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Standards Update on Oncology from the CDISC Therapeutic Area User Groups and ADaM Oncology Sub-team

Terek Peterson, MBA & Gaurab Chakraborty

December 5th, 2015

Lonavala, Maharashtra

** Subject to change*

Established CDISC Expertise

2004
EARLY ADOPTER

- One of First Companies to Submit CDISC Compliant Data
- Corporate Member Since 2005
- Platinum Member and Registered Solutions Provider

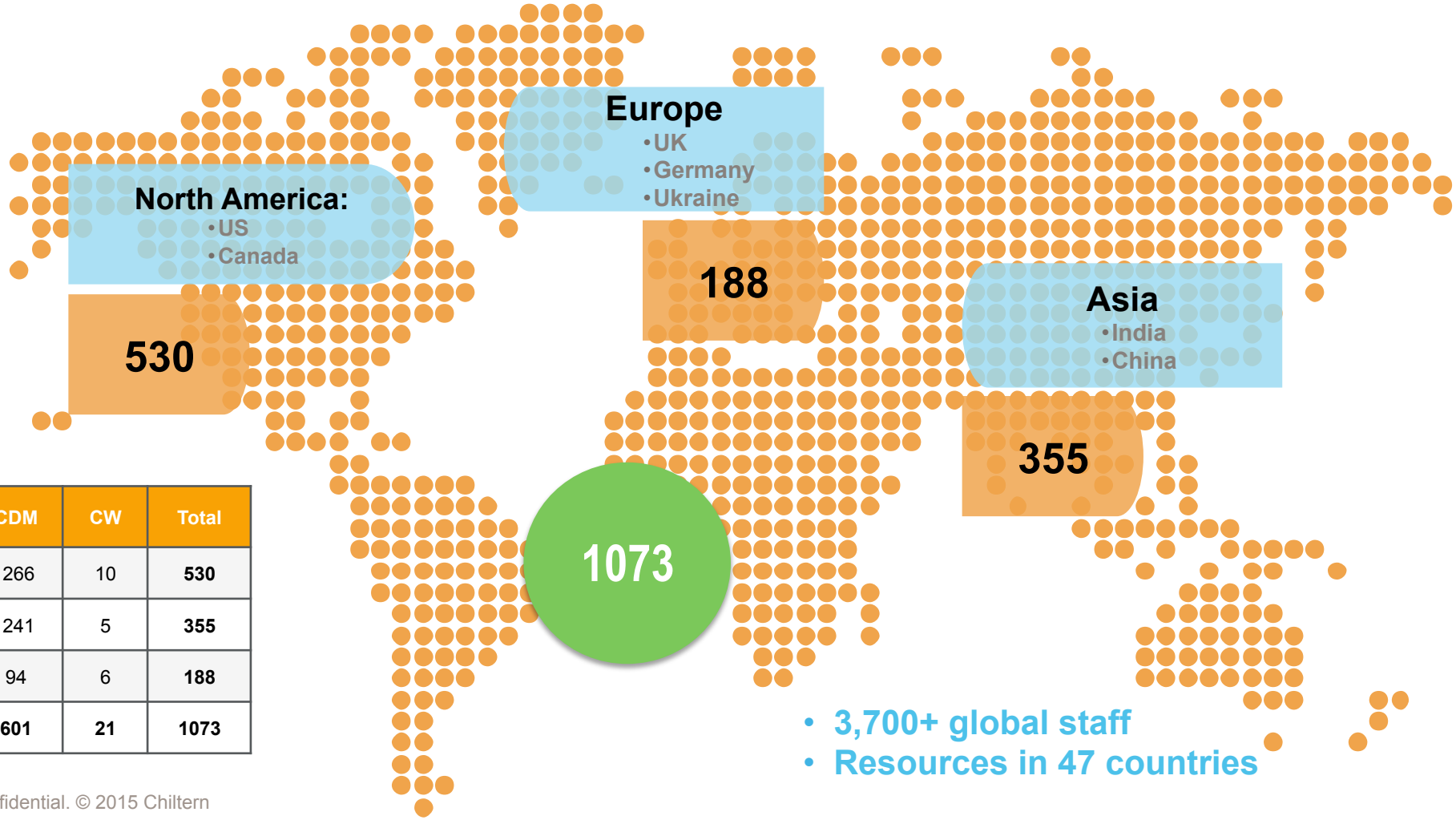
CONTRIBUTION

- 3 Outstanding Performance Awards
- Multiple Interchange Presentations
- PhUSE FDA/CSS Working Groups
- 9 Staff Members on CDISC Committees (Including Oncology)
- CDISC Fellow Sponsorship for 2015

