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

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ABSTRACT

The Clinical Data Interchange Standards Consortium (CDISC) Standard for Exchange of Nonclinical Data (SEND) Safety Pharmacology Working Group has created a proof-of-concept (POC) SEND dataset to model Latin square cardiovascular safety pharmacology studies. In collaboration with the Pharmaceutical Users Software Exchange (PhUSE) Nonclinical Scripts Working Group, an R-Shiny® web application has been developed to validate the utility of this POC dataset. This application will demonstrate how tables and figures can be generated from the dataset, and an explanation of the methods employed by the analysis software will be provided. This POC dataset and open source analysis software may be used to promote best practices across the pharmaceutical industry with respect to the modeling of Latin square study designs in SEND. The POC dataset and the source code for the R Shiny application are both publicly available on GitHub at https://github.com/phuse-org/phuse-scripts, and the application is currently hosted publicly on shinyapps.io at https://phuse-nonclinical-scripts.shinyapps.io/CDISC-SEND-Safety-Pharmacology-POC/.

INTRODUCTION

In December 2014, the United States Food and Drug Administration (FDA) finalized a binding guidance requiring specific types of clinical and nonclinical study reports to be submitted with standardized electronic data. A list of data exchange standards currently supported by the FDA can be found in the FDA Data Standards Catalog, along with requirement dates for each. Any study that can be supported by a data exchange standard and was initiated after that standard's requirement date is required to be submitted with standardized electronic data. The only data exchange standard currently supported for nonclinical study data is the Standard for Exchange of Nonclinical Data (SEND), which was created by the Clinical Data Interchange Standards Consortium (CDISC). The requirement dates for SEND Version 3.0 are December 17, 2016 for study reports included in New Drug Applications (NDAs) and December 17, 2017 for study reports included in Investigational New Drug Applications (INDs), and the nonclinical studies supported by SEND Version 3.0 include single-dose general toxicology, repeat-dose general toxicology, and carcinogenicity studies. The types of studies supported by SEND were expanded in Version 3.1 to also include respiratory and cardiovascular safety pharmacology studies and the requirement dates are March 15, 2019 for NDAs and March 15, 2020 for INDs. This means that for new NDA submissions, any cardiovascular or respiratory safety pharmacology study initiated after March 15, 2019 will need to be submitted with SEND Version 3.1 datasets.

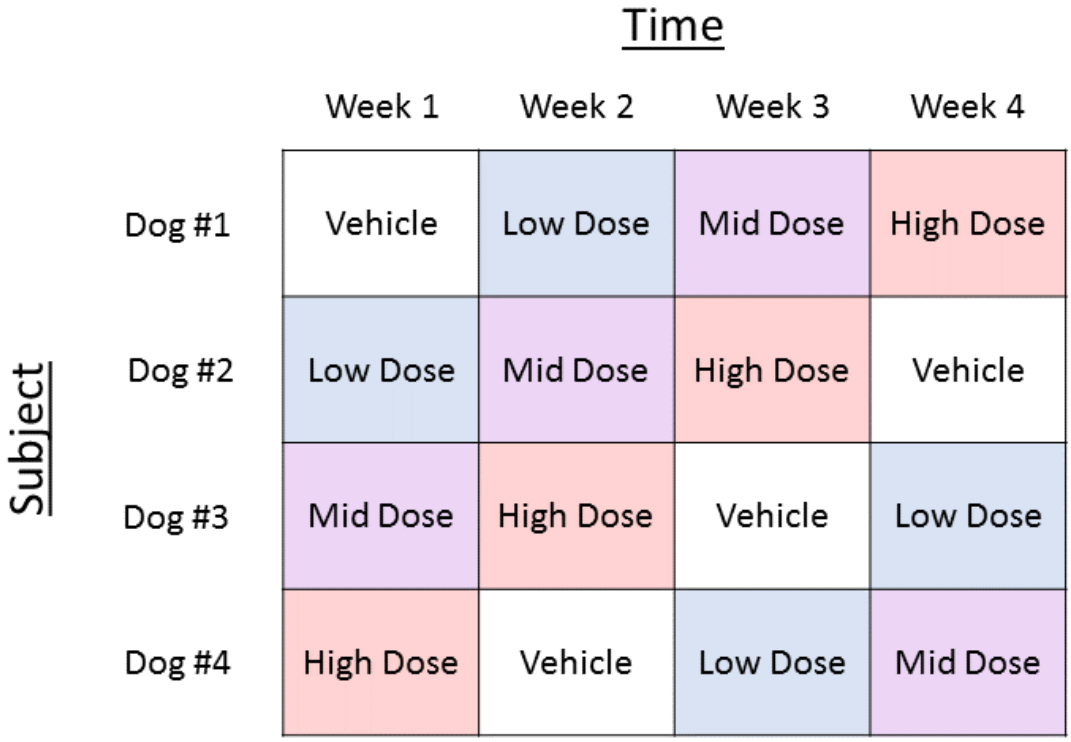
Unlike general toxicology and carcinogenicity studies, which conventionally employ parallel study designs, cardiovascular safety pharmacology studies often employ Latin square study designs. SEND has been theoretically designed to accommodate cross-over study designs such as Latin square, but practical analysis of a SEND dataset modeling a Latin square study design has not yet been publicly demonstrated. As such, the CDISC-SEND Safety Pharmacology Working Group created a proof-of-concept (POC) SEND dataset modeling mock data using a Latin square cardiovascular safety pharmacology study design, and in collaboration with the Pharmaceutical Users Software Exchange (PhUSE) Nonclinical Scripts Working Group, an R Shiny® web application has been developed to validate the utility of this POC dataset.

