Moving up! – SDTM v3.2 – What is new and how to use it

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ABSTRACT

December of 2013 the CDISC world blessed us with SDTM version 3.2. Now that the FDA has approved the use of the new version of the implementation guide and the requirement is on the horizon, we need to consider all that the new IG has in store for our clinical trials and what handling or considerations should be made for the noted exceptions. Don't be overwhelmed by the file size or the fancy, new format, this session will lay out the new IG in easy to understand ways and show you how to apply this to your studies today! It will cover new domains, significant changes to our existing domains and applied examples to walk you through how to transition to this new version. We will cover in depth bigger changes, such as the EX/EC adjustment, but will highlight even in the smaller changes to make sure you don't miss them as you become familiar with the new document. This session will have you SDTM v3.2 fluent in no time!

INTRODUCTION TO SDTM IG V3.2

SDTM IG v3.2 was released to the world in December 2013 containing many enhancements over previous versions. SDTM IG v3.2 was originally identified as SDTM IG v3.1.4 but after considering the broad scope and significance of the changes incorporated, a decision was made to release it as SDTM IG v3.2. One thing you may notice is that CDISC SDTM v1.4 and SDTM IG v3.2 no longer share the numbering alignment of previous versions like SDTM v1.3 and SDTM IG v3.1.3. Don't worry, this is not a mistake, the perceived synchronicity between SDTM and SDTM IG version numbers was never intentional. The SDTM and SDTM IG are meant to be independent documents versioned independently.

As mentioned, SDTM IG v3.2 has gone through a significant update affecting almost every section. In this paper we are going to focus on some of the major updates made, including: new IG format, new Domains, changes to existing domains and changes to controlled terminology. There are many minor changes that will not be within the scope of this paper but can be found in Appendix E – Revision History of SDTM IG v3.2.

NEW DOCUMENT FORMAT

SDTM IG v3.2 was converted from a single document to a PDF Portfolio, or a collection of multiple files assembled into an integrated PDF unit. Although not all PDF viewers can display a PDF portfolio, most current versions of Adobe Reader with Adobe Flash installed can utilize the PDF portfolios full functionality. We'll discuss the core requirements and alternative viewing options later in this paper.

Some of the major changes to the SDTM v3.2 structure:

- Section 1 – Section 4: a single document
- Section 5: a collection of smaller documents, one per domain
- Section 6: a collection of 3 sub-folders (one for each Observation Class), each containing individual documents (one per domain or sets of related domains)
- Section 7: a collection of smaller documents
- Section 8: a single document
- Appendices: a folder containing smaller documents, one per appendix (A through F)
- Every domain document will have consistent sub-sections:
    - Purpose – Description of intended use and related background (Purpose will match Controlled Terminology)
    - Specification – Table of variables and metadata
    - Assumptions – all clarifications, caveats, rules, exceptions, etc.
    - Examples

