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Decrypting SDTM Trial Design Datasets for Complex Study Designs

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ABSTRACT

In recent years, increasing number of intervention studies are conducted using various trial designs to minimize cost, time and failure rates, thus enhancing the efficiency of clinical trial conduct. Complexity levels of trial design change based on the strategy of the study. A clinical study can follow multiple masking techniques and/or multiple interventions based on conditional treatment assignment by re-randomization (based on the outcome of the preceding period of the study).

The Trial Design Model (TDM) in the SDTM provides a standardized way to describe the features of a clinical trial. Creating trial design datasets for complex study designs can be challenging in terms of data presentation because, it requires inferring from the protocol and cannot be created from the electronic data. Through relevant case studies this paper will present some of the possible permutations and combinations in creating, SDTM trial design datasets for complex study designs.

INTRODUCTION

The objective of most clinical trials is to estimate the magnitude of treatment effects or estimate differences in treatment effects. Precise statements about observed treatment effects are dependent on a study design that allows the treatment effect to be sorted out from person-to-person variability in response. An accurate estimate requires a study design that minimizes bias. The design of the clinical trial/trial design of clinical studies is the plan for what assessments will be conducted to the subjects and what data/type of data to be collected to address the trial's objective in analysis perceptive.

The purpose of trial design domains is to provide the standardized description of overall plan and design of the clinical study retrospectively from the protocol in the data form. These datasets should enable quick familiarization with the clinical study handled.

The trial design domains provide rapid understanding of the study and make the information centrally accessible and searchable. Its relatively has small number of rows of data and easy to comprehend; has standard and relatively simple data structures. The TDMs are useful for both FDA reviewers and internal sponsor use.

STUDY PROTOCOL

Experienced investigators/scientists have mostly acknowledged that prestudy planning and peer review is crucial to the scientific success of any research project. The written study protocol, is the most viable manifestation of that planning, is the anvil on which most research proposals come to be tempered.

A protocol is typically the first document created when starting a clinical trial. Although content differs from study to study, most protocols contain similar types of information. For example, protocols have a title and contain information about the drug under study, study objective(s), the study design (e.g., blinded, crossover), inclusion and exclusion criteria, and a schedule of visits with planned activities at each visit. When this type of information is captured as data, rather than as simple text, it can be used throughout all stages of the process, such as when setting up the database, creating dataset metadata, and generating tables in study reports.

SIGNIFICANCE OF PROTOCOL AND ITS AMENDMENTS

The clinical trial protocol provides the design for the study conduct and sets out the endpoints of the study up-front. There is clear guidance on how and when to measure and evaluate the study endpoints.

The primary endpoint usually assesses the treatment efficacy (the ability of an intervention or drug to reproduce a desired effect). A trial may also define one or more secondary endpoints. These typically include secondary efficacy measures (additional evaluations designed to assess the clinical effectiveness of the drug in controlling disease) and safety endpoints (designed to measure tolerability and safety of treatment over the period of study).

STUDY DESIGN

Study Design is a critical activity in the lifecycle of a clinical research study. It is the foundational blueprint for the execution of the study, forming the basis for the study protocol. The trial design refers to the overall strategy that you choose to integrate the different components of the study in a coherent and logical way, thereby, ensuring you will effectively address the research problem; it constitutes the blueprint for the collection, measurement, and analysis of

data. The function of a trial design is to ensure that the evidence obtained enables you to effectively address the research problem logically and as unambiguously as possible.

TYPES OF STUDY DESIGN

SINGLE GROUP DESIGN
Describes a clinical trial in which all participants receive the same intervention/study drug.

PARALLEL DESIGN
Describes a clinical trial in which two or more groups of participants receive different interventions. For example, a two-arm parallel design involves two groups of participants. One group receives drug A, and the other group receives drug B. So, during the trial, participants in one group receive drug A "in parallel" to participants in the other group, who receive drug B.

CROSS-OVER DESIGN
Describes a clinical trial in which groups of participants receive two or more interventions in an order. For example, a two-by-two cross-over design involves two groups of participants. One group receives drug A during the initial phase of the trial, followed by drug B during a later phase. The other group receives drug B during the initial phase, followed by drug A. So, during the trial, participants "cross over" to the other drug. All participants receive drug A and drug B at some point during the trial but in a different order, depending on the group to which they are assigned.

FACTORIAL DESIGN
Describes a clinical study in which groups of participants receive one of several combinations of interventions. For example, a two-by-two factorial design involves four groups of participants. Each group receives one of the following pairs of interventions: 1) drug A and drug B, 2) drug A and a placebo, 3) a placebo and drug B, or 4) a placebo and a placebo. So, during the trial, all possible combinations of the two drugs (A and B) and the placebos are given to different groups of participants.

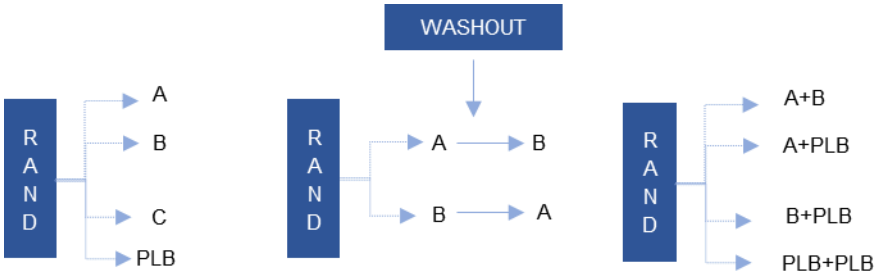

Figure 1. Schematic diagrams of Parallel, Cross-Over and Factorial Study Designs

NECESSITY FOR COMPLEX STUDY DESIGN
Increasing number of clinical studies are conducted with many facets of trial design to minimize cost, time and failure rates especially in oncology trials and to enhance efficiency of clinical trial conduct. The trial design becomes complex because the design of trial changes within a study depending on the strategy of the study. A clinical study can have multiple masking techniques to be followed sequentially in different periods of study and/or multiple interventions based on conditional treatment assignment by re-randomization based on preceding period outcome of the study.

