



CDISC Italian User Network 2019

Milan, Italy | 22 February 2019

cdisc



Therapeutic Area User Guidance (TAUGs) Update

What's in there and
what can we learn from there?

Angelo Tinazzi, Cytel Inc.

CDISC Italian User Network - Milano / 22 February 2019

The number of available CDISC TAUGs (Therapeutic Area User Guides) are continuously evolving now covering a wide range of indications, such as diabetes, oncology (Prostate, Colon and Breast), Rheumatoid Arthritis, etc. **Overall 30 guidances have been released since 2013, with 5 more planned to be finalized in 2019.**

In 2015 *Johannes Ulander and Niels Both* did a review of the content of the existing TAUGs available at that time (“Therapeutic Area standards and their impact on current SDTM implementations”, PhUSE, CD03, 2015). The main **focus was on SDTM and in particular the analysis of differences of similar aspects covered by the different TAUGs**, for example the way ‘Primary Diagnosis’ information are handled in SDTM.

Based on an ongoing Cytel initiative, with the aim of **setting some internal libraries of examples that could be applied across sponsors, projects and indications**, the objective of this presentation is to introduce TAUGs concept and to give **some insights on what’s covered in all TAUGs**. All foundational standards covered by the different TAUGs are assessed, either CDASH or SDTM or ADaM or the Controlled Terminology.

- Introduction and Objectives
- “Lo Stato dell’Arte” (State of Art)
- A deeper insight into TAUGs
 - SDTM Domains Used
 - ADaM Concepts Used
 - ‘Variations’ between TAUGs
 - Other Points of Interest
- Conclusions



Introduction and Objectives

Intro to TAUGs, TAUGs vs Foundational, Concept Map

Introduction and Objectives

What is a TAUG?

- Guides for the implementation of CDISC standards in **specific disease areas**
- Based on **biomedical concepts** identified by **subject matter experts**
- Include examples from across CDISC foundational standards

FOUNDATIONAL CONCEPT	THERAPEUTIC AREA CONCEPT
How to model data from labs (LB domain, SDTMIG)	How to model data from the complete concept of cerebrospinal fluid biomarker labs (Alzheimer's/Huntington's TAUGs)
How to collect labs data (CDASHIG, CDASH Example CRF Library)	How to collect data on Nadir CD4+ T-cell counts (HIV TAUG)
How to structure time-to-event analysis datasets (ADTTE dataset, ADaMIG)	How to structure analysis of time to kidney allograft rejection using ADTTE (Kidney Transplant TAUG)

Specifications for how to structure data of certain types

Vs.

How to implement those specifications in disease-specific use cases

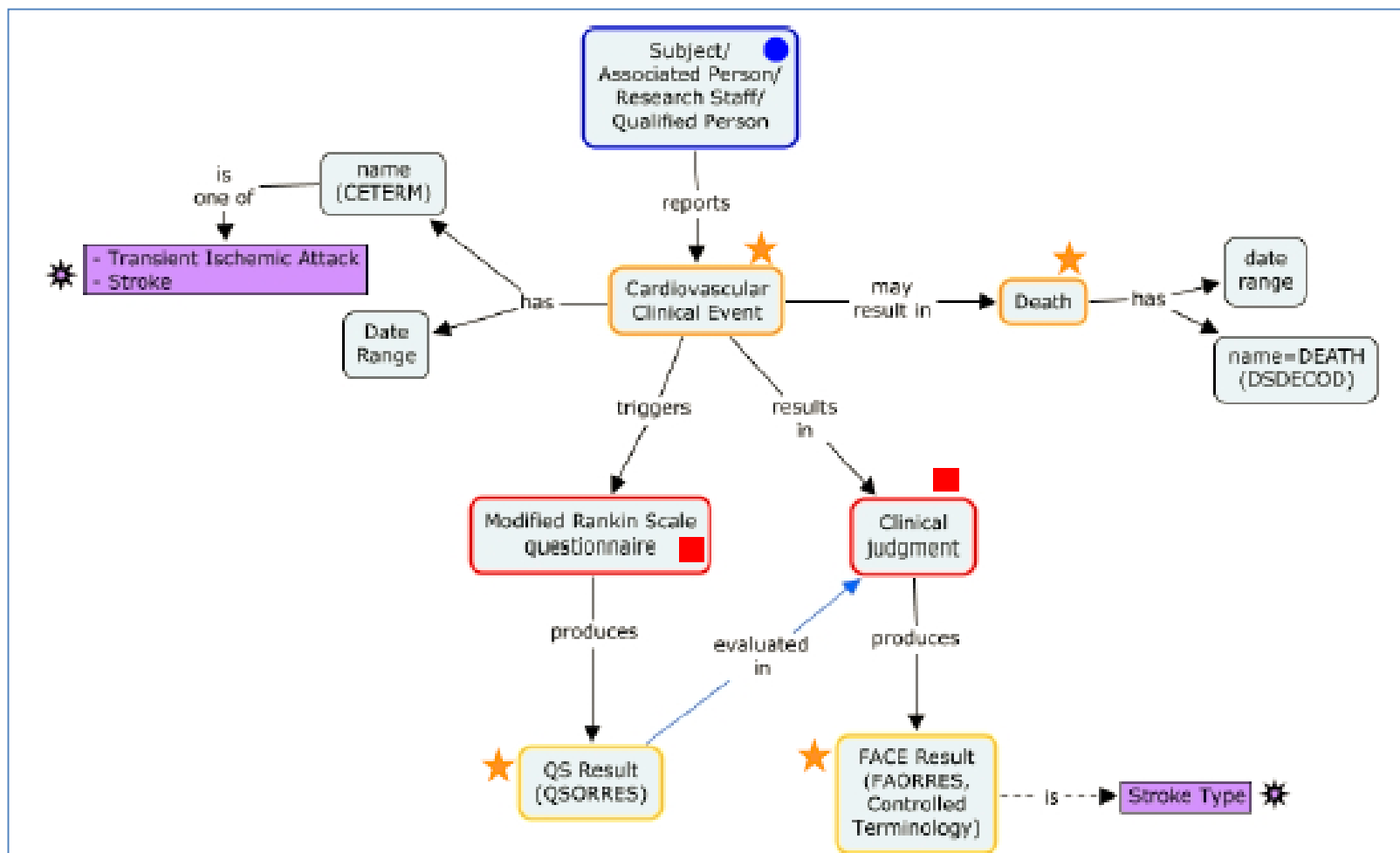
From «Review of Therapeutic Areas for Newcomers», Bess LeRoy, CDISC, CDISC EU Interchange, 2018