CDISC® EXPERTISE

- 40,000+ Domains Created
- Submissions
- Expert Training
- Customized Consulting
- Aggressive Projects Completed On Time Due to Issue Anticipation and Vendor Experience

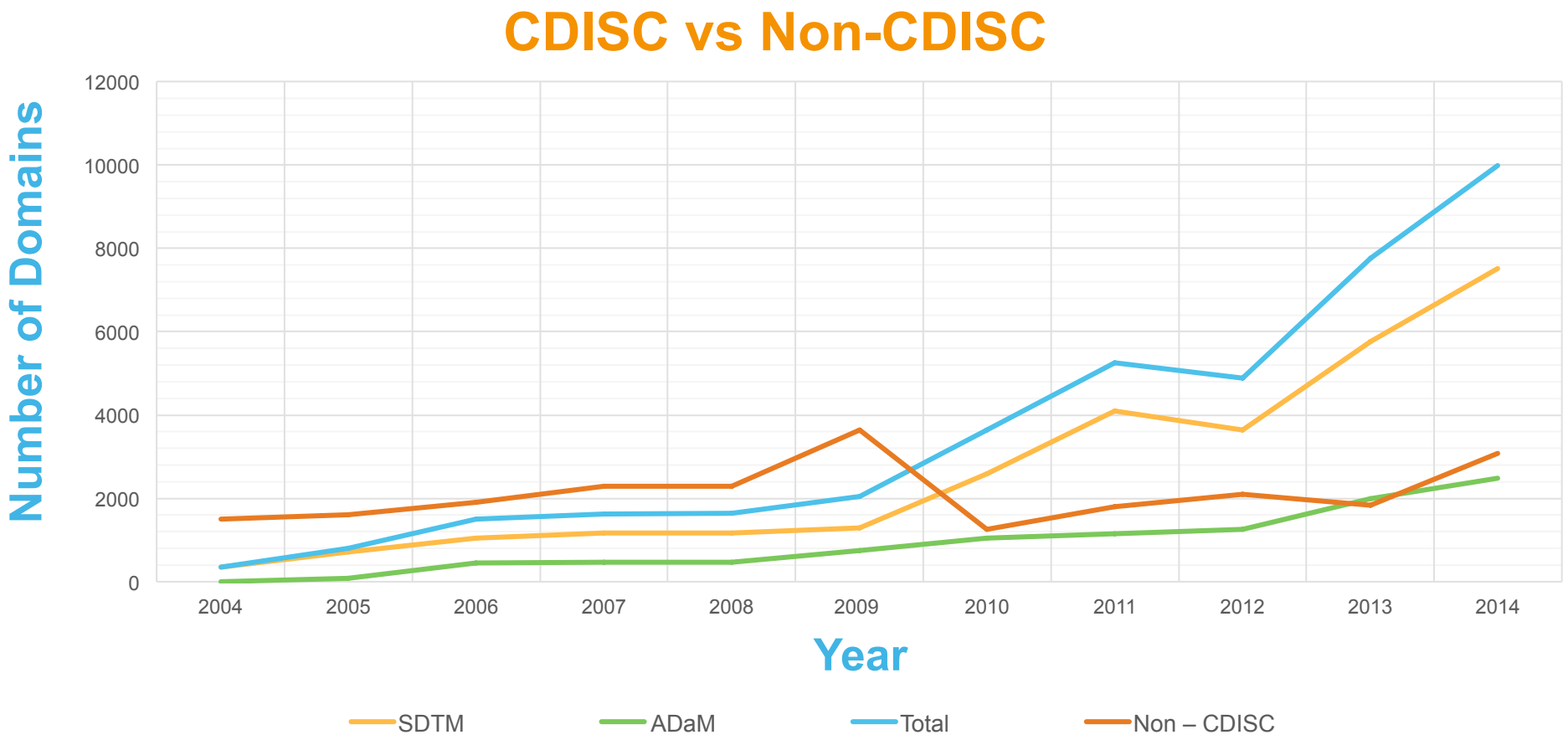
Chiltern's Worldwide Clinical Analytics Presence



Region	BM	CDM	CW	Total
Americas	254	266	10	**530**
Asia Pac	109	241	5	**355**
Europe	88	94	6	**188**
Total	**451**	**601**	**21**	**1073**

- 3,700+ global staff
- Resources in 47 countries

CDISC: SDTM and ADaM Experience



Agenda – Standards Update on Oncology

FDA Guidance & SDTMIG v3.2

- Recent FDA Guidance
- Federal Register Notice SDTMIG v3.2 Accepted with Exceptions

