The Need for Therapeutic Area User Guide Implementation

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ABSTRACT

As regulatory agencies, specifically PMDA at the moment, begin to do cross-product analysis of their accumulated study data, the need for standardization increases. CDISC standards cover much of the data common to clinical trials, but gaps exist. Therapeutic Area User Guides (TAUGs) are created to fill some of these gaps. However, consistent implementation of these provisional guides is lacking, and this will impact the ability of regulatory agencies to analyze data across products. This paper will discuss some possible reasons for the slow adoption of TAUGs, attempt to show why it is increasingly important that the industry implement the TAUGs, and show how the implementation of the TAUGs could be enforced.

INTRODUCTION

It seems that we are finally reaching, or approaching, an era of truly standardized data. Regulatory agencies have begun enforcing the conformance of trial data to standard format. The FDA requires that data for studies starting after December 17, 2016, must be submitted in conformance with data formats listed in the FDA Data Standards Catalog, specifically CDISC format for trial data. PMDA will require standardized data to be submitted starting on April 1, 2020. The regulatory agencies' data standards catalogs also phase out support for older versions of the standards, forcing sponsors to submit data using the newer versions.

We also seem to be approaching the level of 'good-enough' standards, in which the standards adequately account for the majority of data common to trials. New versions of the standards mostly add domains and variables to account for some of the less common data, to correct issues with previous versions, to account for regulatory guidance, or to reorganize and change implementation guidance to a more consistent way. However, the implementation guidance for data common to the majority of trials stays mostly the same, besides wrapping up loose ends or making corrections to previous versions.

Since regulatory agencies are beginning to require the use of data standards, and pushing sponsors to use later versions of the standards, and since these data standards account for the most common data collected in trials, to move forward with data standardization, we must fill in the remaining gaps. The attempt to do this, to provide standards for the remaining data collected in trials, is through creation of Therapeutic Area User Guides.

CURRENT STATE OF DATA STANDARDS

Data standards seem to be at or approaching the level of sufficient for handling the most common types of data collected or derived in a trial. New versions of the standards seem to either handle cases of less common data, or providing adjustments to already handled cases.

To illustrate this point, the latest version of the SDTMIG, version 3.3 (just recently released at the time of this writing), adds 12 new domains.

- One is a domain implemented previously in a TAUG, the AG (Procedure Agents) domain.

- One is a domain implemented previously in a TAUG and already commonly used across the industry, the ML (Meal Data) domain.

- The FT (Functional Tests) domain is new, to handle a somewhat common type of data.

- A number of body system domains were introduced to change previous guidance on how to map this data, which was previously mapped to the MO (Morphology) domain.

- A few domains were introduced to handle less common scenarios, such as: OI (Non-host Organism Identifiers), SM (Subject Disease Milestones), and TM (Trial Disease Milestones).

Examples of new variables added in SDTMIG version 3.3 include:

• DM.ARMNRS (Reason Arm and/or Actual Arm is Null) to remove the seemingly contradictory guidance between regulatory agencies and standards development organization.

• --LOBXFL (Last Observation Before Exposure Flag) to provide a clear, standardized way to represent this information instead of relying on a sponsor-defined baseline flag derivation.

The point here is that standards are now relatively sufficient to handle the most common data, and new versions released mostly wrap up deficiencies or correct previous issues. The industry is now consistently using these standards for these common types of data. But how about the other data not covered by the data standards? This is where TAUGs come in.

CURRENT STATE OF TAUGS

At the time of this writing, there are 30 TAUGs published by CDISC, with 6 more in development. As of the latest version of the FDA's Technical Conformance Guide (March 2019), 21 of these published TAUGs are supported. If a sponsor uses a TAUG that is not listed as supported, they "should explain the rationale in the cSDRG for using TA extensions that are not currently listed in the Guide."[1] The PMDA does not list which TAUGs they support, stating at the CDISC Japan Interchange 2018 that they "basically accept that applicants implement the published TAUGs."[2]

The implementation of TAUGs across the industry however, by all accounts, is lacking.