- SDTM mapping of **key TA concepts** i.e. disease background, endpoints
- Provides additional examples of **situations not covered by current IG**
- New Controlled Terminology
- New Domains
- Identification of **Regulatory and Medical References**
- Developed in **collaboration with TA opinion leaders / organizations**
i.e.
 - Cardiology: American College of Cardiology and Duke Clinical Research Institute
 - Multiple Sclerosis: National Institute for Neurological Disorder and Stroke

- When released, they are **Provisional**
- Creation of **User Guides**
 - PDF → now html
 - Make use Biomedical Concepts (Concept Map)
 - CDASH with SDTM annotations
 - ADaM
- Some are «Validated» and **accepted by the FDA** and listed in the FDA Study Data Technical Conformance Guide (SDTCG)

Introduction and Objectives

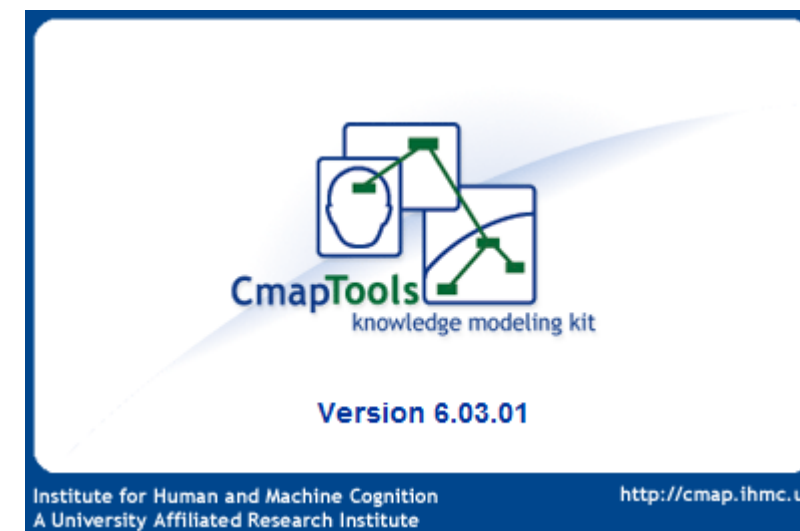
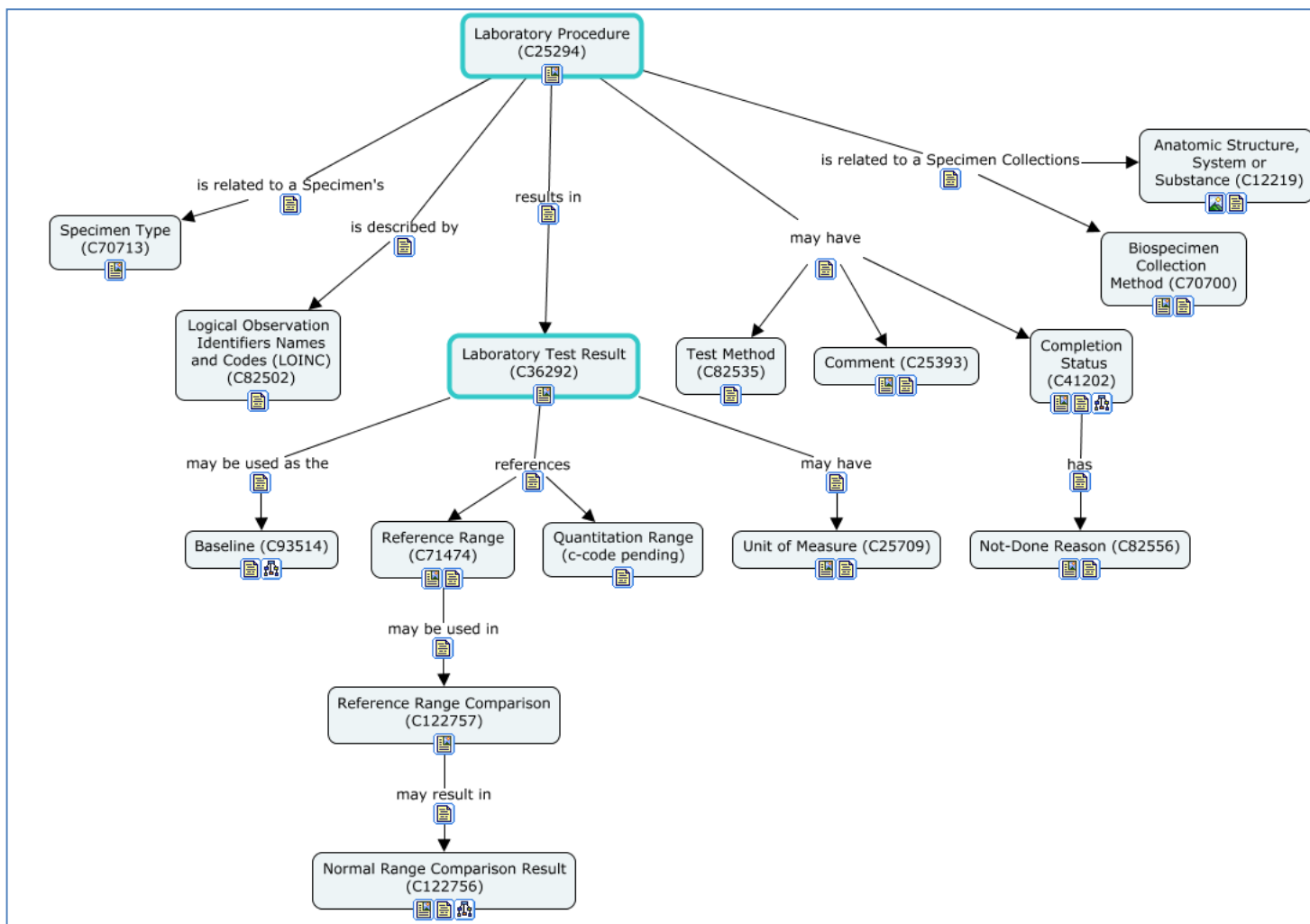
What is a TAUG? Concept Maps / Biomedical Concepts