HOW TO USE THE PDF PORTFOLIO FORMAT
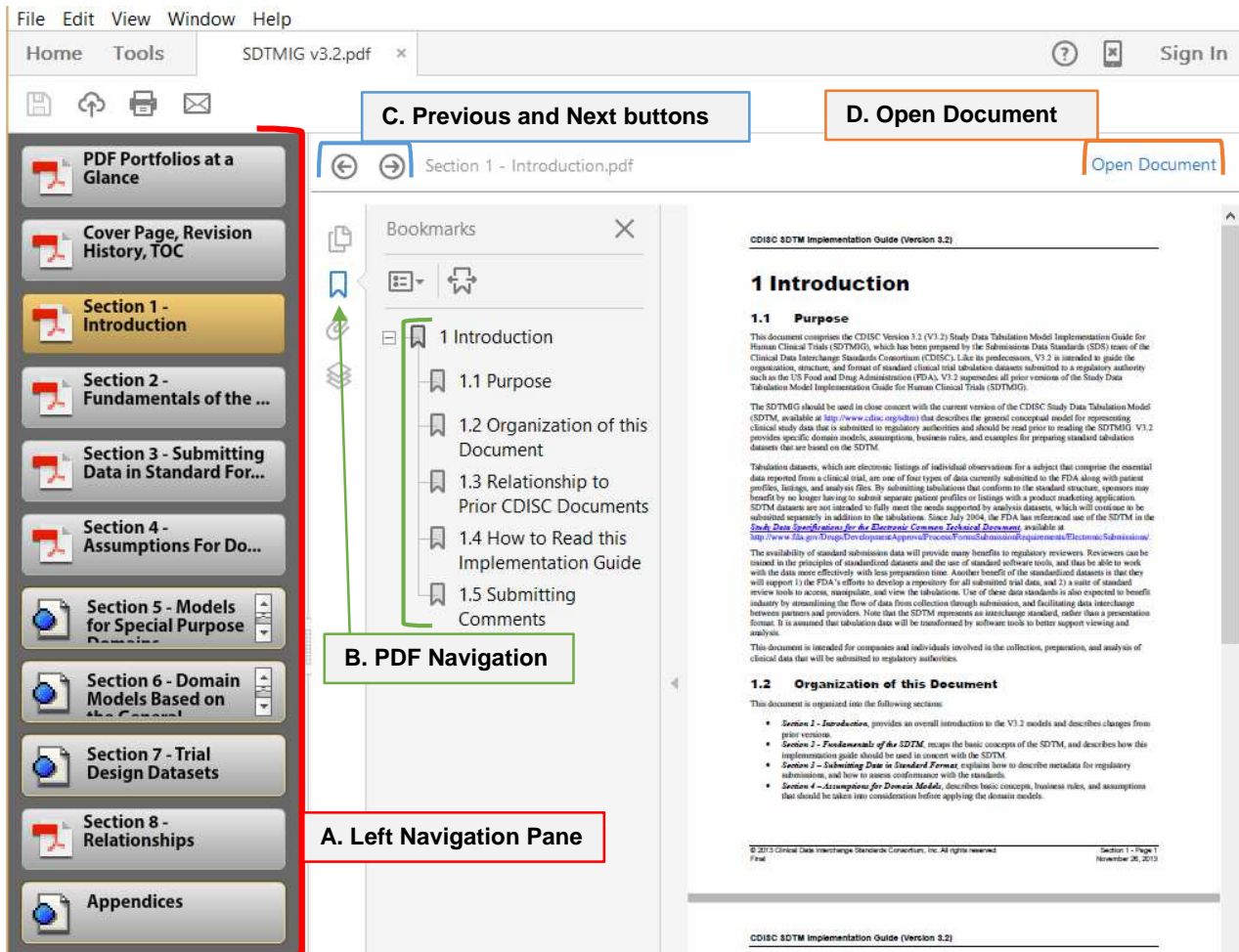
Display 1. SDTM IG v3.2 PDF Portfolio layout

A. Left Navigation Pane: Lists the files and folders included in the SDTM IG v3.2 PDF Portfolio. From here you can select the IG section or folder you want to review. If you click on a section, the corresponding PDF opens in the reader window. If you click on a folder, like Section 5, the left navigation pane will update with the PDFs within that folder. To navigate back to the main PDF navigation pane just click on the 'Home' button highlighted below.
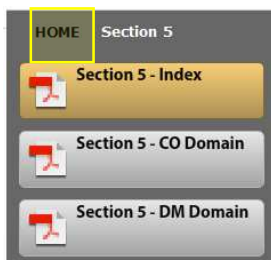
Display 2. SDTM IG v3.2 PDF Portfolio Section Home button

B. PDF Navigation: Files in PDF format have a navigation bar accessible by clicking the blue ribbon. The navigation bar will display the bookmarks within the current PDF.

    C.   Previous and Next buttons: Arrows that allow you to scroll through the files and folders included in the PDF Portfolio.

    D.   Open Document: Any file in PDF format can be opened and viewed separately.

How to navigate to find what you are looking for

Navigation within the PDF Portfolio is made easy and straightforward using the left navigation pane (A) and PDF navigation (B) outlined above. If there is a specific term or topic you need to review, the PDF portfolio still supports full search functionality.

