Multiple Successful Submissions of Medical Device Clinical Trial in the US and China using CDISC

Phil Hall, Tikiri Karunasundera, Subendra Maharjan, Vijaya Vegesna

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 regulatory submissions of four Edwards Lifesciences' trials, three in the US and one in China, 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 approaches.

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), and regulatory agencies around the world, accept clinical trial data in any format, including CDISC format. This paper details how Edwards Lifesciences received four separate approvals of the SAPIEN 3 Transcatheter Heart Valve using analyses performed utilizing SDTMs and ADaMs. This paper builds on previous publications[1, 2] to provide further examples of successful trial submissions across multiple countries, gives more detailed examples of the mapping of key domains and illustrates the evolution of the mapping process from those earlier attempts.

SUBMITTED CLINICAL TRIALS

All four clinical trials detailed in this paper had the SAPIEN 3 Transcatheter Heart Valve (THV) as the investigational product. This is a non-invasively implanted valve, using a catheter instead of open-heart surgery to place it within the heart. These trials were conducted to expand the number of patients who can receive this therapy.

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 (SAVR). 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.

THE PARTNER 3 BICUSPID REGISTRY

The PARTNER 3 Bicuspid Registry is a separate single-arm registry under the PARTNER 3 trial protocol. It is a prospective, single-arm, multicenter study. The objective of the study is to evaluate the safety and effectiveness of the SAPIEN 3 THV in patients with calcific aortic stenosis requiring aortic valve replacement who are at low operative risk for SAVR and who have a bicuspid aortic valve as determined by the CT Core Lab.

CHINA S3 TRIAL

The China SAPIEN 3 trial is a single-arm, multi-center study to assess the safety and effectiveness of the SAPIEN 3 transcatheter heart valve implantation in Chinese patients with symptomatic severe calcific aortic stenosis who are considered at high risk for surgical valve replacement. The primary endpoint is all-cause mortality at 30 days post-index procedure.

COMPASSION S3 TRIAL

The COMPASSION S3 study is a single arm, prospective, multicenter study to demonstrate the safety and effectiveness of the Edwards Lifesciences SAPIEN 3 Transcatheter Heart Valve System in subjects with a dysfunctional right ventricular outflow tract (RVOT) conduit or previously implanted valve in the pulmonic position with a clinical indication for intervention.

SUBMISSION PROCESSES

The submission processes were the same as if we'd submitted in a non-CDISC format except that we replaced the raw data sets, corresponding to the Electronic Data Capture Case Review Forms (EDC CRFs), with SDTMs. With all variables mapped, the SDTMs contain the same information as the raw data sets, just formatted in a way that is recognized by anyone with familiarity to CDISC standards. For the US submissions, annotated CRFs explaining how each variable was mapped to each domain in the zip file that contained SDTM data was provided, along with programs and documentation but not a define.xml. For the China submission, it was not required to send the data sets, but additional Adverse Event listings were provided.

While it cannot be said that submitting in this format led to swifter approvals, we received <u>zero</u> questions across four whole submissions about our data format, so it certainly did not cause any issues. Therefore, we can say that the use of CDISC did not delay, and may have shortened, the approval times.

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."[3]

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.[4]

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 (V3.3).[5]

AE (Adverse Events)

CE Domain (Clinical Events)

CM (Concomitant and Prior Medications)

DD (Death Details)

DM (Demographics)

DS (Disposition)

DV (Protocol Deviations)

EG (ECG Results)

FT (Functional Test)

IE (Inclusion / Exclusion Criteria Not Met)

HO (Healthcare Encounters)

LB (Laboratory Test Results)

MH (Medical History)

MO (Morphology)

QS (Questionnaires)

RS (Disease Response

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.

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) [6] 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 Data sets") 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.

CASE STUDY EXAMPLES

In the case of the SAPIEN 3 trials performed by Edwards Lifesciences, the investigational devices used included the study valve, delivery system and balloon. The primary device is the heart valve. The studies investigated the safety and efficacy of the transcatheter heart valve (THV). The THV implant is a less invasive alternative to a surgical heart valve implanted via open-heart surgery.

The study devices were considered as common devices. That is there was a single record each in the DI domain for the valve, delivery system, and balloon, for a total of three records. The reason for taking this approach was the device tracking information was not available through the CRFs but collected in a separate database and not intended for data summary. The information that was on the CRFs regarding the device was mapped to the DU domain and the DO domain was not used. The device malfunctions were mapped to the DE domain and the date device was implanted was mapped to the DX domain.

DI Domain

DOMAIN	SPDEVID	DISEQ	DIPARAMCD	DIPARAM	DIVAL
DI	Balloon	1	TYPE	Device Type	Balloon
DI	Delivery_System	2	TYPE	Device Type	Delivery system
DI	Study_Valve	3	TYPE	Device Type	Study valve

DU Domain

Domain	USUBJID	SPDEVID	DUSEQ	DUTEST	DUCAT	DUORRES	DUORRESU
DU	SUBJ001	Balloon	1	Width	PREDILATATION	xx	mm
DU	SUBJ001	Balloon	2	Pressure	PREDILATATION	xx	xx
DU	SUBJ001	Study_Valve	3	Size	VALVE IMPLANT	xx	mm

The delivery system had no parameters of interest. The number of records in DU domain was the number of subjects multiplied by the number of parameters of interest. The DX and DE domains had similar formats where the SPDEVID was one of the values from the DI domain.

