

## Are you ready for SEND?

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### ABSTRACT

From December 2016 onwards, according to the US Food and Drug Administration (FDA) binding guidance, nonclinical data must be submitted in SEND standardized electronic format. This paper explains what it takes for an organization with a broad knowledge of SDTM to be able to handle nonclinical data and provide SEND datasets for submission.

### INTRODUCTION

The reality of distributed workflow across multiple organizations makes data harmonization critical for submitting compliant data to Regulatory Authorities. It is important that companies already start to think about how SEND will be implemented in their organization. Therefore it is good to know where SEND comes from and what the pitfalls might be, as well as the advantages to using SEND.

### WHAT IS SEND?

SEND = **S**tandard for **E**xchange of **N**onclinical **D**ata

SEND is an implementation of the Study Data Tabulation Model (SDTM)

You can compare SEND Implementation Guide (SENDIG) with SDTM Implementation Guide (SDTMIG) for clinical trials; SEND is used for preclinical studies (Animal testing).

The latest version of the CDISC SEND Implementation Guide can be found on the CDISC website:

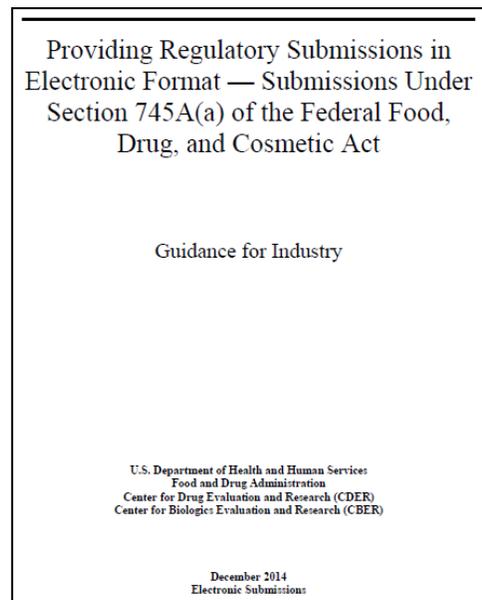
<http://cdisc.org/send>

The CDISC SEND Implementation Guide Version 3.0 is intended to guide the organization, structure, and format of standard nonclinical tabulation datasets for interchange between organizations such as sponsors and CROs and for submission to the US Food and Drug Administration (FDA). Version 3.0 of the SENDIG in the current production version and is designed to support single-dose general toxicology, repeat-dose general toxicology, and carcinogenicity studies. The SENDIG is based upon, and should be used in close concert with Version 1.2 of the CDISC Study Tabulation Model (SDTM).

### WHY NOW?

The FDA has published binding guidance documents regarding the submission of nonclinical data. The bottom line is that from December 2016 onwards nonclinical data must be submitted in SEND standardized electronic format according to the FDA binding guidance:

Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act (17DEC2014), as shown in Fig. 1.



## CDISC STANDARDS

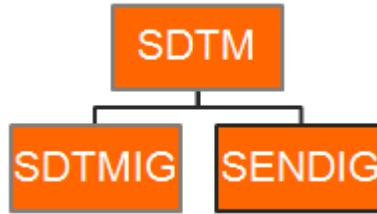


Fig. 2: SDTM standard

Luckily the SEND Implementation Guide finds its foundations in the SDTM standard. Both SDTMIG and SENDIG use the same model, SDTM, as shown in Fig. 2.

This implies that the knowledge gained and the tools built for implementing SDTM in clinical trials can be used to a great extent for the implementation of SEND for nonclinical data as well. In this way organizations can deliver high quality datasets from the start. Relatively small efforts are needed to implement the necessary updates and some processes will need to be adapted to be able to provide SEND compliant data.

### TOOLS AND PROCESSES

Here is a small overview of validated/automated processes (assuming those processes are already in-house) that could be used for SEND as well.

#### ANNOTATION TOOL

This is a tool for uploading the PDF-version of your CRF and creating your annotations. Every trial is linked to a specific standard, a specific implementation of SDTM or SEND. E.g. several sponsors can have different specifications for the annotations and work with their own implementation of SDTM or SEND.

The annotation tool knows exactly which look and feel to apply to the annotations (color, font, font size), which domains and variables can be used, which controlled terminology is available.