You can search the PDF in 2 ways:

- Ctrl+F Search: This search option will search the currently open section for the term you specify. Simply click Ctrl+F, type in the term you are searching for and every page with the section you are looking at will be searched for the given term.
- Ctrl+Shift+F Search: This search option will search the entire integrated PDF portfolio for the term you specify. Simply click Ctrl+Shift+F, type in the term you are searching for and every page within entire integrated PDF portfolio IG will be searched for the given term.

Special versions of Adobe Reader and Adobe Flash Player are needed

To get the most out the SDTM IG v3.2 PDF Portfolio you need to have a PDF Viewer with Adobe Flash support and have Adobe Flash player installed on your system. Having a version of Adobe Reader of at least X is recommended but Adobe Reader DC is ideal. Note, whatever version you have, you have to have Adobe Flash player installed on your system also. Adobe Flash player is now a standalone program when downloading and installing Adobe Reader or any other PDF Viewer. Having the Adobe Flash web browser plugin is not the same as Flash player so you'll need the additional installation in order to utilize PDF Portfolios full functionality.

How to navigate if you cannot view in intended layout

If you are unable to view the SDTM IG PDF Portfolio with your current system configuration you can download a single PDF Version from the CDISC website (www.CDISC.org/sdtm) which will open in any PDF viewer. Although the single file PDF has bookmarks like the previous versions, you will not be able to capitalize on the portfolio's advanced navigation features.

NEW DOMAINS

SDTM IG v3.2 introduces 11 new domains across 5 sections, including: Section 6.1 (Interventions), Section 6.2 (Events), Section 6.3 (Findings), Section 6.4 (Findings About) and Section 7.4 (Trial Design). We'll provide a high-level overview of the new domains. For a more detailed description and examples refer to the relative section of the SDTM IG v3.2.

SECTION 6.1 (INTERVENTIONS)

Exposure as Collected (EC)

The Exposure as Collected domain model reflects protocol-specified study treatment administrations, as collected. The expected data structure for EC is one record per protocol-specified study treatment, per collected-dosing interval, per subject, per mood. EC reflects protocol-specified study treatment administrations, as collected on the CRF. EC can used in all cases where collected exposure information cannot be directly represented in EX. For example, administrations not collected in protocol-specified units (tablets instead of mg) would be mapped to EC not EX. If the entire EC dataset is an exact duplicate of the entire EX dataset, then EC is optional and at the sponsor's discretion.

Procedures (PR)

The Procedures domain model reflects collected details describing a subject's therapeutic and diagnostic procedures. The expected data structure of PR is one record per recorded procedure per occurrence per subject. PR reflects collected details describing a subject's therapeutic and diagnostic procedures.

Example procedures include:

- Disease screening (e.g., mammogram, pap smear)
- Endoscopic examinations (e.g., arthroscopy, diagnostic colonoscopy, therapeutic colonoscopy)
- Diagnostic tests (e.g., amniocentesis, biopsy, catheterization, cutaneous oximetry, finger stick, fluorophotometry, imaging techniques (e.g., DXA scan, CT scan, MRI), phlebotomy, pulmonary function test, skin test, stress test)

- Therapeutic procedures (e.g., ablation therapy, catheterization, cryotherapy, mechanical ventilation)
- Surgical procedures (e.g., curative surgery, diagnostic surgery, palliative surgery, therapeutic surgery, prophylactic surgery, resection, stenting, hysterectomy, tubal ligation, implantation)

The protocol design should pre-specify whether procedure information will be collected and all collected procedures are represented in this domain. Measurements obtained from procedures captured in the PR domain will be captured in their respective Findings domain.

SECTION 6.2 (EVENTS)

Healthcare Encounters (HO)

The Healthcare Encounters domain model includes inpatient and outpatient healthcare events (e.g., hospitalizations, nursing home stay, rehabilitation facility stays, ambulatory surgery). The expected data structure of HO is one record per healthcare encounter per subject. HO will represent the collected data about the location or place of the healthcare encounter, date of admission and date of discharge.