LATIN SQUARE CARDIOVASCULAR SAFETY PHARMACOLOGY STUDY DESIGN

Cardiovascular safety pharmacology studies are included in the core battery of safety pharmacology studies that are required to be conducted prior to the initiation of clinical studies in accordance with ICH S7A, and ICH M3(R2). These studies typically evaluate the endpoints such as blood pressure, heart rate, and electrocardiogram parameters, including QT interval, following single-dose administration of test article in beagle dogs at dose levels high enough to establish a concentration-effect relationship if one exists. As these studies evaluate the effects of single-dose administration of the test article, they are amenable to cross-over study designs in which each subject receives multiple treatments separated by a washout period without treatment. A Latin square design is a special case of a cross-over design in which each subject receives all treatment levels throughout the course of the study

(Figure 1). By employing a Latin square experimental design, variation can be controlled across two blocking factors, e.g. subject and time, simultaneously increasing statistical efficiency and decreasing the number of animals required to be used in the study. A Latin square cardiovascular safety pharmacology study employing only one dog per treatment level can achieve the same level of statistical power as a parallel design with several dogs per dose level. Due to the ethical and financial benefits of the reduced animal requirements of the Latin square design, cardiovascular safety pharmacology studies are commonly implemented with this design.

Figure 1: Schematic of a Latin Square Cardiovascular Safety Pharmacology Study Design