TRIAL DESIGN MODEL(TDM)

A Trial Design Model (TDM) domain is a special purpose data set, which represent information about the study design but do not contain subject data. The purpose of Trial Design Model domain is to provide the clear description of overall plan and design of the study basically the Clinical study report in the data form. There are six TDM domains that are well defined on the SDTM Implementation Guide. They are:

TRIAL ARMS (TA)	This TDM describes the sequence of elements in each epoch for each treatment arm and thus describes the complete sequence of elements in each treatment arm. It is always recommended to design treatment arm the study cell level then the element level to cover each planned element to be covered in study
TRIAL ELEMENTS (TE)	This TDM contains the information regarding the planned elements that are included in the study and subjects are assigned to these elements. In the TE domain, important thing to note that there are no gaps between elements, as one element starts right after that the other.
TRIAL INCLUSION EXCLUSION (TI)	This TDM contains all the inclusion and exclusion criteria for the trial, and thus provides information that may not be present in the subject-level data on inclusion and exclusion criteria.

TRIAL VISITS (TV)	This TDM represents the planned visits, or "clinical encounters" that are defined with the protocol's time and event schedule. These visits basically are described in VISIT, VISITNUM, and VISITDY.
TRIAL SUMMARY (TS)	This TDM domain allows the sponsor to submit a summary of the trial in a structured format.
TRIAL DISEASE ASSESSMENTS (TD)	This TDM domain provides information on the protocol-specified disease assessment schedule.

Trial Design Basics

ELEMENT	Building block for creating study cells
ARM	Arm is composed of study cells. A path through the study which describes what activities the subject will be involved.
EPOCH	An interval of time in the planned conduct of a study during which treatment is constant.
STUDY CELLS	These are combination of arm and epoch. Each study cell represents an implementation of the purpose of its associated epoch. Since the trial is divided into epochs, each planned path through the trial (i.e., each arm) is divided into pieces, one for each epoch. Each of these pieces is called a study cell.
VISIT	A Visit is defined as a clinical encounter that encompasses planned and unplanned trial interventions, procedures, and assessments that may be performed on a subject.

TRIAL DESIGN MATRIX

A Trial Design Matrix, an alternative format for representing most of the information in the diagram that shows Arms and Epochs, and emphasizes the Study Cells.

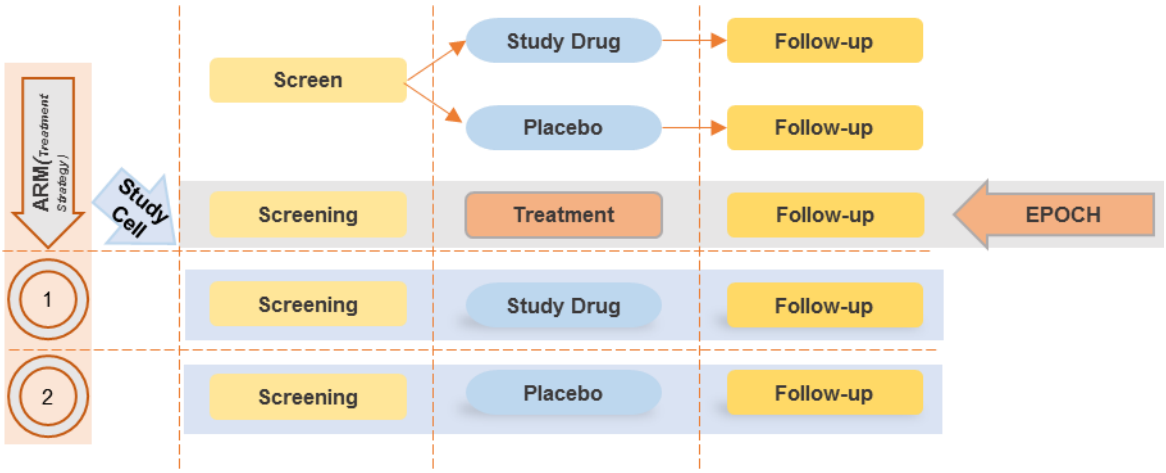

Figure 2. Schematic Diagram Showing Epochs, Study Cells and Treatment Arms Together Forming Trial Design Matrix

CASE STUDY 1

This case study discusses about constructing the TI dataset when the inclusion/exclusion criteria were amended during the trial. The complexity surges when there is alteration/addition in the inclusion/exclusion criteria of the study during the study conduct. During this scenario, each complete set of criteria will be included in the TI domain. TIVERS is used to distinguish between the versions. A protocol may have many versions or amendments, but the TI is appended is with different versions only when there are any amendments in the inclusion/exclusion criteria and only the amended version is only included.

The following listed are the two versions of inclusion/exclusion criteria available in the study protocol. In the listed we can identify that some inclusion/exclusion are amended/altered and some new criteria are added in the later version of protocol.

