

Modeling Safety Pharmacology Study Designs in
SEND:
An Analysis of a Proof-of-Concept Dataset

Paper SI09

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- Compatibility of safety pharmacology studies and SEND
- Latin square cardiovascular safety pharmacology study designs
- Modeling Latin square study designs in SEND
- Analysis of a Latin square cardiovascular safety pharmacology proof-of-concept dataset using an R Shiny web application

Standard for Exchange of Nonclinical Data (SEND)



- SEND is a data standard created by the Clinical Data Interchange Standards Consortium (CDISC) to enable collection and presentation of nonclinical data in a consistent format.
- In December 2014, the FDA finalized a binding guidance requiring that certain clinical and nonclinical studies be submitted with standardized electronic data, formatted in accordance with the standards recognized in FDA Data Standards Catalog, which currently includes SEND versions 3.0 and 3.1.

SEND Compatibility of Safety Pharmacology Studies



- Core Battery (ICH S7A)

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 - Cardiovascular System
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 - Cardiovascular System
 - ✓ Endpoints modeled in the CV and EG domain in SEND version 3.1
- ? Latin square study designs have *theoretically* been modeled in SEND but use for analysis has not been *practically* demonstrated.

When are Safety Pharmacology Studies Compatible with SEND Version 3.1 Required?



- All studies supported by SEND version 3.1, including cardiovascular and respiratory safety pharmacology studies, initiated after March 15, 2019 for new drug applications (NDAs) or after March 15, 2020 for commercial investigation new drug applications (INDs) will be required to be submitted with SEND data, as specified in the FDA Data Standards Catalog.
 - Can data from Latin square design cardiovascular safety pharmacology studies modeled using SEND version 3.1 be used for analysis?
 - Short Answer: YES
 - Long Answer: *see rest of this presentation...*

Latin Square Study Designs

- What is a Latin square study design?
 - A study design in which each level of the independent variable of interest, e.g. drug treatment, occurs the same number of times with each level of two blocking factors, e.g. subject and time.
 - For example, one may measure the impact of drug treatment on cardiovascular parameters, e.g. QT interval, in dogs by recording ECG during treatment of one dog per dose level followed by a one-week washout period for one week per dose level.

Latin Square Study Designs

		<u>Time</u>			
		Week 1	Week 2	Week 3	Week 4
<u>Subject</u>	Dog #1	Vehicle	Low Dose	Mid Dose	High Dose
	Dog #2	Low Dose	Mid Dose	High Dose	Vehicle
	Dog #3	Mid Dose	High Dose	Vehicle	Low Dose
	Dog #4	High Dose	Vehicle	Low Dose	Mid Dose

Latin Square Study Designs

- Why do we use Latin square study designs?
 - Increase statistical efficiency → Decrease # of animals required
 - By blocking across both time and subject, the impact of a treatment can be assessed using only 1 animal per dose level, yet each dose level will be evaluated in as many animals as there are dose levels.
 - If a particular animal or study day is associated with abnormal results, this will increase the observed variability but not bias the assessment of treatment effects as the abnormal results will be evenly distributed across all treatment levels.

Modeling Latin Square Designs in SEND

- In traditional parallel toxicology study designs, e.g. repeat-dose toxicology studies, each animal is assigned to a trial set denoting the treatment level administered. Study findings can be linked to treatment levels by grouping animals by trial set.
- In a Latin square design, each animal is assigned to a trial set denoting the sequence of treatment levels administered. Study findings cannot be directly linked to treatment levels based only on Animal ID or trial set.

CDISC-SEND Safety Pharmacology Proof-of-Concept Pilot



- The CDISC-SEND Safety Pharmacology Working Group has created a proof-of-concept SEND dataset to model a Latin square cardiovascular safety pharmacology study.
 - Objective: To determine if SEND datasets for Latin square safety pharmacology study designs can be used for analysis.