EXAMPLE FROM CARDIOVASCULAR TRANSIENT ISCHEMIC ATTACK (TIA)

Introduction and Objectives

What is a TAUG? Concept Maps / Biomedical Concepts



EXAMPLE FROM COPD-Chronic-Obstructive-Pulmonary-Disease

Introduction and Objectives

Typical Table of Contents

- Clinical Overview / Disease Background
- Trial Design
- Subject and Disease Characteristics i.e. Diagnosis
- Disease Assessments i.e. Symptoms, QRS, Response Measurements
- Routine Data i.e. Concomitant Medications
- Analysis Data (when covered) i.e. key efficacy endpoints with ADaM examples
-
- Known Issues
- Questionnaires, Rating and Scales (list and approval status)
- Some provide some sort of xls metadata summarizing what the TAUG is covering i.e. SDTM domains mentioned in the TAUG

Introduction and Objectives

Example from Schizophrenia

User Guide Section Number	Section Name	Examples	SDTM Domains used	"New" SDTM variables used	Comments
2.0	Clinical Overview				
2.1	Clinical Case Examples				
2.1.1	Clinical Case 1. Patient with Acute Schizophrenia				
2.1.2	Clinical Case 2. Patient with Negative Symptoms in Adjunctive Treatment Trial				
3.0	Trial Design				
3.1	Example Trial 1. Acute Schizophrenia				
3.1.1	Acute Schizophrenia Trial Design Datasets	2.1 Example 1	TA, TE, TV, TI, TS		
3.2	Example Trial 2. Randomized Withdrawal to Assess Maintenance of Response				
3.2.1	Randomized-Withdrawal to Assess Maintenance of Response Trial Design Datasets	2.1 Example 2	TA, TE, TV, TI, TS		
3.3	Example Trial 3. Adjunctive Treatment				
3.3.1	Adjunctive Treatment Trial Design Datasets	2.1 Example 3	TA, TE, TV, TI, TS		
4.0	Subject and Disease Characteristics				
4.1	Schizophrenia Diagnosis				
4.1.1	Diagnosing Schizophrenia_ DSM-IV-TR versus DSM-5	4.1.1 Example 1	MH	EVDTYP, DSMAXS, DSM4CD, DSM5CD, DIAMTH	Includes CRF: Psychiatric History
		4.1.1 Example 2	MH, FA	EVDTYP, CRNORD	
		4.1.1 Example 3	MH, FA, RELREC	EVDTYP, CRNORD, DSMAXS, DSM4CD, DIAMTH, MHAGE	
4.2	Medical History of Special Interest to Schizophrenia	4.2 Example 1	MH		
4.3	Additional Disease History	4.3 Example 1	MH, HO, FA	EVNUM, REAS,	Includes CRF: Psychiatric

Introduction and Objectives

New in Recent SDTM CDISC-CT

- Specific TSPARMCD in TS to reference TAUG(s) used
- Proposed by FDA with Study Technical Conformance Guide (October 2018)
- Added in CDISC-CT

TSPARMCD=CTAUG

Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition
Trial Summary Parameter Test Code	CTAUG	CDISC Therapeutic Area User Guide	The name and version of the CDISC therapeutic area user guide that is being used in the study submission.