TABLE 1. SDTM.TI

IETESTCD	IETEST	IECAT	TIVERS
INCL01	The subject is 18 years of age or older.	INCLUSION	Version1 Amendment 3 dated 08DEC2013
INCL02	The subject agrees to use adequate contraception during the study period and for 12 weeks after the last dose of study therapy.	INCLUSION	Version1 Amendment 3 dated 08DEC2013
INCL03	The subject has provided signed informed consent.	INCLUSION	Version1 Amendment 3 dated 08DEC2013
INCL04	The subject is accessible for treatment and follow-up; subjects enrolled in this trial must be treated at the study center.	INCLUSION	Version1 Amendment 3 dated 08DEC2013
EXCL01	The subject has a concurrent active malignancy other than adequately treated non melanomatous skin cancer / in situ neoplasm [Subject with a prior malignancy is eligible being disease-free for > 3 yrs.]	EXCLUSION	Version1 Amendment 3 dated 08DEC2013
EXCL02	The subject has received treatment with agents specifically targeting the CSF-1 or CSF-1R.	EXCLUSION	Version1 Amendment 3 dated 08DEC2013
EXCL03	The subject has an active infection; symptomatic congestive heart failure; uncontrolled hypertension; unstable angina pectoris; serious cardiac arrhythmia; active bleeding or any serious medical disorders	EXCLUSION	Version1 Amendment 3 dated 08DEC2013
EXCL04	The subject has leukemia or lymphoma.	EXCLUSION	Version1 Amendment 3 dated 08DEC2013
EXCL05	The subject is pregnant (confirmed by serum beta human chorionic gonadotropin test performed within 7 days prior to first dose of study therapy) or breastfeeding.	EXCLUSION	Version1 Amendment 3 dated 08DEC2013
EXCL06	The subject has a known active hepatitis B or C infection, human immunodeficiency virus infection, or acquired immunodeficiency syndrome.	EXCLUSION	Version1 Amendment 3 dated 08DEC2013
EXCL07	The subject has received a solid organ transplant.	EXCLUSION	Version1 Amendment 3 dated 08DEC2013
INCL01	The subject is 18 years of age or older.	INCLUSION	Version 7 dated 20APR2015
INCL02A	The subject has CK within normal limits.	INCLUSION	Version 7 dated 20APR2015
INCL03A	The subject agrees to use adequate contraception during the study period and for 12 weeks after the last dose of study therapy.	INCLUSION	Version 7 dated 20APR2015
INCL04A	The subject has provided signed informed consent.	INCLUSION	Version 7 dated 20APR2015
INCL05A	The subject is accessible for treatment and follow-up; subjects enrolled in this trial must be treated at the study center.	INCLUSION	Version 7 dated 20APR2015
INCL06A	The subject is accessible for treatment and follow-up; subjects enrolled in this trial must be treated at the study center.	INCLUSION	Version 7 dated 20APR2015
EXCL01A	Patient receiving conc trt with other anticancer therapy, including chemotherapy/immunotherapy/hormonal therapy/radiotherapy/chemoembolization/targeted therapy/invest agent <4weeks prior to study entry	EXCLUSION	Version 7 dated 20APR2015
EXCL02A	The subject has received treatment with agents specifically targeting the CSF-1 or CSF-1R including (but not limited to) imatinib, nilotinib, and sunitinib	EXCLUSION	Version 7 dated 20APR2015
EXCL03A	Subjects with known muscle damage due to a primary, traumatic, or other muscle disease.	EXCLUSION	Version 7 dated 20APR2015
EXCL04A	Subjects who are known to be HIV seropositive.	EXCLUSION	Version 7 dated 20APR2015
EXCL05A	The subject has a known and uncontrolled infection (presumed or documented) with progression after appropriate therapy for greater than one month.	EXCLUSION	Version 7 dated 20APR2015
EXCL06A	Subjects known to have active tuberculosis, leishmaniasis, or listeriosis.	EXCLUSION	Version 7 dated 20APR2015
EXCL07A	Subjects with active bleeding	EXCLUSION	Version 7 dated 20APR2015
EXCL08	The subject has leukemia or lymphoma.	EXCLUSION	Version 7 dated 20APR2015

CASE STUDY 2

As the trial design paper (Wood and Lenzen, 2011) stated, constructing the Trial design datasets is more a matter of art than it is pure science. The design of clinical trials can change vividly depending on the necessity in the study, which impacts how the trial is modeled within the trial design datasets. It is sensible to create the Trial Elements, followed by Trial Arms and Trial Visits. The identification of Elements and Epochs should consider how the data will be analyzed.

The following case studies uses prospective approach of creating trial design datasets and discuss about identification of elements, EPOCH considerations and construction of TE and TA using line diagram of the study available in the protocol.

CASE STUDY 2A

STUDY DESIGN WITH DIFFERENT MASKING TECHNIQUE

DESCRIPTION

In this clinical study, the treatment phase follows different masking techniques. The complexity in this design is different masking technique in one epoch. The subjects are treated with the study drug in the open-label and after certain period, the study follows double-bind technique. This enhances the efficiency of the trial conducted by minimizing time and cost.

This study will have two baseline characteristics, which can be analyzed extensively by comparing among themselves and by comparing with other visits. Therefore, it minimizes the need to have another trial to compare its efficacy.

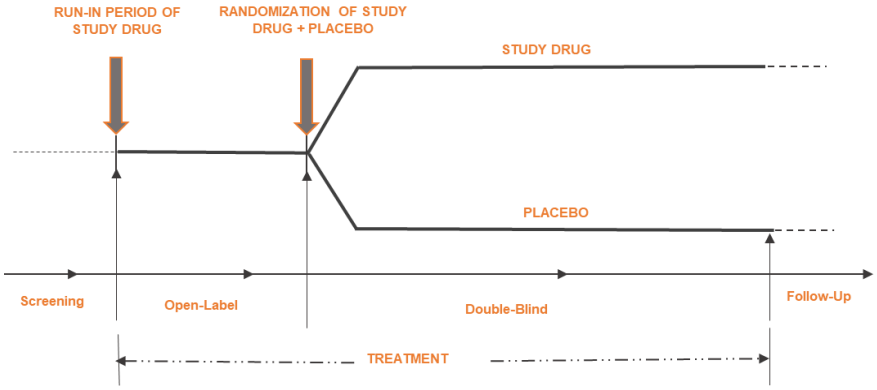

Figure 3. Line Diagram of Study Design

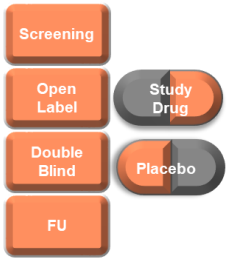

Figure 4. Identification of Elements

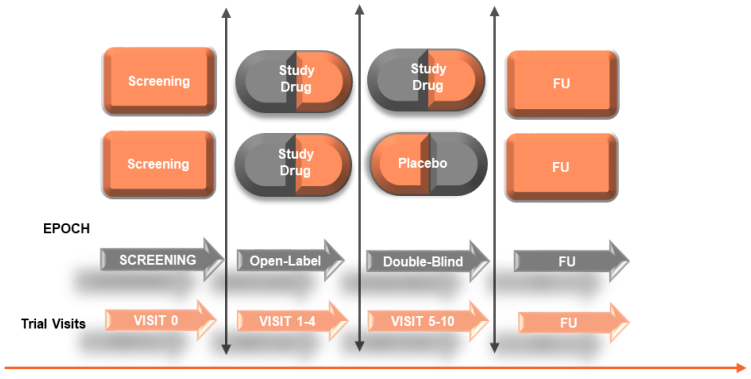

Figure 5. Treatment Arms Creation with Elements

TABLE 2. TRIAL DESIGN MATRIX

	Screening	Open-Label	Double-Blind	Follow-Up
Study Drug	SCRN	Study Drug	Study Drug	FU
Placebo	SCRN	Study Drug	Placebo	FU

