Life Sciences

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The Standard for the Exchange of Nonclinical Data (SEND): History, Basics, and Comparisons with Clinical Data

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PharmaSUG SDE
RTP, October 2016

accenture

Strategy | Digital | Technology | Operations

Outline

- Development and Relationship to the SDTM
- Similarities to the SDTMIG
- SENDIG/SDTMIG Domain Comparison
- SDTM Variables Resulting from SEND
- SEND Location Variables
- SEND Standardization of MA and MI
- Pool Definition
- Trial Sets

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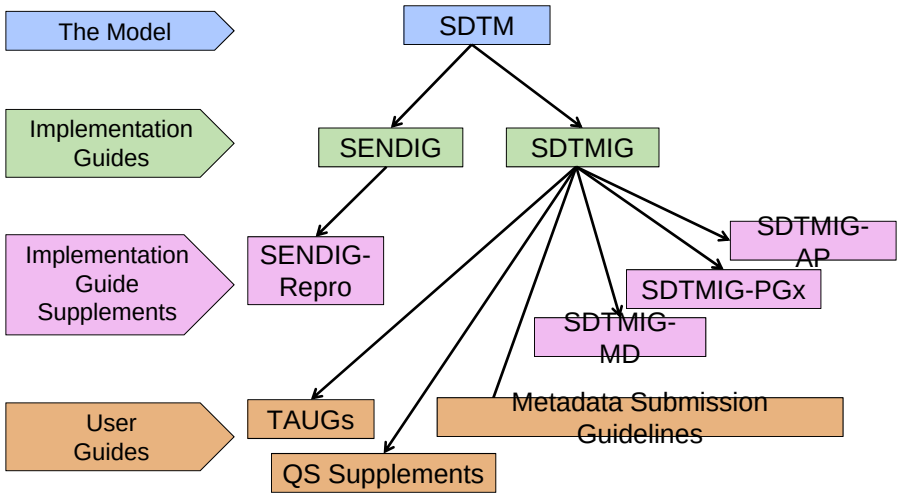
SDTM, Implementation Guide, and User Guide Relationships



History of SEND (Standard for the Exchange of Nonclinical Data)

Late 2002- early 2003	First (non-SDTM-based) versions of SEND domains created
January 2003	Announcement of a pilot project for standardized nonclinical data
June 2003	(Clinical) Submission Data Standards v3.0 (precursor to the SDTM)
Summer 2003	v3 domains SEND domains modeled to SDTM
August 2003	v1 SEND standard published as specification for pilot
Late 2004	Pilot completed
November 2005	SEND IG v2.3 published
2005-2007	Team dormant
May 2007	SEND effort restarted by industry; discussion with CDER reinitiated
October 2007	FR Notice for SEND Pilot
March 2009	SENDIG Draft 3.0A published for second pilot
December 2010	SENDIG Draft 3.0B posted for public review
May 2011	SENDIG v3.0 published
November 2014	SENDIG v3.1 posted for first public review
May 2015	SENDIG v3.1 posted for second public review
June 2016	SENDIG v3.1 published

Similarities to the SDTMIG

- SENDIG Appearance and Organization
- Domain Models, Assumption, and Examples
- Extensive CT Managed by CDISC/NCI EVS

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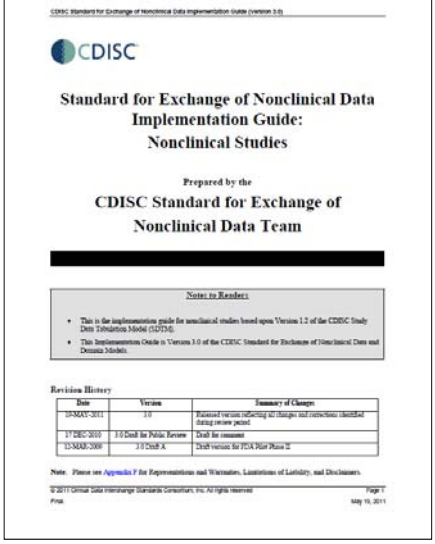
The SEND Implementation Guide



CDISC

Standard for Exchange of Nonclinical Data Implementation Guide: Nonclinical Studies

Prepared by the CDISC Standard for Exchange of Nonclinical Data Team

Note to Reader:

- This is the implementation guide for nonclinical studies based upon Version 1.2 of the CDISC Study Data Tabulation Model (SDTM).
- This Implementation Guide is Version 3.0 of the CDISC Standard for Exchange of Nonclinical Data and Domain Models.