Mapping SEND Findings to Treatment: Parallel Study Design



Findings

Body Weight

BW Domain
USUBJID

Clinical Pathology

LB Domain
USUBJID

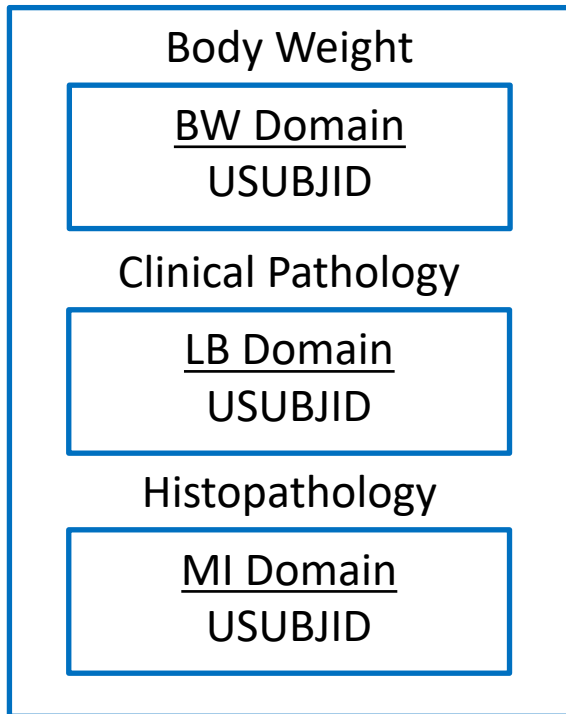
Histopathology

MI Domain
USUBJID

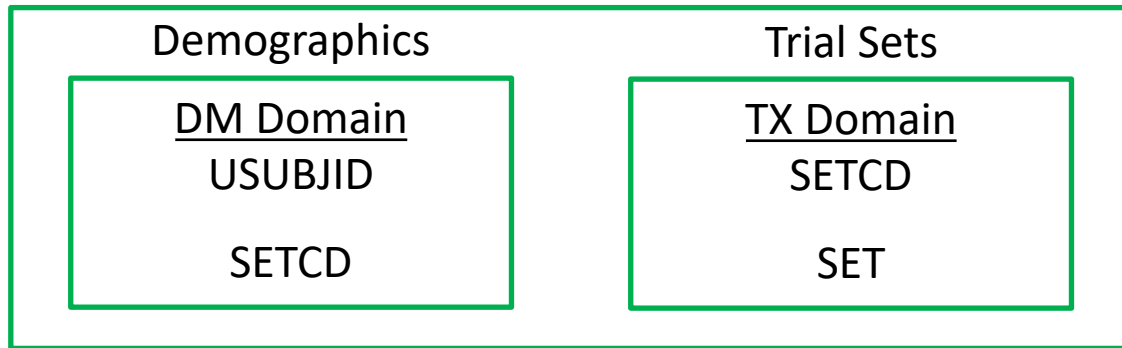
Mapping SEND Findings to Treatment: Parallel Study Design



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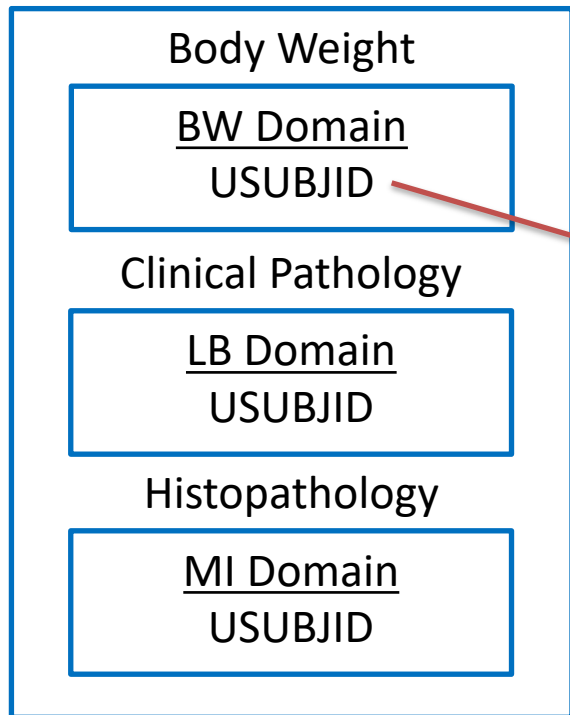


