CDISC Standards for Medical Devices: Historical Perspective and Current Status

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ABSTRACT

Work on SDTM domains for medical devices was begun in 2006. Seven SDTM domains were published in 2012 to accommodate medical device data. Minor updates to these seven SDTM domains were published in 2018. These seven SDTM domains are intended for use by medical device companies in getting their products approved/cleared by regulatory authorities and for use by pharmaceutical companies to put ancillary device data. As evidenced by the Therapeutic Area User Guides, pharmaceutical companies are using these seven SDTM domains for ancillary devices. However, adoption of these seven SDTM domains by medical device companies seems to be happening rather slowly. In 2014, a statistician at the Centers for Radiologic Health and Devices (CDRH) presented the issues that CDRH has with medical device submission and in 2015 the CDISC medical device team presented how the CDRH issues could be solved with CDISC standards. Recently CDRH published a document titled 'Providing Regulatory Submissions for Medical Devices in Electronic Format.' In 1999, the FDA published a similar document for pharmaceutical products which was the beginning of the development of CDISC standards for the pharmaceutical industry. While CDRH has not made a statement that they are moving towards the requirement of CDISC standards for medical device submissions the publishing of this document is a step in the right direction.

HISTORY

The CDISC team for Medical Devices was founded in May 2006. Representatives from the SDTM and CDASH teams joined in 2007 and 2009, respectively. In 2012, seven SDTM domains were published as SDTMIG-MD v1.0 (Smoak et al, 2012). These seven SDTM domains were developed by comparing 138 CRF pages from various medical device companies with the CDASH standard (Shiralkar et al 2010). These seven SDTM domains were developed to fill-in the gaps in data collected in medical device clinical trials. SDTMIG-MD v1.1 was published in 2018 with minor updates.

SDTM DOMAINS FOR MEDICAL DEVICES

Briefly, the seven Medical Device domains (SDTMIG-MD v1.1) are:

DEVICE IDENTIFIERS (DI)

This study reference domain contains the data that identifies a specific device unit under study. It has one record per device identifier per device.

DEVICE PROPERTIES (DO)

The Device Properties domain is a Findings domain and reports the characteristics of the device that are important to include in the submission, and that do not vary over the course of the study, but do not uniquely identify the device. It has one record per property per device.

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 another target. It has one record per property or setting per time point per visit or test date per subject.

DEVICE EXPOSURE (DX)

Device Exposure is an Interventions domain that records the details of a subject's exposure to a medical device under study. It has one record per recorded intervention occurrence or constant treatment interval per subject.

DEVICE EVENTS (DE)

Device Events is an Events domain that contains information about various kinds of device-related events, such as malfunctions. It has One record per event per device.

DEVICE TRACKING AND DISPOSITION (DT)

The Device Tracking domain is an Events domain that represents a record of tracking events for a given device. It has one record per device tracking event.

DEVICE-SUBJECT RELATIONSHIPS (DR)

The Device-Subject Relationships domain is a relationship domain that links each subject to the devices used in the study. It has one record per device/subject combination.

The seven SDTM domains were developed with two purposes in mind. First, for medical device sponsors to have a place to put data that would be used in medical device submission to regulatory authorities. Second, a place for pharmaceutical companies to put ancillary medical device data.

The use of these medical device SDTM domains by pharmaceutical companies is evidenced by 22 of 26 (as of 2017) of the Therapeutic Area User Guides (TAUG) showing the use of medical device data (Smoak 2018). Sixteen of the TAUGs have actual examples of device data as indicated by the "DI" column in Table 1. Eight of the TAUGs mention device data, but do not provide examples (Could Have Device Domains column in Table 1). Two of the TAUGs fall into both categories (actual examples of device data and could have device domains). Thus, actual device examples (n=16) and could have device domains (n=8) adds up to 24. But two of the TAUGs are counted in both categories. Thus, twenty-two of the TAUGs have examples of device data because the Cardiovascular and Duchenne Muscular Dystrophy TUAGs are being counted twice.

	DI	DO	DU	DX	DT	DE	DR	PR without DI Domain	Could Have Device Domains	None
Totals	16	5	7	2	0	1	2	5	8	4

Table 1. Summary of Device Domains in TAUGs

HOW CDISC CAN HELP CDRH

The need for CDISC standards in medical device submission has been clearly demonstrated by a statistician at CDRH. In 2014, this CDRH statistician presented six areas of medical device submissions which create difficulties for statisticians to do their reviews of the data submitted by medical device companies (Nair, Lu 2014) – see Tables 2-7. The six areas of issues that were presented are:

- Protocol Deviations
- Data Traceability
- Missing Data
- Patient Accountability
- Missing Coding Tools
- Trial Data Issues

The CDISC Medical Device team took this presentation and showed how CDISC standards could solve each of these six difficulties (Nair et al 2015).

Tables 2-7 show the CDRH Reviewer Request and the CDISC Solution to that request. In these tables, there is not a one-to-one correspondence for the bullet points in the CDRH Reviewer Request and the CDISC solutions columns. Rather the CDSIC Solution column should be seen as a set of solutions to the set of requests. Thus, the CDISC solutions in Tables 2-7 clearly demonstrate the usefulness of adopting CDISC standards for medical device submissions.

PROTOCOL DEVIATIONS

The issue here is that protocol deviations are hard to identify and determine their impact.

