Paper DS05

Implementation of SDTM IG v.3.3 for Neurological Therapeutic Area

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ABSTRACT

A number of new domains included in the recently released SDTM IG v.3.3 such as nervous system findings, domains for biofluid biomarkers, device domains, PROs etc will be studied based on Therapeutic Area User Guides for Neurology as well as the best practices to implement standards for the study.

- Introduction to TAUGs in Neurological Therapeutic Area in general;
- Types of new domains, examples of raw data and how it should be mapped according to new standards;
- Comparison of its implementation (in Multiple Sclerosis, Alzheimer's TAUGs etc in Neurology) on SDTM level;
- Pros and cons;
- Contradictions between TAUGs (if any).

INTRODUCTION

The standards for mapping of data in therapeutic areas are becoming more and more clear, and it involves a lot of changes. For easier understanding of the most challenging cases of mapping in Neurology several Therapeutic Area User Guides (TAUGs) have been created since 2012. The purpose of TAUGs is to display specific domain examples. Analysis rules and define.xml are out of scope. Below you can see the TAUGs which are mentioned in this paper. For better understanding of specific domains and because Huntington's disease has lot in common with Neurology, TAUG HD has been used as an example.

Table 1. TAUGs which are studied

#	TAUGs	Based on	Date and Version	SDTM version	SDTMIG
1	Therapeutic Area User Guide for Parkinson's Disease NEUROLOGY	This is the provisional Parkinson's disease user guide for Human Clinical Trials corresponding to the CDISC Study Data Tabulation Model. It is based on the CDISC Submission Data Standards and domain models but includes draft domains slated for a future release of the SDTM Implementation Guide. ·This work was funded by National Institute of Neurological Diseases and Stroke (NINDS), funded under a subcontract with KAI Research, Inc., via NINDS contract N01-NS-7-2372.	2012-12-18 v1.0 - Provisional	-	-
2	Therapeutic Area Data Standards User Guide for Alzheimer's Disease and Mild Cognitive Impairment NEUROLOGY	CFAST Alzheimer's Development Team • This document corresponds to the SDTM v1.4 and SDTMIG v3.2.	2013-12-16 2.0 TAUG-Alzheimer's v2.0	1.4	3.2

#	TAUGs	Based on	Date and Version	SDTM version	SDTMIG
3	Therapeutic Area Data Standards User Guide for Multiple Sclerosis NEUROLOGY	Multiple Sclerosis Outcome Assessments Consortium and the CFAST Multiple Sclerosis Development Team • This document corresponds to the SDTM v1.4 and SDTMIG v3.2.	2014-05-02 Provisional Multiple Sclerosis User Guide v1.0 release	1.4	3.2
4	Therapeutic Area Data Standards User Guide for Traumatic Brain Injury NEUROLOGY	This document is based on SDTM v1.4 and SDTMIG v3.2, and on CDASH v1.1 and CDASHUG v1.0. • This document is based on SDTM v1.4 and SDTMIG v3.2, and on CDASH v1.1 and CDASHUG v1.0.	2015-12-02 Version 1.0 for provisional use	1.4	3.2
5	Therapeutic Area User Guide for Huntington's Disease RARE DISEASE	CFAST Huntington's Disease Standards Team • This document is based on SDTM v1.5, SDTMIG v3.2, SDTMIG-PGx v1.0, and SDTMIG-MD v1.0 (provisional).	2018-10-01 1.0 Provisional	1.5	3.2

Table 2. TAUGs releases (based on latest versions)

#	Year	TAUGs	TAUGs in Neurology
1	2012	1	1
2	2013	3	1
3	2014	3	1
4	2015	5	1
5	2016	9	
6	2017	5	
7	2018	4	
8	2019	5	
9	2020	6+	

Origin of domains used in latest TAUGs:

- SDTMIG v.3.2;
- SDTMIG Medical Devices v.1.0 (SDTMIG-MD v1.0);
- SDTMIG Associated Persons v1.0 (SDTMIG-AP v1.0);
- Draft domains proposed (TAUG draft domains not yet in any SDTMIG), most of them already represented in SDTMIG v.3.3;
- SDTMIG Pharmacogenomics/Genetics v1.1 (SDTMIG PGx).