Study Design

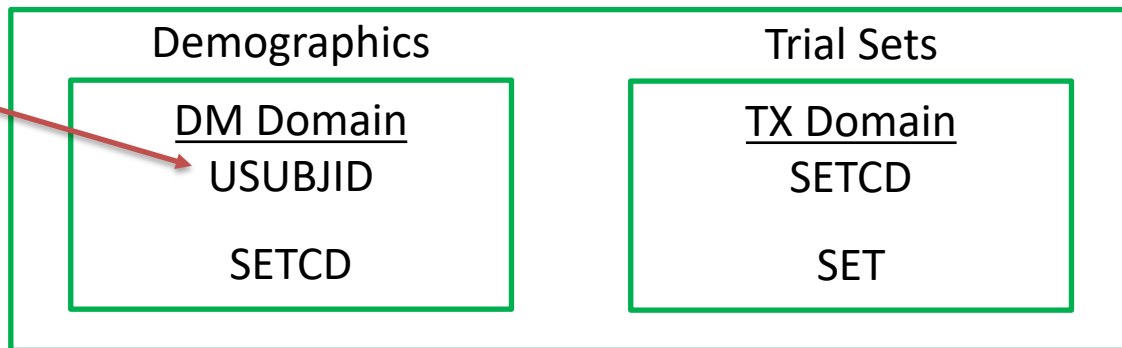


Mapping SEND Results to Treatment: Parallel Study Design

Findings



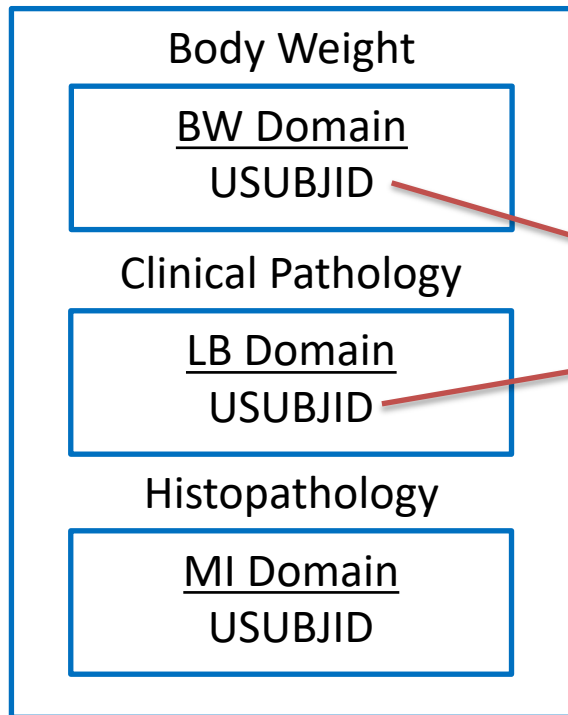
Study Design



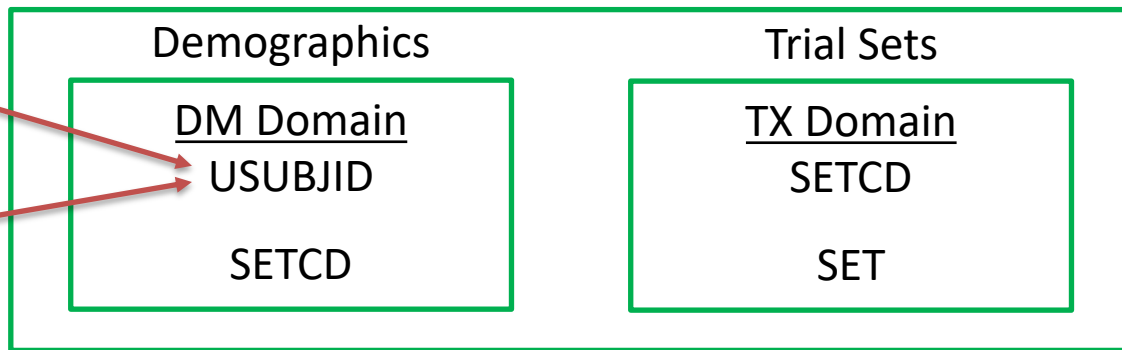
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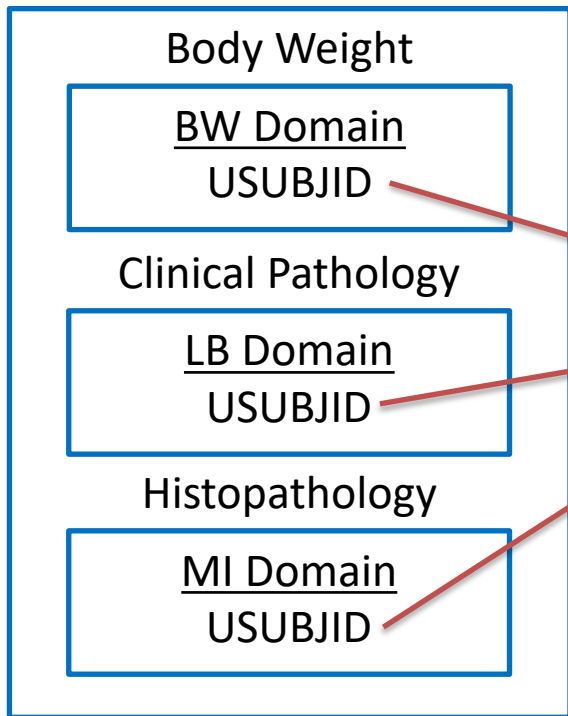
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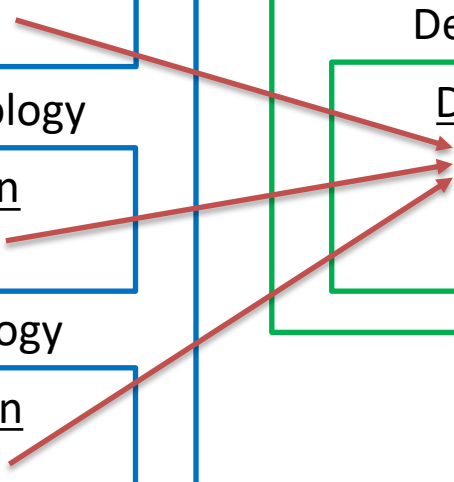
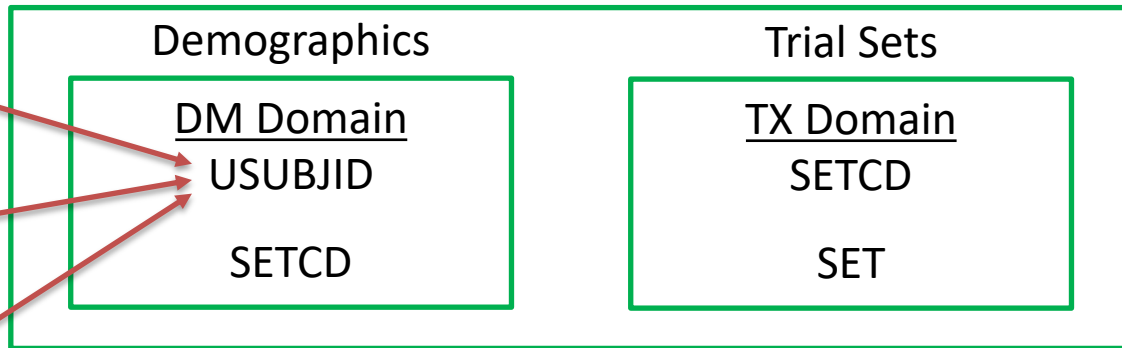
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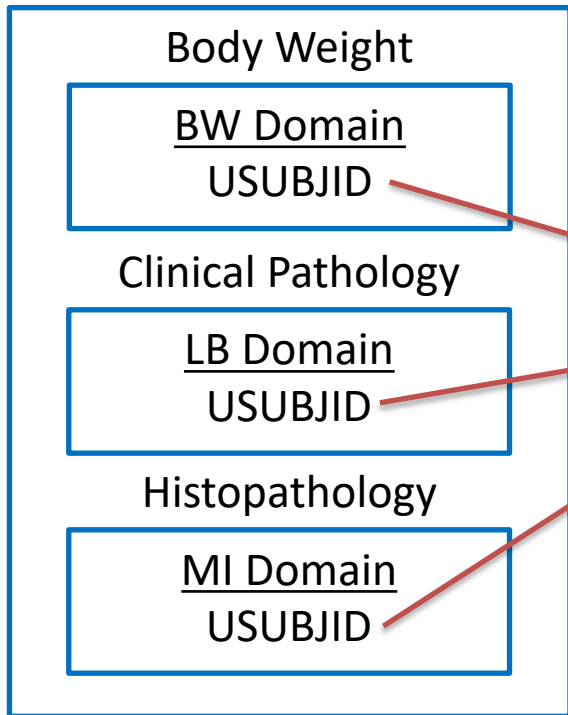
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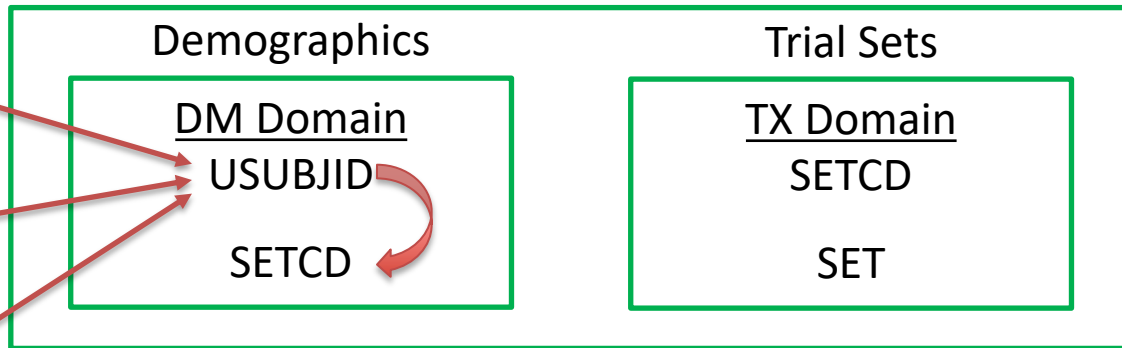
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Findings