Revision History

Date	Version	Summary of Changes
19-MAY-2011	3.0	Retained version reflecting no changes and corrections identified during review period.
17-DEC-2010	3.0 Draft for Public Review	Draft for comment
12-MAR-2009	3.0 Draft X	Draft version for FDA Pilot Phase II

Note: Please see Appendix F for Representations and Warranties, Limitations of Liability, and Disclaimers.

Final May 19, 2011

Describes:

- Names for commonly submitted datasets
- Names for commonly used variables (columns)
- Extensive harmonized controlled terminology (data values)
- A set of business rules for implementing SDTM concepts

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- Trial Sets

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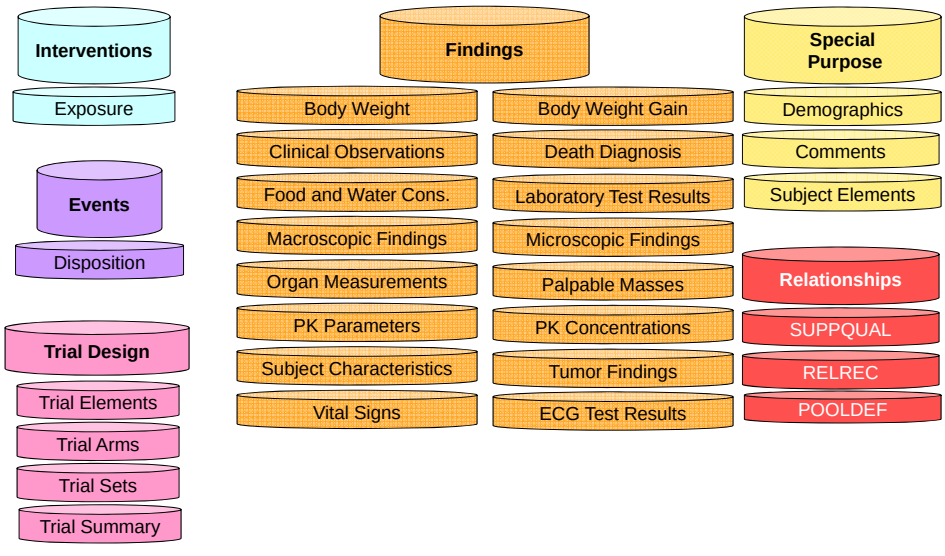
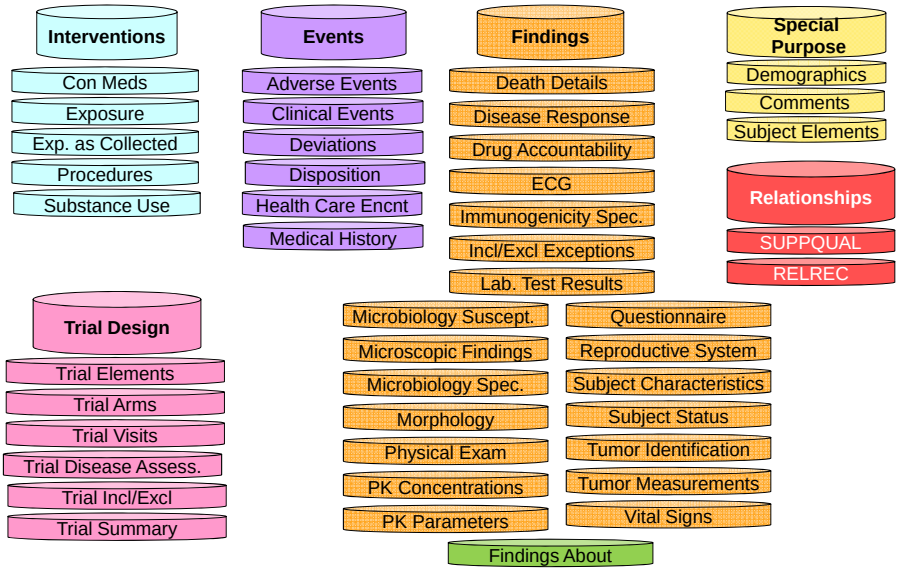
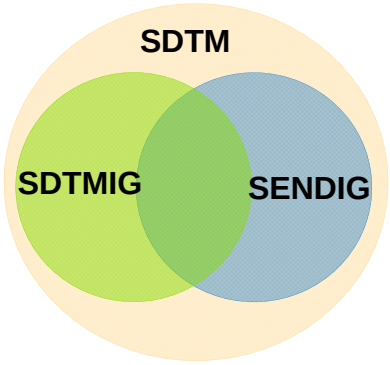
SENDIG (Nonclinical) Domains (v3.0)