CHALLENGES OF TAUG IMPLEMENTATION

While TAUGs are very useful and important in providing guidance on how to use CDISC standards for certain types of data, there are some challenges with using TAUGs:

IS MY TYPE OF DATA IN A TAUG?

There are situations where the indication for your study doesn't have an applicable TAUG, but the type of data you collect may be mentioned somewhere in a TAUG. Unless the indication for your study matches that therapeutic area, you wouldn't necessarily know that guidance exists for that type of data. There is currently no way to know this information at the moment. An example of this is the Asthma TAUG, which contains guidance for data such as allergen skin tests. A study with an indication of allergic rhinitis, for example, may typically contain this type of data, but as the indication is asthma, would the sponsor know that there is guidance for this type of data in the asthma TAUG? Currently, unless a study falls under an indication for which there is a TAUG, and the sponsor is aware of the publication of this TAUG, and chooses to implement their study according to this guidance, the data will not adhere to guidance.

MAPPING IS PROVIDED AS 'EXAMPLES', AND NOT GUIDANCE

Most people would agree that an example is not a requirement. There is no strong guidance for mapping data in the TAUGs, only examples. For example, in the Asthma TAUG, allergen skin tests are listed with the wording "These examples use the Skin Response (SR) domain, which is not final at the time of publication of this document."[3] Is it possible to use other SDTM domains, and not follow the examples provided? Implementers want very clear guidance on mapping data, and while examples are certainly beneficial, stronger guidance may be preferred.

PREVIOUS GUIDANCE IS SOMETIMES DEPRECATED

Occasionally, guidance in a TAUG is changed between versions. For example, per the Virology v2 TAUG, "The Viral Resistance (VR) domain has been deprecated. Drug sensitivity testing is now consolidated in the Microbiology Susceptibility (MS) domain with the addition of some variables that had been previously used only in VR."[4] Studies that had used version 1 of the TAUG will now be inconsistent with other studies that use the newer version of the TAUG, resulting in the same data mapped to different SDTM domains.

TAUGS MAY BE INCOMPLETE

It is possible that the TAUGs do not address all important types of data, or how to handle certain data points, for a therapeutic area. An example of this is the Kidney Transplant Therapeutic Area User Guide v1.0, for with the FDA's TCG (March 2019) states "The Kidney Transplant TAUG does not address two important data elements. First, the date of the request for a biopsy is important for review, not just the date the biopsy was performed. Second, evidence of C4d staining status in renal allografts (+ or -) is important in the Banff classification criteria for the diagnosis of acute and chronic antibody-mediate rejection. Sponsors should discuss these two data elements with the appropriate review division."[1] In these cases, the same exact data for a therapeutic area may be mapped differently across the industry, as sponsors will either create their own implementation, or ask each review division for advice (and implement accordingly).

INCONSISTENCY IN MAPPING SIMILAR DATA

Authors have previously discussed inconsistency in mapping similar data across the TAUGs. An example is the PhUSE 2015 paper Therapeutic Area standards and their impact on current SDTM Implementations[5], which discusses variations in the mapping to the Medical History domain across various TAUGs.

SUGGESTED REASONS FOR LACK OF IMPLEMENTATION

REGULATORY GUIDANCE MIGHT NOT REQUIRE IT

At the time of this writing, the Technical Conformance Guide (TCG) states: "Sponsors may use new TA extensions of a CDISC standard, but are not required to until the extensions have been incorporated into a SDTMIG version supported by FDA (the supported SDTMIGs are listed in the Catalog). Sponsors should explain the rationale in the cSDRG for using TA extensions that are not currently listed in the Guide."[1]

From this statement, it is not exactly clear if sponsors are required to use a TAUG for their study. A point that could use clarity is: does the statement "…are not required to until the extensions have been incorporated into a SDTMIG version supported by FDA…" mean that any study for one of these therapeutic areas listed in the FDA's Technical Conformance Guide is actually required to use one?

