STANDARD FOR EXCHANGE OF NONCLINICAL DATA

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Introduction to SEND

What is SEND?

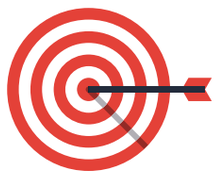
CDISC SEND is the Clinical Data Interchange Standards Consortium Standard for Exchange of Nonclinical Data, an FDA standard data format/terminology that is now required for submission of preclinical study data to the FDA. SEND is defined in the SEND Implementation Guide (SENDIG).

Scope of SEND

SENDIG v3.0 supports single-dose general toxicology, repeat-dose general toxicology, and carcinogenicity studies. SENDIG v3.1 adds support for cardiovascular and respiratory data collected during some safety pharmacology studies. At this time, reproductive toxicology study data is exempt from SENDIG v3.0 and v3.1, but will be included in future mandates.

What do the SENDIGs v3.0 encompass?

The SENDIGs are intended to guide the industry about the structure, organization, and format of standard nonclinical tabulation datasets for exchange between organizations (e.g., sponsors and CROs) and for submission to the FDA. The SENDIGs are based on the CDISC Study Data Tabulation Model (SDTM) for clinical data.



The goal of SEND

SEND seeks to increase efficiency and the quality of scientific review by the Center for Drug Evaluation and Research (CDER) pharmacologists and toxicologists, and to improve communication between the US Food and Drug Administration (FDA) and the industry. The ultimate goal is to phase out paper submissions.

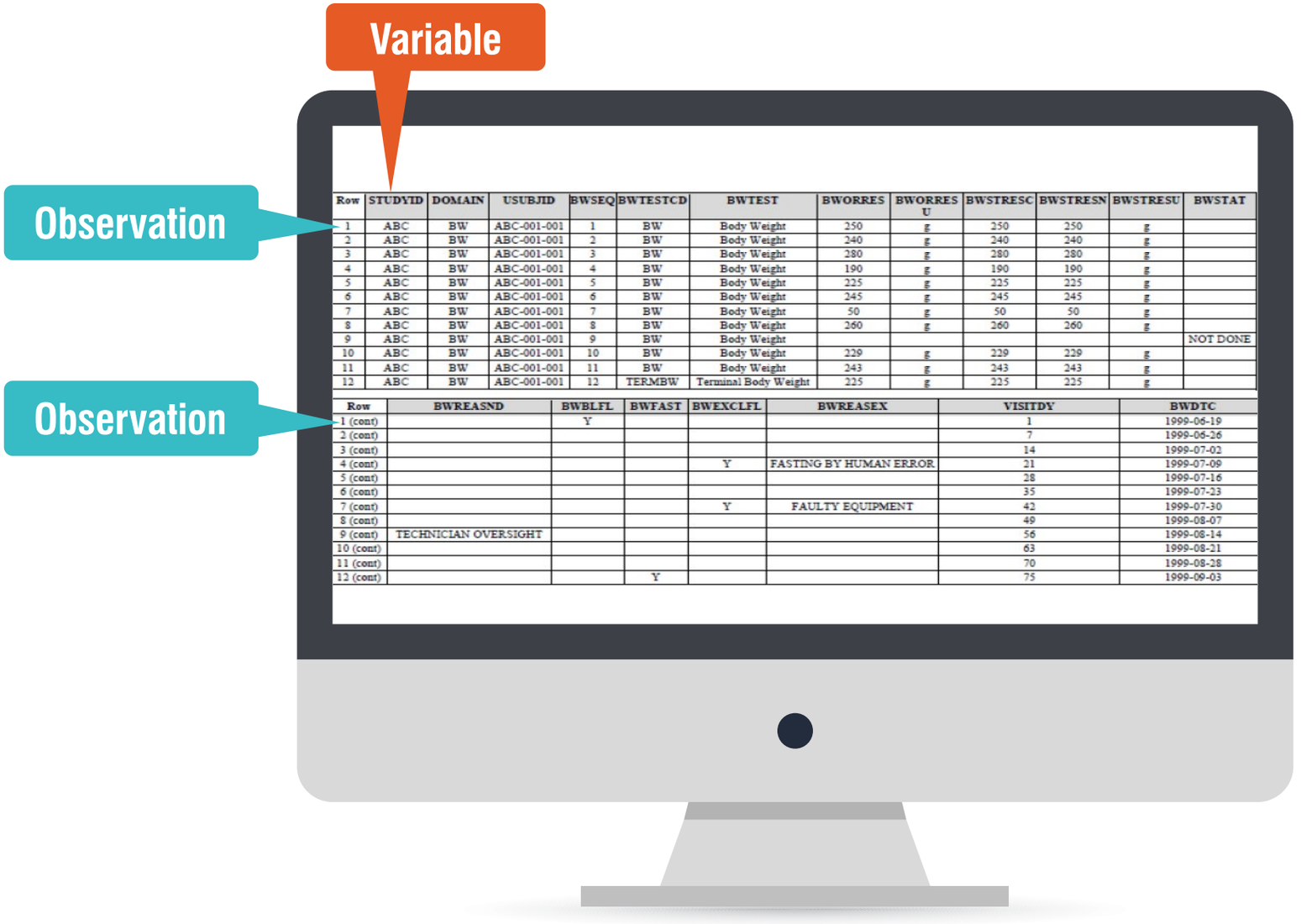
What does SEND look like?