#### CONVERSION PROCESS

This process enables you to map, merge and convert source data such as: EDC, third party data, raw data files, etc to a specific standard, e.g. different CDISC SDTMIG versions or a sponsor specific implementation of SDTMIG. It also enables you to schedule/follow-up the complete conversion process. E.g. Schedule the download and conversion of data to the specific standard overnight.

#### TRANSFERS OF DATASETS

At different time points in the course of a study the sponsor may require datasets. The process of transfer of datasets allows you to create datasets and send them out to the sponsor. The process should allow you for example to send out draft datasets from the TEST environment or send only a sub selection of data because of an interim analysis or the full SDTM datasets which can be used for submission.

#### FORMAT OF TRANSFERRED DATASETS

The data should eventually end up in datasets in order to be able to exchange them. Different formats of datasets may be required depending on the purpose. For example during the course of a study SAS® datasets are used in our organization to exchange data. On the other hand, for submission purposes XPT or Dataset-XML format is used.

#### CREATION OF DEFINE METADATA

This tool allows you to create a define.xml and/or a define.pdf file based on the metadata of your datasets.

#### SDTM CHECKS

These are checks that will validate your data, metadata, define.xml against the implementation guide used. Because SENDIG is also based on SDTM, these checks could easily be extended to for SEND. E.g. the OpenCDISC Community tools already contain rules for SEND v3.0.

## DIFFERENCES BETWEEN SEND & SDTM

Differences between the implementation of SDTM and SEND may have an impact on those processes and tools and may require updates. Observations about study subjects are normally collected for all subjects in a series of domains. A domain is defined as a collection of logically related observations with a common topic. The logic of the relationship may pertain to the scientific subject matter of the data or to its role in the trial. Each domain is represented by a single dataset. Since both SDTMIG and SENDIG are an implementation of the same model, SDTM, they are based on the same fundamental principles:

- General observation classes
  - Findings
  - Interventions
  - Events
- Special Purpose
- Relationships
- Trial Design domains

## SENDIG V3.0 DOMAIN MODEL

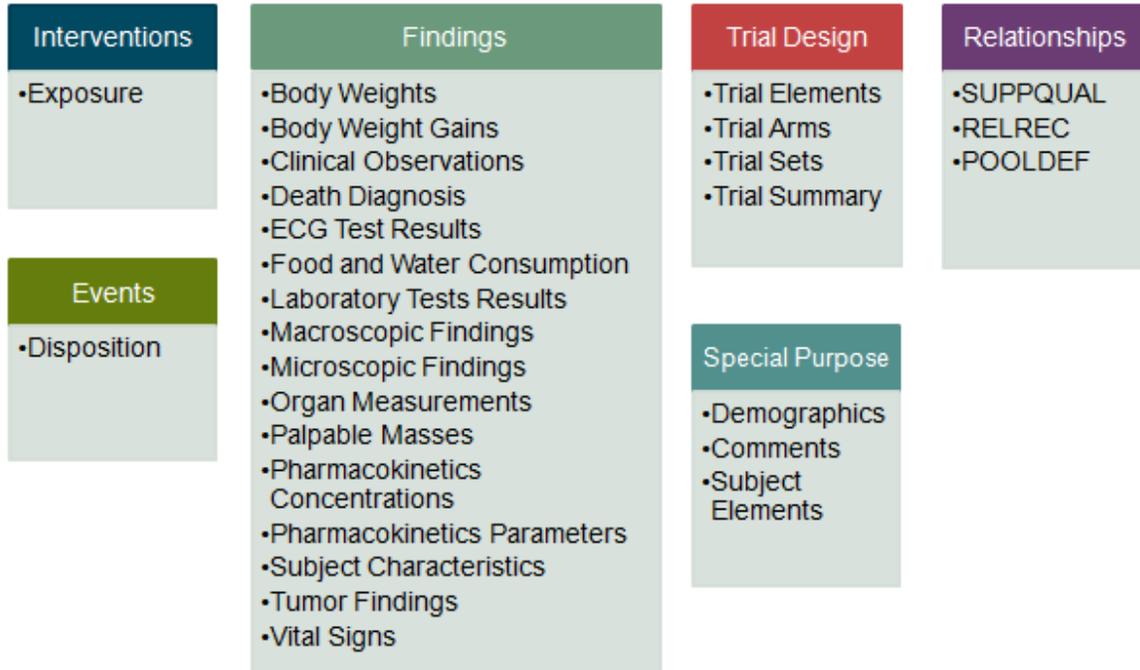


Fig. 3: SENDIG v3.0 domain model

In Fig. 3 the SEND standard domain models are shown. If you are familiar with the SDTM standard domain models, you will discover some similarities and differences between the two models. An overview of all the standard domains for both SDTM and SEND is shown in fig. 4. In the middle you can find the common domains.

