

The Need for Therapeutic Area User Guide Implementation

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Data Standards – Good Enough?

- › Regulatory agencies are beginning to require submission in these standards
- › Data standards catalogs are ending support for older versions of these standards
- › Use of newer versions of the standards seems to be trending upwards
- › Compliance to the standards seems to be trending upwards

Data Standards – Good Enough?

- › Foundational 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
 - › Provide adjustments to already handled cases

Example Of New Version Of A Standard – SDTMIG v3.3

- › New Domains
 - › FT (Functional Tests) domain - handles a somewhat common type of data
 - › AG (Procedure Agents) domain – from a TAUG
 - › ML (Meal Data) domain – from a TAUG and already commonly used across the industry
 - › A few domains to handle less common scenarios - OI (Non-host Organism Identifiers), SM (Subject Disease Milestones), and TM (Trial Disease Milestones)
 - › Many body system domains - change to previous guidance (MO (Morphology) domain)

Example Of New Version Of A Standard – SDTMIG v3.3

- › Changes to the existing standard
 - › Dataset Description changed for 6 datasets
 - › Core changed for 29 variables
 - › Variable Label changed for 86 variables
 - › Codelist removed for 2 variables
 - › Codelist added for 21 variables
 - › Codelist changed for 8 variables
 - › Role changed for 33 variables

New Versions Of Standards – Unnecessary Complications

- Example - Label changes for --STRESC variables

Dataset	Variable	SDTMIG v3.2 Label	SDTMIG v3.3 Label
DA	DASTRESC	Assessment Result in Std Format	Result or Finding in Standard Format
IS	ISSTRESC	Result or Finding in Standard Format	Character Result/Finding in Std Format
MB	MBSTRESC	Character Result/Finding in Std Format	Result or Finding in Standard Format
MI	MISTRESC	Result or Finding in Standard Format	Character Result/Finding in Std Format
MS	MSSTRESC	Character Result/Finding in Std Format	Result or Finding in Standard Format
PC	PCSTRESC	Result or Finding in Standard Format	Character Result/Finding in Std Format
PE	PESTRESC	Result or Finding in Standard Format	Character Result/Finding in Std Format
PP	PPSTRESC	Result or Finding in Standard Format	Character Result/Finding in Std Format
QS	QSSTRESC	Result or Finding in Standard Format	Character Result/Finding in Std Format
RP	RPSTRESC	Character Result/Finding in Std. Format	Character Result/Finding in Std Format
RS	RSSTRESC	Response Assessment Result in Std Format	Character Result/Finding in Std Format
SR	SRSTRESC	Result or Finding in Standard Format	Character Result/Finding in Std Format
TU	TUSTRESC	Tumor Identification Result Std. Format	Tumor/Lesion ID Result Std. Format

New Versions Of Standards – Consistency Problems

- › Inconsistent mapping of ARM values for screen failures
 - › New Variables in SDTMIG v3.3
 - › DM.ARMNRS (Reason Arm and/or Actual Arm is Null)
- › Baseline Flags
 - › New Variable in SDTMIG v3.3
 - › --LOBXFL (Last Observation Before Exposure Flag)
- › Body system domains to replace MO domain
 - › New Domains in SDTMIG v3.3
 - › 6 new body system domains

New Versions Of Standards – Changing Existing Standards

- › While updates to existing standards may be valid...
- › At some point, do changes to existing standards need to stop so that we have consistent standardized data across the industry?
- › Additions to standards however are welcome

Extensions Of Standards - TAUGs

- › So, if foundational standards are (practically) good-enough, we need to focus on truly standardizing the rest of the data common to clinical trials
- › TAUGs (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.
- › We need to focus on increased implementation of TAUGs

Therapeutic Area User Guides – Current State

- › Released by CDISC
 - › 31 – Total
 - › 10 more in development
 - › 18 – Acceptance by FDA (Referenced in TCG)
 - › All* – Acceptance by PMDA

*Based on PMDA statement at CDISC Japan Interchange: “We basically accept that applicants implement the published TAUGs”