How extensive is SEND data?

A six-month study in rats with four weeks of recovery: The LB (clinpath) domain contains approximately 18 columns and 36,000 rows of data.

What does SEND data look like?

The graphic displays an example of what the “Body Weight” domain may look like.



Row	STUDYID	DOMAIN	USUBJID	BWSEQ	BWTESTCD	BWTEST	BWORRES	BWORRESU	BWSTRESC	BWSTRESN	BWSTRESU	BWSTAT
1	ABC	BW	ABC-001-001	1	BW	Body Weight	250	g	250	250	g	
2	ABC	BW	ABC-001-001	2	BW	Body Weight	240	g	240	240	g	
3	ABC	BW	ABC-001-001	3	BW	Body Weight	280	g	280	280	g	
4	ABC	BW	ABC-001-001	4	BW	Body Weight	190	g	190	190	g	
5	ABC	BW	ABC-001-001	5	BW	Body Weight	225	g	225	225	g	
6	ABC	BW	ABC-001-001	6	BW	Body Weight	245	g	245	245	g	
7	ABC	BW	ABC-001-001	7	BW	Body Weight	50	g	50	50	g	
8	ABC	BW	ABC-001-001	8	BW	Body Weight	260	g	260	260	g	
9	ABC	BW	ABC-001-001	9	BW	Body Weight						NOT DONE
10	ABC	BW	ABC-001-001	10	BW	Body Weight	229	g	229	229	g	
11	ABC	BW	ABC-001-001	11	BW	Body Weight	243	g	243	243	g	
12	ABC	BW	ABC-001-001	12	TERMBW	Terminal Body Weight	225	g	225	225	g	

Row	BWREASND	BWBLFL	BWFAST	BWEXCLFL	BWREASEX	VISITDY	BWDTC
1 (cont)		Y				1	1999-06-19
2 (cont)						7	1999-06-26
3 (cont)						14	1999-07-02
4 (cont)				Y	FASTING BY HUMAN ERROR	21	1999-07-09
5 (cont)						28	1999-07-16
6 (cont)						35	1999-07-23
7 (cont)				Y	FAULTY EQUIPMENT	42	1999-07-30
8 (cont)						49	1999-08-07
9 (cont)	TECHNICIAN OVERSIGHT					56	1999-08-14
10 (cont)						63	1999-08-21
11 (cont)						70	1999-08-28
12 (cont)			Y			75	1999-09-03