Also, if a sponsor must explain why they used a TAUG for which something in it is not supported in an SDTMIG, would this discourage sponsors from using the TAUG?

VALIDATION AGAINST TAUGS DOESN'T EXIST

Should a TAUG have been used?

There is currently no (standard) way to know if TAUG should have been used. The indications of studies could possibly be used to identify studies that should implement a TAUG, however there are issues with this. Using the indication provided by the sponsor in the Trial Summary (TS) domain would be ideal, however this requires that sponsors map the data correctly. The trial summary parameter INDIC (Trial Disease/Condition Indication) requires the use of SNOMED CT, but we see that many times this is not the case.

The table below shows examples of actual values used for prostate cancer studies, many of which do not use SNOMED CT values.

INDICATION
Carcinoma of prostate (disorder)
PROSTATE CANCER
CASTRATION RESISTANT PROSTATE CANCER
Adenocarcinoma of prostate
Prostate Cancer

Hormone sensitive prostate cancer (disorder)
Hormone Refractory Prostate Cancer (disorder)
Metastatic Castration-Resistant Prostate Cancer
Castration-resistant prostate cancer
Hormone refractory prostate cancer
Metastasis from malignant tumor of prostate
CARCINOMA OF PROSTATE (DISORDER)
PROSTATE CANCER Carcinoma of prostate (disorder)
HORMONE REFRACTORY PROSTATE CANCER (DISORDER)
Metastatic Castration- Resistant Prostate Cancer (mCRPC)
Hormone refractory prostate cancer (disorder
Non-Metastatic Castration-Resistant Prostate Cancer
Adenocarcinoma of the prostate
CARCINOMA OF PROSTATE
Metastatic castration resistant prostate cancer (mCRPC)
Progressive Castration-Resistant Prostate Cancer
HORMONE REFRACTORY PROSTATE CANCER
Hormone-naive prostate cancer
Metastatic prostate cancer
Men with newly diagnosed high-risk metatastatic hormone-naive prostate cancer
Progressive Metastatic Castration-Resistant Prostate Cancer
Carcinoma of prostate

Table 1. Examples of different values of Trial Disease/Condition Indications for one indication

This lack of standardization for this parameter creates a challenge in identifying studies that should have used a TAUG (in this case, the Prostate Cancer Therapeutic Area User Guide v1.0).

Another parameter exists for use (in CDISC CT), the THERAREA (Therapeutic Area) parameter. This parameter is listed in the FDA's Technical Conformance Guide as an FDA desired parameter for sponsors to use. However, the inclusion of this parameter in sponsors' trial summary datasets seems to be rare.

Was a TAUG used?

There is also the issue of determining if a TAUG was used. There had been no (standard) way to know this, other than the sponsor volunteering the information in the reviewers guide, even though there is no explicit section in the reviewers guide (PhUSE cSDRG template) to list this information. Therefore, until October 2018, it was only known that a study was implemented according to a TAUG if the sponsor volunteered this information somewhere (anywhere) in the reviewers guide.

As of October 2018, however, the FDA's Technical Conformance Guide now lists a trial summary parameter to indicate if a study was implemented according to a TAUG. The Trial Summary Parameter Code (TSPARMCD) "CTAUG", and the Trial Summary Parameter Name (TSPARM) is "CDISC Therapeutic Area User Guide". This should be very useful to help solve the issue of knowing whether or not a study was implemented according to a TAUG.

FDA's TCG (March 2019):

TSPARMCD value	TSPARM value	TSVAL value
CTAUG	CDISC Therapeutic Area User Guide	*Should be the exact listing in section 5.2 of the TCG for TAUGs* Ex. Chronic Hepatitis C Therapeutic Area User Guide v1.0

Display 1. FDA's TAUG parameter in Technical Conformance Guide (March 2019)

This trial summary parameter is also listed in CDISC controlled terminology.