- › Released by FDA
 - › 2 - Total
 - › HIV
 - › Vaccines
- › Implemented by industry
 - › Practically nonexistent

Suggested Reasons For Lack Of Implementation

- › Challenges of Implementation
 - › Is my type of data in a TAUG?
 - › Mapping is provided as 'Examples', and not guidance
 - › Previous guidance is sometimes deprecated
 - › TAUGs may be incomplete
 - › Inconsistency across TAUGs in mapping similar data
 - › Has been addressed in other papers
- › Lack of Enforcement
 - › Regulatory guidance doesn't seem to require it
 - › Validation for compliance to TAUGs doesn't exist

Is My Type Of Data In A TAUG?

- > Your study indication may not use a TAUG, but is your data represented in a TAUG anyway?
- > Example: Asthma TAUG

2.3.1 Examples for Allergen Skin Tests

These examples use the Skin Response (SR) domain, which is not final at the time of publication of this document.

Example 1

In this example, the subject is dosed with a positive (histamine) control, negative control, and allergens at screening, which the sponsor has designated “VISIT 1”. This case differs from the example shown in the diagram above: both wheal and flare were measured, and no interpretation of combined wheal and flare was performed.

Row 1-6: Show wheal diameter responses associated with the administration of a histamine (positive control), negative control, and specific allergens.

Rows 7-12: Show testing for wheal flare response.

sr.xpt

Row	STUDYID	DOMAIN	USUBJID	SRSEQ	SRTESTCD	SRIEST	SROBJ	SRORRES	SRORRESU	SRSTRESC	SRSTRESN	SRSTRESU	SRLOC	VISITNUM	VISIT
1	ABC-001	SR	ABC-001-1234	1	WHEALDIA	Wheal Diameter	Histamine Control	10	mm	10	10	mm	FOREARM	1	VISIT 1

- > Would implementers for a study with an indication of Allergic Rhinitis know to look in the Asthma TAUG?

Mapping Is Provided As ‘Examples’, Not Guidance

- › Mapping is provided as “Examples” in the TAUGs
- › “Example” does not equal “Requirement”

- › From Asthma TAUG:

2.3.1 Examples for Allergen Skin Tests

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- › Is it possible to use a domain other than SR? A user may interpret it as not being required

Previous Guidance Is Sometimes Deprecated

- › Guidance sometimes changes between versions of a TAUG
- › From Virology TAUG:

CDISC Therapeutic Area Data Standards User Guide for Virology

- 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.
- Handling of virus nomenclature now makes use of a draft variable (NHOID) and a draft domain (Non-Host Organism Identifiers—OI). The variable –NSPCES (non-host species) is still available, but –NSTRN (non-host strain) is deprecated since the concept of “strain” is not relevant to all viruses. See section 4.2 and the OI domain for more information.

- › Studies mapped using v1.0 will now be inconsistent with studies using v2.0

TAUGs May Be Incomplete

- › TAUGs may not address:
 - › All important types of data for the therapeutic area, or
 - › How to handle certain data points

- › Example 1, from FDA's Technical Conformance Guide:

5.2.14 Schizophrenia Therapeutic Area User Guide v1.1

The Schizophrenia TAUG **does not address two important data elements**. **First**, the subjects daily living situation for the past 12 months. **Second**, when a protocol violation prompts study termination, sponsors should use the existing Disposition domain as appropriate and provide a referential link to any detailed information regarding the protocol violation. Sponsors should consult with the appropriate FDA review division on the best approach for each specific study.

- › Example 2, from FDA's Technical Conformance Guide:

5.2.11 Prostate Cancer Therapeutic Area User Guide v1.0

The TAUG v1.0 **does not include a guidance** on where to capture "Reason Not Done" information for the tumor lesions that were Inevaluable (this is a known issue)). In addition, the Agency considers it more accurate use the phrase 'tumor lesions' rather than 'tumors'.

Does Regulatory Guidance Require It?