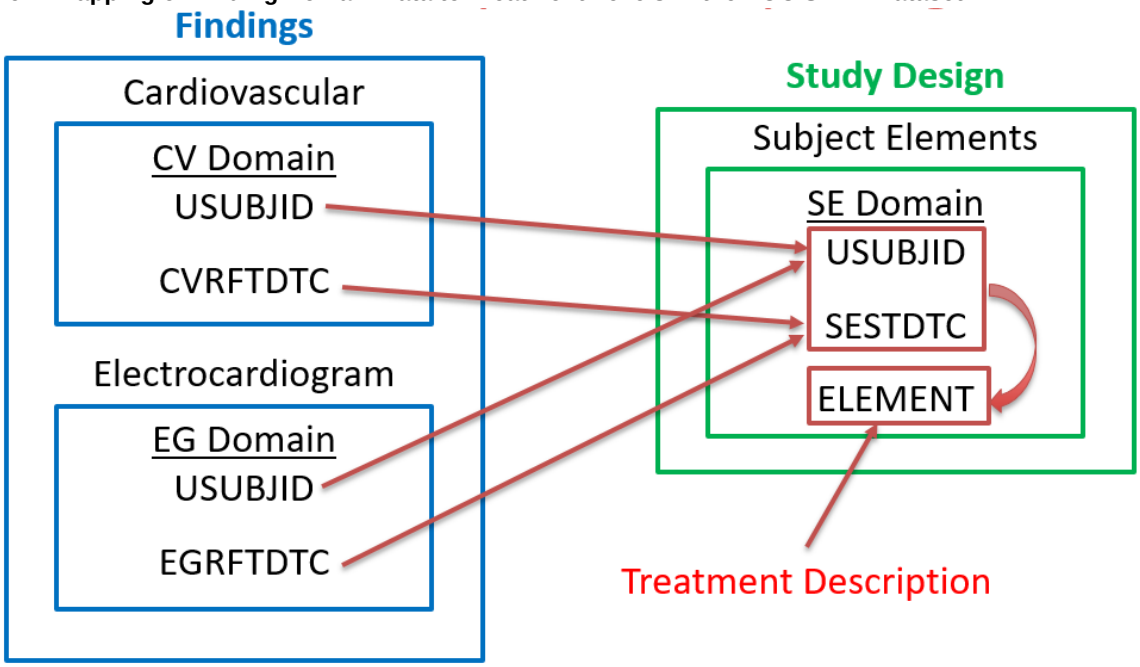


MODELING LATIN SQUARE CARDIOVASCULAR SAFETY PHARMACOLOGY STUDIES IN SEND

SEND datasets are now being routinely created and analyzed for parallel-design toxicology studies, but the use of SEND to model Latin square study designs is still novel. The primary difference between parallel and Latin square study designs is that in a parallel study design, each subject receives the same treatment throughout the entire study whereas in a Latin square design, each subject receives all the treatments throughout the course of the study. Consequently, in a Latin square study design, the treatment associated with a study endpoint cannot be simply inferred from study subject's treatment group allocation as it could in a parallel study. Instead, both the subject and time of dosing must both be known in order to ascertain which treatment was administered.

The POC dataset created by the CDISC-SEND Safety Pharmacology Working Group provides an example of how a Latin square study design can be modeled in SEND. The SEND standard is flexible such that the implementation chosen by the working group to generate the POC dataset is not the only way that this study design can be modeled, but the POC dataset can be used as a publicly available template to aid in the creation of SEND datasets for these types of studies. Furthermore, as it was created by a panel of SEND and safety pharmacology experts, the conventions used may serve as best practices to facilitate the creation and analysis of these datasets. Two noteworthy conventions were used in the creation the of the POC dataset: (1) the ELEMENT variable in the SE domain was populated with human readable descriptions of the treatment levels and (2) the SESTDTC variable in the SE domain was populated to match exactly with the --RFTDTC variable in the finding domains. This allowed treatment levels to be matched with study endpoint data by simultaneously finding the ELEMENT in the SE domain that matched both the USUBJID from the finding domain and the SE domain along with the --RFTDTC from the finding domain and the SESTDTC from the SE domain as shown in Figure 2.

Figure 2: Mapping of Finding Domain Data to Treatment Levels in the POC SEND Dataset



The logic of this double-join is also demonstrated in the following SQL code using CV as the relevant finding domain:

```
SELECT * FROM CV, SE
JOIN CV, SE
ON CV.USUBJID = SE.USUBJID
AND CV.CVRFTDTC = SE.SESTDTC
```

ANALYSIS OF A LATIN SQUARE CARDIOVASCULAR SAFETY PHARMACOLOGY STUDY MODELED IN SEND USING R SHINY

In order to demonstrate the practical utility of the POC dataset created by the CDISC-SEND Safety Pharmacology Working Group, the PhUSE Nonclinical Scripts Working Group created a publicly available, interactive R Shiny web application that can be freely accessed at:

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

The application displays summary tables (Figure 3) and figures (Figure 4) as well as a view of the raw SEND data (Figure 5) and a brief explanation of the analysis logic (Figure 6). By default, the application displays the group mean values at each treatment level within each sex, but users can interactively select from several options to alter the display, e.g. show individual animal data rather than group means or exclude results from analysis by finding domain, sex, treatment level, subject ID, or dosing day. The application does not present an exhaustive representation of all possible analyses and visualizations that could be generated from the data but is designed to highlight the advantages that SEND datasets can offer over the static summary tables and figures typically included in traditional study report submissions.

R SHINY

R is a free and open source software environment for statistical computing and graphics that is publicly available at https://www.r-project.org. Shiny is an R package developed by RStudio® to enable R programmers to easily build interactive web applications without requiring R developers to know or write any HTML, CSS, or javascript code, although it does include functions that allow advanced users to embellish their web applications with custom HTML, CSS, and/or javascript code. The R Shiny web application is currently hosted on a public R Shiny server provided by RStudio.