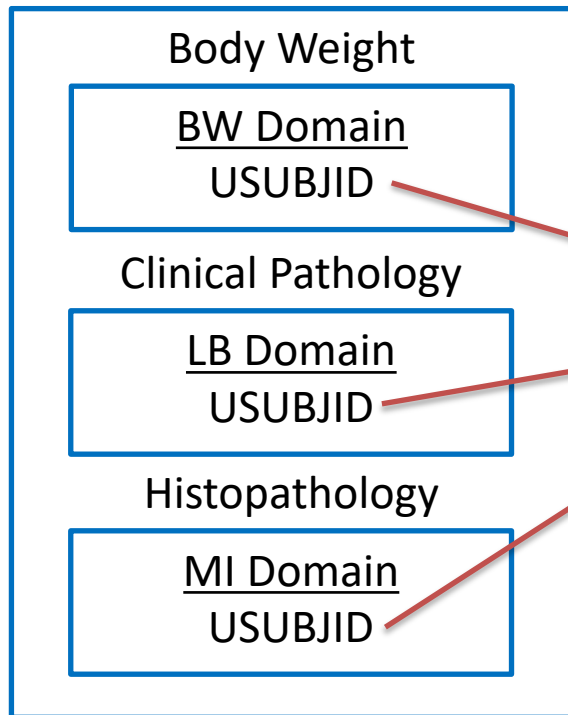
Study Design



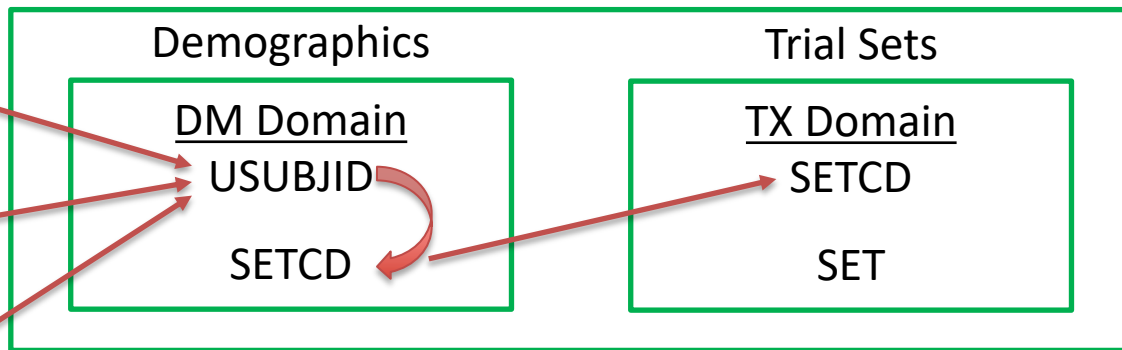
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Findings