SDTMIG (Human Clinical) Domains (v3.2)



Domain Overlap



Domain Comparison: Nonclinical vs. Clinical (2)

Nonclinical Only	Clinical Only	
Findings • Body Weights • Clinical Observations • Food and Water Consumption • Macroscopic Findings • Microscopic Findings • Palpable Masses • Organ Measurements • Tumor Findings **Special Purpose** • POOLDEF	**Interventions** • Concomitant Medications • Procedures • Substance Use **Events** • Adverse Events • Clinical Events • Deviations • Healthcare Encounters • Medical History **Findings** • Disease Response • Drug Accountability • Immunogenicity Specimen • Inclusion Exclusion Exceptions • Microbiology Specimen	**Special Purpose** • Subject Visits **Trial Design** • Trial Visits • Trial Inclusion/Exclusion • Microbiology Susceptibility • Physical Exam • Questionnaire • Subject Status • Tumor Identification • Tumor Measurements

Domain Comparison: Nonclinical vs. Clinical (1)

Both	
Interventions • Exposure **Events** • Disposition **Findings** • Death Diagnosis • ECG Test Results • Laboratory Test Results • Microscopic Findings • PK Concentrations • PK Parameters • Subject Characteristics • Vital Signs	**Special Purpose** • Demographics • Comments • Subject Elements • SUPPQUAL • RELREC **Trial Design** • Trial Elements • Trial Arms • Trial Sets • Trial Summary

SDTM Variables Resulting from SEND (1)

SDTM Table	Variable *	Variable Label	Example Value(s)	Used in Clinical Trials **
2.2.1, Interventions	--UNSCHFL *	Unscheduled Flag	Y or null	N
2.2.2, Events	--UNSCHFL *	Unscheduled Flag	Y or null	N
2.2.3, Findings	--CHRON *	Chronicity of Finding		P
	--DISTR *	Distribution Pattern of Finding		P
	--REPNUM *	Repetition Number		P
	--EXCLFL *	Exclude from Statistics	Y or null	N
	--REASEX	Reason for Exclusion from Statistics	Text	N
	--UNSCHFL *	Unscheduled Flag	Y or null	N
2.2.4, Identifiers	POOLID	Pool Identifier	Text	U
	FOCID *	Focus of Study Specific Interest	Text	P
	--RECID *	Invariant Record Identifier	Text	P

** Denotes new variables in SDTM v1.5. Unless noted, variables shown appeared in SDTM v.1.4.*
*** N = No, U = Unlikely, P = Possible*

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SDTM Variables Resulting from SEND (2)