Benefits of SEND

As an evolving standard – and one with several challenges to address before the industry can fully meet requirements – it may take some time for both the FDA and the industry to fully realize SEND benefits. The benefits the CDISC SEND team hopes to achieve are:

FDA

- Standard mechanism for review of data
- Comparative and more in-depth analysis of data
- Harmonized terminology

Industry

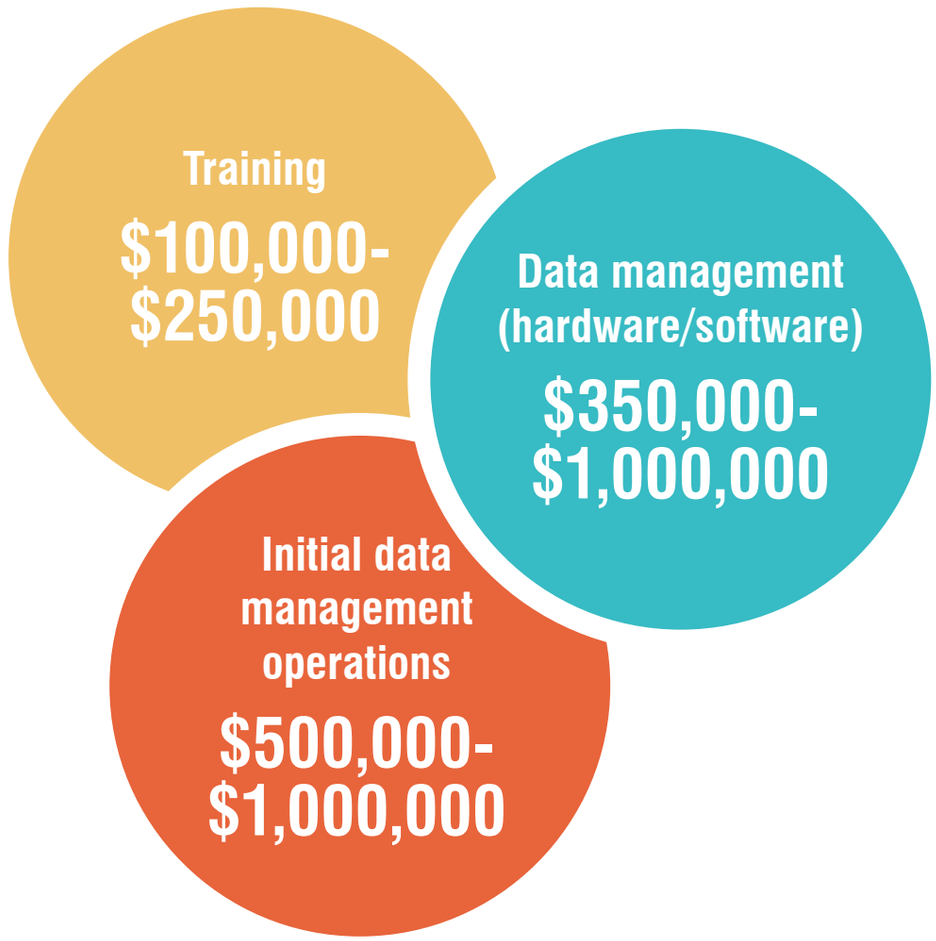
- Standard format and delivery mechanism
- Efficient interactions with both vendors and regulators
- Faster time to market; for a blockbuster drug, this could be significant

Excerpt from Final Guidance

"For many years sponsors and applicants have been submitting electronically using the electronic common technical document format and have included electronic study data in both legacy and standardized formats.

For some sponsors and applicants there may be new costs, including capital costs or operating and maintenance costs, which would result from the requirements under FDASIA and guidance, because some sponsors and applicants would have to change from submissions that have included legacy (non-standard) study data to submissions in compliance with the final guidance."