# SDTM & SEND DOMAINS

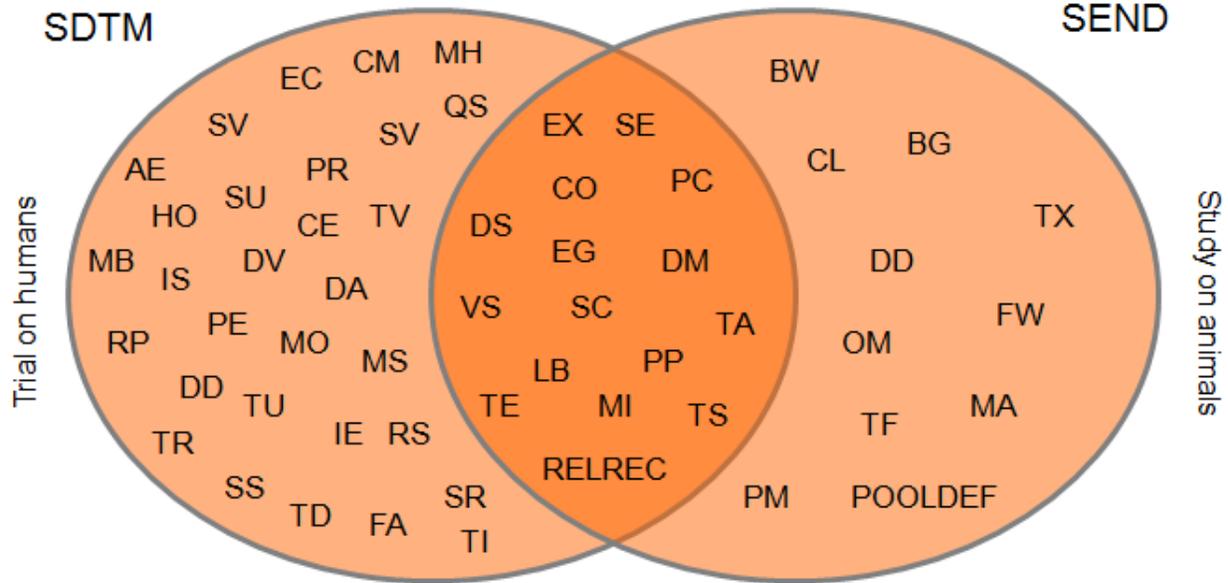


Fig. 4: SDTM & SEND domains

## TRIAL DESIGN

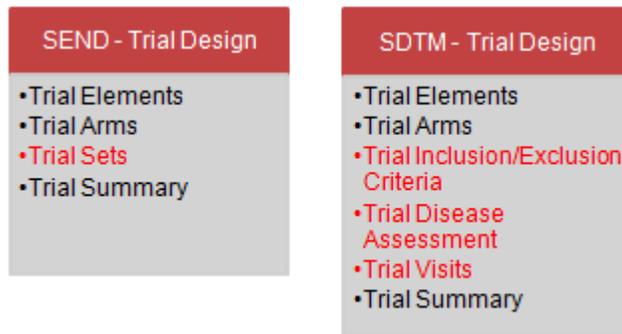


Fig. 5: Trial Design

In SENDIG there is no Trial Visits (TV), Trial Inclusion/Exclusion Criteria (TI) or Trial Disease Assessment (TD) domain, as shown in Fig. 5. However, a new domain Trial Sets (TX), which is not present in SDTMIG, is introduced.

The Trial Sets domain enables you to further subdivide ARM's into different sets. Or group different ARM's together with the Sponsor Defined Group Code (SPGRPCD). As shown in Fig. 6, ARM with ARMCD = 1 is subdivided in 2 sets with SETCD = 1 and SETCD = 1.TK. The two sets are grouped together with the SPGRPCD = 1.