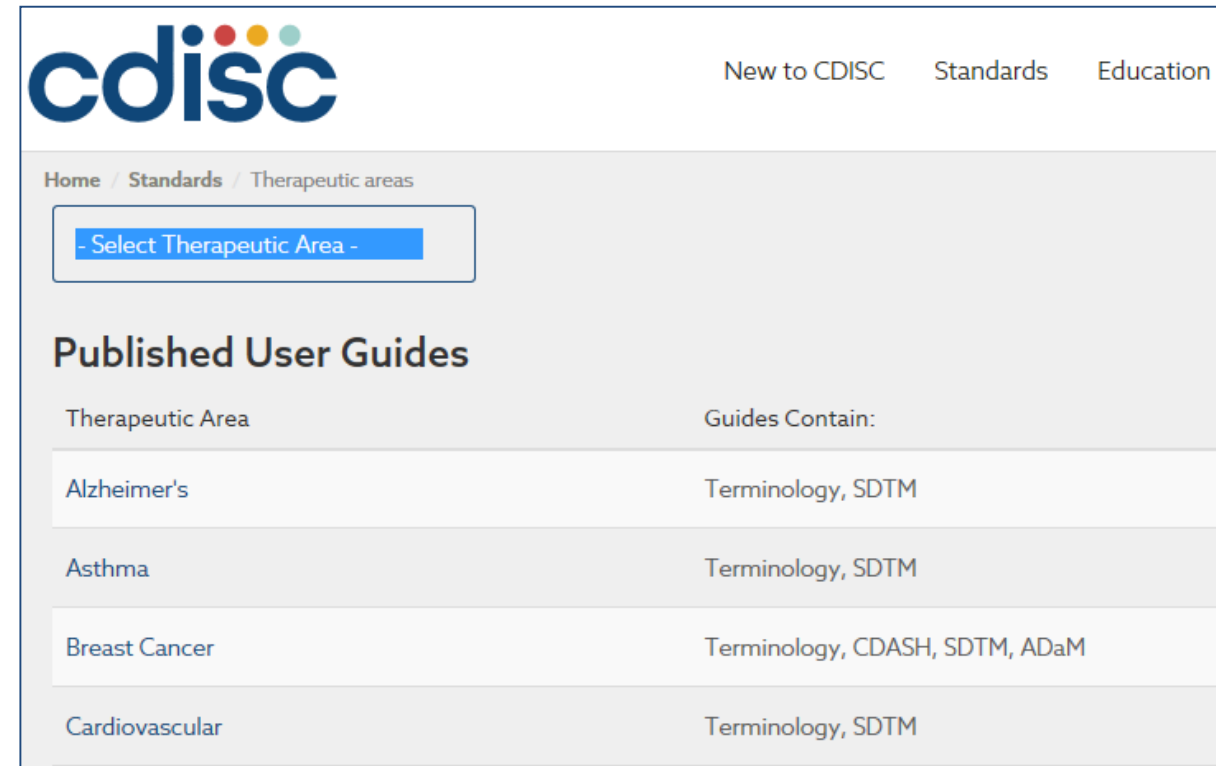
LO STATO DELL'ARTE



Available TAUGs

- First TAUG released in **2011** (Alzheimer)
- **30** TAUGs released up to End of 2018
- **5** more in the pipeline for 2019
- **10** different Area of Specialty
 - Autoimmune (1) i.e. Rheumatoid Arthritis
 - Cardiovascular (2) i.e. QT Studies
 - Endocrine (5) i.e. Diabetes
 - Infectious (6) i.e. Influenza
 - Mental Health (3) i.e. Schizophrenia
 - Neurology (4) i.e. Multiple Sclerosis
 - Oncology (3) i.e. Breast
 - Rare Disease (2) i.e. Huntington's Disease
 - Respiratory (2) i.e. Asthma
 - Treatments (2) i.e. Pain

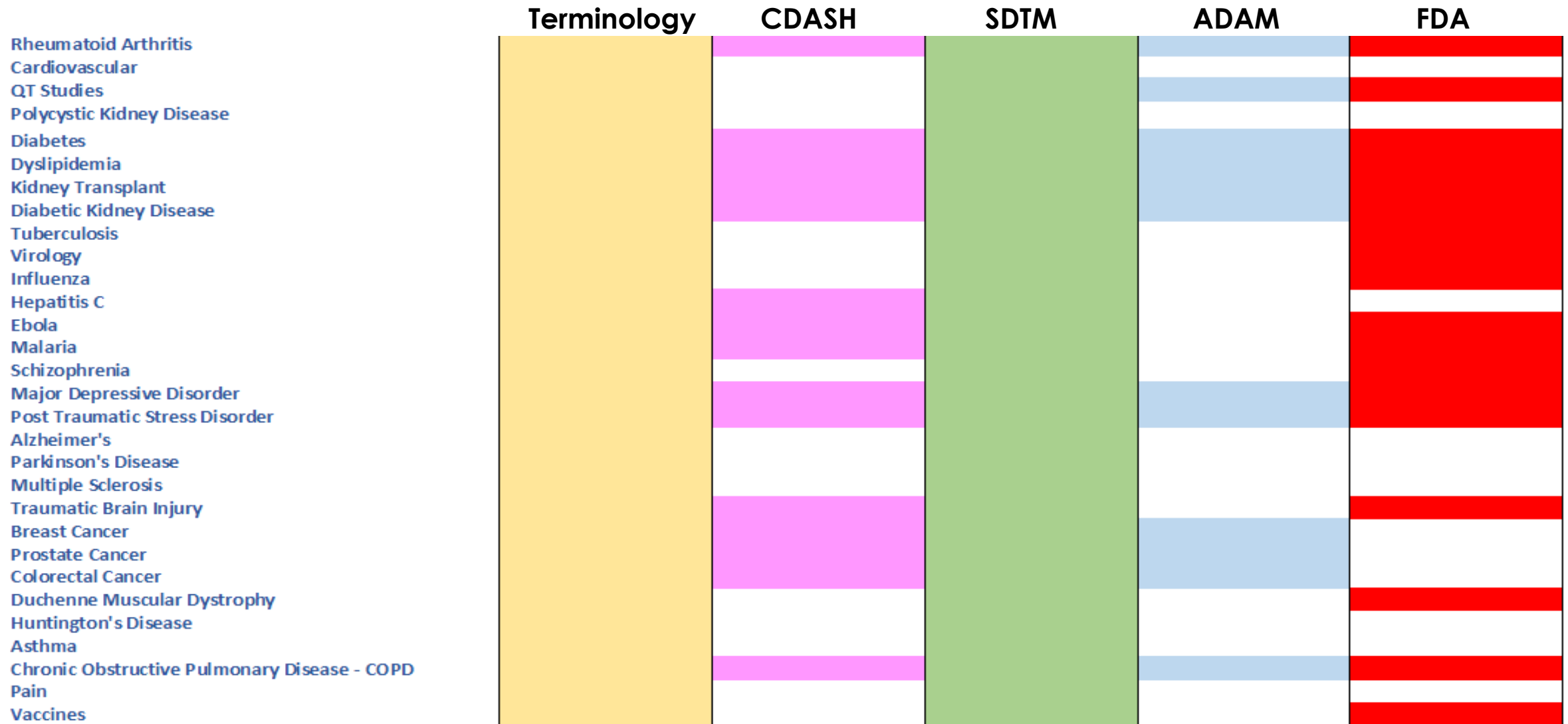
<https://www.cdisc.org/standards/therapeutic-areas>