TABLE 3. SDTM.TE

STUDYID	DOMAIN	ETCD	ELEMENT	TESTRL	TEENRL	TEDUR
XXX	TE	SCRN	SCREENING	Informed consent	5 days after start of the element	P5D
XXX	TE	OL	OPEN-LABEL	First dose of study drug	4 weeks after start of the element	P4W
XXX	TE	DB	DOUBLE-BLIND	First dose of study drug after randomization	8 weeks after start of the element	P8W
XXX	TE	DB	DOUBLE-BLIND	First dose of placebo after randomization	8 weeks after start of the element	P8W
XXX	TE	FU	FOLLOW-UP	24 hrs. after last dose of study drug/placebo administration	30 days after start of the element	P30D

TABLE 4. SDTM.TA

STUDYID	DOMAIN	ARMCD	ARM	TAETORD	ETCD	ELEMENT	TABRANCH	TATRANS	EPOCH
XXX	TA	PLB	Placebo	01	SCRN	Screening			Screening
XXX	TA	PLB	Placebo	02	OL	Open-Label			Treatment
XXX	TA	PLB	Placebo	03	DB	Double-Blind	Randomized to Placebo		Treatment
XXX	TA	PLB	Placebo	04	FU	Follow-Up			Follow-Up
XXX	TA	SD	Study Drug	01	SCRN	Screening			Screening
XXX	TA	SD	Study Drug	02	OL	Open-Label			Treatment
XXX	TA	SD	Study Drug	03	DB	Double-Blind	Randomized to Study Drug		Treatment
XXX	TA	SD	Study Drug	04	FU	Follow-Up			Follow-Up

CASE STUDY 2B

STUDY WITH MULTIPLE ARMS AND RE-RANDOMIZATION WITH STRATEGY

DESCRIPTION

This clinical study is a multi-period multiple arm trial where subjects are assigned to multiple arms after screening and rerandomized to multiple arms based on the strategy of the trial at different periods of time. It effectively combines facets of the clinical study. These kinds of design are generally employed for phase 2 and above. The complexity in this study we must encounter too many study periods i.e., epochs. And each arm changes its pattern in an identified epoch.

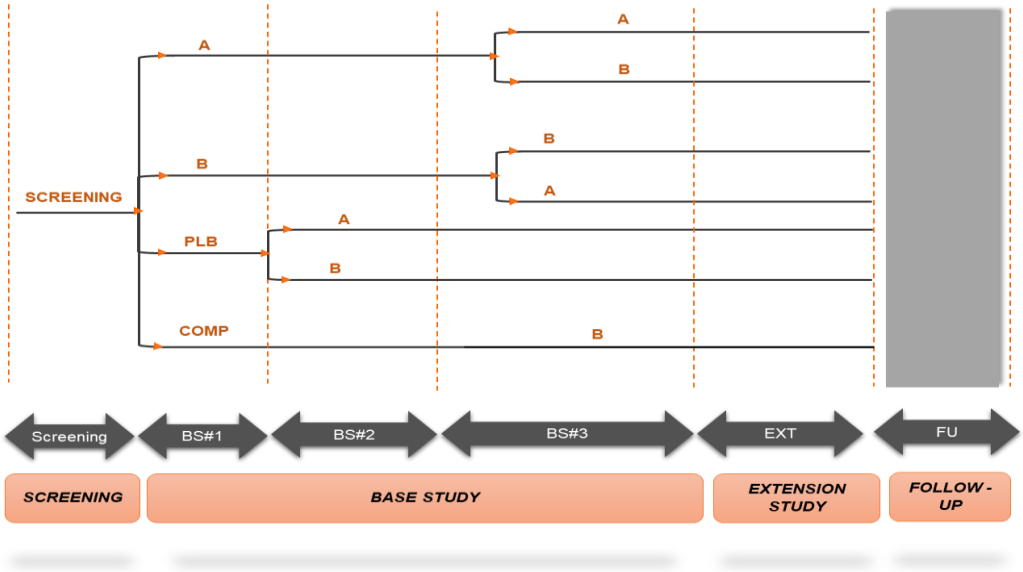

Figure 6. Line Diagram of Study Design

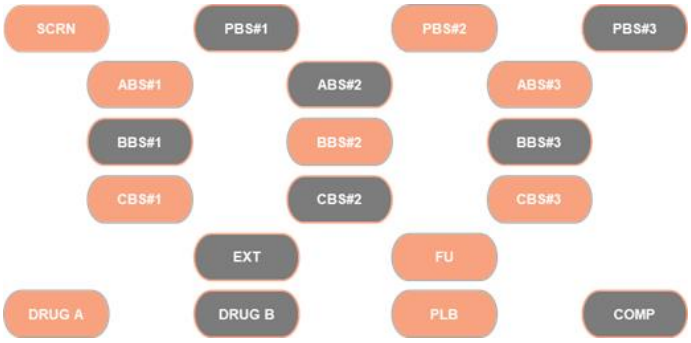

Figure 7. Identification of Elements

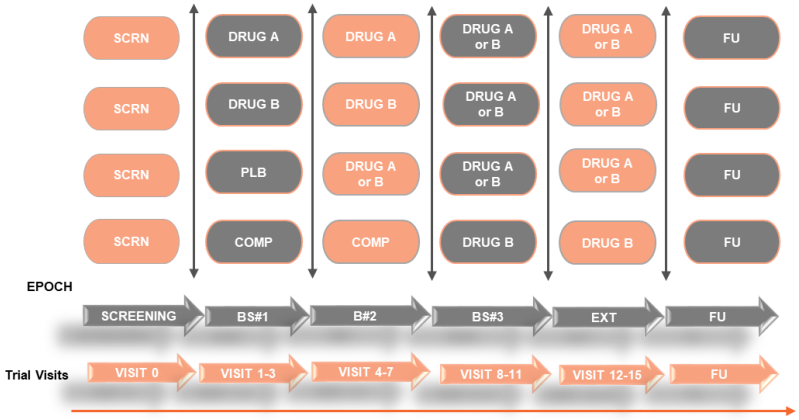

Figure 8. Treatment Arms Creation with Elements

TABLE 5. TRIAL DESIGN MATRIX

	SCREENING	PART 1	PART 2	PART3	EXTENSION	FOLLOW-UP
A	SCRN	A	A	A or B	A or B	FU
B	SCRN	B	B	A or B	A or B	FU
PLB	SCRN	PLB	A or B	A or B	A or B	FU
COMP	SCRN	COMP	COMP	B	B	FU