Therapeutic Area User Groups

- Current Available TAUGs
- CDISC SHARE Metadata Spec Project

ADaM Oncology Sub-team Update

- Suggested Analysis dataset structures
- Handling RECIST

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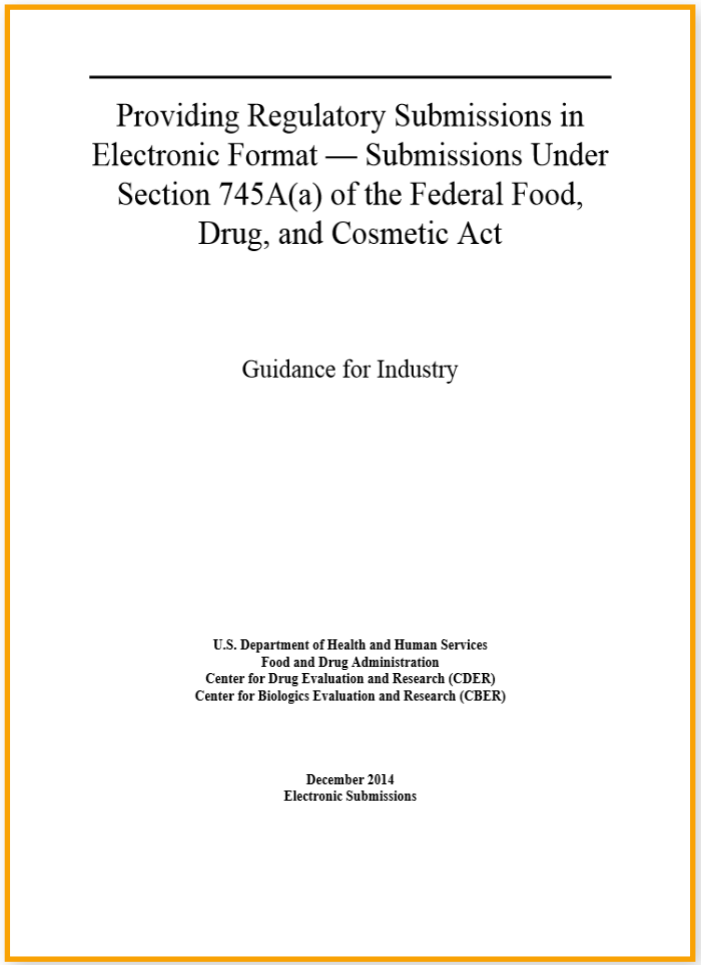
FDA Guidance & SDTMIG v3.2

