (AVR). The primary safety and effectiveness endpoint is the composite of all-cause mortality, all stroke, or rehospitalization (valve-related or procedure-related and including heart failure) at 1-year post procedure. Secondary endpoints were

- New onset atrial fibrillation at 30 days
- Length of index hospitalization
- Composite of death and KCCQ < 45 or KCCQ decrease ≥ 10 points from baseline to 30 days
- Death/All Stroke composite at 30 days
- All Stroke at 30 days

SUBMISSION PROCESS

The submission process was the same as if we'd submitted in a non-CDISC format except that we replaced the raw datasets, corresponding to the Electronic Data Capture Case Review Forms (EDC CRFs), with SDTMs. With all variables mapped, the SDTMs are the same as the raw datasets, just formatted in a way that is recognized by anyone with familiarity to CDISC standards. We included annotated CRFs explaining how each variable was mapped to each domain in the zip file that contained SDTM data, programs and documentation but not a define.xml. There were 147 raw EDC datasets in a unique format mapped to 51 datasets (including supplemental domains) in the standard SDTM format as well as 25 derived datasets in standard ADaM format.

We submitted the PMA on April 1st, 2019 to CDRH, received zero questions about the datasets or corresponding documentation and got approval on 16th August 2019, four and half months after submission. It is certain that the use of CDISC did not delay, and may have significantly shorted, the approval time. In the case of many medical devices, saved approval time means saved lives!

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]

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, DT and DO 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. The PR domain in the SDTM Implementation Guide is an obvious place for this data but what is a ‘procedure’? We defined a procedure as something that has a start or stop date / time, a dosage or if stated to have occurred or not. This means that values of PRSTDTM, DOSE or PROCCUR can be entered and each of these procedures is entered as a separate observation per subject and given its own value of PRTRT. For example, the administration of anesthesia is considered to be its own procedure as is pre-stenting and fluoroscopy.

PRTRT	PRSTDTC	PRENDTC	PRDOSE	PRDOSEU	PROCCUR
General Anesthesia	2017-01-01T12:00:00	2017-01-01012:35:00			
Fluoroscopy			400	mL	
Pre-stenting					Y

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

It is not claimed that this was a fully CDISC-compliant submission but went a long way towards it and makes Edwards Lifesciences a lot more prepared for the time when CDISC is mandatory. Submitting datasets, both raw (SDTM) and analysis (ADaM) in a format that it recognizable by the reviewers, along with supporting documentation, can only speed up the approval process compared with submitted data in a non-standard format.

As was stated earlier, there is currently no regulatory requirement (as of 2020) for medical device trials to conform to CDISC standards and there is work to be done before it is feasible to do so. Clarification could be made to the PR domain so that it's explicitly stated that this is to be used for medical devices and the controlled terms updated to include individual aspects of a medical device procedure such as administration of anesthesia.

It should be noted that having CRFs that conform to CDASH conventions makes it much easier to create SDTMs. It's important to work with your Data Management group to ensure this. 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.

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. Note that why it's tempting to map a CRF based on its title (Adverse Events to the AE domain, for example), this form may contain data that is best mapped to another domain such as details of re-interventions which should be mapped to the PR domain. Map question by question, not form by form!

CONCLUSION

Don't be scared to submit data in the style of SDTMs and ADaMs as a step to being fully CDISC-compliant. As long as you map all data and document properly, you're helping the reviewer by providing recognizable dataset names, variables and formats. Most medical device trial data can be mapped to the same SDTM domains as pharmaceutical trial data. Even if you mapped just 80% of data to the documented domains and 20% to custom domains, the reviewer would recognize most of the datasets, including the fundamentals of demographics, disposition and adverse events which can only reduce the time from submission to approval.

It is not known when it will be mandatory for medical device trials to be submitted in CDISC, but I recommend all professionals in this field ask themselves the following questions;

- Would you be ready if it became mandatory in two years' time?
- Would you be ready if it became mandatory in five years' time, but you don't start preparing for it for another three years?

The point is that it's worth starting to prepare now. It allows you take the process step-by-step. Remember, CDRH will accept clinical trial data in any format which includes CDISC format or a format that is partially CDISC.

Any trial data following CDISC standards can be combined. We know future data will be in CDISC format so studies done now in another format will have to be reworked if it is to be combined with those future studies. Time spent now will be time saved in the future. Try it. There is nothing to lose!

REFERENCES

[1] https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device

[2] https://www.fda.gov/medical-devices/consumers-medical-devices/learn-if-medical-device-has-been-cleared-fda-marketing

[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/qrs

CONTACT INFORMATION

Contact the author at:

Phil Hall
Edwards Lifesciences
One Edwards Way
Irvine, CA 92614
phil_hall@edwards.com
949-250-4881