Figure 3: Screenshot of Summary Table from R Shiny Web Application

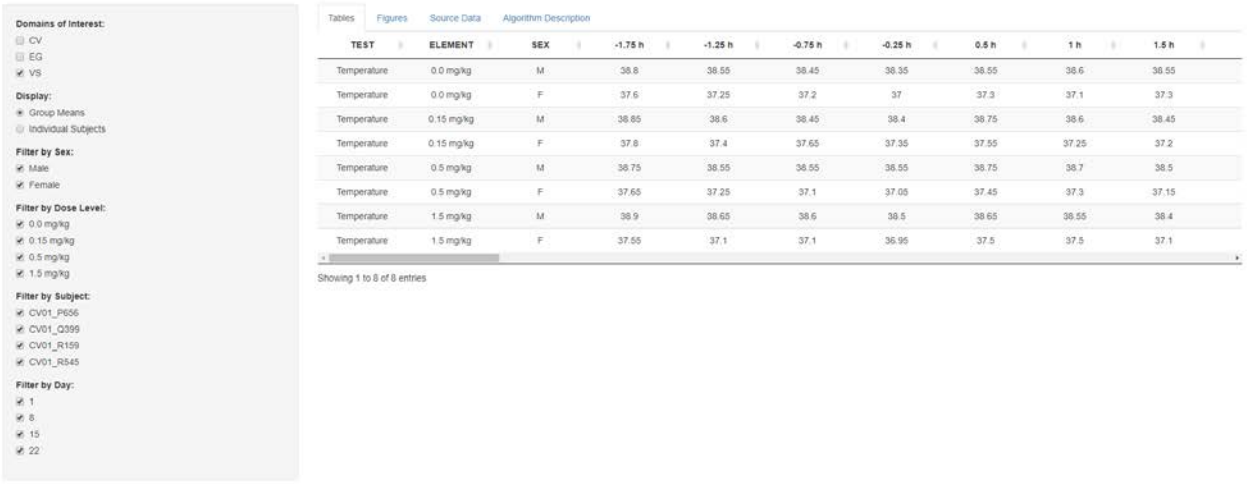


Figure 4: Screenshot of Summary Figure from R Shiny Web Application

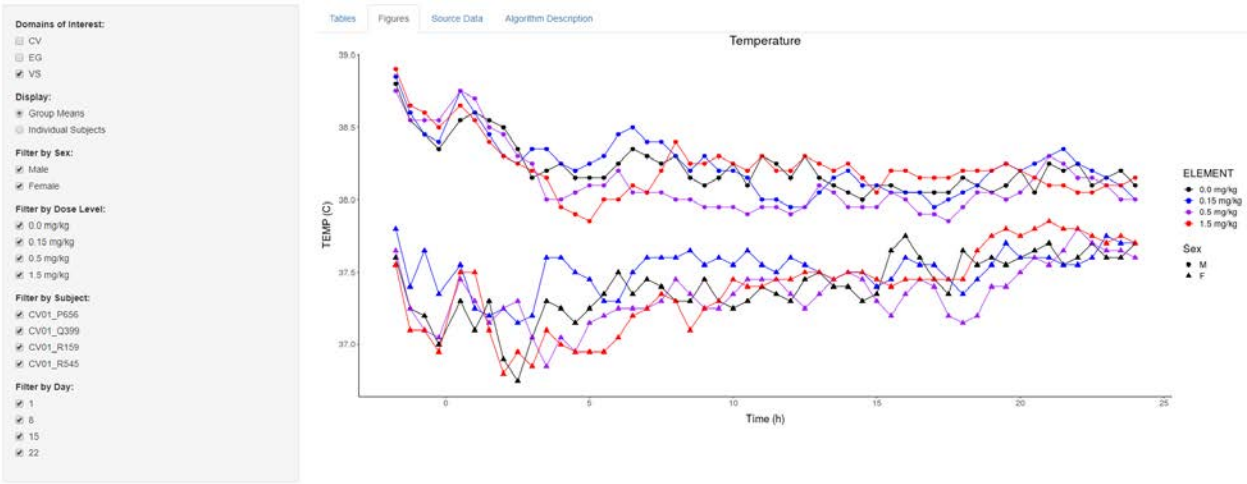


Figure 5: Screenshot of Raw SEND Data View from R Shiny Web Application

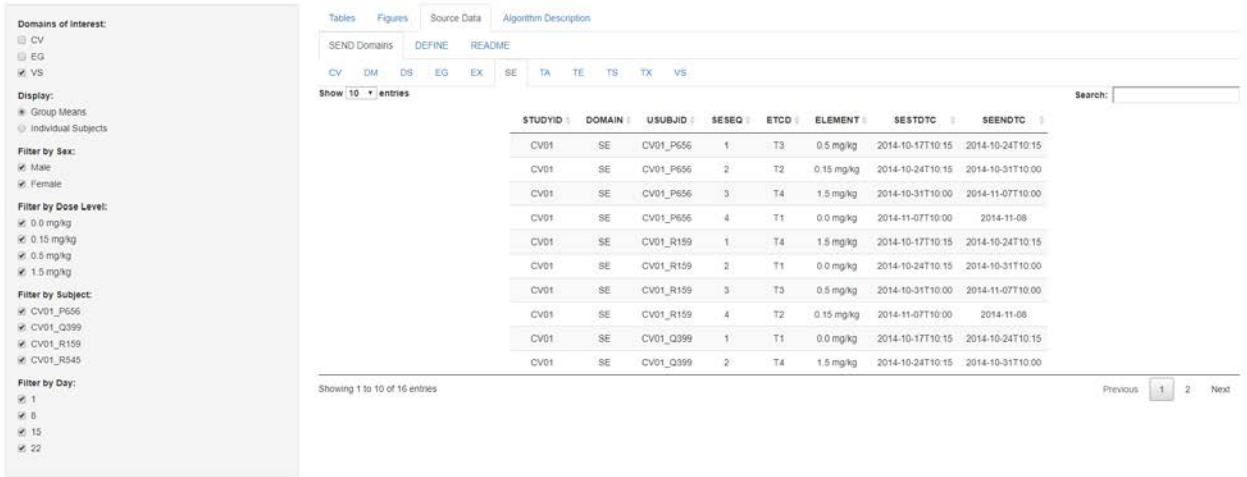
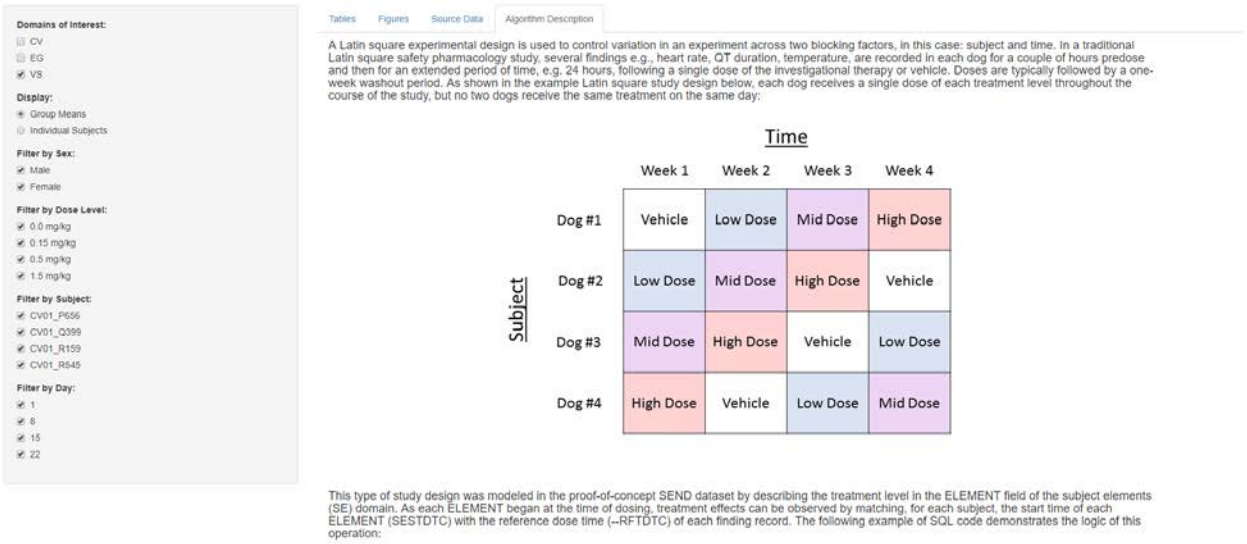


Figure 6: Screenshot of Brief Description of Analysis Logic from R Shiny Web Application



CONCLUSION

Taken together, the POC dataset, created by the CDISC-SEND Safety Pharmacology Working Group, along with the analysis produced by the R Shiny web application, created by the PhUSE Nonclinical Scripts Working Group, provide an end-to-end demonstration of how Latin square cardiovascular safety pharmacology studies can be effectively modeled and analyzed using SEND. Both the dataset and analysis application are publicly available at https://github.com/phuse-org/phuse-scripts and can be used to promote best practices in the creation and analysis of SEND data with respect to these studies.

DISCLAIMER

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

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