SECTION 6.3 (FINDINGS)

Death Details (DD)

The Death Details domain model will contain supplemental data that is collected when a death occurs. It is not intended to replace existing data collection practices around deaths nor introduce new requirements in data collection not already indicated as Good Clinical Practice or defined in regulatory guidelines. DD does provide a consistent place within the SDTM model to map information that was not clearly defined before.

Immunogenicity Specimen Assessment (IS)

The Immunogenicity Specimen Assessment domain model is intended to be used only for data collected regarding the immunogenic potential of materials under study. The expected data structure of IS is one record per test per visit per subject. IS holds data representing whether a therapy provoked/caused/induced an immune response. The response can be negative, positive or represent the concentration of an immune response marker.

Microscopic Findings (MI)

The Microscopic Findings domain model provides a record for each microscopic finding observed. MI follows the data structure of one record per finding per specimen per subject. MI holds findings resulting from the microscopic examination of tissue samples that were prepared with a stain. Careful consideration should be taken as some specimen examinations could be mapped to other domains. For example, biomarkers assessed by histologic or histopathological examination (by employing cytochemical / immunocytochemical stains) will be stored in the MI domain. However, examinations of cells in fluid specimens should be mapped to LB if the fluid collection occurred in blood or urine.

Morphology (MO)

The Morphology domain model provides microscopic morphology data (e.g. size, shape, color) of specimens observed through the naked eye or via procedures. Many morphology observations can be made from a given sample. MO follows the data structure of one record per Morphology finding per location per time point per visit per subject.

Reproductive System Findings (RP)

The Reproductive System Findings domain model captures all Reproductive information related to a subject. RP follows the data structure of one record per Reproductive System Finding per time point per visit per subject. In previous versions of the SDTM IG, reproductive information was mapped to various SDTM domains. RP was created so all reproductive related information for a subject could be consolidated into one domain. RP contains information like the subject's reproductive ability, reproductive history (e.g. number of previous pregnancies, number of births, etc) but does not contain information about reproductive medications.

Subject Status (SS)

Subject Status domain model contains data relating to general subject characteristics that are evaluated periodically to determine if they have changed. SS follows the data structure of one record per finding per visit per subject. SS does not contain details about the circumstances of a subject's status SS contains information about the collection of the subject's status including: collection date, the status question and the status response.

SECTION 6.4 (FINDINGS ABOUT)

Skin Response (SR)

The Skin Response domain model contains dermal responses to antigens normally assessed from skin-pricks. SR follows the data structure of one record per test per visit per subject. Different dermal response tests can be used to evaluate the response of different antigens at varying concentrations.

SECTION 7.4 (TRIAL DESIGN)

Trial Disease Assessments (TD)

The Trial Disease Assessments domain model provides information on the protocol-specified disease assessment schedule. The defined scheduled is then used to determine actual occurrence of efficacy assessment in order to determine assessment compliance. The expected data structure of TD is one record per planned constant assessment period. Although TD has limited utility within oncology studies it makes possible an evaluation of 'assessment time bias' for studies with progression-free survival (PFS) endpoints. TD model was developed specifically studies using RECIST criteria and where an assessment time bias analysis is appropriate.

CHANGES TO EXISTING DOMAINS

Many domains were updated in some form or another in the SDTM IG v3.2. These updates include changes to the CDISC Notes and Definitions verbiage, Controlled Terminology, Variables and Variable metadata. All changes can be found in Appendix E – Revision History of the IG. We'll highlight some of the more notable changes below.

NEW CONTROLLED TERMINOLOGY

There are several variables that had control terminology either added or updated.