2.2.5, Timing	--DETECT	Time in Days to Detection of Tumor	Needed for the creation of the tumor.xpt file for carcinogenicity studies	U
	--NOMDY *	Nominal Study Day for Tabulations	Number	N
	--NOMLBL	Label for Nominal Study Day	WEEK 1	N
2.2.6, Demographics	SPECIES	Species	RAT, MOUSE	U
	STRAIN	Strain/Substrain	FISCHER 344, B6C3F1	U
	SBSTRAIN	Strain/Substrain Details	Text description of additional STRAIN details	U
	AGETXT	Age Text	4-6 weeks	U
	SETCD	Set Code	Used to divide or group animals within Arms	P
4.1.1, RELREC; 4.1.2, SUPPQUAL	POOLID	Pool Identifier	Text	U

** Denotes new variables in SDTM v1.5. Unless noted, variables shown appeared in SDTM v.1.4.*
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Location Variables

- SEND benefits from having the BRIDG Model, which distinguishes between test and result locations.

Test	Result
Look at the kidney	In the cortex, we observed [Finding]
Look at the kidney cortex	[Finding]

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SEND Location Variables (1)

Test Variables	Result Variables
--SPEC	--ORRES
--ANTREG	--STRESC, --RESMOD Possibly coming: --RESLAT, --RESDIR
--LAT	
--DIR	
--PORTOT	

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SEND Location Variables (2)

Two concepts:

- **SDTMIG:** The same finding in multiple locations is represented using MULTIPLE in --LOC and the multiple locations in SUPP--.

AETERM	AELOC
RASH	MULTIPLE

QNAM	QLABEL	QVAL
AELOC1	Location of the Reaction 1	FACE
AELOC2	Location of the Reaction 2	NECK
AELOC3	Location of the Reaction 3	CHEST

- **SENDIG:** One finding in one location with multiple descriptors keep them in the same field as per the SENDIG. Example: “medial;anterior”.

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Controlled Terminology

- SEND terminology has its own lists, but every effort is made to harmonize.
- SEND terminology includes 31 codelists that were initially developed for clinical data.
- SDTM terminology includes three codelists initially developed by the SEND CT Subteam.

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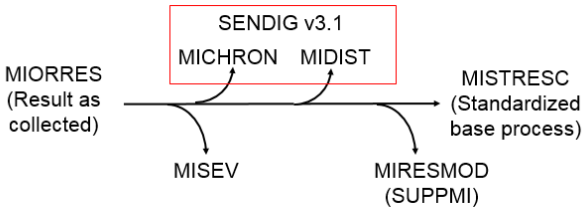
SEND Standardization of Macroscopic and Microscopic Findings (1)



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SEND Standardization of Macroscopic and Microscopic Findings (2)

Row	STUDYID	DOMAIN	USUBJID	MISEQ	MIGRPID	MIREFID	MITESTCD	MITEST
1	2016-1	MI	2016-1-001	12	67	LIV-154	MIEXAM	Microscopic Examination
2	2016-1	MI	2016-1-001	13	67	LIV-154	MIEXAM	Microscopic Examination

Row	MIORRES	MISTRESC	MICHRON	MIDISTR	MISPEC	MISEV
1	Moderate subacute necrosis surrounded by mild diffuse inflammation	NECROSIS	SUBACUTE		LIVER	MODERATE
2	Moderate subacute necrosis surrounded by mild diffuse inflammation	INFLAMMATION		DIFFUSE	LIVER	MILD

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POOLDEF – Pool Definition

- Sometimes data may be collected for a group of animals, rather than for any single animal.
- POOLDEF shows the animals in a pool.
- Whenever a pool composition changes, a new POOLID must be created.

STUDYID	POOLID	USUBJID
2009-008	CAGE 1	**2009-008-001**
2009-008	CAGE 1	**2009-008-002**
2009-008	CAGE 1	**2009-008-003**
2009-008	PK1	**2009-008-001**
2009-008	PK1	**2009-008-002**
2009-008	PK1	**2009-008-003**
2009-008	PK1	**2009-008-004**
2009-008	PK1	**2009-008-005**
2009-008	CAGE 1-A	**2009-008-001**
2009-008	**CAGE 1-A**	**2009-008-003**

Animals group housed, with pooled food and water consumption collected.