CDISC CT (2018-12-21):

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)
C156602	C66738		Trial Summary Parameter Test Code	CTAUG	CDISC Therapeutic Area User Guide
C156602	C67152		Trial Summary Parameter Test Name	CDISC Therapeutic Area User Guide	CDISC Therapeutic Area User Guide

Display 2. CDISC CT TAUG parameter

There are two potential issues with the new trial summary parameter, however:

- The first is that it is listed as "Conditional" in the TCG, with the FDA Notes indicating it should only be provided if applicable. Therefore, since it is not a required parameter, it seems likely that many sponsors will simply not include it in their trial summary dataset.

- The second is that there is no CDISC controlled terminology for this parameter. The FDA does, however, specify that the values "should be the exact listing in section 5.2 of the TCG for TAUGs".

IMPACT OF LACK OF TAUG IMPLEMENTATION

Lack of TAUG implementation means that although there is guidance for how to map similar data for the same therapeutic area, the industry is not mapping it consistently.

An important impact of this is that PMDA is doing cross-product analysis from accumulated study data, as can be seen from this information from the PMDA website[6], which specifies that the cross-product analysis is done by therapeutic area with their statement circled in red below.

Accumulation and utilization of data
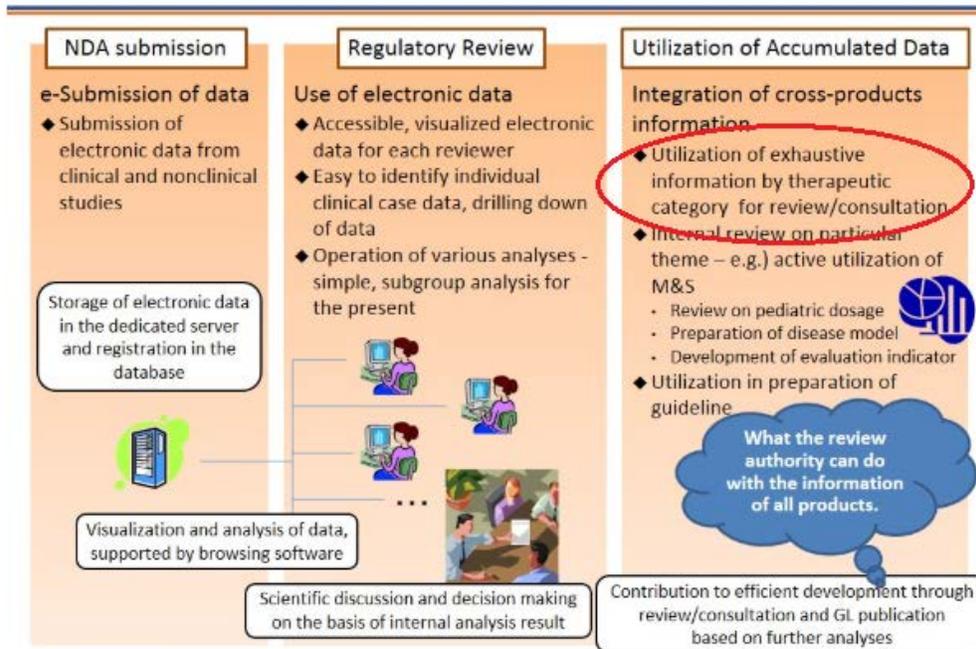
Display 3. PMDA's Accumulation and utilization of data, from PMDA website

If the same data common to certain therapeutic areas is mapped inconsistently across studies submitted to an agency, it makes this cross-product analysis much less useful. Instead, this cross-product analysis would only be useful for data common to all trials (those mapped in implementation guides instead of therapeutic area user guides), and not other important data commonly collected for that therapeutic area.