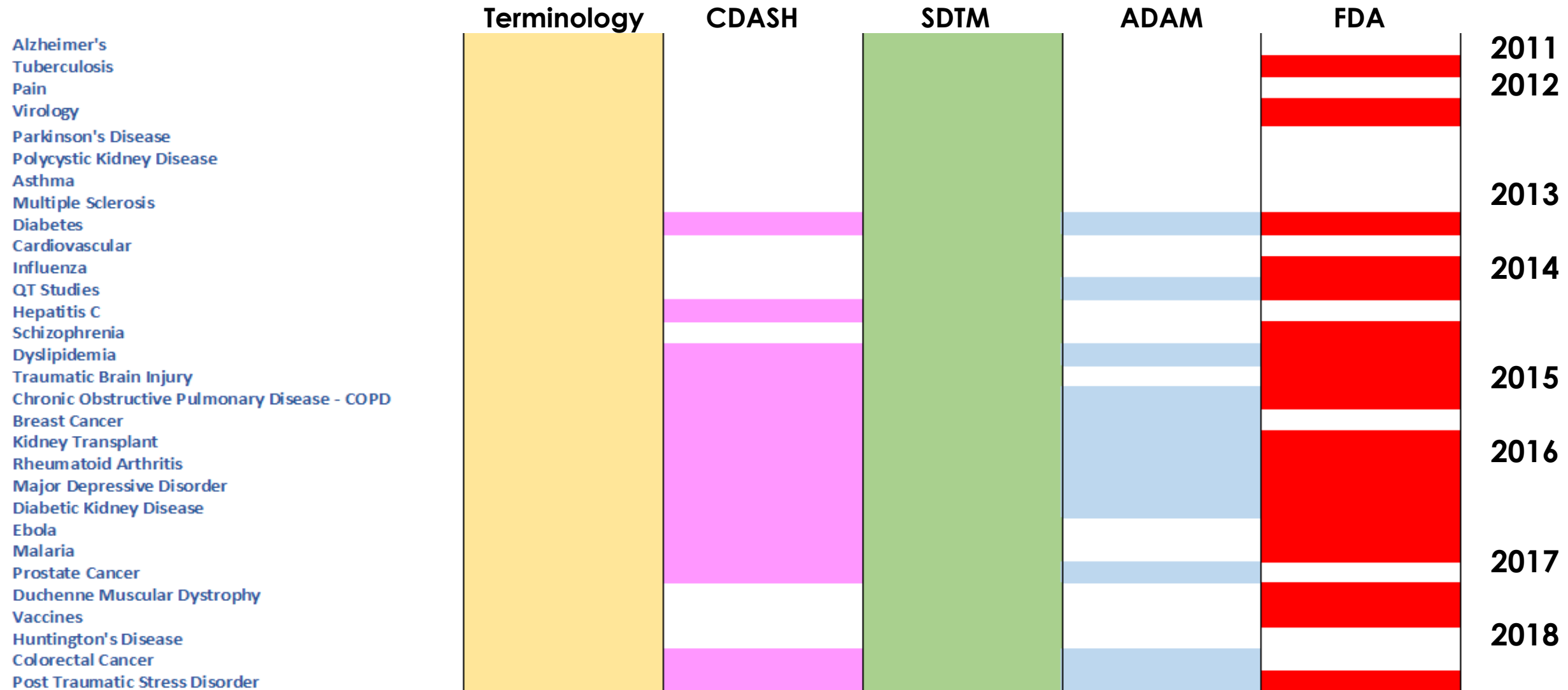
The screenshot shows the CDISC website interface. At the top, there is a navigation bar with 'New to CDISC', 'Standards', and 'Education'. The main content area is titled 'Home / Standards / Therapeutic areas' and features a dropdown menu labeled '- Select Therapeutic Area -'. Below this, a section titled 'Published User Guides' displays a table of therapeutic areas and their associated guides.