TABLE 6. SDTM.TE

STUDYID	ETCD	ELEMENT	TESTRL	TEENRL	TEDUR
XXX	SCRN	Screening	Informed Consent	5 Days After Start of the Element	P5D
XXX	PBS #1	Placebo BS Part 1	First Dose of Placebo	2 Weeks After Start of the Element	P2W
XXX	PBS #2	Placebo BS Part 2	First Dose of Study Drug A or B After Re-Randomization	8 Weeks After Start of the Element	P8W
XXX	PBS #3	Placebo BS Part 3	Continuation of the Previous Element	8 Weeks After Start of the Element	P8W
XXX	ABS #1	Drug A BS Part 1	First Dose of Drug A	2 Weeks After Start of the Element	P2W
XXX	ABS #2	Drug A BS Part 2	Continuation of the Previous Element	8 Weeks After Start of the Element	P8W
XXX	ABS #3	Drug A BS Part 3	First Dose of Study Drug A or B After Re-Randomization	8 Weeks After Start of the Element	P8W
XXX	CBS #1	Comparator BS Part 1	First Dose of Comparator	2 Weeks After Start of the Element	P2W
XXX	CBS #2	Comparator BS Part 2	Continuation of the Previous Element	8 Weeks After Start of the Element	P8W
XXX	CBS #3	Comparator BS Part 3	First Dose of Study Comparator	8 Weeks After Start of the Element	P8W
XXX	EXT	Extension Part	Continuation of the Arms Followed in BS #3	20 Weeks After Start of the Element	P20W
XXX	FU	Follow-up	24 Hrs. After Last Dose of Study Drug/ Placebo/Comparator Administration	30 Days After Start of the Element	P30D

TABLE 7. SDTM.TA

STUDY ID	ARMCD	ARM	ETCD	ELEMENT	TABRANCH	TATRANS	EPOCH
XXX	PLB	PLACEBO	SCRN	Screening			SCREENING
XXX	PLB	PLACEBO	PBS #1	Placebo BS Part 1	Randomized to placebo		BASE STUDY
XXX	PLB	PLACEBO	PBS #2	Placebo BS Part 2	Re-randomized to drug A or B		BASE STUDY
XXX	PLB	PLACEBO	PBS #3	Placebo BS Part 3			BASE STUDY
XXX	PLB	PLACEBO	EXT	Extension Part			EXTENSION STUDY
XXX	PLB	PLACEBO	FU	Follow-up			FOLLOW-UP
XXX	A	DRUG A	SCRN	Screening			SCREENING
XXX	A	DRUG A	ABS #1	Drug A BS Part 1	Randomized to drug A		BASE STUDY
XXX	A	DRUG A	ABS #2	Drug A BS Part 2			BASE STUDY
XXX	A	DRUG A	ABS #3	Drug A BS Part 3	Re-randomized to drug A or B		BASE STUDY
XXX	A	DRUG A	EXT	Extension part			EXTENSION STUDY
XXX	A	DRUG A	FU	Follow-up			FOLLOW-UP
XXX	B	DRUG B	SCRN	Screening			SCREENING
XXX	B	DRUG B	BBS #1	Drug B BS Part 1	Randomized to drug B		BASE STUDY
XXX	B	DRUG B	BBS #2	Drug B BS Part 2			BASE STUDY
XXX	B	DRUG B	BBS #3	Drug B BS Part 3	Re-randomized to drug A or B		BASE STUDY
XXX	B	DRUG B	EXT	Extension Part			EXTENSION STUDY
XXX	B	DRUG B	FU	Follow-up			FOLLOW-UP
XXX	COMP	COMPARATOR	SCRN	Screening			SCREENING
XXX	COMP	COMPARATOR	CBS #1	Comparator BS Part 1	Randomized to Comparator		BASE STUDY
XXX	COMP	COMPARATOR	CBS #2	Comparator BS Part 2			BASE STUDY
XXX	COMP	COMPARATOR	CBS #3	Comparator BS Part 3	Re-randomized to drug B		BASE STUDY
XXX	COMP	COMPARATOR	EXT	Extension part			EXTENSION STUDY
XXX	COMP	COMPARATOR	FU	Follow-up			FOLLOW-UP

CASE STUDY 2C

STUDY DESIGN WITH THE RUN-IN PERIOD AND WASH-OUT PERIOD

DESCRIPTION

This clinical study consists of obligatory washout period for clear and cleaner data collection of the study medication and to rule out the effects of the previous medications. It also has a run-in period with Placebo administration followed by the randomization treatment. The treatment period has rescue components as well, which makes the design trickier.

