Paper DS09

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SEND 3.1: Giving Your Submission a “Vital” Upgrade

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ABSTRACT

The SEND [Standard for Exchange of Nonclinical Data] Implementation Guide v3.1, "SEND 3.1," changes the model for the reporting of cardiovascular and respiratory endpoints. SEND 3.1 will become effective 15 March 2019 for NDA submissions and 15 March 2020 for IND submissions, and will overlap with the effective period of the previous version, SEND 3.0. Through the introduction of two new domains, Cardiovascular Test Results [CV] and Respiratory Test Results [RE], content changes will be enacted in the Vital Signs [VS] domain. Gaining familiarity with the key changes to ensure compliance with both SEND 3.0 and SEND 3.1 are important to build confidence in upcoming submissions, which are likely to include SEND datasets of both versions.

INTRODUCTION

Gaining a new implementation guide can provide challenges all on its own, despite that many organizations are still learning to interpret the 3.0 guide. While SEND 3.1 includes changes for general toxicity and carcinogenicity studies, the primary focus here is on cardiovascular and respiratory safety pharmacology studies and endpoints, namely on the Latin square design and amended data presentation for principal endpoints. Finally, upcoming regulatory submissions will likely include not only SEND 3.0 datasets, but also SEND 3.1 datasets and abbreviated trial summary [TS] files.

DISCUSSION

The CDISC SEND Implementation Guide [IG] v3.1 introduces new modeling for endpoints of cardiovascular, respiratory, electrocardiographic [ECG], and vital signs data types. Previously in SEND 3.0, these endpoints were placed into two domains: (1) VS and (2) EG. Understanding the proper placement of different endpoints will be key to ensuring compliance with the new standard and guaranteeing successful use by agency reviewers.

The SEND 3.1 document includes a summary of the changes in Section 1.3, “Relationship to Prior CDISC Documents” [Figure 1] and a detailed listing of changes between versions 3.0 and 3.1 in Appendix D. SEND 3.1 introduces two new domains, CV and RE, for the reporting of cardiovascular and respiratory data, while also maintaining the VS and EG domains.

1.3 Relationship to Prior CDISC Documents

The most significant changes since the prior version, v3.0, include:

- Realignment with SDTM v1.5.
- Reclassified the use of VISITDY from Expected to Permissible and added three new variables to relevant domains (--USCHFL, --NOMLBL, --NOMDY)
- New FOCID variable added to several domains (EX, CL, MA, and MI). FOCID, described further in Section 4.2.7, is available to all general observation classes to specify a study-specific point of interest.
- Updated Microscopic Findings domain (Section 6.3.8); added three new variables (FOCID, --CHRON, --DISTR).
- Updated Vital Signs domain (Section 6.3.15). With the addition of new domains for nonclinical safety pharmacology study data, CV and RE, the Vital Signs domain was revised, blood pressure measurements were moved to the Cardiovascular (CV) domain, and respiratory rate was moved to the Respiratory (RE) domain. For nonclinical study data, the Vital Signs domain is now intended to hold vital signs measurements, such as body temperature, that are not otherwise covered in domains for respiratory and cardiovascular test data.
- Updated ECG Test Results domain (Section 6.3.16); added two new Timing variables (--STINT and --ENINT).
- New Cardiovascular domain (Section 6.3.17) including blood pressure measurements, which were previously submitted in Vital Signs domain.
- New Respiratory domain (Section 6.3.18) including respiratory rate, which was previously submitted in Vital Signs domain.

Figure 1: Excerpt from CDISC SEND IG v3.1, summarizing the changes from CDISC SEND IG v3.0.

SEND 3.0

The SEND 3.0 guide specifies that the standard applies to single- and repeat-dose toxicity studies and carcinogenicity studies. It is common for the general toxicology studies to include ECG data collection as well as physical examinations, particularly for canines and nonhuman primates, with various endpoints commonly referred to as "vitals." In SEND 3.0, two findings domains are used to present these data types. The EG domain is used to report ECG tests such as ECG mean heart rate, QRS duration, PR interval, QT interval, QTc interval, and RR interval. The VS domain is used to report heart rate, body temperature, respiratory rate, blood pressures, oxygen saturation, mean arterial pressure, and pulse pressure. In this version, the VS domain can be quite lengthy for a study containing all of the aforementioned endpoints.

SEND 3.1

The SEND 3.1 guide includes the previously-mentioned study types [with some updates] and adds stand-alone cardiovascular and respiratory studies that will be included in the Safety Pharmacology section of the electronic regulatory submission.

The Latin-square design is often used on stand-alone cardiovascular studies. In the Latin-square design, the dosing regimen is designed to ensure that all dose levels are represented on each dosing day, with each subject receiving each dose only once, and every subject in each square receiving a unique dosing sequence [Figure 2].