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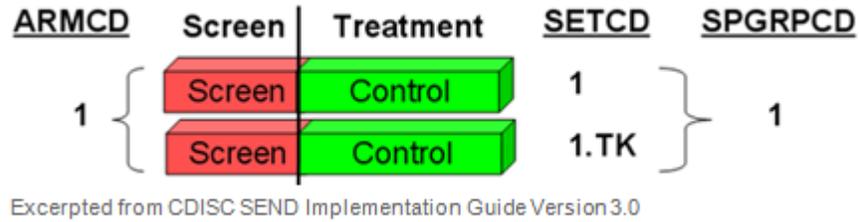


Fig. 6: Trial Sets (TX)

## SUBJECT POOLING



Fig. 7: POOLDEF

As shown in Fig.7, the domain POOLDEF is introduced in the Relationships class of SENDIG.

In nonclinical studies it is common that a single finding may be captured for multiple subjects. The SENDIG specification handles this by introducing pools. The use of a POOLID column has been introduced to the LB, FW, PC, and CL domains to support subject pooling in conjunction with the POOLDEF.

POOLID and USUBJID are mutually exclusive. When POOLID is used, USUBJID will be null and if a USUBJID is recorded, the POOLID will be null.

Note that POOLID values are unique for a given set of subjects. While the same value of POOLID may not be re-used to refer to different sets of subjects, different POOLIDs may be used to refer to the same set of subjects.

A Pool is defined as a set of subjects or practically speaking a cage of multiple animals. A set of subjects is defined in the POOLDEF domain. As shown in Fig 8, the POOLDEF domain consists of 2 pools with POOLID = CAGE1 P1 and CAGE1 P2. Any change in the population of subjects will result in a new POOLID. In this example a new pool had to be created because USUBJID = ABC1-1002 was removed from pool with POOLID = CAGE1 P1.

Row	STUDYID	POOLID	USUBJID
1	ABC1	CAGE1 P1	ABC1-1001
2	ABC1	CAGE1 P1	ABC1-1002
3	ABC1	CAGE1 P1	ABC1-1003
4	ABC1	CAGE1 P2	ABC1-1001
5	ABC1	CAGE1 P2	ABC1-1003

Excerpted from CDISC SEND Implementation Guide Version 3.0

Fig. 8: POOLDEF example

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## TUMOR.XPT

The Tumor.xpt datasets is a dataset that is composed of data from other SEND domains. Domains required for creation tumor.xpt file:

- DM (Demographics)
- DS (Disposition)
- EX (Exposure)
- MI (Microscopic Findings)
- TF (Tumor Findings)
- TX (Trial Sets)

At this moment according to regulatory guidelines for the submission of carcinogenicity data, the tumor.xpt file is expected at submission. The long term intent is to no longer require the tumor.xpt at submission where you already have these datasets available.

Fig. 9 shows how the TUMOR.XPT is composed by the Mapping of SEND variables to TUMOR.XPT variables.