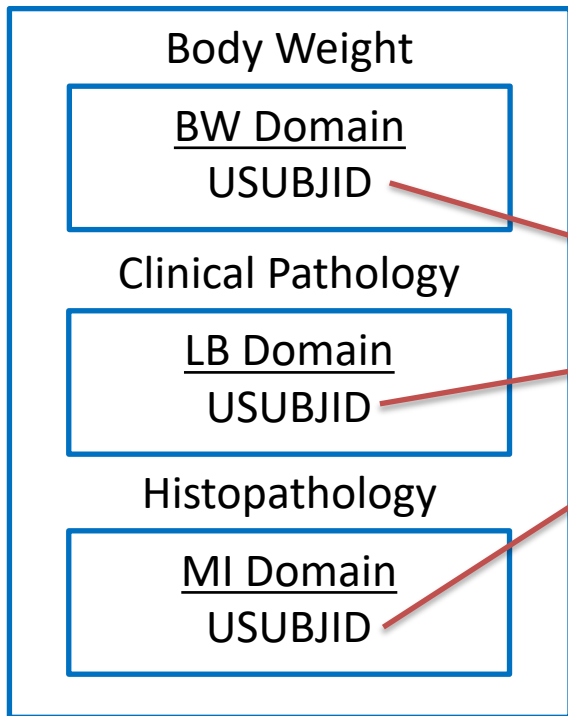
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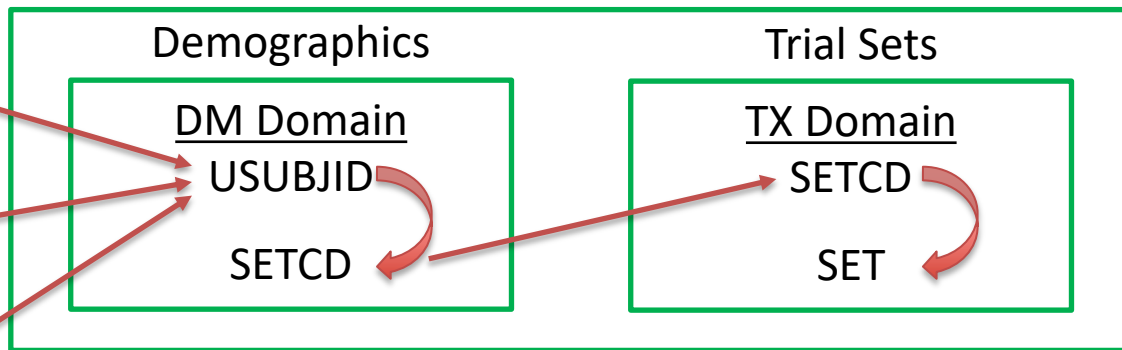
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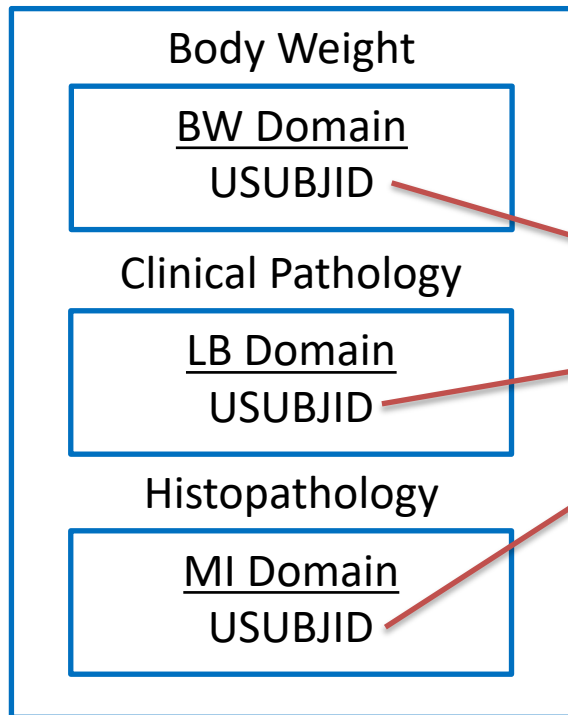
Study Design



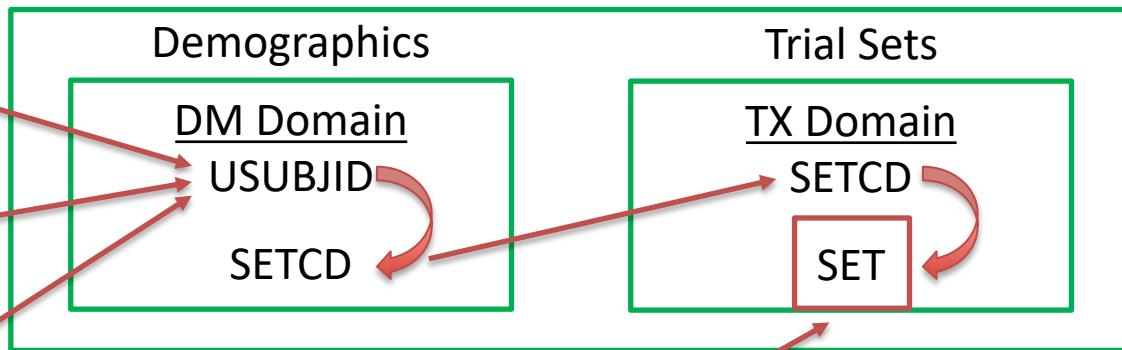
Mapping SEND Results to Treatment: Parallel Study Design