Binding FDA Guidance

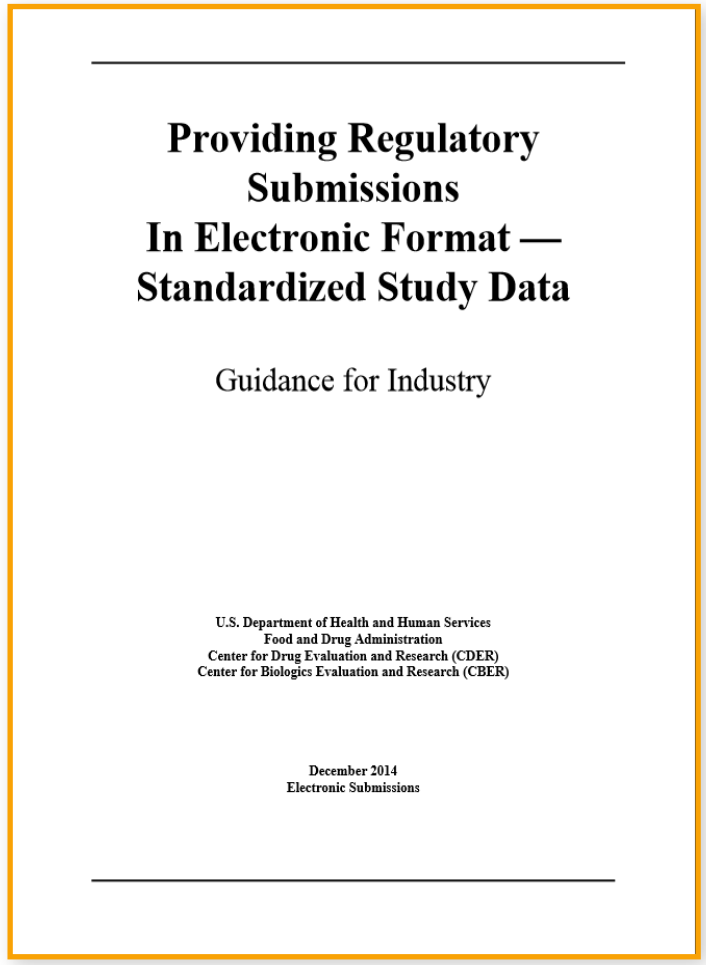


Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2014
Electronic Submissions

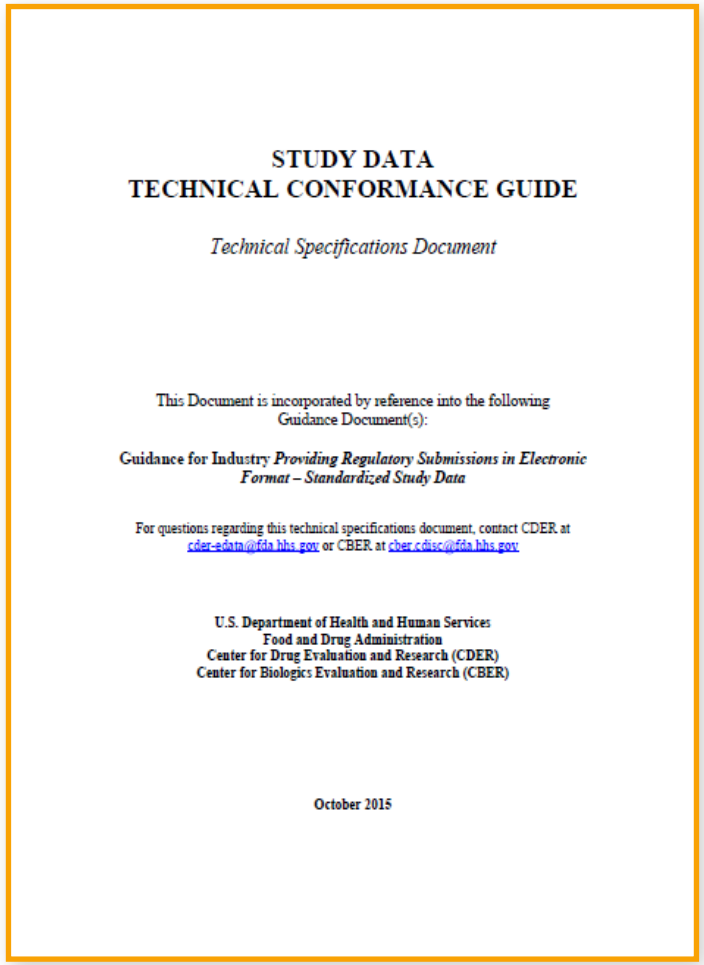


Providing Regulatory Submissions In Electronic Format — Standardized Study Data

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2014
Electronic Submissions



STUDY DATA TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

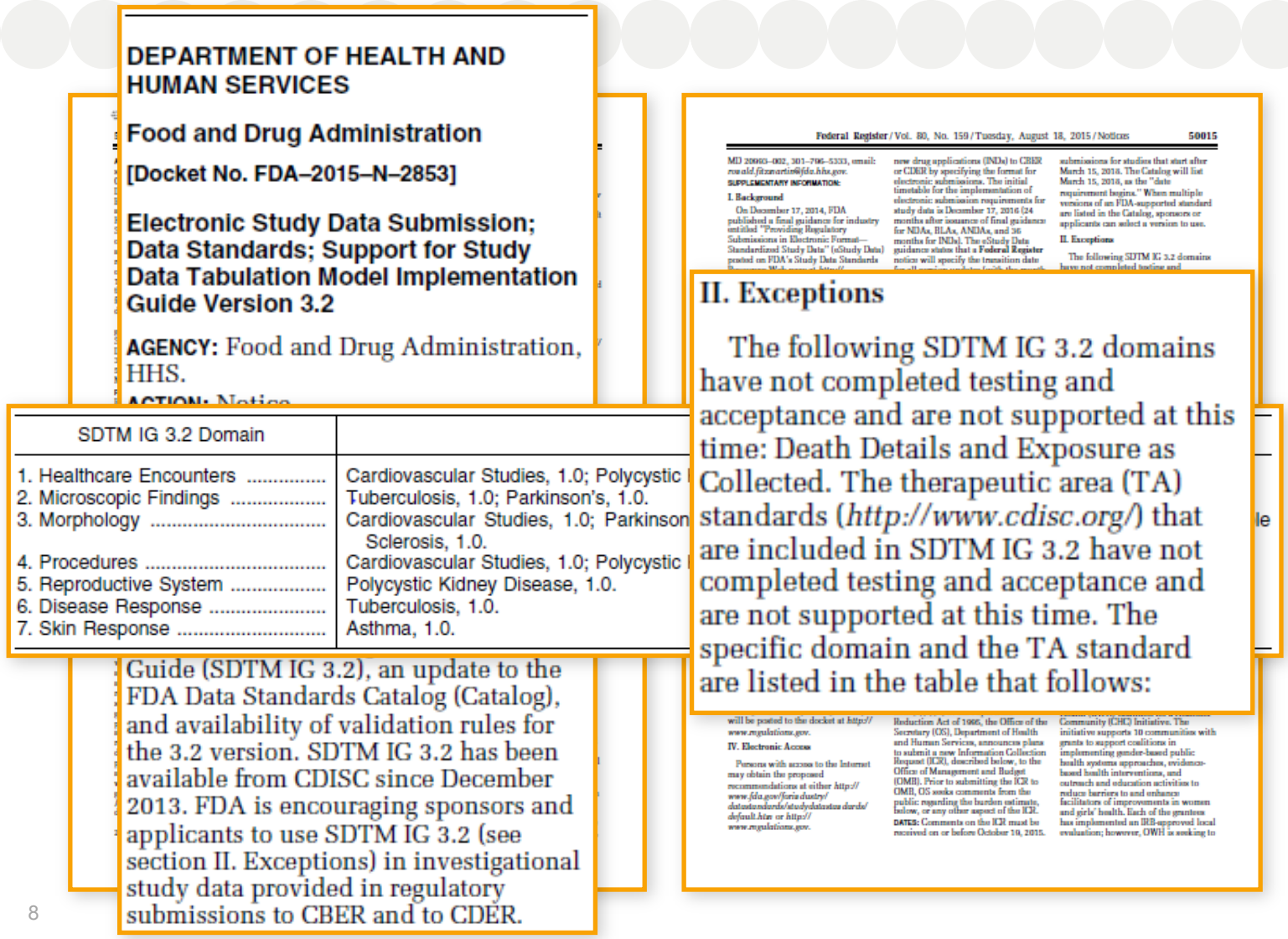
Guidance for Industry ***Providing Regulatory Submissions in Electronic Format – Standardized Study Data***