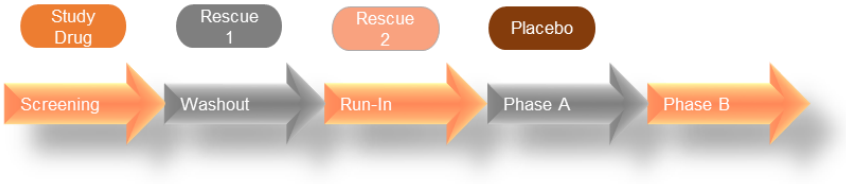

Figure 9. Identification of Elements

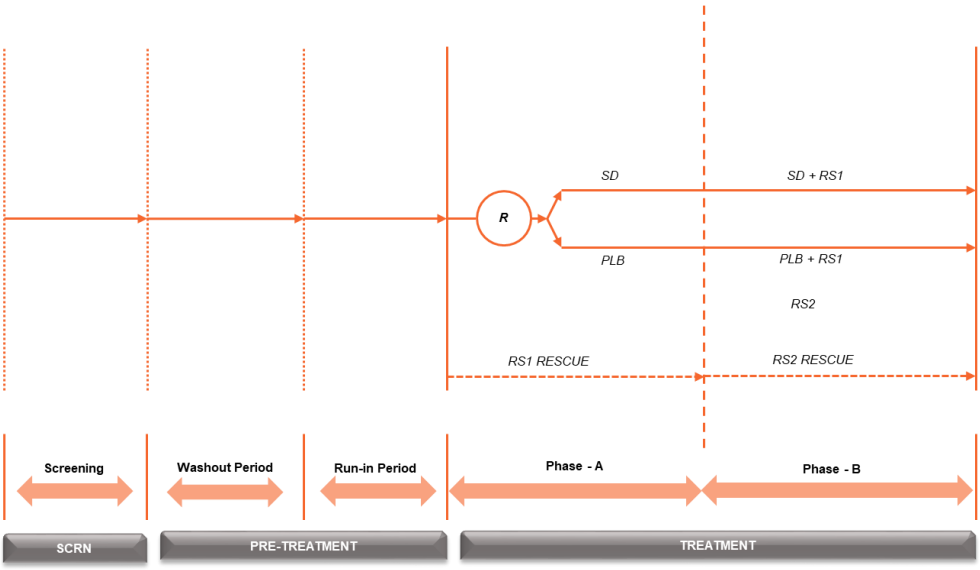

Figure 10. Line diagram of study design

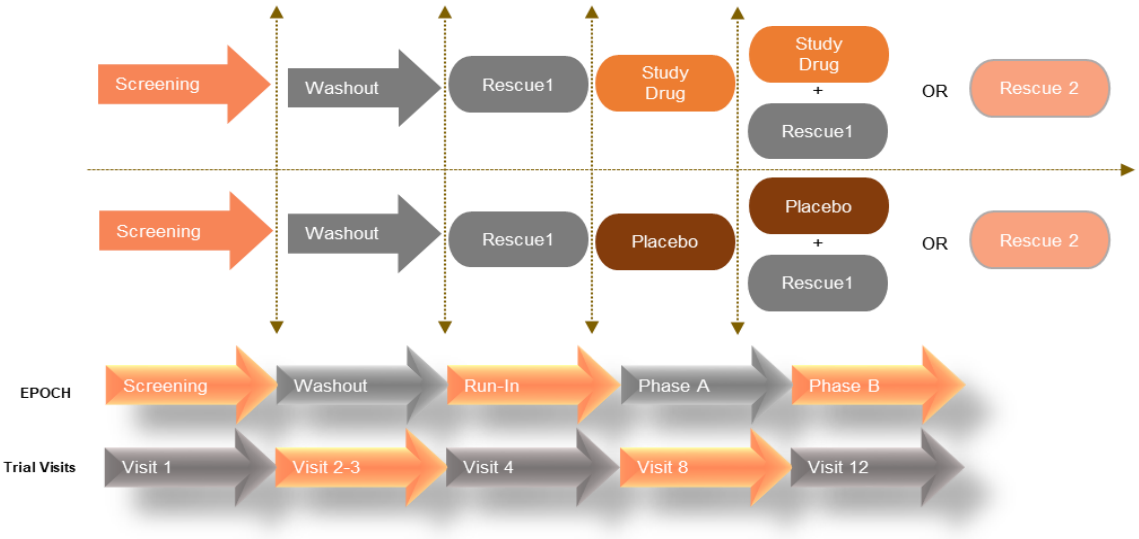

Figure 11. Treatment Arms Creation with Elements

TABLE 8. TRIAL DESIGN MATRIX

	SCREENING	WASHOUT PERIOD	RUN-IN PERIOD	PHASE - A	PHASE - B
Study Drug	SCRN	Other Method	Placebo	Study Drug	(Study Drug + Rescue 1) / Rescue 2
Placebo	SCRN	Other Method	Placebo	Placebo	(Placebo + Rescue 1) / Rescue 2

TABLE 9. SDTM.TE

STUDYID	ETCD	ELEMENT	TESTRL	TEENRL	TEDUR
XXX	SCRN	Screening	Date of Screening	Date of Visit 2	
XXX	PBORUNIN	Placebo Run-in	Date of Visit 2	Date of first non-zero dose of Phase A	
XXX	DRUGA	Study Drug (Phase A)	Date of first non-zero dose of Phase A	Date of first non-zero dose of Phase B	
XXX	RESCDRUGA	Study Drug (Phase A Rescue)	Date of first non-zero dose of Phase A	Date of first non-zero dose of Phase B	
XXX	DRUGB	Study Drug (Phase B)	Date of first non-zero dose of Phase B	Date of Visit 12	
XXX	RESCDRUGB	Study Drug (Phase B Rescue)	Date of first non-zero dose of Phase B	Subjects will complete at Visit 12	
XXX	POSTA	Follow-up No Rescue Phase A	Date of first non-zero dose of Phase B	At Visit 8, subject will enter Phase B	
XXX	POSRESCA	Follow-up Rescue Phase A	Date of first non-zero dose of Phase B considering the rescue therapy in Phase A	Subjects will complete at Visit 12	
XXX	POSTB	Follow-up No Rescue Phase B	Date of first non-zero dose of Phase B considering the rescue therapy in Phase A	Subjects will complete at Visit 12	
XXX	POSRESCB	Follow-up Rescue Phase B	Date of last non-zero dose of Phase B		
XXX	PLBA	Placebo (Phase A)	Date of first non-zero dose of Phase B		
XXX	PLBRESCA	Placebo (Phase A Rescue)	Date of first non-zero dose of Phase B		
XXX	PLBB	Placebo (Phase B)	Date of first non-zero dose of Phase B	Subjects will complete at Visit 12	
XXX	PLBRESCB	Placebo (Phase B Rescue)	Date of first non-zero dose of Phase B		