Some of the same animals were included in another pool, where PK samples were combined for five animals.

Animal 2009-008-002 was removed from the original CAGE 1 pool.

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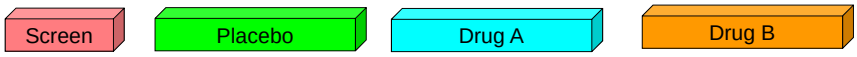
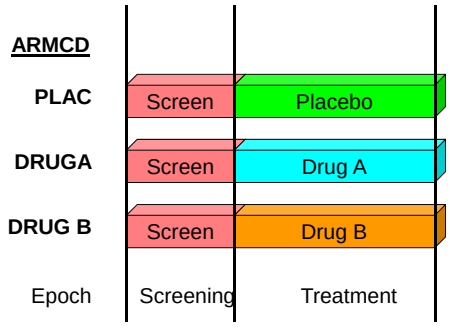
Trial Design Similarities

Trial Elements



Trial Arms



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Trial Design Difference (Potential): Trial Sets

- A Trial Set represents the most granular subdivision of all the experimental factors, treatment factors, inherent characteristics, and distinct sponsor designations as specified in the design of the study.
- The Set Code (SETCD) is Required in DM for SEND data.
- Trial Sets allows for:
  - The subsetting of subjects within an Arm (treatment path)
  - The "grouping" of multiple Arms

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Trial Sets in Clinical Trials Subsetting Arms (1)

- While the Trial Sets (TX) table is not in the SDTMIG, it is in the SDTM.
- Trial Sets has possible uses in human clinical trials when randomization may be based upon factors other than treatment.
  - Subjects who have undergone previous heart surgery vs. or therapies vs. those who have not)
  - Subjects who smoke vs, subjects who don't smoke

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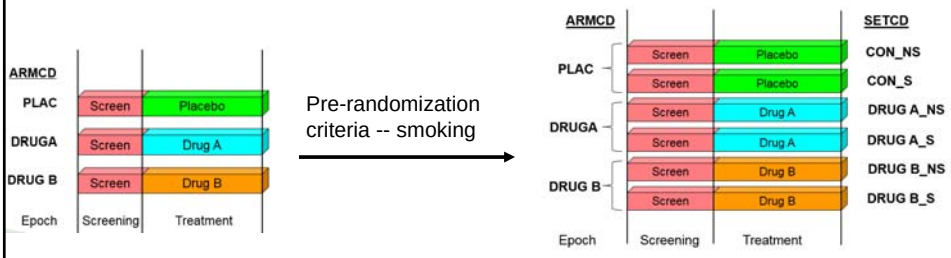
Trial Sets in Clinical Trials
Subsetting Arms (2)



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How Trial Sets Are Described (1)