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov or CBER at cber.cdisc@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2015

FDA Acceptance SDTMIG v3.2 with TAUG Exceptions



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2015–N–2853]

Electronic Study Data Submission; Data Standards; Support for Study Data Tabulation Model Implementation Guide Version 3.2

AGENCY: Food and Drug Administration, HHS.

SDTM IG 3.2 Domain	
1. Healthcare Encounters	Cardiovascular Studies, 1.0; Polycystic
2. Microscopic Findings	Tuberculosis, 1.0; Parkinson's, 1.0.
3. Morphology	Cardiovascular Studies, 1.0; Parkinson
	Sclerosis, 1.0.
4. Procedures	Cardiovascular Studies, 1.0; Polycystic
5. Reproductive System	Polycystic Kidney Disease, 1.0.
6. Disease Response	Tuberculosis, 1.0.
7. Skin Response	Asthma, 1.0.

Guide (SDTM IG 3.2), an update to the FDA Data Standards Catalog (Catalog), and availability of validation rules for the 3.2 version. SDTM IG 3.2 has been available from CDISC since December 2013. FDA is encouraging sponsors and applicants to use SDTM IG 3.2 (see section II. Exceptions) in investigational study data provided in regulatory submissions to CBER and to CDER.

Federal Register / Vol. 80, No. 159 / Tuesday, August 18, 2015 / Notices 50015

II. Exceptions

The following SDTM IG 3.2 domains have not completed testing and acceptance and are not supported at this time: Death Details and Exposure as Collected. The therapeutic area (TA) standards (*http://www.cdisc.org/*) that are included in SDTM IG 3.2 have not completed testing and acceptance and are not supported at this time. The specific domain and the TA standard are listed in the table that follows:

- First announced in Federal Register notice August 18, 2015
- Access exceptions of several TAUG domains
- Death Details (DD) and Exposure as Collected (EC) not currently supported

FDA Data Standards Catalog Note Lists without Exceptions

FDA Data Standards Catalog v4.4 (08-17-2015) - Supported and Required Standards

This table contains a listing of the data exchange, file formats and terminology standards supported at FDA. These standards have gone through all the steps necessary to make this part of the regulatory review process, including posting of regulatory guidance documents and associated implementation guidelines and technical specifications. The submission of standardized data using any standard not listed, or to an FDA Center not listed, should be discussed with the Agency in advance. This catalog is incorporated by reference in the guidance to industry, *Providing Regulatory Submissions in Electronic format-Standardized Study Data (http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf)*.