Findings



Study Design

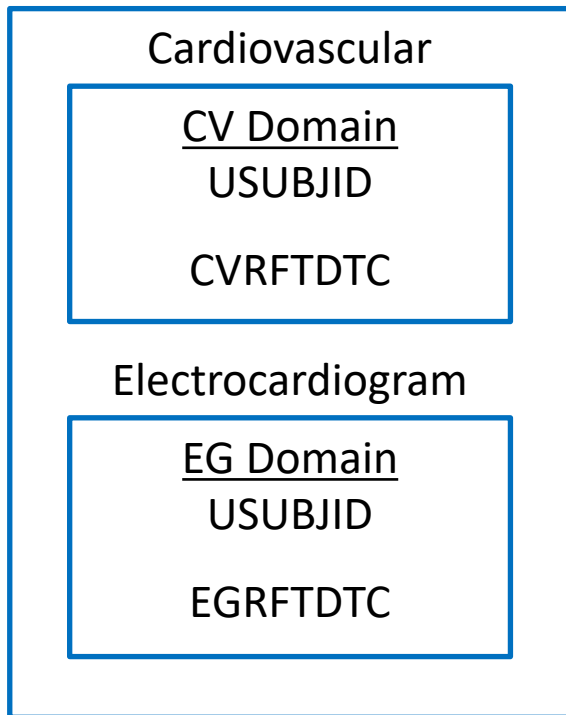


Treatment Description

Mapping SEND Findings to Treatment: Latin Square Study Design

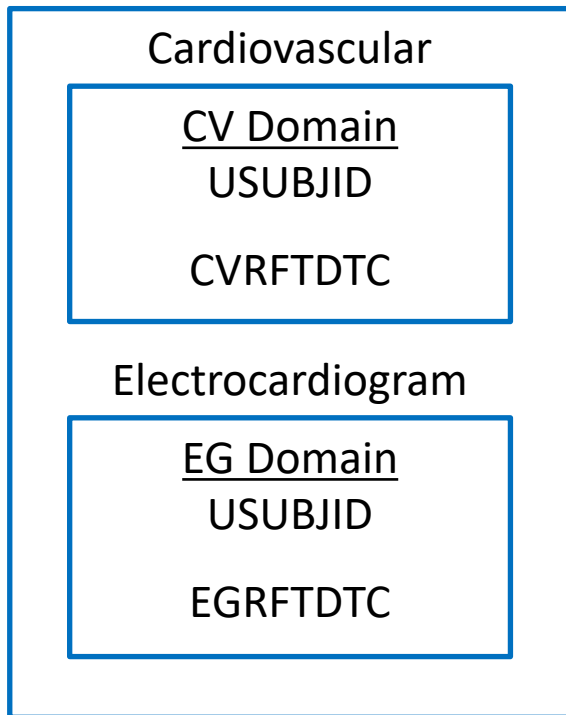


Findings

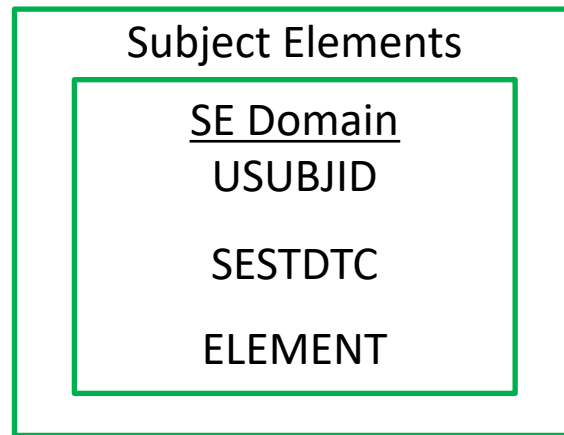


Mapping SEND Findings to Treatment: Latin Square Study Design

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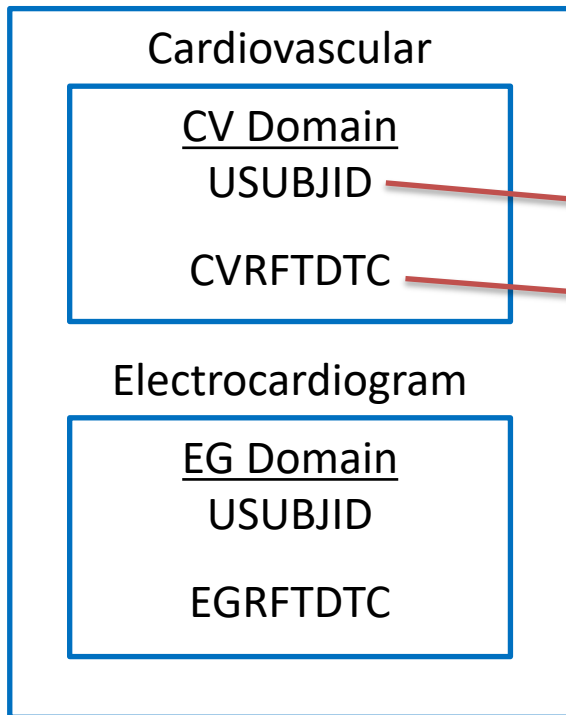


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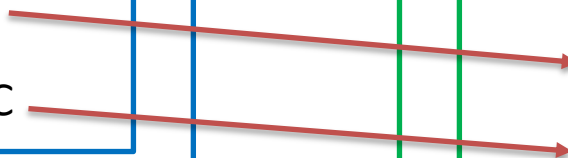
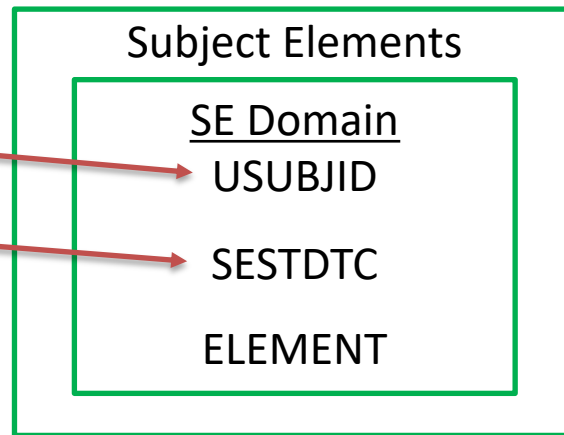