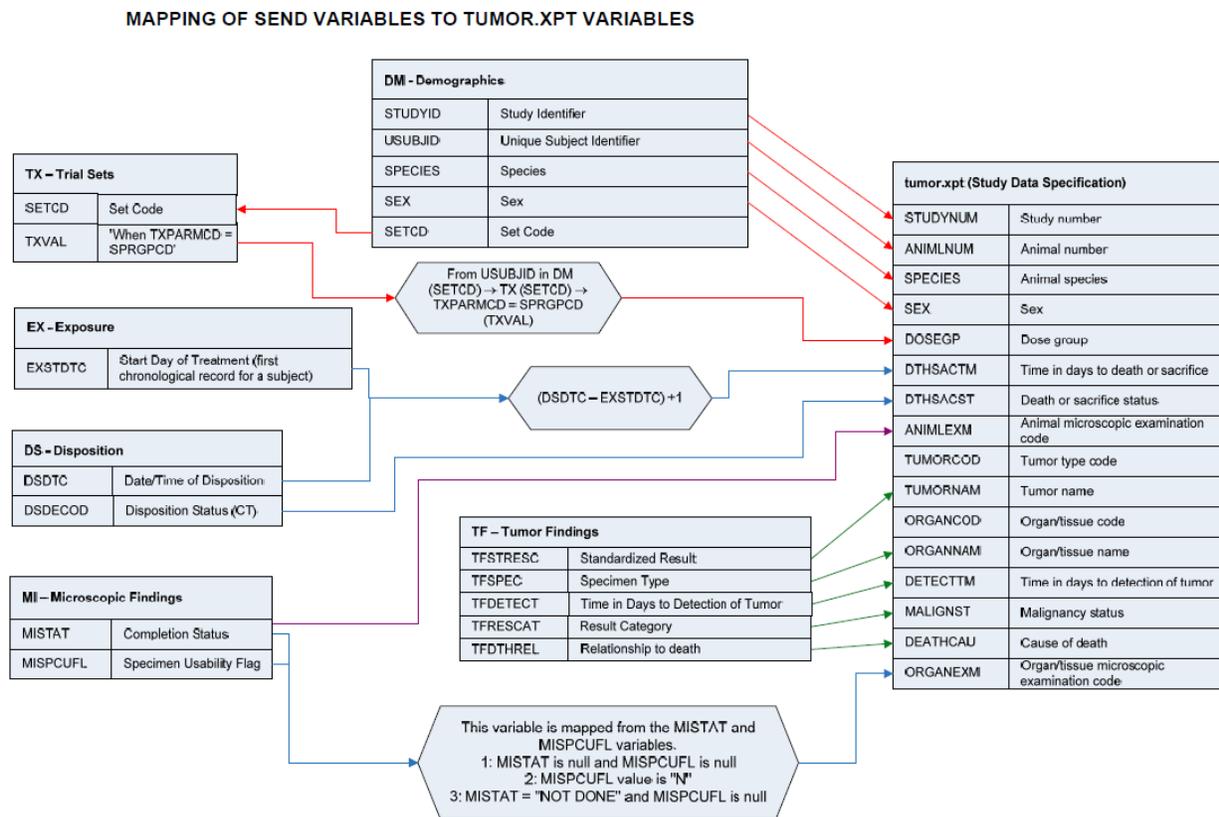


Fig. 9: Mapping of SEND variables to TUMOR.XPT variables

Excerpted from CDISC SEND Implementation Guide Version 3.0

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## DM DIFFERENCES

SEND - Demographics		SDTM - Demographics	
•STUDYID	•AGETXT	•STUDYID	
•DOMAIN	•AGEU	•DOMAIN	•AGEU
•USUBJID	•SEX	•USUBJID	•SEX
•SUBJID	•SPECIES	•SUBJID	
•RFSTDTC	•STRAIN	•RFSTDTC	
•RFENDTC	•SBSTRAIN	•RFENDTC	
		•RFXSTDTC	•RACE
		•RFXENDTC	•ETHNIC
	•ARMCD	•RFICDTC	•ARMCD
	•ARM	•RFPENDTC	•ARM
		•DTHDTC	•ACTARMCD
		•DTHFL	•ACTARM
•SITEID		•SITEID	•COUNTRY
		•INVID	•DMDTC
		•INVNAM	•DMDY
•BRTHDTC	•SETCD	•BRTHDTC	
•AGE		•AGE	

Fig. 10: Demographics

Fig. 10 shows the difference between the demographics domain for SEND and SDTM. In SEND neither DTHDTC nor DTHFL is used. The date of death is stored in DS. The AGETXT variable can be used in SEND if you don't know the exact age of the animal. No RACE information is present in SEND, instead SPECIES, STRAIN and SBSTRAIN is used. Next to the ARM information, the ARM set (SETCD) can be specified.

In SEND supplemental qualifiers are only used for general observation domains (Events, Interventions or findings), not for Special Purpose domains. Therefore, in SEND, the DM domain cannot have a SUPPDM domain.

## VISITS

SEND - Special Purpose	SDTM - Special Purpose
•Demographics	•Demographics
•Comments	•Comments
•Subject Elements	•Subject Elements
	•Subject Visits

Fig. 11: Subject Visits

In SEND only the planned study day variable is used: VISITDY (no VISITNUM/VISIT). As shown in Fig. 11, Subject Visits (SV) domain is not present in SEND.

## CONCLUSION

The SEND format will become necessary for submitting nonclinical data from December 2016 onwards. Luckily SEND finds its foundations in the SDTM standard and therefore SDTM knowledge gained and tools built can be used to a great extent. Some specific SEND – SDTM differences might trigger updates.

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### REFERENCES

CDISC Standard for Exchange of Nonclinical Data Implementation Guide (Version 3.0)  
Study Data Tabulation Model Implementation Guide: Human Clinical Trials Version 3.2  
Study Data Tabulation Model (SDTM) V1.2

### CONTACT INFORMATION

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