Use	Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Regulatory Reference and Information Sources
Clinical study datasets	Study Data Tabulation Model (SDTM)	XPT	Interchange Standards Consortium (CDISC)	1.4	3.2	CDER, CBER	8/17/2015		03/15/2018 [1] 03/15/2019 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.3	3.1.3	CDER, CBER	12/01/2012		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.2	Version 3.1.2 Amendment 1	CDER, CBER	08/07/2013		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.2	3.1.2	CDER, CBER	10/30/2009		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1.1	3.1.1	CDER, CBER	Ongoing	01/28/2015			CDISC.org - SDTM
Clinical study datasets	Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.0	CDER, CBER	Ongoing		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - ADaM
Animal study datasets	Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1.2	3.0	CDER	06/13/2011		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SEND

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Therapeutic Area User Groups

Therapeutic Area User Guides (TAUGs) - Development

- The Coalition for Accelerating Standards & Therapies (CFAST) drives development of Therapeutic Area User Guides (TAUGs).
- Focus – identify core TA concepts and translate into CDISC standards
- SDTM mapping of key TA endpoints results in
  - New domains/variables
  - New control terminology
  - Modelling strategies
- Domains used in TAUGs are distributed across:
  - SDTMIG v3.2
  - SDTMIG Medical Devices v1.0
  - SDTMIG Associated Persons v1.0
  - TAUG draft domains not in any SDTMIG

Therapeutic Area User Guides (TAUGs) - Status

- Pipeline of TAUG release/updates

Year	2011	2012	2013	2014	2015	2016
TAUGs	1	4	7	9	12	10

- Projected publication timeline for upcoming TAUG releases/updates

Therapeutic Area	Timeline	Therapeutic Area	Timeline
Traumatic Brain Injury v1	Q4 2015	CV Imaging v1	Q2 2016
COPD v1	Q4 2015	Prostate Cancer v1	Q3 2016
ADaM Supplement to Diabetes v1	Q4 2015	Major Depressive Disorder	Q3 2016
Breast Cancer v1	Q1 2016	General Anxiety Disorder v1	Q3 2016
Diabetic Kidney Disease v1	Q1 2016	Bi-polar Disorder v1	Q3 2016
Tuberculosis v2	Q1 2016	Solid Organ Transplant	Q3 2016
Rheumatoid Arthritis v1	Q2 2016		

Available Therapeutic Area Standards

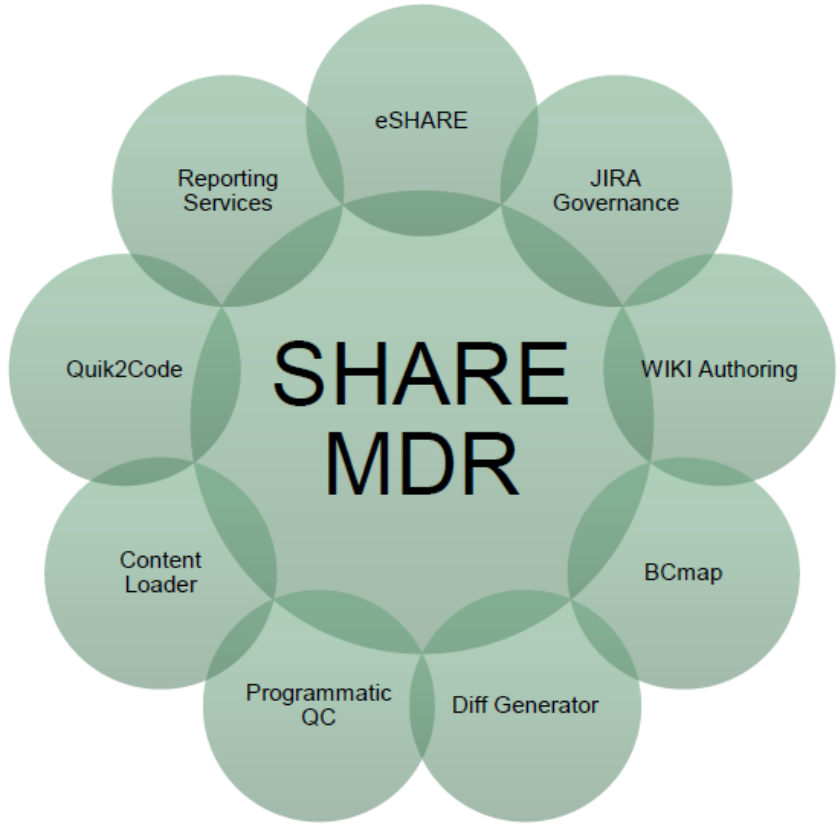
TA Standards	TA Concepts/Endpoints
Alzheimer's Disease v2	Clinical scales, Biomarkers
Asthma v1	Medical history, Pulmonary functions tests, Exacerbations of Asthma, QoL and composite outcomes, symptoms assessment
Cardiovascular v1	Cardiovascular and stroke endpoints, Imaging, data elements relevant to acute coronary care
Chronic Hepatitis C v1	Medical history, PRO, cirrhosis, progression of liver disease, AE & CM of special interest, HCV Viral load testing
Diabetes v1	Diabetes history, PRO, lab assessments
Dyslipidemia v1	Diagnosis, PRO, AE & CM of special interest, Imaging, treatment history, dietary
Influenza v1	Diagnosis, exposure, symptoms, medical history, AE & CM of special interest