- › The Technical Conformance Guide 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).”
- › Does that mean that any study for one of these therapeutic areas listed in the FDA’s TCG is actually required to use the TAUG?

Does Regulatory Guidance Require It?

- › The Technical Conformance Guide also states:
 - › “Sponsors should *explain the rationale in the cSDRG for using TA extensions* that are not currently listed in the Guide.”
- › If a sponsor must explain why they used a TAUG, would this discourage sponsors from using the TAUG?

TAUG Validation Doesn't Currently Exist

- › There is currently no (standard) way to know if:
 - › A TAUG should have been used, or
 - › A TAUG was used
- › For validation purposes, we need answers to these two important questions, but there are issues with each

TAUG Validation – Should A TAUG Have Been Used?

- › How to know if a TAUG should have been used?
 - › *Issue #1* – Use the Trial Summary INDIC (Trial Disease/Condition Indication) parameter?
 - › *Problem* - TS Indication should use SNOMED, but not always implemented correctly

- › Indication problem examples –
Prostate Cancer:

Trial Summary Indication
Carcinoma of prostate (disorder)
PROSTATE CANCER
Metastasis from malignant tumor of prostate
Adenocarcinoma of the prostate
CARCINOMA OF PROSTATE
Adenocarcinoma of prostate
Metastatic prostate cancer

- › Indication problem examples –
Diabetes:

Trial Summary Indication
Type 2 Diabetes mellitus (disorder)
Diabetes mellitus type 2 (disorder)
Diabetes mellitus type 2
TYPE 2 DIABETES MELLITUS
Type II diabetes mellitus
TYPE 1 DIABETES
DIABETIES
Diabetes mellitus type 1 (disorder)
Type 2 diabetes mellitus with moderate to severe chronic kidney disease

TAUG Validation – Should A TAUG Have Been Used?

- › How to know if a TAUG should have been used?
- › *Issue #2* – If a study indication doesn't have a TAUG, should one have been used anyway?
 - › For example, should the PAIN TAUG only be used for pain studies, or should they be referenced for any study that collects data on pain?
 - › Should a study potentially reference multiple TAUGs depending on the types of data collected?

TAUG Validation – Was A TAUG Used?

- › How to know if a TAUG was used?
 - › New Trial Summary parameter to indicate TAUG
 - › This is great news, however:
 - › *Issue #1* - Trial Summary Parameter inconsistency

- › FDA's Technical Conformance Guide TSPARMCD value:

TSPARMCD value	TSPARM value	TSVAL value
TAUG	TAUG and version used	<i>Should be the exact listing in section 5.2 of the TCG for TAUGs</i> Ex. Chronic Hepatitis C Therapeutic Area User Guide v1.0

- › CDISC Controlled Terminology TSPARMCD value:

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

TAUG Validation – Was A TAUG Used?

- › How to know if a TAUG was used?
 - › New Trial Summary parameter to indicate TAUG
 - › *Issue #2* - No Controlled Terminology for the values of the Trial Summary Parameter
 - › FDA's TCG does state, however:

TSPARMCD value	TSPARM value	TSVAL value
TAUG	TAUG and version used	<i>Should be the exact listing in section 5.2 of the TCG for TAUGs</i> Ex. Chronic Hepatitis C Therapeutic Area User Guide v1.0