CDRH Reviewer Request	CDISC Solution
• Summary tables by type of deviation (major / minor) • Protocol deviations by investigational site	• SDTM: designed to facilitate summary table production • CDASH: defines deviation data capture, including narratives; facilitates categorization

Table 2. CDISC Solutions for Protocol Deviations

DATA TRACEABILITY

The issue here is that lack of data traceability means the reviewer cannot assess data validity.

CDRH Reviewer Request	CDISC Solution
• Provide mechanism to trace each data point from the study report back to the CRF	• ADaM, SDTM, associated define-xml and CDASH-conformant CRFs are specifically designed for this: hyperlink each variable to associated algorithm(s), source dataset(s), controlled terms and annotated CRF(s)

Table 3. CDISC Solutions for Data Traceability

MISSING DATA

The issue here is that missing data may impact the validity of conclusions and the choice of statistical model.

CDRH Reviewer Request	CDISC Solution

• Show why and when data are missing (missed visits, value not recorded, etc.)
• No undisclosed data omissions; justify all data omissions
• Clearly note all imputed data
	• SDTM and ADaM define-xml:
	  ○ Origin of each variable is defined as collected, derived or imputed
	  ○ Algorithms for all derivations and imputations included
	  ○ Can show what data were included or omitted and why
	• CDASH can indicate what data were missing, with associated dates

Table 4. CDISC Solutions for Missing Data

PATIENT ACCOUNTABILITY

The issue here is that it is hard to determine the accountability for all subjects..

CDRH Reviewer Request	CDISC Solution
• Provide patient accountability charts with discussions of missing data	• CDASH and SDTM: Subject Disposition domain captures status of each subject at each defined time point, which can be used to produce accountability charts; see also “Missing Data” box

Table 5. CDISC Solutions for Patient Accountability

MISSING CODING TOOLS

The issue here is that it is hard to identify and determine the impact of missing coding tools.

CDRH Reviewer Request	CDISC Solution
• Include PROC FORMAT program that creates the format catalog	• Controlled Terminology contains standard "formats" • define-XML contains customized ones and external terms

Table 6. CDISC Solutions for Missing Coding Tools

TRIAL DATA ISSUES

There are several issues in the following table..

CDRH Reviewer Request	CDISC Solution
• Include electronic datasets in PMA submission • Adverse Event listings for medical reviewers • Study endpoints analysis dataset(s) and raw data to minimize complicated manipulations and merges required to validate results • Analysis datasets to support key effectiveness/safety analyses • Include basic demographic variables and important covariates in analysis datasets • Define/README file for datasets and program files • Document datasets and code sufficiently	• SDTM and ADaM provide subject- and device-level tabulation and analysis datasets • Data transmitted in SAS transport files • Standardized AE data support listings from data visualization tools • ADaM defines key effectiveness / safety analyses and datasets, and permits inclusion of any/all relevant variables

Table 7. CDISC Solutions for Trial Data Issues

CURRENT STATUS OF CDISC STANDARDS FOR MEDICAL DEVICES

Currently, CDRH accepts data in any format, including CDISC-conforming data. They do state on their webpage (Center for Devices and Radiologic Health, 2018) they recommend medical device companies to use data standards for pre-market and post-market reports. Furthermore, they give the following rationale for the use of data standards:

> "The FDA can review and analyze data and information more quickly when manufacturers and user facilities have used our standards."

Furthermore, on this webpage they state that if a sponsor is planning to use data standards in a pre-market submission that they should discuss the use of data standards in a pre-submission meeting with the FDA.

In 1999, the FDA published a document for pharmaceutical submissions titled 'Providing Regulatory Submissions in Electronic Format — General Considerations' (U.S. Department of Health and Human Services 1999). This document was instrumental in staring the discussion about CDISC standards for pharmaceutical submissions. In September of 2019, CDRH published a document titled 'Providing Regulatory Submissions for Medical Devices in Electronic Format' (U.S. Department of Health and Human Services 2019). While this does mean that CDRH is definitely moving towards requiring CDISC standards for medical device submissions, it is a step in the right direction.

WORK REMAINING TO BE DONE

Currently, there is much work to be done on the CDSIC Medical Device team. We need to complete work on SDTM, CDASH and ADaM. An updated SDTIMIG-MD will be forthcoming.

CONCLUSION

SDTM domains for submission of medical device data has been available since 2012. Many pharmaceutical companies use these seven medical device domains for ancillary device data. Based on my interactions with people at medical device companies, I know that some medical device companies have started implementing SDTM. I also know that some medical device companies are waiting for CDRH to require CDISC standards before adopting CDISC data standards. My response to this position is three-fold:

- First, CDRH has clearly stated that data standards make reviews easier and quicker.
    - Why wouldn't a sponsor want to have their review done more quickly?
- Second, the CDISC Medical Device team has clearly demonstrated that CDISC data standards can solve issues that statisticians at CDRH have with reviewing data submitted by medical device companies.
    - Why wouldn't a sponsor want to make their submissions easier to review?
- Third, data standards when implemented at the earliest stages of a clinical trial has a downstream effect on saving time and money (CDISC 2014).
    - Why wouldn't a sponsor want to save time and money?

Finally, CDRH recently published a document on submitting data in electronic format. In 1999, a similar document was published by the FDA that was the beginning of CDISC standards being developed for pharmaceutical submissions. While CDRH has not made an official announcement about requiring CDISC standards for medical device submission, the document that they recently put out for commenting purposes on submission of electronic data would is a step in the right direction.

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