Therapeutic Area	Guides Contain:
Alzheimer's	Terminology, SDTM
Asthma	Terminology, SDTM
Breast Cancer	Terminology, CDASH, SDTM, ADaM
Cardiovascular	Terminology, SDTM

"Lo Stato dell'Arte" Standards Covered – Ordered by Area



"Lo Stato dell'Arte" Standards Covered – Ordered by Date of First Version



A Deeper Insight



Covered concepts, SDTM domains used,
ADaM concepts used, 'variations' between TAUGs

- Get **all TAUGs** from cdisc.org
- **Map all covered items** : SDTM ADaM CDASH CT
 - SDTM domains usage
 - Non Standard Domains Proposed
 - Specific Nomenclature i.e. QNAM
 - ADaM concepts
 - Covered Endpoints
- Special Mention on topic further **clarifying the Ig**
- Any **major ‘variation’** between TAUGs
- Assessment and internal Cytel «governed» library by end of Q1*

* Final outcome to be presented at CDISC-EU Interchange in May (Poster Session)

A Deeper Insights SDTM Most Common Domains Implemented



Domain	Count	Comment
MH/FAMH – Medical History	20	How to store diagnosis-related information → covered later
Devices (DI/DR/DU/DO)	18	
AE / CE	17	AE of Special Interest / Symptoms
Morphology	16	i.e. NV (Nervous System) and RE (Respiratory System Findings)
CM – Concomitant Medications	14	
PR – Procedures	14	
LB – Laboratory	14	
Microbiology Specimen (MB/MS/MI)	13	i.e. MI Pathology (Estrogen Receptor) in Breast Ca
Pharmacogenomic/genetic biomarkers (PF/PG/PB/BS)	13	i.e. PF Drug Resistance (genetic variation) in Influenza Ca
Questionnaires/ Rating (QS/FT/RS)	12	Use of RS in non-Oncology domains
Associated Persons	9	i.e. Family History
EC / EX / DA	7	
Trial Design – TDM	7	i.e. Schizophrenia Various example of TA: Acute Schizophrenia, Maintenance of Response, Adjunctive Treatment
TU TR HO AG ML IS DS SC VS SU SR DM DD EG		

A Deeper Insights

Additional SDTM Concepts Used / Discussed

- How to handle **Disease Diagnosis** related data → covered later
- **Kidney Transplant** makes use of several Associated Persons (AP) datasets to stores information about the donor
 - Blood Group in **APLB** with **LBCAT=BLOOD GROUP**
 - Score to assess eligibility of Organ Transplant **APUR**
 - Donor Characteristics i.e. DEAD vs ALIVE in **APSC**
 - Family History (**APMH**) in other TAUGs i.e. Parkinson's Disease
 - Demographics (**APDM**) in Ebola TAUG for "Suspect Source Case" and Survival Status (**APSS**)

A Deeper Insights

Additional SDTM Concepts Used / Discussed

- Use of **Devices Ig domains** in a non-device study
 - DX for “Wheelchair, Powered” in Duchenne Muscular Dystrophy
 - DI for “Protective Device” such as Airbag in Traumatic Brain Injury TAUG
- Laboratory Parameters of Specific Interest i.e. HIV Antibody and CD4 for Tuberculosis
- No specific examples for PC/PP (Pk studies)

A Deeper Insights ADaM Concepts Used

- 12/x30 TAUGs provide details about analysis topics specific to the TA
i.e. how to handle missing data
- The most significant examples
 - Breast and Colon Cancer TAUGs
 - Diabetes, Diabetic Kidney Disease, Dyslipidemia
 - Chronic Obstructive Pulmonary Disease – COPD
 - QT Studies
 - Rheumatoid Arthritis
- Most of them describe key efficacy endpoints with some ADaM mapping examples



ADaM Examples in Commonly Used Statistical Analysis Methods

A Deeper Insights

ADaM Concepts Used (conc)

■ Oncology TAUGs - Breast

- Use of **Intermediate ADaM** datasets prior to Best Overall Response-BOR (ADRESP) and Progression Free Survival (ADTTE) and other related TTE Endpoints
- Identification of **Cancer Related 'Baseline Characteristics'** i.e. Staging
- **Key Efficacy Endpoints** discussed i.e. Progression Free Survival, Disease Free Survival
- Colorectal Cancer **reference Breast TAUG** for BOR / TTE Endpoints modelling in ADaM

■ Diabetic Kidney Disease

- Good Example of **Composite Endpoints** i.e. an event that is triggered by the occurrence one of several events, that could be the value of a lab parameter and its 'persistence' i.e. confirmation xx weeks after
- Make use of **AP--** suffix for variables belonging to Associated Persons

■ Rheumatoid Arthritis

- Concept of **pre-ADSL** → some wording/recommendation also in ADaM Ig 1.2 draft

■ COPD-Chronic-Obstructive-Pulmonary-Disease

- Identification of Disease Baseline Variables
- ‘Rich’ of examples of intermediate ADaMs and ADaM from multiple ADaMs and SDTMs
- Key Efficacy Endpoints:

- Exacerbation

Identification of Individual Events: ADEXAC – Exacerbation Events (ADaM OCCDS, from SDTM.AE, CM, FA, etc.)



Total Number of Events: ADXACSUM – Exacerbation Events Summary (ADaM BDS from ADEXAC)

- Bode Index

ADFEV, ADVS (for BMI), AD6MWT (6-minutes walk test), ADMMRC (Dyspnea Test)



ADBODE: Sum individual score parameters from ADFEV/ADVS/AD6MWT/ADMMRC

A Deeper Insights ADaM Concepts Used (cont)

- Diabetes – ADaM Supplement (38 pages)
 - Examples of Analysis Results Metadata (ARM)
 - Standard for Randomization Stratification Factors → now « proposed » standard in ADaM Ig 1.2