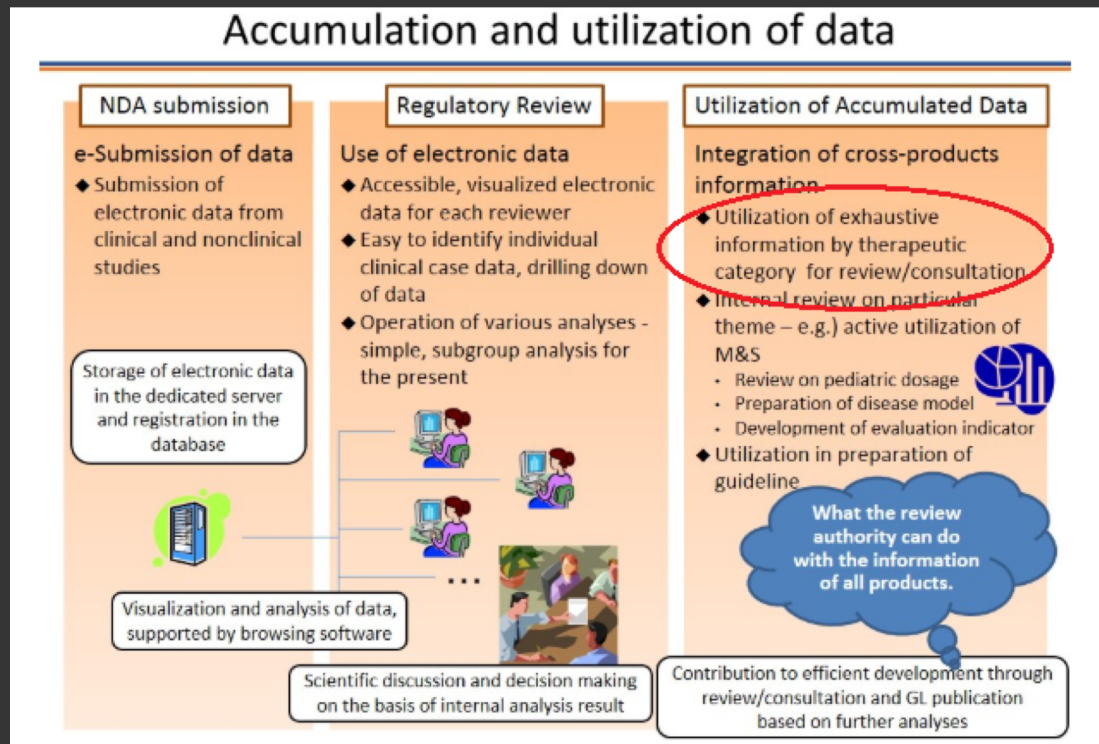
- › How can this parameter be used in automated validation, if values aren't controlled?

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 indication, the industry is not mapping it consistently
- › Affects ability of regulatory agencies to do cross-product analysis

Impact Of Lack Of TAUG Implementation

- An important impact of this is that PMDA is doing cross-product analysis from accumulated study data.



TAUG Implementation Inconsistency Example 1

- › Breast Cancer indication
 - › Estrogen receptor data – same data mapped inconsistently

Type of receptor	LBSCAT	ER ☐
Test method	LEMETHOD	IHC ☐ FISH ☐ CISH ☐ ISET ☐ VERIDEX ☐ NISH ☐ SISH ☐ Not Done ☐
Receptor result	LBORRES	Negative ☐ Positive ☐

Study A – Mapped to the LB domain

Study B – Mapped to the PF domain

2. Estrogen Receptor Status [Estrogen Receptor Status]	PFTTEST	☐ Positive ☐ Negative	PFORRES
3. Pathological Diagnosis Progesterone Receptor Status [Patholog Diag Progester Recept Stat]	PFTTEST	☐ Positive ☐ Negative	PFORRES
4. Pathological Diagnosis HER2 Status [Pathological Diagnosis HER2 Status]	PFTTEST	☐ Positive ☐ Negative	PFORRES

MITESTCD = ESTRCPT		Progesterone Receptor ☐
		Estrogen Receptor ☐
		ErbB2 ☐
Date of Sample		MIDTC
Qualitative Result		Positive ☐ Negative ☐ Unknown ☐
MIORRES, MISTRESC		

Study C – Mapped to the MI domain

★ This matches the example in the TAUG.

TAUG Implementation Inconsistency Example 2

- Diabetes indication
 - Hypoglycemia signs/symptoms data – same data mapped **and collected** inconsistently

Q1B - Result in **loss of consciousness**? **FAOBJ = this episode resulted in loss of consciousness**
FAORRES

Q1C - Result in a **seizure**?
 If response to ALL of the above is "No", then Severe Hypoglycemia is assessed not to have occurred: jump to Question #3.
 If response to ANY of the above is "Yes", complete Question #2 to collect additional data regarding the Severe Hypoglycemia episode AND Question #3 to assess whether this episode also meets criteria for Documented Hypoglycemia.