The FDA estimates that the costs for some sponsors and applicants to implement data standards may be as follows:



SEND 3.0 and SEND 3.1 Mandatory Timelines

Final Guidance Published	NDA/ANDA and certain* BLA studies MUST be submitted in SEND v3.0.	certain* IND studies MUST be submitted in SEND v3.0.	NDA/ANDA and certain* BLA studies MUST be submitted in SEND v3.1.	certain* IND studies studies MUST be submitted in SEND v3.1.

SEND 3.0 includes single dose, repeat dose, and carcinogenicity studies.
SEND 3.1 also includes some safety pharmacology studies.

*For details, please reference the FDA Study Data Catalog and the Providing Regulatory Submissions in Electronic Format – Standardized Study Data Guidance for Industry (December 2014)

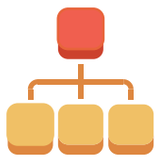
Industry Challenges

This is new to the industry.

Although companies have been creating SENDIG v3.0 datasets, most are still refining their SEND dataset creation processes. With the introduction of new SENDIGs, continuous process changes will be needed to fully adjust to the evolving system modifications, controlled terminology, and electronic data collection practices.

SEND software is still in development

As new standards are released, the SEND software will continue to evolve at a rapid pace to ensure customers have the necessary capabilities when the standard becomes mandatory for submissions.



Merging data from several sources

Merging data from multiple sources can be a challenge. Vendors differ in their ability to produce complete SEND datasets, making it important that companies are selecting a provider that can meet their SEND needs.

SEND is an evolving standard

Current SEND requirements are extensive, and still evolving.The FDA has recently published that indicated support for SENDIG v3.1 and CDISC has published the SENDIG-DART v1.1. As future IG versions are published by CDISC and accepted by the FDA, new study designs will be in scope for SEND (e.g., embryo-fetal development).

Creating SEND Files

The process of creating SEND files presents its own challenges. Data generated from several internal and vendor-based sources can vary in quality, completeness and readiness for submission.

This is compounded if gaps exist in the population of the original data source. In addition, the current lack of automation tools for some datasets requires the manual population of data, which can be a time-consuming process. In the future, the introduction of new technologies will continue to address these difficulties.

What's Next?

- Define 2.0 will be required for all in scope studies that start on March 15, 2018. Tools are just becoming available to produce Define 2.0 for preclinical studies.
- SENDIG includes the following:
  - Updates to PC/PP Domains
  - Updates to Microscopic Findings (MI) Domain
  - Other implementation guide fixes
  - SENDIG v3.2
- Developmental and Reproductive Toxicology Implementation Guide (SENDIG-DART v1.1) has been published to support embryo-fetal development studies.
- Vendors are currently developing tools to support the SENDIG-DART v1.1.

Summary

SEND data is now a submission requirement for all in-scope nonclinical study designs.

Sponsor companies are ultimately responsible for the submission of SEND datasets. SEND datasets are submitted to the FDA as part of the eCTD submission. Sponsor should have the ability to receive, review, submit and archive the SEND data.

SEND implementation requires planning and dedicated resources but this investment results in the long-term benefit of an improved FDA approval process for the industry.

With decades of experience and a commitment to providing comprehensive regulatory support, Charles River has made such an investment, and will continue to do so. Our involvement with the SEND initiative dates back to 2007, and has only grown since then.

Charles River has been producing validated SEND packages since 2015. As we move forward, Charles River clients can continue to rely on our regulatory expertise and guidance through these new requirements.

Resources

Click on the links below for additional resources and contact information.

- SEND Implementation Guide (IG)
- CDISC Controlled Terminology
- FDA Study Data Standards Resources
- FDA Federal Register Notice
- Study Data Standards for Submission to CDER
- SEND Implementation User Group
- PhUSE - SEND Implementation Wiki
- Questions and General Information Regarding Preparation of Submissions - CDER
- Questions and General Information Regarding Preparation of Submissions - CBER
- FDA Electronic Regulatory Submission and Review

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