Variable Name	Variable Label	Type	Length/Display Format	Codelist/Controlled Terms	Source/Derivation/Comment
USUBJID	Unique Subject Identifier	text	\$15		DM.USUBJID
STRATA	Randomized Strata	text	\$30	>7-<9% Metformin alone; >=9% Metformin alone; >7-<9% Metformin + insulin; >=9% Metformin + insulin	Obtained from QVAL in SUPPDM where QNAM = "STRATA" <i>Note: At present there is not a standard approach for capturing stratification factors in SDTM-based datasets. This variable represents the combination of individual stratum values used for randomization. The above text is an example and uses a pipe () as a delimiter between individual stratum values. These data could come from other sources as well depending on methodologies used for the design and the management of the randomization schedule.</i>
STRATAN	Randomized Strata (N)	integer	1	1; 2; 3; 4	= 1 when ADSL.STRATA = ">7-<9% Metformin alone"; = 2 when ADSL.STRATA = ">=9% Metformin alone"; = 3 when ADSL.STRATA = ">7-<9% Metformin + insulin"; = 4 when ADSL.STRATA = ">=9% Metformin + insulin"
STRAT1NM	Description of Stratum 1	text	\$20	HbA1c at Baseline	Assigned based on stratification factors defined a given trial. The value is the same across all subjects and is intended to provide a full text description of the first stratification factor.
STRAT1	Randomized Value of Stratum 1	text	\$6	>7-<9%; >=9%	Derived from ADSL.STRATA and is the text string up to the first delimiter of " "
STRAT1N	Randomized Value of Stratum 1 (N)	integer	1	0; 1	= 0 when ADSL.STRAT1 = ">7-<9%"; = 1 when ADSL.STRAT1 = ">=9%"

A Deeper Insights 'Variations' between TAUGs

'Variations' in 'Primary Diagnosis' in MH discussed by Ulander 2015, Where do we stand?

TAUG	Year	MHTERM	MHCAT	MHSCAT	MHEVDTYPE New in Ig 3.3	FAMH	TM/SM New in Ig 3.3
Chronic Obstructive Pulmonary Disease - COPD	2016	CHRONIC OBSTRUCTIVE PULMONARY DISEASE	COPD HISTORY		SYMPTOMS vs DIAGNOSIS	Nr of Occurrences	
Diabetic Kidney Disease	2016	<ul style="list-style-type: none"> TYPE 1 DIABETE TYPE 2 DIABETES 	DIABETES		DIAGNOSIS		
Ebola	2016	EVD for Ebola Diagnosis	<ul style="list-style-type: none"> EVD SYMPTOMS Empty when diagnosis with MHTERM=EVD 		SYMPTOMS ONSET when MHTERM=EVD		
Hepatitis C	2015	HEPATITIS C	<ul style="list-style-type: none"> HEPATITIS C COMORBIDITIES OF INTEREST FOR HEPATITIS C 		INFECTION vs DIAGNOSIS		
Malaria	2017		MALARIA SYMPTOMS				
Major Depressive Disorder	2016	MAJOR DEPRESSIVE DISORDER	PSYCHIATRIC HISTORY	MDD SYMPTOM	DIAGNOSIS		
Post Traumatic Stress Disorder	2018	POST TRAUMATIC STRESS DISORDER	PTSD HISTORY	PTSD HISTORY / PTSD SYMPTOMS	DIAGNOSIS vs SYMPTOM ONSET		
Prostate	2017	PROSTATE CANCER			DIAGNOSIS		Diagnosis as trial milestone
Traumatic Brain Injury	2015		TRAUMATIC BRAIN INJURY	<ul style="list-style-type: none"> RELATED INJURY vs QUALIFYING EVENT i.e. TBI episode SIGNS AND SYMPTOMS 		Nr of Events	

A Deeper Insights 'Variations' between TAUGs (cont)

'Variations' in 'Primary Diagnosis' in MH discussed by Ulander 2015, Where do we stand?

Possible Recommendations (as per Ig 3.3)

sm.xpt

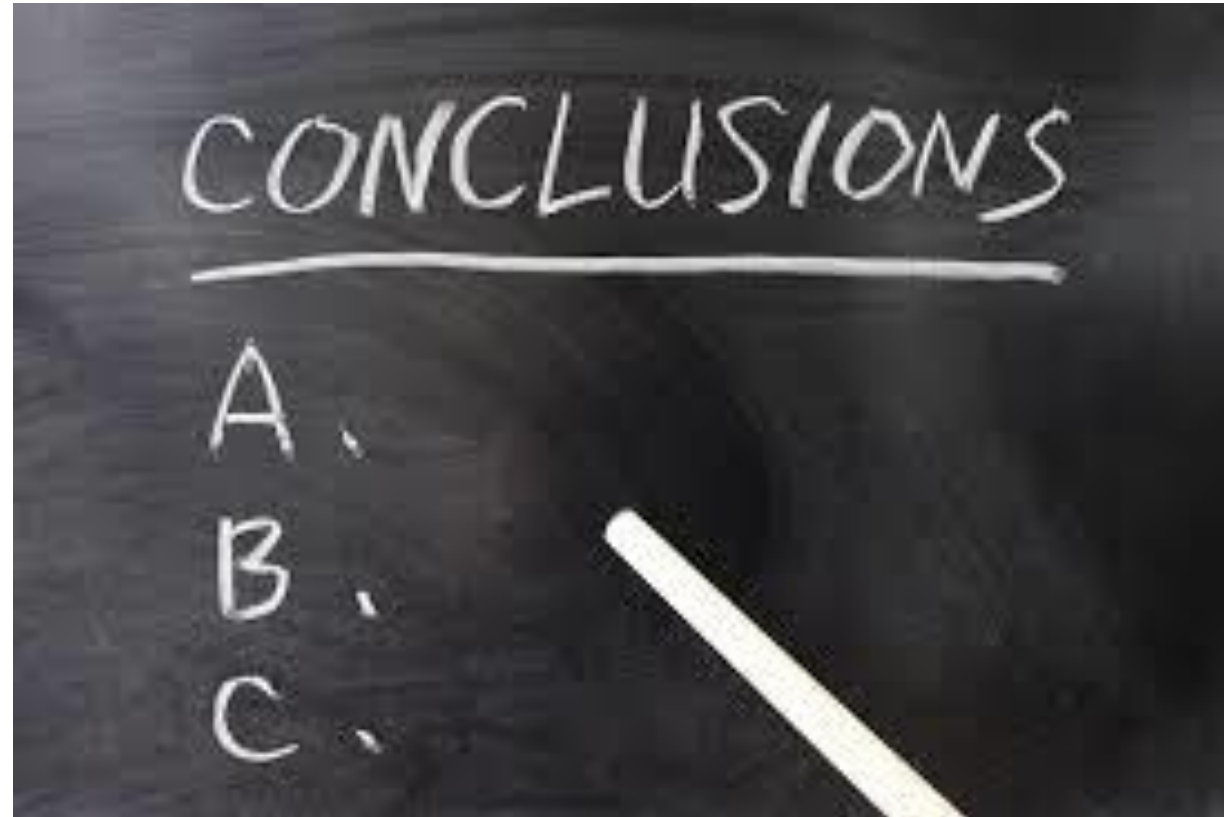
Row	STUDYID	DOMAIN	USUBJID	SMSEQ	MIDS	MIDSTYPE	SMSTDTC
1	XYZ	SM	001	1	DIAG	DIAGNOSIS	2005-10
2	XYZ	SM	001	2	HYP01	HYPOGLYCEMIC EVENT	2013-09-01T11:00
3	XYZ	SM	001	3	HYP02	HYPOGLYCEMIC EVENT	2013-09-24T8:48
4	XYZ	SM	002	1	DIAG	DIAGNOSIS	2010-05-15