Available Therapeutic Area Standards - continued

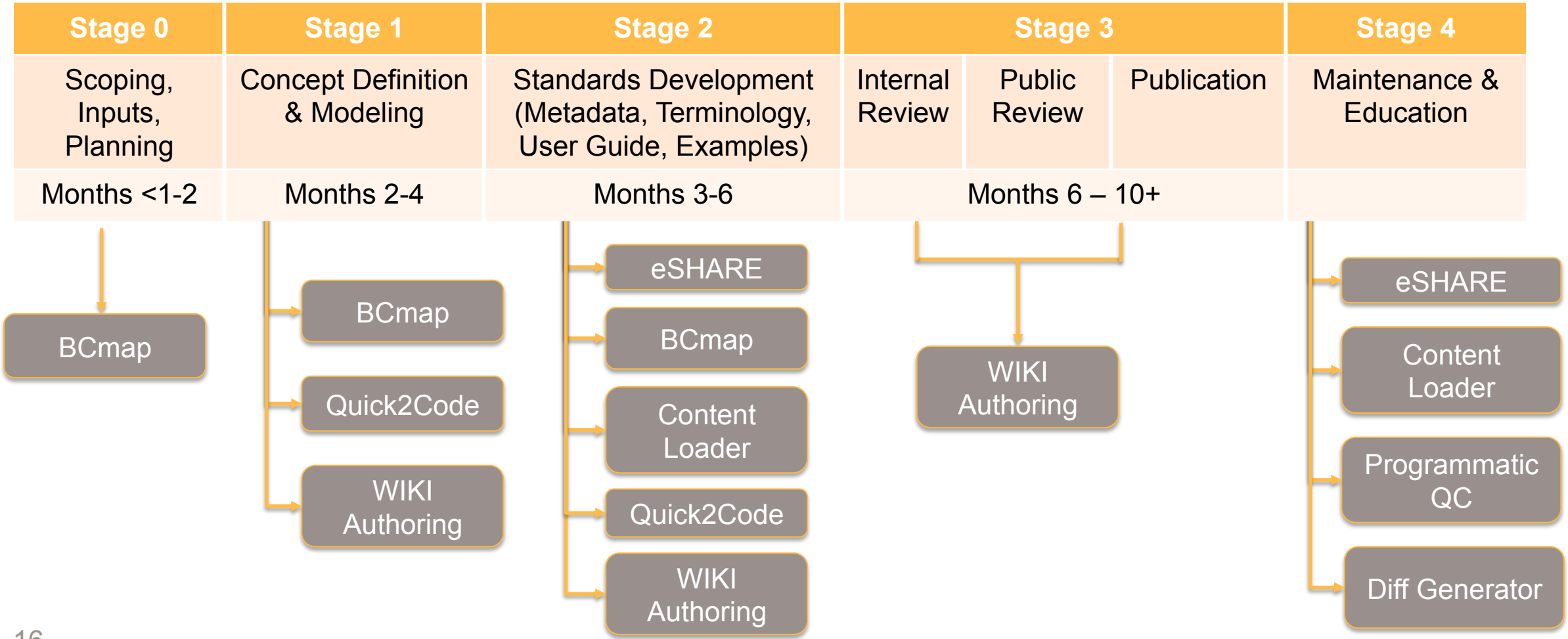
TA Standards	TA Concepts/Endpoints
Multiple Sclerosis v1	Disease course, assessment, Questionnaires
Pain v1	Pain conditions, areas of interest in acute/chronic pain, Questionnaires
Parkinson's Disease v1	Guidance on mapping strategy, ad-hoc SUPP, ad-hoc terminology
Polycystic Kidney Disease v1	Guidance on mapping strategy, ad-hoc SUPP, ad-hoc terminology
QT Studies v1	ECG related variables, dosing, PK & relevant pharmacogenomics data
Schizophrenia v1	Diagnosis, course of illness, family psychiatric history, psychiatric hospitalizations, rating scales
Tuberculosis v1	Guidance on mapping strategy, ad-hoc SUPP, ad-hoc terminology
Virology v2	Measurements of viral concentrations from in-vitro resistance testing, ad-hoc domains/variables

SHARE Ecosystem

- Reusable biomedical concept templates
  - BCmap
  - Quick2Code
  - Content Loader
- TA Specification – new variable/domain/CT
  - Content Loader
  - Diff Generator
- eSHARE – TA metadata published from SHARE MDR
  - WIKI Authoring
  - Programmatic QC
  - Diff Generator
- WIKI & JIRA Integration - publishing and standards governance
  - WIKI Authoring
  - JIRA Governance