TREATMENT DESIGN AND DOSE LEVEL DESIGNATION					
Animal	Gender	Dose Level Designation on Specified Dosing Days			
		Day 1	Day 8	Day 15	Day 22
1	M	Low	Control	High	Mid
2	M	Mid	High	Control	Low
3	M	High	Low	Mid	Control
4	M	Control	Mid	Low	High

Figure 2: Example of the Latin square design for dosing on a cardiovascular safety pharmacology study.
Source: Covance training study

In the SEND dataset, special consideration must be given to the trial design domain details, particularly trial arms [TA] and trial sets [TX]. Following the example in Figure 2, assume a single dose is given at each level with a 7-day washout period between each dose.
Control = 0 mg/kg
Low = 30 mg/kg
Mid = 100 mg/kg
High = 300 mg/kg

The trial arm is descriptive, showing the dosing order each subject underwent with the dose level integer. Subject 1 has a trial arm of 30-0-300-100, Subject 2 has a trial arm of 100-300-0-30, and so forth [Figure 3].

DOMAIN	ARMCD	ARM	TAETORD	ETCD	ELEMENT
TA	1	30-0-300-100	1	T2	30 mg/kg
TA	1	30-0-300-100	2	T1	0 mg/kg
TA	1	30-0-300-100	3	T4	300 mg/kg
TA	1	30-0-300-100	4	T3	100 mg/kg
TA	2	100-300-0-30	1	T3	100 mg/kg
TA	2	100-300-0-30	2	T4	300 mg/kg
TA	2	100-300-0-30	3	T1	0 mg/kg
TA	2	100-300-0-30	4	T2	30 mg/kg

Figure 3: Example excerpt of the TA domain for a Latin square design. Source: Covance training study
ARMCD = Planned arm code; TAETORD = Order of element within arm; ETCD = Element code

The trial set contains the description of the dosing sequence. Subject 1 has a trial set of “Low, Control, High, Mid” [Figure 4]. The dose frequency and washout period can also be included in the trial set, e.g., “Low, Control, High, Mid once with a 7-day rest period,” but is not considered to be required content.

DOMAIN	SETCD	SET	TXSEQ	TXPARMCD	TXPARM	TXVAL
TX	1	Low, Control, High, Mid	1	ARMCD	Arm Code	1
TX	2	Mid, High, Control, Low	2	ARMCD	Arm Code	2
TX	3	High, Low, Mid, Control	3	ARMCD	Arm Code	3
TX	4	Control, Mid, Low, High	4	ARMCD	Arm Code	4
TX	1	Low, Control, High, Mid	5	TCNTRL	Control Type	Vehicle Control
TX	2	Mid, High, Control, Low	6	TCNTRL	Control Type	Vehicle Control
TX	3	High, Low, Mid, Control	7	TCNTRL	Control Type	Vehicle Control
TX	4	Control, Mid, Low, High	8	TCNTRL	Control Type	Vehicle Control
TX	1	Low, Control, High, Mid	9	TRTDOS	Dose Level	30;0;300;100
TX	2	Mid, High, Control, Low	10	TRTDOS	Dose Level	100;300;0;30
TX	3	High, Low, Mid, Control	11	TRTDOS	Dose Level	300;30;100;0
TX	4	Control, Mid, Low, High	12	TRTDOS	Dose Level	0;100;30;300

Figure 4: Example excerpt of a TX domain for a Latin square design. Source: Covance training study
SETCD = Set code; TXSEQ = Sequence number; TXPARMCD = Trial set parameter short name; TXPARM = Trial set parameter; TXVAL = Trial set parameter value

For the presentation of data in the SEND 3.1 model, the introduction of two new domains splits the various tests previously appearing in a SEND 3.0 VS domain into three separate domains - CV, RE, and VS [Table 1]. The new domains, CV and RE, are also findings domains and present data in a similar format as the EG and VS domains from SEND 3.0. New variables introduced in SEND 3.1 will be included in all four domains [CV, EG, RE, and VS] as well. All of these domains rely heavily on the population of timing variables to provide various options for grouping and evaluating the data.

Domain	SEND 3.0		SEND 3.1			
	EG	VS	CV	EG	RE	VS
Test/Data Type						
ECG Mean Heart Rate	X			X		
PR Interval	X			X		
QRS Duration	X			X		
QT Interval	X			X		
QTc Interval	X			X		
RR Interval	X			X		
Body Temperature		X				X
Diastolic Blood Pressure		X	X			
Heart Rate		X	X			
Mean Arterial Pressure		X	X			
Minute Volume		X			X	
Oxygen Saturation		X				X
Pulse Pressure		X	X			
Respiratory Rate		X			X	
Systolic Blood Pressure		X	X			
Tidal Volume		X			X	

Table 1: Placement of endpoints in SEND 3.0 vs SEND 3.1.

While the VS domain from SEND 3.0 undergoes an overhaul in SEND 3.1, all ECG endpoints remain in the EG domain. The VS domain is greatly minimized, with all blood pressure measurements and other cardiovascular-related vitals [that are not electrocardiography] tests moving to the CV domain and all respiratory results transferring to the RE domain.

It is important to note that while many tests are moving from the VS domain to other domains, the CT [Controlled Terminology] issued by CDISC does not differentiate between the 3.0 and 3.1 versions of the IGs [Figures 5, 6, and 7]. While the name of the tests that SHOULD be in the CV and RE domain is provided, all of the tests are available in the VSTEST/VSTESTCD [Vital Signs Test Name/Vital Signs Test Short Name] lists as well. Keeping a list of what data types should be found in each domain in each SEND version will help determine what is expected in each new section.