TABLE 10. SDTM.TA

STUDY ID	ARMCD	ARM	ETCD	ELEMENT	TABRANCH	TATRANS	EPOCH
XXX	SD	Study Drug	SCRN	Screening			Screening
XXX	SD	Study Drug	PBORUNIN	Placebo Run-in	Randomized to SD	Placebo	Run-in
XXX	SD	Study Drug	DRUGA	Study Drug (Phase A)		Study Drug	Phase A
XXX	SD	Study Drug	RESCDRUG A	Study Drug (Phase A Rescue)		Study Drug	Phase A
XXX	SD	Study Drug	DRUGB	Study Drug (Phase B)		Study Drug	Phase B
XXX	SD	Study Drug	RESCDRUGB	Study Drug (Phase B Rescue)		Rescue 2	Phase B
XXX	SD	Study Drug	POSTA	Follow-up No Rescue Phase A			Phase A
XXX	SD	Study Drug	POSRESCA	Follow-up Rescue Phase A		Rescue 1	Phase A
XXX	SD	Study Drug	POSTB	Follow-up No Rescue Phase B			Phase B
XXX	SD	Study Drug	POSRESCB	Follow-up Rescue Phase B			Phase B
XXX	PLB	Placebo	SCRN	Screening			Screening
XXX	PLB	Placebo	PBORUNIN	Placebo Run-in	Randomized to PLB	Placebo	Run-in
XXX	PLB	Placebo	DRUGA	Study Drug (Phase A)		Placebo	Phase A
XXX	PLB	Placebo	RESCDRUG A	Study Drug (Phase A Rescue)		Placebo	Phase A
XXX	PLB	Placebo	DRUGB	Study Drug (Phase B)		Placebo	Phase B
XXX	PLB	Placebo	RESCDRUGB	Study Drug (Phase B Rescue)		Rescue 2	Phase B
XXX	PLB	Placebo	POSTA	Follow-up No Rescue Phase A			Phase A
XXX	PLB	Placebo	POSRESCA	Follow-up Rescue Phase A			Phase A
XXX	PLB	Placebo	POSTB	Follow-up No Rescue Phase B			Phase B
XXX	PLB	Placebo	POSRESCB	Follow-up Rescue Phase B			Phase B

CASE STUDY 2D

STUDY DESIGN WITH MULTIPLE TITRATIONS WITHIN ONE ARM

DESCRIPTION

This clinical study is a randomized, dose-adaptive, multicenter, double-blind, parallel group, placebo-controlled study with the primary objective to define the optimal therapeutic dose(s) of study medication. Combination dosing with dose escalation for subjects with insufficient response at Week 12 and Week 24, with a withdrawal point at Week 36 and with a 12-week follow-up visit after the last dose.

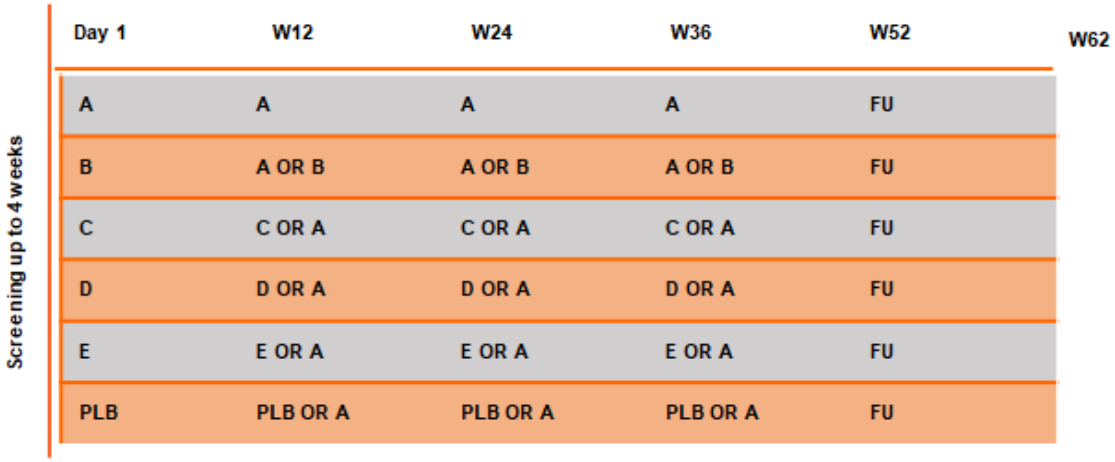

Figure 12. Line Diagram of Study Design

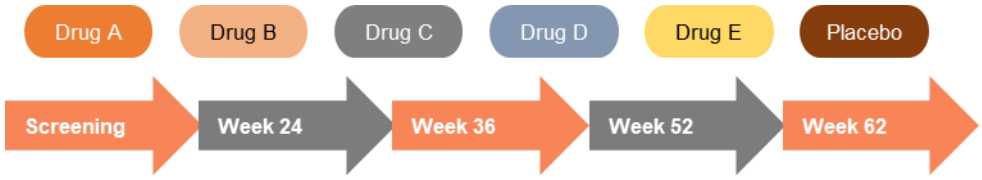

Figure 23. Identification of Elements

TABLE 11. TRIAL DESIGN MATRIX

	SCREENING	Week 24	Week36	Week 52	Week 62
Study Drug A/B/C/D/E	SCRN	Study Drug A/B/C/D/E	Study Drug A/B/C/D/E	Study Drug A/B/C/D/E	Follow-Up
Placebo	SCRN	Placebo	Study Drug A	Study Drug A	Follow-Up