Prostate Cancer TAUG Development and SHARE



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ADaM Oncology Sub-team Update & Handling RECIST

ADaM Oncology Sub-team Document Creation

- ADaM Oncology Sub-team includes members from Sponsor companies and CROs
- Will be creating a document similar to other supplemental ADaM documents (like ADTTE, ADAE, OCCDS)
- Document targeted for draft release in 2016
- “Provisional content” may be included for certain topics; anything that is “provisional” (i.e., not in the current ADaM IG) will be clearly documented as such
- NOTE: All Sub-team activity is subject to change

ADaM Oncology Sub-team Document Topics

- Current ***planned**** topics for discussion:
  - **ADSL** – include common baseline characteristics for oncology (e.g., baseline ECOG performance status)
  - **ADCYCLE** – analysis dataset for cycle start/stop dates, dosing start/stop dates within each cycle
    - Vertical structure, help avoid size explosion of ADSL
    - This dataset will be useful if, for example, AEs need to be slotted into cycles. As opposed to needing to carry many period start/stop dates (APxxSDT & APxxEDT up to the maximum # of cycles across patients) within ADSL.

** Subject to change*

ADaM Oncology Sub-team Document Topics

- Current ***planned**** topics for discussion:
  - **Labs** – National Cancer Institute Common Terminology Criteria (NCI-CTC) toxicity grading
    - *May get pulled out of oncology document and moved into its own separate document*
  - **Exposure** – parameters common to oncology trials (e.g. cumulative dose, dose intensity, dose delays)
  - **Survival analysis** – parameters common to oncology trials (e.g. overall survival [OS], progression-free survival [PFS], duration of response)
    - Will not be specifying algorithm/derivation rules, but rather suggesting naming conventions for PARAM/PARAMCD
  - **Best response** – based on RECIST criteria – like survival analysis, will mainly suggest naming conventions

** Subject to change*

ADaM Oncology Sub-team Document Contents

- Current ***planned**** sections underneath each topic:
  - Purpose
  - Background
  - Analysis results (expected to include a sample mock and analysis results metadata)
  - Variable metadata
  - Controlled terminology when proposed
  - Provisional content

** Subject to change*

Handling RECIST Response Evaluation Criteria In Solid Tumors

- Set of published rules that define when cancer patients improve ("respond"), stay the same ("stable") or worsen ("progression") during treatments.
- Both SDTM and ADaM have mechanisms to store RECIST Scores
  - SDTM may store algorithmically created scores created by the EDC system or Site personnel in SDTM.RS (Response)
    - Maybe used for Inclusion/Exclusion criteria
    - Considered Operationally derived
    - Collected data with minimal derivation
  - ADaM ADORS or TTE is more robust allowing for SAP directions and programming instructions
    - Imputations, Interpolations, Missing observations, etc.
    - Analysis Derived
- All the data in SDTM RS are collected in eCRF, but response data should be derived or check response data to determine the investigator calculated correctly

Operationally Derived (SDTM) vs. Analysis Derived (ADaM)

- Operationally Derived data is typically computed at the point of data capture or by data management systems during study conduct
  - Prior to making data available for analysis
  - Values not statistically adjusted
  - Stored in SDTM as part of a domain
  - May not be suitable for analyses due to lack of methods for statistical adjustment or selection
- Analysis Derived (ADaM) value typically computed after data capture
  - Associated with derivation logic specified by a statistician and SAP
  - Handling of missing or ill conditioned data
  - Operationally Derived may not equal the same Analysis Derived value
- In conclusion, derive the best responses in ADaM using tumor results from the TR domain and compare those against the responses provided by investigators in the RS domain within an ADaM structure

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Conclusion and Contact Information

Agenda – Standards Update on Oncology

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- CDISC SHARE Metadata Spec Project

ADaM Oncology Sub-team Update

- Suggested Analysis dataset structures
- Handling RECIST

Many Thanks!

Gaurab and Terek would like to thank Beth Seremula for providing content to this presentation from the ADaM Oncology subteam. Beth has been involved with standards for many years and presented on standards related topics including most recently a presentation on different approaches to the integration of data from SDTM or ADaM. She is actively involved in the ADaM team and ADaM Oncology subteam.

Questions?

Contact:

Terek Peterson, MBA

Senior Director, Global Statistical Standards

Terek.Peterson@Chiltern.com

Direct: +1 610 627 9436

Mobile: +1 484 560 8960

King of Prussia, Pennsylvania

USA

Contact:

Gaurab Chakraborty

Associate Director, Statistical Programming

Gaurab.Chakraborty@Chiltern.com

Direct: +91 80 4065 0413

Mobile: +91 96864 83145

Bengalore, Karnataka

India