SDTMIG V3.3 DOMAINS IN THERAPEUTIC AREA USER GUIDES

Table 3. SDTMs mentioned in TAUGs

#	SDTM	PD	AD	HD	MS	TBI	Total	Comments
1	DI	+	+	+	+	+	5	
2	DU	+	+	+	+	+	5	
3	MO	+	+		+	+	4	Is decommissioning
4	***DO**	+	+	+		+	4	SDTMIG-MD
5	MH		+		+	+	3	
6	PR		+	+		+	3	
7	NV		+	+	+		3	
8	BS	+	+	+			3	
9	LB		+	+			2	
10	AG		+	+			2	
11	CE	+			+		2	
12	OE				+	+	2	
13	FA				+	+	2	
14	BE		+	+			2	
15	***PF**		+				1	SDTMIG PGx
16	***APMH**	+					1	SDTMIG-AP
17	***APBS**	+					1	SDTMIG-AP
18	***APDM**	+					1	SDTMIG-AP
19	***ED**	+					1	Now Education Details is mapped into SC
20	MI	+					1	
21	RELSPEC			+			1	
22	TS				+		1	
23	RS					+	1	
24	SU					+	1	
25	HO					+	1	

**domains which don't exist in SDTMIG v3.3*

DISEASE ASSESSMENT

Table 4. Symptoms and Signs

AD	PD	MS	TBI	HD
Cognitive Impairments	Tremor	Depression	Loss of Consiousness	Irritability
Speech Problems	**Walking Impairment**	Pain	Memory Loss	Depression
Depression	**Gait Impairment**	Numbiness/Tingling	**Speech Problems**	Pain
Sleeping Changes	Spacticity	Sexual Dysfunction	Confusion	Fatigue
Gait Slowed	Pain	Fatigue	**Dizziness/Vertigo**	**Sleeping Problems**
Dizziness/Vertigo	Depression	Spacticity	Nausea and/or Vomiting	Spacticity
Swalllowing (Advanced Stages)	Bowel/Bladder Problems	Lower And Upper Extremity Impairments	Blurry Vision	**Walking Impairment**
Pain	Fatigue	**Walking Impairment**	Tinnitus	Upper And Lower Extremity Impairments
	Sleeping Impaired	Bowel/Bladder Problems	**Sleeping Impaired**	**Dizziness/Vertigo**
	Dizziness/Vertigo	**Dizziness/Vertigo**	Changes in Behavior and/or Mood	Cognitive Impairments
	Cognitive Impairments	Cognitive Impairments		**Speech Problems**
	Speech Problems			

As you can see, all these symptoms have a functional impact on:

- Social life and social participation;
- Work life;
- Relationships and family;
- Independence.

The above reasons are why the questionnaires, functional tests and rating scales are very important in Neurology therapeutic area. And as the result of the development of TAUGs in SDTMIG v3.3 there are new domains to make information easier to analyze.

New domains which are released now in SDTMIG v3.3 and are important for Neurology:

Table 5. New domains in SDTMIG v3.3 which are connected with Neurology

Section	Domain Type	Domain Name and Code
6.1	Interventions	Procedure Agents (AG)
6.3	Findings	Nervous Systems Findings (NV)
		Ophthalmic Examinations (OE)
		Functional Tests (FT)
9	Study References	Device Identifiers (DI)
		Pharmacogenomic/Genetic Biomarker Identifiers (PB)

PROCEDURE AGENTS (AG)

This Interventions domain is used to represent agents administered to the subject as part of a procedure, as opposed to drugs, medications and, therapies administered with therapeutic intent. Examples so far have included a shortacting bronchodilator administered as part of a reversibility assessment for asthma, glucose or meals administered as part of a tolerance test in subjects with diabetes, and contrast agents and radio-labeled substances used in imaging studies.

NERVOUS SYSTEM FINDINGS (NV)

This domain was first introduced as part of the TAUG for Multiple Sclerosis. It is a physiology domain intended for the representation of results from active neurological processes. Examples of what tests and results can be included:

- Glucose metabolism by various regions of the brain, assessed by using radiotracers and PET scans.
- Visual evoked potential (VEP), which assesses a subject's response to a visual stimulus via an EEG.
- MRI imaging.

The modeling of this data does not differ from that of most Findings domains, and no new variables were needed.

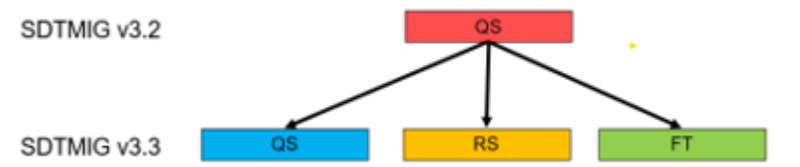
OPHTHALMIC EXAMINATIONS (OE)