PROCEDURE DATA

A medical device, by its nature, must be placed on or in a patient in order to give the effect to the patient which involves some kind of procedure. In the case of these Edwards Lifesciences trials involving Transcatheter Aortic Valve Replacement (TAVR) and in one case, a comparator of 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 the obvious place for this data. The implantation of a transcatheter heart valve is not one single procedure, but a collection of procedures. 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 a concomitant procedure such as a percutaneous coronary intervention (PCI). The study case review forms (CRF) may collect a lot of information. Some of these elements would be in the PR supplement domain (e.g. valve is inserted in correct position). The device data may also be in the procedure CRF (e.g. valve size). Care should be taken to include the device data in the device-specific domains.

It was decided that we would split the data into two domains. The data relating to implanting the device was captured in what we named the PRID domain. This is the same as the PR domain, but the granularity of the data was more detailed than one record. This consisted of a collection of procedures.

The interventions due to AEs were less granular and considered as one single procedure. The data was mapped as PRAE, again using the naming conventions of the PR domain.

PRID EXAMPLE

PRSEQ	PRCAT	PRTRT	PRSTDTC	PRENDTC	PROCCUR
1	Anesthesia	General anesthesia	2020-08-11T08:15	2020-08-11T13:25	Y
2	Study procedure preparation	Skin incision	2020-08-11T08:20	2020-08-11T12:25	Y
3	Study procedure	Delivery system inserted	2020-08-11T08:50	2020-08-11T12:20	Y
4	Study procedure	Transcatheter heart valve implanted	2020-08-11T09:15	2020-08-11T10:20	Y
5	Concomitant procedures	Percutaneous coronary intervention (PCI)	2020-08-11	2020-08-11	Y

The PRAE domain was less granular compared to the PRID domain. This contained procedures that were performed due to a device-related AE. These are procedures performed after leaving the operating room. The primary interest was the procedure performed (PRTRT), procedure date (PRSTDTC), and the reason for the intervention (PRINDC). An example is shown below.

PRAE EXAMPLE

PRSEQ	PRCAT	PRTRT	PRSTDTC	PRINDC
1	Permanent Pacemaker	Dual Chamber	2020-06-10	Atrial fibrillation
2	Other Intervention - ARRHY	Intervention - Ablation	2020-06-10	Atrial fibrillation
3	Transfusion	Transfusion of Plasma	2020-06-10	Bleeding
4	Percutaneous Coronary Intervention	Coronary Stent	2020-09-10	Cardiac failure

ADJUDICATED DATA

It's not unique to medical device trials to have a committee to adjudicate Adverse Events, the procedure by which clinical events identified as potential endpoints are submitted to a panel of independent experts to be assessed in a blinded way, but it's much more common than in drug trials. Adjudication is used in clinical trials to manage subjective evaluations like severity or whether an event is cardiovascular related or not. It was determined that we would use the CE (Clinical Events) domain for this data. The raw data sets were organized such that each type of event was contained within its own data set. By combining these in a single SDTM domain, we demonstrate the efficiency of standardization both for the sponsor and the reviewers.

CESEQ	CESPID	CETERM	CECAT	CESCAT1	CESEV	CEOCCUR	CESTDTC
1	001	Arrhythmia / Conduction Injury	Arrhythmia / Conduction Injury	LBBB		Event	2020-09-24
2	002	Rehospitalization	Rehospitalization	Cardiovascular		Event	2020-11-13
3	003	Bleeding	Bleeding		Major	Event	2020-05-01

ADVERSE EVENTS

Although the AE domain is used, as in pharmaceutical trials, there are some differences. AERELDEV is mapped from a CRF variable that assesses the relationship to the transcatheter heart valve but there are additional variables that assess the relationship to other parts of the procedure. These are mapped to SUPPAE. Similarly, AEACNDEV (Action relating to the device) is simply mapped to AE but with multiple other actions taken, we have AEACNOTH='MULTIPLE' and the details again provided in SUPPAE.

AE Domain

AETERM	AEACNDEV	AEACNOTH	AERELDEV
Worsening related RVOT pressures	TPV Reintervention	None	None
Sinus Infection	None	Multiple	None
Flu	None	Medication	Possibly Related

SUPPAE Domain

QNAM	QLABEL	QVAL
AERELBC	Relationship to EW Balloon Catheter	None
AERELDS	Relationship to EW Delivery System	None
AERELIP	Relationship to Procedure	None
ACNOTH1	Other Action 1	Medication
ACNOTH2	Other Action 2	Other: Placement of urinary catheter on 24 May 2020

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 these were fully CDISC-compliant submissions but went a long way towards it and makes Edwards Lifesciences a lot more prepared for the time when CDISC is mandatory. Submitting data sets, 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 2021) 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. We are actively working with the authors of the CDISC literature, including Implementation Guides (IGs) and Therapeutic Area User Guides (TAUGs), to include more examples for medical devices.

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 CRFs compliant. Then, at your next 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 while 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!

CONCLUSIONS

This paper proves that submitting data in a CDISC-style to global regulatory agencies is not only possible, but a successful strategy. Don't be scared! You don't need to get it perfect first time. You still have time to prepare and adapt your mapping. As long as you map all data and document properly, you're helping the reviewer by providing recognizable data set 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 data sets, including the fundamentals of demographics, disposition and adverse events which can only reduce the time from submission to approval.

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

An additional benefit is that 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

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[5] CDISC Study Data Tabulation Model Implementation Guide (SDTM IG): Human Clinical Trials Version 3.3

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CONTACT INFORMATION

Contact the authors at:

Phil_Hall@Edwards.com
Tikiri_Karunasundera@Edwards.com
Subendra_Maharjan@Edwards.com
Vijaya_Vegesna@Edwards.com

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