Below is an example of how the exact same data is mapped inconsistently across three sponsors, taken from actual studies. These three studies have an indication of breast cancer, for which Estrogen Receptor Status is typically collected. The Breast Cancer Therapeutic Area User Guide v1.0 does contain an example of how this data should be mapped to SDTM.

Study 1. This study has the data mapped to the Laboratory Test Results (LB) domain.

Display 3. Study 1 mapping

Study 2. This study has the data mapped to the Pharmacogenomics/Genetics Findings (PF) domain.

Display 4. Study 2 mapping

Study 3. This study has the data mapped to the Microscopic Findings (MI) domain. This is the approach that matches the example in the Breast Cancer TAUG for Estrogen Receptor Status data.

Display 5. Study 3 mapping

RECOMMENDATIONS TO INCREASE IMPLEMENTATION

TRACKING OF DATA POINTS, TYPES OF DATA BY TAUG

A publicly available tracking of data points, or types of data, would be helpful in industry-wide adoption of standard implementation. Implementers should be able to quickly see where their type of data is represented in CDISC guidance, without having to open and search 30+ TAUG files to see if anything exists. Also, this would possibly assist in the creation of TAUGs, as it could be quickly determined where else a type of data is referenced, so that consistency could be ensured.

STRONGER GUIDANCE WOULD HELP

If stronger guidance were to be created for therapeutic areas, from collection to mapping to analysis, it would be less ambiguous as to if the guidance was required to be followed or not. Currently, examples could be dismissed as just that, only 'examples.'

CLARITY ON REGULATORY GUIDANCE IS NEEDED

As mentioned above, clarity is needed on the regulatory requirements around TAUG implementation. But regardless, without regulatory agencies requiring the use of these TAUGs, industry-wide implementation is unlikely to occur.

INDUSTRY NEEDS TO ADOPT AND IMPLEMENT

Industry needs to adopt and implement the extensions of the standards, to further the advancement of data standardization, for the following reasons:

- the improvement of data quality that occurs with standardization,
- the improvement of efficiency of collecting and standardizing clinical trial data,

- and to improve the reviewability of clinical trial data.

TAUG IMPLEMENTATION AND COMPLIANCE ENFORCEMENT NEEDED

Without enforcement, industry-wide implementation and compliance is unlikely to occur. Validation rules and data quality assessments need to be created to check for the compliance to the extensions of the standards. In order to do this, the following items are needed:

- a standard way to check if a TAUG was used (one has recently been provided),

- a standard way to check if a TAUG should have been used,

- validation rules extracted from the TAUGs.

CONCLUSION

To cover the gaps in guidance for standardizing clinical trial data, Therapeutic Area User Guides are a critical component. These extensions of the standards provide necessary guidance on how to handle types of data common to certain therapeutic areas, that aren't covered in the implementation guides. However, these extensions must be adopted and implemented on a larger scale than they currently are, in order to see the benefits of the increased standardization for clinical trial data across the industry. Increased enforcement in the adherence to these extensions seems like an important next step to fill the current gaps in standardized clinical trial data.

REFERENCES

[1] U.S. Food & Drug Administration, Study Data Technical Conformance Guide (current version at time of access – v4.3/ March 2019)

[2] CDISC Japan Interchange 2018, Electronic Data Submission in Japan: Current Status and Future, Dr. Yuki Ando, PMDA

[3] CDISC, Therapeutic Area Data Standards User Guide for Asthma Version 1.0, CFAST Asthma Team, 2013

[4] CDISC, Therapeutic Area Data Standards User Guide for Virology Version 2.0 Provisional, CFAST Virology v2.0 Standards Team, 2015

[5] Phuse 2015, Therapeutic Area standards and their impact on current SDTM Implementations, Johannes Ulander, S-cubed, Niels Both, S-cubed (CD03, 2015)

[6] PMDA website, Office of Advanced Evaluation with Electronic Data, http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html

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