C67153 VSTEST

NCI Code	CDISC Submission Value	CDISC Synonym	CDISC Definition	NCI Preferred Term
C49679	Mean Arterial Pressure	Mean Arterial Pressure	The mean pressure of the blood within the arterial circulation. The arterial pressure may be directly measured by insertion of an intra-arterial catheter connected to a transducer. The mean arterial pressure (MAP) can be calculated by subsequent analysis of the waveform. MAP can be approximated without an invasive procedure using the following formula: diastolic pressure plus 1/3 of the pulse pressure, where pulse pressure is systolic pressure - diastolic pressure. (NCI)	Mean Arterial Pressure
C49678	Respiratory Rate	Respiratory Rate	The rate of breathing (inhalation and exhalation) measured within in a unit time, usually expressed as breaths per minute. (NCI)	Respiratory Rate

Figure 5: Excerpt of the VSTEST Controlled Terminology options available in the 2018-12-21 version. Source: CDISC.org

SCVTST (SEND Cardiovascular Test Name)

NCI Code: C120533, Codelist extensible: Yes

C120533 SCVTST

NCI Code	CDISC Submission Value	CDISC Synonym	CDISC Definition	NCI Preferred Term
C49679	Mean Arterial Pressure	Mean Arterial Pressure	The mean pressure of the blood within the arterial circulation. The arterial pressure may be directly measured by insertion of an intra-arterial catheter connected to a transducer. The mean arterial pressure (MAP) can be calculated by subsequent analysis of the waveform. MAP can be approximated without an invasive procedure using the following formula: diastolic pressure plus 1/3 of the pulse pressure, where pulse pressure is systolic pressure - diastolic pressure. (NCI)	Mean Arterial Pressure

Figure 6: Excerpt of the SCVTST Controlled Terminology options available in the 2018-12-21 version demonstrating that the option for Mean Arterial Pressure is identical in all fields to VSTEST. Source: CDISC.org

SRETST (SEND Respiratory Test Name)

NCI Code: C120535, Codelist extensible: Yes

C120535 SRETST

NCI Code	CDISC Submission Value	CDISC Synonym	CDISC Definition	NCI Preferred Term
C49678	Respiratory Rate	Respiratory Rate	The rate of breathing (inhalation and exhalation) measured within in a unit time, usually expressed as breaths per minute. (NCI)	Respiratory Rate

Figure 7: Excerpt of the SRETST Controlled Terminology options available in the 2018-12-21 version demonstrating that the option for Respiratory Rate is identical in all fields to VSTEST. Source: CDISC.org

Other test types that are found in the CV domain include Activity, Diastolic/Systolic Blood Pressure, Heart Rate, Left Ventricular Minimums and Maximums, Pressure Minimums and Maximums, Pulse Pressure, and Peripheral Resistance.

Other test types that are found in the RE domain include Airway Resistance, Inspiration and Expiration Times, Pauses, Peaks and Flows, Pulmonary Pressure, and Total Lung Capacity.

Other test types that are found in the VS domain include Basal Metabolic Rate, Body Measurements, and Pulse Rate.

REGULATORY SUBMISSIONS

Following on the specifics contained within the SEND datasets, the next information to understand is what will be included in regulatory submissions. The start date of the study [protocol finalization date] is the key piece of information used to determine if a SEND dataset and what version is required. As of 15 March 2019, new in-scope studies appearing in an NDA submission will be required to have a SEND 3.1 dataset. If a legacy cardiovascular or respiratory study is included in an NDA submission [study start date prior to 15 March 2019], an abbreviated TS file will need to be included.

Consider the following studies for an NDA submission filing in August 2019. The following studies will appear in Module 4, Section 4.2.1.3.

Study 1: Cardiovascular dog study started on 25 September 2017; abbreviated TS file required
Study 2: Respiratory rat study started on 12 February 2018; abbreviated TS file required
Study 3: Cardiovascular monkey study started on 18 March 2019; full SEND 3.1 dataset required
Study 4: Irwin rat study started on 25 September 2017; out-of-scope – no SEND or TS file requirement

CONCLUSION

Consulting the protocol, report, and SEND dataset will provide the easiest way to identify that the content of the documents align.

(1) Check the finalization date of the study protocol to determine whether the study is in-scope for the SEND 3.1 reporting requirement.
(2) If the study used the Latin square design, confirm that the trial arms and trial sets have been properly populated.
(3) Look for the two newest domains, CV and RE. Remember that these domains will be used in single- and repeat-dose toxicity studies as well as the cardiovascular and respiratory safety pharmacology studies.
(4) Ensure that the vital signs domain includes only data not covered under the cardiovascular and respiratory domains.

Knowing what to expect before receiving your first SEND 3.1 dataset by gaining familiarity with these key changes between SEND 3.0 and SEND 3.1 is important to building confidence in and avoiding delays when preparing for upcoming submissions.

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