FAOBJ = this episode resulted in a seizure
FAORRES

Study A – Mapped to the **FA** domain

Study B – Mapped to the **CF** domain

4. Symptoms of Hypoglycemia
 [Symptoms of Hypoglycemia]
CFORRES when CFTESTCD='HYPOGSYM'

[Symptoms of Hypoglycemia]
 [A:NO SYMPTOMS] ☐ No Symptoms
 [A:MARKEDLY DEPRESSED LEVEL OF CONSCIOUSNESS] ☐ Markedly Depressed Level of Consciousness
 [A:LOSS OF CONSCIOUSNESS] ☒ Loss of Consciousness
 [A:SEIZURE] ☒ Seizure
 [A:OTHER SYMPTOMS NOT LISTED ABOVE] ☐ Other Symptoms not Listed Above

Were Signs/Symptoms Present?	No	Yes (If yes complete following)	
CECAT= HYPO SYMPTOMS		CEYN	
CETERM= SWEATING	No	Yes	CEOCCUR with CEPRESP=Y
CETERM= TREMORS/TREMBLING	No	Yes	
CETERM= DIZZINESS	No	Yes	
CETERM= COGNITIVE IMPAIRMENT	No	Yes	
CETERM= LOSS OF CONSCIOUSNESS	No	Yes	
CETERM= CONVULSIONS/SEIZURE	No	Yes	
CETERM= COMA	No	Yes	
Other (Specify)	No	Yes (if yes enter below)	

For reference, this is how it is collected and mapped in the TAUG

TAUG Implementation Inconsistency Example 3

- Multiple Sclerosis indication
 - Recovery from relapse data – same data mapped inconsistently, **but no guidance available**

 Study A – ‘Recovery from relapse’ mapped to a suppqual

Start date of relapse symptoms	CESTDTC
End date of relapse symptoms	CEENDTC
Recovery from relapse	None ☐ Partial ☐ Complete ☐
SUPPCE.QVAL where QNAM=RECOVER	

 Study B – same exact ‘Recovery from relapse’ data, mapped to a **different** suppqual

Recovery from relapse 0=None 1=Partial 2=Complete	Hospitalization 0=No 1=Yes	Steroid used 0=No 1=Yes	Confirmed relapse 0=No 1=Yes	Severity 1=Mild 2=Moderate 3=Severe	Affects daily activities 0=No 1=Yes
--	----------------------------------	-------------------------------	------------------------------------	--	---

Start date of relapse symptoms CESTDTC	End date of relapse symptoms CEENDTC	Recovery from relapse 0 1 2 ☐ ☐ ☐	Hospitalization 0 1 ☐ ☐
CEOUTOR in SUPPCE		CESHOSP	



If it is data common to a therapeutic area, shouldn't the TAUG clearly define a mapping?

Recommendations To Improve Implementation

- › Tracking of data points, or types of data, by TAUG
 - › Would allow implementers to quickly determine which TAUG to reference
 - › Could assist in TAUG development consistency
- › Stronger guidance within the TAUGs would help
 - › Would eliminate ambiguity in mapping decisions
- › Clarity on regulatory guidance/requirements is needed
 - › Enforcement is really the key way to increase implementation

Recommendations To Improve Implementation

- › Industry needs to make TAUG implementation a priority
 - › Reasons:
 - › The improvement of data quality that occurs with standardization
 - › The improvement of efficiency of collecting and mapping clinical trial data
 - › To improve the reviewability of clinical trial data

Recommendations To Improve Implementation

- › TAUG compliance validation is needed
 - › Without enforcement, widespread implementation is unlikely
- › 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
- › To see the benefits of increased standardization, these extensions must be implemented on a larger scale than they currently are
- › Increased enforcement in the use of extensions is an important next step to fill the current gaps in standardized clinical trial data

Questions

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