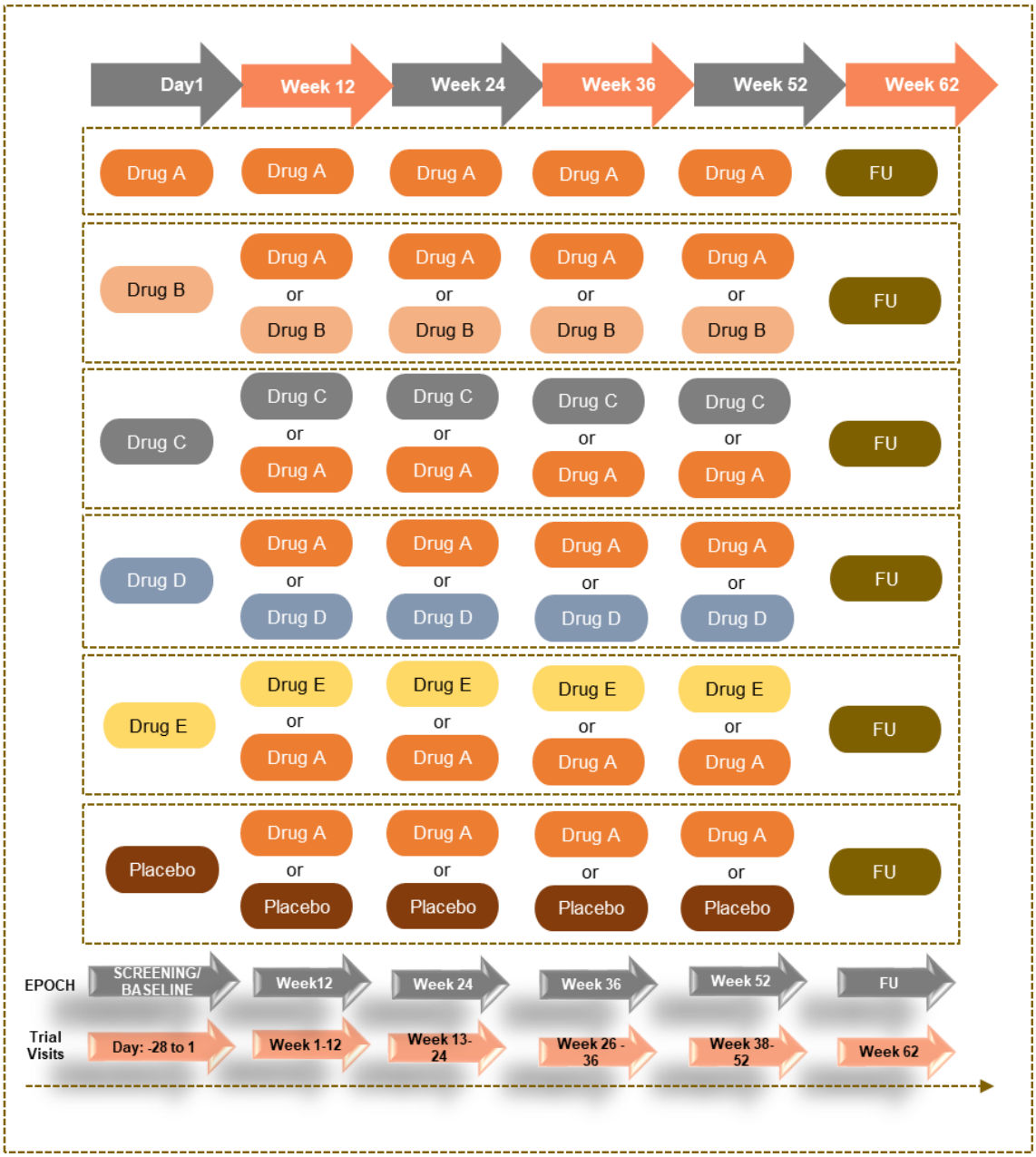

Figure 14. Treatment Arms Creation with Elements

TABLE 12. SDTM.TE

STUDYID	ETCD	ELEMENT	TESTRL	TEENRL	TEDUR
XXX	SCRN	Screening	Date of Screening	Date of Day 1	P28D
XXX	W24	Week 24	Date of Day 1	Last date of visit WEEK 24	P24W
XXX	W36	Week 36	First Date of visit WEEK 26	Last date of visit WEEK 36	P12W
XXX	W52	Week 52	First Date of visit WEEK 38	Last date of visit WEEK 52	P16W
XXX	FU	Follow-Up	Start of Follow-Up	End of Follow-Up	P12W

TABLE 13. SDTM.TA

STUDY ID	ARMCD	ARM	ETCD	ELEMENT	TABRANCH	TATRANS	EPOCH
XXX	SDA	Study Drug A	SCRN	Screening			Screening
XXX	SDA	Study Drug A	W24	Week 24	Randomized to Study Drug A		Week 24
XXX	SDA	Study Drug A	W36	Week 36			Week 36
XXX	SDA	Study Drug A	W52	Week 52			Week 52
XXX	SDA	Study Drug A	FU	Follow-Up			Week 62
XXX	SDB	Study Drug B	SCRN	Screening			Screening
XXX	SDB	Study Drug B	W24	Week 24	Randomized to Study Drug B		Week 24
XXX	SDB	Study Drug B	W36	Week 36		Dose escalated to Study Drug A	Week 36
XXX	SDB	Study Drug B	W52	Week 52		Dose escalated to Study Drug A	Week 52
XXX	SDB	Study Drug B	FU	Follow-Up			Week 62
XXX	SDC	Study Drug C	SCRN	Screening			Screening
XXX	SDC	Study Drug C	W24	Week 24	Randomized to Study Drug C		Week 24
XXX	SDC	Study Drug C	W36	Week 36		Dose escalated to Study Drug A	Week 36
XXX	SDC	Study Drug C	W52	Week 52		Dose escalated to Study Drug A	Week 52
XXX	SDC	Study Drug C	FU	Follow-Up			Week 62
XXX	SDD	Study Drug D	SCRN	Screening			Screening
XXX	SDD	Study Drug D	W24	Week 24	Randomized to Study Drug C		Week 24
XXX	SDD	Study Drug D	W36	Week 36		Dose escalated to Study Drug A	Week 36
XXX	SDD	Study Drug D	W52	Week 52		Dose escalated to Study Drug A	Week 52
XXX	SDD	Study Drug D	FU	Follow-Up			Week 62
XXX	SDE	Study Drug E	SCRN	Screening			Screening
XXX	SDE	Study Drug E	W24	Week 24	Randomized to Study Drug E		Week 24
XXX	SDE	Study Drug E	W36	Week 36		Dose escalated to Study Drug A	Week 36
XXX	SDE	Study Drug E	W52	Week 52		Dose escalated to Study Drug A	Week 52
XXX	SDE	Study Drug E	FU	Follow-Up			Week 62
XXX	PLB	Placebo	SCRN	Screening			Screening
XXX	PLB	Placebo	W24	Week 24	Randomized to Placebo		Week 24
XXX	PLB	Placebo	W36	Week 36	Dose escalated to Study Drug A		Week 36
XXX	PLB	Placebo	W52	Week 52			Week 52
XXX	PLB	Placebo	FU	Follow-Up			Week 62

CONCLUSION

It is generally advised and encouraged to keep these datasets as simple as possible and present the overall picture of the trial, but still within the framework of the model and the intent of the study protocol. It takes a lot of practice and experience with trials of many types of designs before one can become adept at creating Trial Design datasets. This paper attempts at easing the path to create simple trial design datasets for complex study designs.

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