Action	Domain	Variable	Attribute (updated)	Action	Domain	Variable	Attribute (updated)
Added	AE	AEDECOD	MedDRA	Added	PE	PEEVAL	(EVAL)
Updated	AE	AEENRTPT	(STENRF)	Added	PE	PEMETHOD	(METHOD)
Updated	CE	CEENRTPT	(STENRF)	Updated	PP	PPORRESU	(PKUNIT)
Updated	CE	CESTRTPT	(STENRF)	Added	PP	PPSPEC	(SPECTYPE)
Added	DS	EPOCH	(EPOCH)	Updated	PP	PPSTRESU	(PKUNIT)
Added	DV	EPOCH	(EPOCH)	Added	PP	PPTESTCD	(PKPARMCD)
Updated	MH	MHENRTPT	(ENRTPT)	Added	PP	PPTEST	(PKPARM)
Added	FA	FAEVAL	(EVAL)	Added	QS	QSCAT	(QSCAT)
Added	FA	FATESTCD	(FATESTCD)	Added	QS	QSTESTCD	(QSTESTCD)
Added	FA	FATEST	(FATEST)	Added	QS	QSTEST	(QSTEST)
Added	LB	LBMETHOD	(METHOD)	Updated	SC	SCTESTCD	(SCTESTCD)
Added	LB	LBNRIND	(NRIND)	Added	SC	SCTEST	(SCTEST)
Added	LB	LBSPCCND	(SPECCOND)	Updated	CM	CMENRTPT	(STENRF)
Added	LB	LBSPEC	(SPECTYPE)	Updated	CM	CMSTRTPT	(STENRF)
Added	LB	LBSTRESC	(LBSTRESC)	Added	EX	EPOCH	(EPOCH)
Added	MB	MBMETHOD	(METHOD)	Updated	SU	SUENRTPT	(STENRF)
Added	MB	MBSPCCND	(SPECCOND)	Updated	SU	SUSTRTPT	(STENRF)
Added	MB	MBSPEC	(SPECTYPE)	Updated	RELREC	RELTYPE	(RELTYPE)
Added	MS	MSMETHOD	(METHOD)	Updated	DM	COUNTRY	(COUNTRY)
Added	MS	MSRESCAT	(MSRESCAT)	Added	SE	EPOCH	(EPOCH)

Added	PC	PCMETHOD	(METHOD)	Added	TA	EPOCH	(EPOCH)
Added	PC	PCSPCCND	(SPECCOND)				
Added	PC	PCSPEC	(SPECTYPE)				

Table 1. List of changes to SDTM IG v3.2 Controlled Terminology.

Additionally, all controlled terminology links in the Domain/Dataset Specification table where updated to link to the NCI Enterprise Vocabulary Service website. CDISC partners with NCI EVS to develop and support controlled terminology for all CDISC foundational standards (SDTM, CDASH, ADaM, SEND) and all CFAST Therapeutic Area standards. CDISC Controlled Terminology is maintained and distributed as part of NCI Thesaurus and is available for direct download in Excel, text, odm.xml, pdf, html and OWL/RDF formats.

EXPOSURE (EX)

EX has been updated to better comply with the new EX/EC interventions model. EX represents the records details of a subject's exposure to protocol-specified study treatment so it will capture records for exposure administrations done per protocol.

Notable changes to EX:

- EXENDTC core was update from Permissible to Expected
- New variables: EXDIR, EXFAST, EXLAT, EXLNKGRP, EXLNKID, EXREFID, EXRFTDTC
- Removed Variables: EXVAMT, EXDOSTOT, EXVAMTU, EXTRTV, TAETORD

SU

Notable changes to SU:

- Changes to CDISC Notes and Definitions verbiage for SUCLAS, SUDOSTOT, SUDOSTXT and SUDOSU.
- Roles for SUDOSFRM and SUPRESP was updated from Variable Qualifier to Record Qualifier

AE

Notable changes to AE:

- Changes to CDISC Notes and Definitions verbiage for AEACN, AEDECOD, AELOC, AEREFID, AEREL and AETOXGR.
- Role for AEPRESP was updated from Variable Qualifier to Record Qualifier

MH

Notable changes to MH:

- Changes to CDISC Notes and Definitions verbiage for MHDECOD, MHREASND and MHSTAT
- Role for MHPRESP was updated from Record Qualifier to Variable Qualifier of --TERM

EG

Notable changes to EG:

- New variable: EGLEAD
- Removed Variable: EGLOC

MB

Notable changes to MB:

- Changes to CDISC Notes and Definitions verbiage for MBLOC, MBMETHOD and MBORRES

PC

Notable changes to PC:

- PCSPEC core was update from Required to Expected
- Changes to CDISC Notes and Definitions verbiage for PCDRVFL
- Added Variable: PCULOQ

PP

Notable changes to PP:

- Changes to CDISC Notes and Definitions verbiage for PPTESTCD and PPTEST
- Added Variable: PPENINT and PPSTINT

VS

Notable changes to VS:

- Changes to CDISC Notes and Definitions verbiage for VSLOC and VSTPT
- Added Variable: VSLAT

TV

Notable changes to TV:

- Changes to CDISC Notes and Definitions verbiage for ARM and VISITDY

DISCUSSION OF FDA ACCEPTANCE OF SDTM IG V3.2

In August 2015, the FDA announced support and availability of validation rules for CDISC SDTM IG v3.2. They encouraged sponsors and applicants to use SDTM IG 3.2 in investigational study data provided in regulatory submissions to the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). The transition date for support of CDISC STDM IG v3.2 is March 15, 2017. Although SDTM IG v3.2 is currently supported and sponsors or applicants are encouraged to begin using it, the new version will only be required in submissions for studies that start after March 15, 2018. The FDA Data Standards Catalog will list March 15, 2018, as the date SDTM IG v3.2 implementations requirement begins. At that time, if the FDA Data Standards Catalog lists multiple versions of an FDA-supported standard, sponsors or applicants can select a version to use.

NOTED EXCEPTIONS TO FDA ACCEPTANCE

Although the FDA announced support of SDTM IG v3.2, not all domains are supported at this time since they have not completed the testing and acceptance process. Death Details and Exposure as Collected as currently not fully supported by the FDA at this time. Additionally, the therapeutic area standards included in SDTM IG v3.2 have not completed testing and acceptance and are not supported at this time.

The specific domain and the therapeutic area standard are listed in the table that follows:

SDTM IG 3.2 Domain	TA User guide
Healthcare Encounters	Cardiovascular Studies, 1.0; Polycystic Kidney Disease, 1.0; Asthma, 1.0.
Microscopic Findings	Tuberculosis, 1.0; Parkinson's, 1.0.
Morphology	Cardiovascular Studies, 1.0; Parkinson's, 1.0; Polycystic Kidney Disease, 1.0; Alzheimer's, 1.0; Multiple Sclerosis, 1.0.
Procedures	Cardiovascular Studies, 1.0; Polycystic Kidney Disease, 1.0; Alzheimer's, 1.0.
Reproductive System	Polycystic Kidney Disease, 1.0.
Disease Response	Tuberculosis, 1.0.
Skin Response	Asthma, 1.0.

Table 2. Therapeutic area exceptions

CONCLUSION

There were many enhancements to the SDTM IG when v3.2 was released in December 2013. The new PDF Portfolio format was a massive improvement to the overall flow and structure of the IG. Although it may be intimidating at first glance and some additional software may be required, once you acclimate yourself to the new layout some benefits should be apparent. SDTM IG v3.2 introduced 11 new domains across 5 sections. These new domains allow more consistent mapping across studies for items that did not have an apparent home before. They provide direct mapping for some items that may have been mapped to different supplemental domains across studies while giving a more rigid structure for the future. Several domains had updates to their CDISC Notes and Definitions verbiage, Controlled

Terminology, Variables or Variable metadata. All changes are conveniently summarized in Appendix E – Revision History of the IG. The FDA encouraged sponsors and applicants to use SDTM IG v3.2 in investigational study data provided in regulatory submissions in August 2015. Considering they also announced it will be required in submissions for studies that start after March 15, 2018, there is no better time than the present to implement SDTM IG v3.2 changes.

REFERENCES

FDA Data Standards Catalog v4.4

Available at: www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm340684.xlsx

CDISC Study Data Tabulation Model (SDTM) v1.4, Study Data Tabulation Model Implementation Guide (SDTMIG)
Available at: http://www.cdisc.org/sdtm

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