STUDYID	DOMAIN	SETCD	SET	TXSEQ	TXPARMCD	TXPARM	TXVAL
TDM10	TX	CON_NS	Control Non-Smokers	1	ARMCD	Arm Code	PLAC
TDM10	TX	CON_NS	Control Non-Smokers	2	GRPLBL	Group Label	Control, Non
TDM10	TX	CON_NS	Control Non-Smokers	3	TRTDOS	Dose Level	0
TDM10	TX	CON_NS	Control Non-Smokers	4	TRTDOSU	Dose Units	mg/day
TDM10	TX	CON_NS	Control Non-Smokers	5	POPTYPE	Population Type	Non-Smokers
TDM10	TX	CON_S	Control Smokers	1	ARMCD	Arm Code	PLAC
TDM10	TX	CON_S	Control Smokers	2	GRPLBL	Group Label	Control, Smoke
TDM10	TX	CON_S	Control Smokers	3	TRTDOS	Dose Level	0
TDM10	TX	CON_S	Control Smokers	4	TRTDOSU	Dose Units	mg/day
TDM10	TX	CON_S	Control Smokers	5	POPTYPE	Population Type	Smokers
TDM10	TX	DRUG A_NS	Drug A Non-Smokers	1	ARMCD	Arm Code	DRUGA
TDM10	TX	DRUG A_NS	Drug A Non-Smokers	2	GRPLBL	Group Label	Drug A, Non
TDM10	TX	DRUG A_NS	Drug A Non-Smokers	3	TRTDOS	Dose Level	200
TDM10	TX	DRUG A_NS	Drug A Non-Smokers	4	TRTDOSU	Dose Units	mg/day
TDM10	TX	DRUG A_NS	Drug A Non-Smokers	5	POPTYPE	Population Type	Non-Smokers
TDM10	TX	DRUG A_S	Drug A Smokers	1	ARMCD	Arm Code	DRUGA
TDM10	TX	DRUG A_S	Drug A Smokers	2	GRPLBL	Group Label	Drug A, Smoke
TDM10	TX	DRUG A_S	Drug A Smokers	3	TRTDOS	Dose Level	200
TDM10	TX	DRUG A_S	Drug A Smokers	4	TRTDOSU	Dose Units	mg/day
TDM10	TX	DRUG A_S	Drug A Smokers	5	POPTYPE	Population Type	Smokers
TDM10	TX	DRUG B_NS	Drug B Non-Smokers	1	ARMCD	Arm Code	DRUGB
TDM10	TX	DRUG B_NS	Drug B Non-Smokers	2	GRPLBL	Group Label	Drug B, Non
TDM10	TX	DRUG B_NS	Drug B Non-Smokers	3	TRTDOS	Dose Level	200
TDM10	TX	DRUG B_NS	Drug B Non-Smokers	4	TRTDOSU	Dose Units	mg/day
TDM10	TX	DRUG B_NS	Drug B Non-Smokers	5	POPTYPE	Population Type	Non-Smokers
TDM10	TX	DRUG B_S	Drug B Smokers	1	ARMCD	Arm Code	DRUGB
TDM10	TX	DRUG B_S	Drug B Smokers	2	GRPLBL	Group Label	Drug B, Smoke
TDM10	TX	DRUG B_S	Drug B Smokers	3	TRTDOS	Dose Level	200
TDM10	TX	DRUG B_S	Drug B Smokers	4	TRTDOSU	Dose Units	mg/day
TDM10	TX	DRUG B_S	Drug B Smokers	5	POPTYPE	Population Type	Smokers

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How Trial Sets Are Described (2)

Example TX records for Drug A smokers and non-smokers

STUDYID	DOMAIN	SETCD	SET	TXSEQ	TXPARMCD	TXPARM	TXVAL
TDM10	TX	DRUG A_NS	Drug A Non-Smokers	1	ARMCD	Arm Code	DRUGA
TDM10	TX	DRUG A_NS	Drug A Non-Smokers	2	GRPLBL	Group Label	Drug A, Non
TDM10	TX	DRUG A_NS	Drug A Non-Smokers	3	TRTDOS	Dose Level	200
TDM10	TX	DRUG A_NS	Drug A Non-Smokers	4	TRTDOSU	Dose Units	mg/day
TDM10	TX	DRUG A_NS	Drug A Non-Smokers	5	POPTYPE	Population Type	Non-Smokers
TDM10	TX	DRUG A_S	Drug A Smokers	1	ARMCD	Arm Code	DRUGA
TDM10	TX	DRUG A_S	Drug A Smokers	2	GRPLBL	Group Label	Drug A, Smoke
TDM10	TX	DRUG A_S	Drug A Smokers	3	TRTDOS	Dose Level	200
TDM10	TX	DRUG A_S	Drug A Smokers	4	TRTDOSU	Dose Units	mg/day
TDM10	TX	DRUG A_S	Drug A Smokers	5	POPTYPE	Population Type	Smokers