Mapping SEND Findings to Treatment: Latin Square Study Design

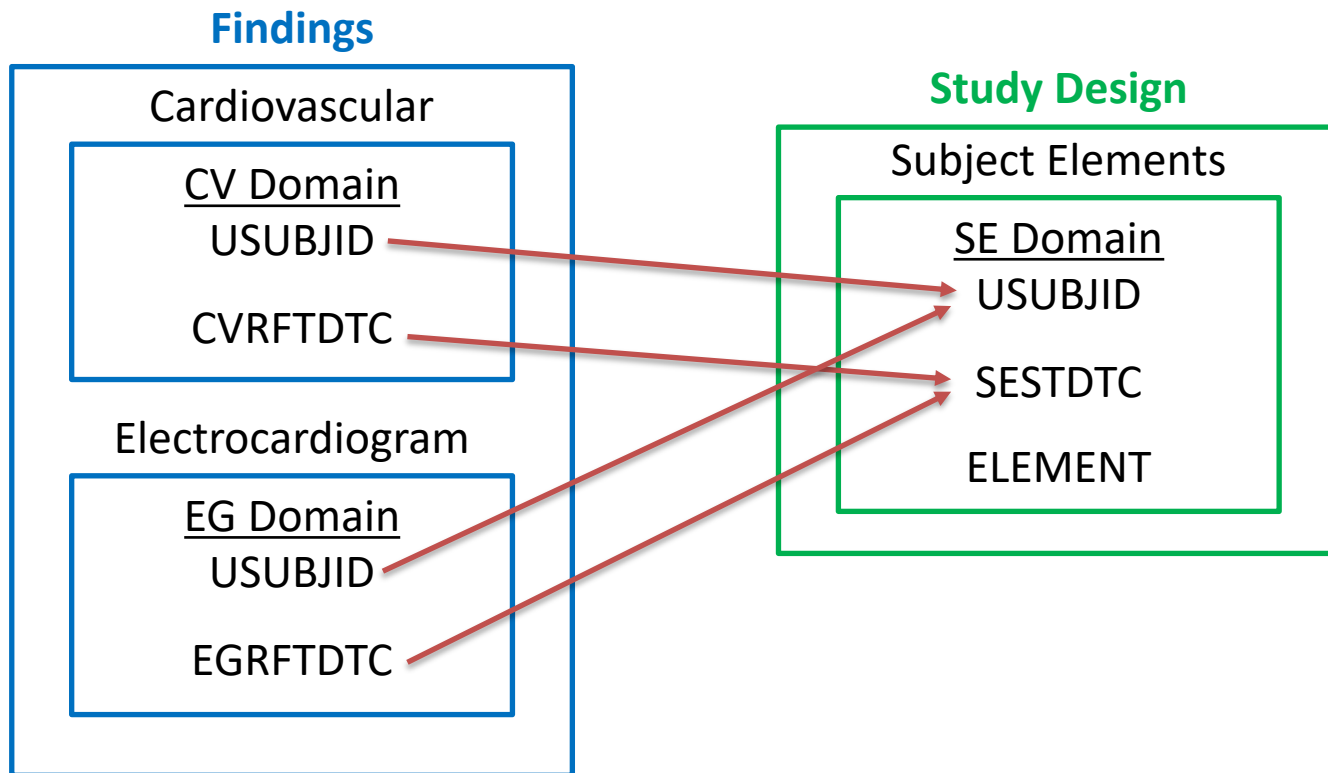
Findings



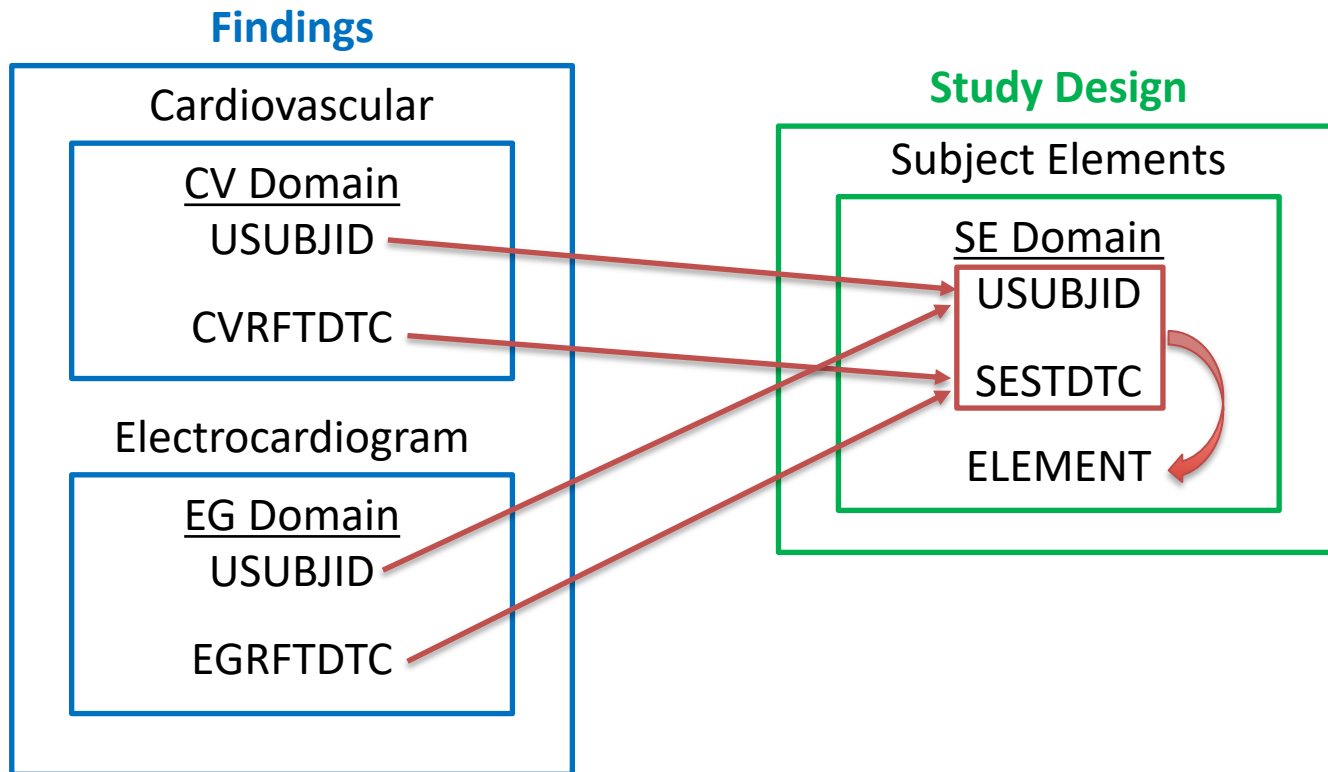
Study Design



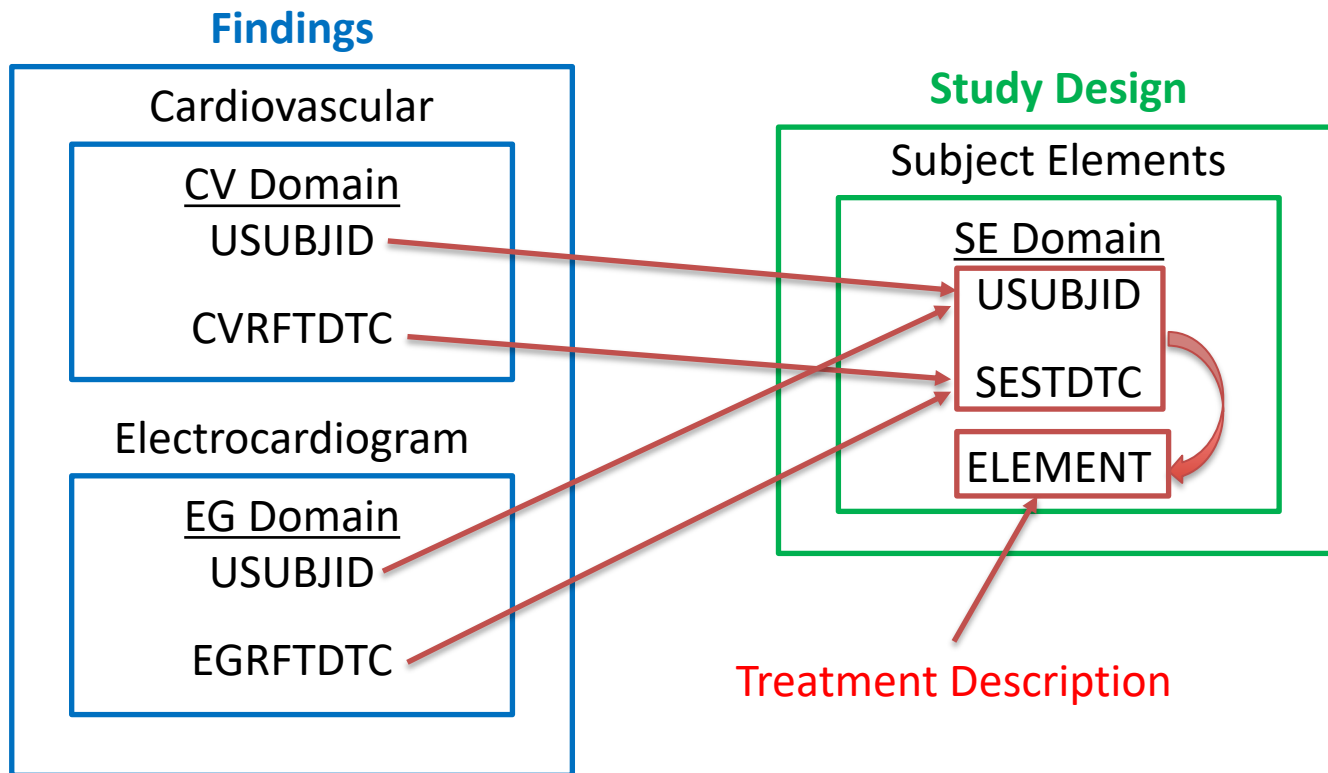
Mapping SEND Findings to Treatment: Latin Square Study Design



Mapping SEND Findings to Treatment: Latin Square Study Design



Mapping SEND Findings to Treatment: Latin Square Study Design



CDISC-SEND Safety Pharmacology Proof-of-Concept Pilot



- This dataset illustrates use of the Subject Elements (SE) domain to provide a direct link between study results and treatment levels.
 - Conventions used in proof-of-concept dataset SE domain:
 - Treatment levels are recorded in the ELEMENT variable.
 - The start of the treatment element in SESTDTC contain the date of dose to match exactly with the –RFTDTC variable values in the findings domains.

CDISC-SEND Safety Pharmacology Proof-of-Concept Pilot



- In collaboration with the Pharmaceutical Users Software Exchange (PhUSE) Nonclinical Scripts Working Group, an interactive R Shiny web application has been developed to demonstrate the utility of the proof-of-concept dataset for analysis.
- The application provides tables, figures, a view of the raw SEND data, and a brief explanation of the analysis logic.

R Shiny Web Application

- R is a free software environment for statistical computing and graphics (<https://www.r-project.org>).
- Shiny is an R package developed by RStudio to enable R programmers to easily build interactive web applications (<https://shiny.rstudio.com>).
- The R Shiny web application is currently hosted on a public R Shiny server provided by RStudio (<https://www.shinyapps.io>).
 - <https://phuse-nonclinical-scripts.shinyapps.io/CDISC-SEND-Safety-Pharmacology-POC>

Application Details

- The application was developed in collaboration with the Pharmaceutical Users Software Exchange (PhUSE) Nonclinical Scripts Working Group.
- The proof-of-concept SEND dataset and the source code for the R Shiny application are both available on GitHub:
 - <https://github.com/phuse-org/phuse-scripts/tree/master/data/send/CDISC-Safety-Pharmacology-POC>
 - <https://github.com/phuse-org/phuse-scripts/tree/master/contributed/Nonclinical/R/Safety%20Pharmacology%20Pilot>

Software Demonstration

<https://phuse-nonclinical-scripts.shinyapps.io/CDISC-SEND-Safety-Pharmacology-POC>