The OE domain is a Findings domain used for tests that measure a person's ocular health and visual status. Included are tests of visual acuity, color vision, ocular comfort (e.g., dryness, itching), and intraocular pressure. Excluded are morphological measurements such as pupil diameter and macula thickness. The variable FOCID (Focus of Study-Specific Interest) will appeared as a result of this domain, as well as several domains expected for the SENDIG. FOCID is an Identifier variable which has no domain prefix. This is because the focus of specific interest within the subject should be identified the same way across all domains. For example, the right eye (FOCID = OD) might be treated (EX) and then evaluated, with results in OE. This domain uses controlled terminology for FOCID: OD (Oculus Dexter, Right Eye), OS (Oculus Sinister, Left Eye), and OU (Oculus Uterque, Both Eyes). The Findings variables --LOC (e.g., EYE) and --LAT (e.g., RIGHT), and to a lesser extent, --DIR, and --PORTOT may also be used. In fact, the Assumptions state that "the variables --LOC and --LAT are recommended to be populated in all cases for ophthalmic findings, since the benefits of facilitating grouping and data aggregation for other needs are recognized." Other implementations of FOCID are expected to use protocol-defined terminology.
of a tolerance test in subjects with diabetes, and contrast agents and radio-labeled substances used in imaging studies. Whether or not FOCID is used in a study, --LOC and --LAT should be populated in records related to the eyes. The value in OELOC may be "EYE" but may also be a part of the eye, such as "RETINA", "CORNEA", etc.

FUNCTIONAL TESTS (FT)

In SDTMIG v3.3 the data previously represented in the QS domain should be split into three domains for making the data that was collected easier and more adequately to represent:

Figure 6. Updates to QS



Many instruments and assessments that had been categorized as questionnaires were really not (since some had no question.

In SDTMIG v3.2 QS domain includes many instruments and assessments which technically were not questionnaires (there were no questions). That's why now it's split and below is the criteria how to distinguish them:

- QS Questionnaires - questions with responses;
- FT Functional Tests meaning that the subject is asked to perform a task and is evaluated (tests for mobility, dexterity and cognitive ability). FSTEST and FSTESTCD have CDISC Controlled Terminology.

- RS Response and Clinical Classifications – subject and objective assessments of a subject's status.RSCAT is required for clinical classifications other than oncology response criteria (to classify, rank or grade the status of a disease or other physiological or biological status). RSCAT, RSTEST and RSTESTCD have CDISC Controlled Terminology.

DEVICE IDENTIFIERS (DI)

DI domain is a Special-Purpose domain that was designed to capture multiple identifiers such as model, serial number, lot identifier, manufacturer, etc. to create a single identifier (SPDEVID) for each device to link data across the device domains. DI contains only identifier characteristics that cannot be changed during the study. DI domain must exist if SPDEVID is used in any domain in a study.

- SPDEVID can be at any level of granularity – to identify an individual device or it may be used to specify only the type of device (for example, in studies w here device is not the product under study and is used only to conduct assessments). SPDEVID is required to be present in all device domains.
- At least one identifier element (DIPARMCD='TYPE') must be populated for each device. TYPE uses controlled terminology defined by FDA as Global Medical Device Nomenclature (GMDN).
- Device Identifiers exist independently from subjects and therefore the DI domain does not contain USUBJID.

PHARMACOGENOMICS/GENETICS BIOMARKER (PB)

PB domain is independent from study subjects. This domain defines the biomarker and contains known associations between observed biomarkers and medical conclusions (e.g., disease diagnosis, drug resistance). PB data relates a set of genetic variations to an inference about that set of genetic variations (i.e., a medical statement) and is structured with one record per genetic biomarker. The medical statement (PBSTMT) describes the medical conclusion of the genetic variation for use of a drug, (in PBDRUG) or the diagnosis of a medical condition (in PBDIAG). PBSTMT can be inferred from the presence of a single genetic variant or all genetic variations in a set must be present for an inference to be drawn. PBMRKR identifies the individual variant. PBMRKRID is used to group genetic variation records which belong to a set and which form the basis for medical statement inference.

PROS AND CONS

\+ Very specific and difficult data has rules to follow and codelists, which are very clear and makes impossible to have something mapped differently;

\+ As time goes we can notice that the main principles of how to map not changed, and now the specific domains which were only ideas in TAUG are present in the latest SDTMIG v3.3;

- Information may be duplicated as it's used for different purposes;
- Some of domains (like BE) is not a very important to analyze per se, though it can be used for identifying and sorting purposes;
- TAUGs need to be up to date to stay aligned with latest standards.

CONTRADICTIONS BETWEEN

1) In TAUG PD there is a domain which now doesn't exist: ED (information from ED is mapped into SC now);
2) MO is decommissioning but still mentioned in TAUGs.

CONCLUSION

As it's shown, the ideas from TAUGs are now implemented in SDTMIG v.3.3, so as far as we understand what drives changes – we can assume what will appear in the standards next.

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