Show the same Arm is divided into two Sets

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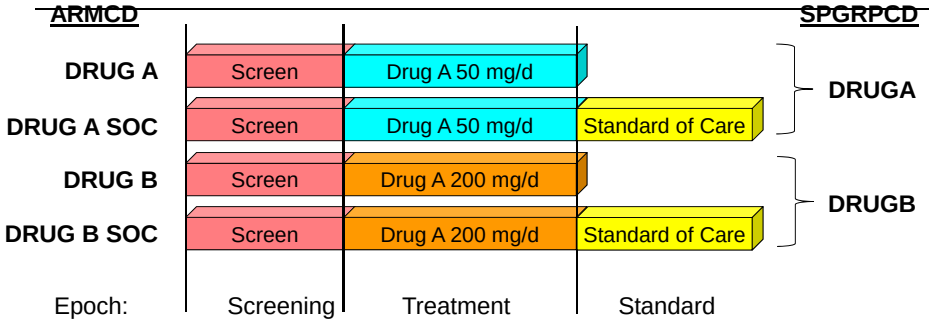
Trial Sets for Grouping Arms



STUDYID	DOMAIN	SETCD	SET	TXSEQ	TXPARMCD	TXPARM	TXVAL
2004-1	TX	DRUGA	Drug A	1	ARMCD	Arm Code	DRUG A
2004-1	TX	DRUGA	Drug A	2	SPGRPCD	Sponsor Group Code	DRUGA
2004-1	TX	DRUGASOC	Drug A Standard of Care	3	TRTDOS	Arm Code	DRUG A SOC
2004-1	TX	DRUGASOC	Drug A Standard of Care	4	TRTDOSU	Sponsor Group Code	DRUGA

Show the same Sponsor group Code for the two Arms

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SEND Team Update – Projects Underway

- Dermal/Ocular domains
- GeneTox studies
- Additional Types of Repro Studies
- SEND Model Limits
- Creation of Conformance Rules
- Multiple Codelists per Variable - How to Validate
- Protocol Amendments - Original Plan vs. Changed Plan
- PK Domains - Time vs. Concentration values may come from different animals at different time points

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PhUSE Nonclinical Working Groups – Completed Projects

- Nonclinical Standardization Roadmap Team
- NICE: Nonclinical Data Interconnectivity for Clinical Endpoint Predictivity
- Nonclinical Historical Controls
- Interorganizational SEND
- Nonclinical Working Group Industry Discussion Group
- Emerging Technologies Collaboration

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PhUSE Nonclinical Working Groups – Current Projects

- Nonclinical Study Data Reviewers Guide
- SEND Implementation User Group
- Application of SEND Data for Analysis
- Investigating Endpoint Modeling - Biomarkers, ADA data and Immunophenotyping
- Visualization of Group Related Differences in Histopathology Data
- Industry SEND Progress Survey
- Test Submission Forum Group
- Nonclinical Script Assessment Project
- Data Consistency: SEND Datasets and the Study Report

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What Nonclinical Studies Are Covered?

As of this date, the FDA is accepting SEND data for the following study types:

- Single-Dose Toxicology
- Repeat-Dose Toxicology
- Safety Pharmacology
- Carcinogenicity

In the future, these study types will be accepted:

- Reproductive Toxicology
- Ocular and Dermal Toxicity
- In Vitro Assays

Summary

- While the SENDIG and the SDTMIG have many differences, there are many similarities.
  - Many domains are shared
  - Many SDTM Variables were created as a result of SEND
  - Controlled Terminology is maintained separately, but harmonized wherever possible
- The POOLDEF table is specific to SEND, and allows for the identification of animals that contribute to data collected for a pool.
- Trial Sets was developed specifically for the SENDIG, but has potential applicability in human clinical trials. Trial Sets can be used to
  - Subdivide Arms
  - Group Arms

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