mh.xpt

Row	STUDYID	DOMAIN	USUBJID	MHSEQ	MHTERM	MHDECOD	MHEVD TYP	MHPRESP	MHOCCUR	MHDTC	MHSTDTC
1	XYZ	MH	001	1	TYPE 2 DIABETES	Type 2 diabetes mellitus	DIAGNOSIS	Y	Y	2013-08-06	2005-10
2	XYZ	MH	002	1	TYPE 2 DIABETES	Type 2 diabetes mellitus	DIAGNOSIS	Y	Y	2013-08-06	2010-05-15

- SM - Subject Disease Milestones (New in Ig 3.3) is designed to record the **timing, for each subject, of disease milestones** that have been defined in the Trial Disease Milestones (TM) domain
- MHEVD TYP – Medical History Event Date Type (New in Ig 3.3) Specifies **the aspect of the medical condition or event by which MHSTDTC and/or the MHENDTC is defined**
 - It has a standard CT (extensible): DIAGNOSIS, EPISODE, EXACERBATION, SYMPTOM ONSET
- Make use of **MHCAT** to distinguish between GENERAL MEDICAL HISTORY vs more specific/study disease medical history. **MHSCAT** can be used to further categorize
- FAMH** can contains additional details related to the diagnosis i.e. nr. of episodes, age at first episode, etc.

- New Proposed Domains
 - **QT** - ECG QT Correction Model Data (QT Studies TAUG)
 - **ER** - Environmental Risk Factor (Ebola, Malaria and Tuberculosis TAUGs)
- Make us of **CMGRPID** to group drugs making the same regimen and **RS** to tumor response to prior therapies in CM (Breast and Prostate TAUGs)
- **Use of RS** in other non-onco TAUG (i.e. Schizophrenia, Traumatic Brain Injury)
- **Use of TU/RR** in other non-onco TAUG (i.e. Tuberculosis and Cardiovascular)
- Some TAUGs have ‘**reach**’ set of **aCRF** (i.e. Malaria, Parkinson’s, Diabetes, Major Depressive Disorder, Rheumatoid Arthritis, Onco TAUGs)



What's Next

- Focus on beginning-to-end (B2E) development in all TAUGs
 - CDASH
 - SDTM
 - ADaM
- Continue to leverage growing body of developed concepts and focus on consistent, reusable solutions

From «Review of Therapeutic Areas for Newcomers», Bess LeRoy, CDISC, CDISC EU Interchange, 2018

Opens Issues

- Still some variations between TAUGs
- Recommend CDISC to revise older TAUGs i.e. >2 years, and align with Ig 3.3 enhancement i.e. EVDTYP

Next for Cytel

- Complete the 'Map' (Review)
- Build the library of good examples:
 - CDASH and SDTM examples
 - Good mapping examples by groups of domains i.e. morphology domains
 - Additional ADaM Implementation Example



Angelo Tinazzi – Director – Standards, Systems, CDISC Consulting (CDISC E3C Member)

angelo.tinazzi@cytel.com

Cytel, Shaping the Future of Drug Development

- “CDISC Therapeutic Area Standard User Guide Highlights”, Angelo Tinazzi – PhUSE SDE Basel 2014
- “Therapeutic Area standards and their impact on current SDTM implementations”, Johannes Ulander and Niels Both – PhUSE 2015 – CD03
- “Assessing CDISC Therapeutic Area User Guides in a machine readable format”, Johannes Ulander and Niels Both – PhUSE 2016 – CD04
- “Easing Your Pain with Biomedical Concepts” – PhUSE -2018 – SI19
- “Review of Therapeutic Areas for Newcomers“, Bess LeRoy, CDISC, CDISC EU Interchange, 2018