A Guide for the Guides: Implementing SDTM and ADaM Standards for Parallel and Crossover Studies

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Introduction

In clinical studies, dataset structures are heavily impacted by the study design and how treatment groups are compared. The two most common study designs used in clinical research are Parallel and Crossover. Parallel studies are straightforward when assigning treatments and deriving other analysis variables. Crossover studies require some additional work when creating treatment variables and other analysis variables. This poster will examine both study designs and explain how CDISC implementation will be different in parallel and crossover studies.

Study Descriptions

Parallel design

A parallel study is a type of clinical study where participants are randomly assigned to a single treatment. The treatment can include placebo, a specific dose of the drug being investigated, or a standard-of-care treatment. For example, group 1 receives Placebo, group 2 receives 2mg of Treatment A, and group 3 receives 1mg of standard-of-care Treatment X. A schematic representation of the parallel study design can be seen in Figure 1. This example has three Arms (Placebo, Drug A, and Drug B) and three Epochs (Screening Epoch, Run-in Epoch, and Treatment Epoch).

Crossover design

A crossover study randomly assigns participants to a specified sequence of treatments. When one treatment is completed, the subject will then “crossover" to another treatment during the course of the trial, resulting in each subject acting as its own control group. Typically, all subjects will receive the same number of treatments and be involved in the same number of periods. This means that even if participants are initially put into a placebo group, they may also eventually receive the study drug or standard-of-care during the trial. Usually, a cross-over study also includes a washout period which enables the effects of the preceding treatments to dissipate and eliminate any carry-over effect. The washout period is a predetermined amount of time during which patients receive no treatment.

A schematic representation of the crossover study design can be seen in Figure 3. In a crossover study, the objectives of the trial will be addressed by comparisons between the arms and by within-subject comparisons between treatments. The design thus depends on differentiating the periods during which the subject receives the different treatments and so there are different respective treatment epochs.

References & Acknowledgements

1. *CDISC, Study Data Tabulation Model Implementation Guide: : Human Clinical Trials Version 3.2, November 2013.*

The authors would like to thank Jeff Jackson for his guidance on this poster.

Parallel Trial Design

Figure 1

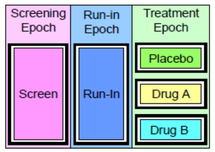

Figure 2

Row	STUDYID	DOMAIN	ARMCD	ARM	TAETORD	ETCD	ELEMENT	TABRANCH	TATRANS	EPOCH
1	EX1	TA	P	Placebo	1	SCRN	Screen			Screen
2	EX1	TA	P	Placebo	2	RI	Run-In	Randomized to Placebo		Run-In
3	EX1	TA	P	Placebo	3	P	Placebo			Treatment
4	EX1	TA	A	A	1	SCRN	Screen			Screen
5	EX1	TA	A	A	2	RI	Run-In	Randomized to Drug A		Run-In
6	EX1	TA	A	A	3	A	Drug A			Treatment
7	EX1	TA	B	B	1	SCRN	Screen			Screen
8	EX1	TA	B	B	2	RI	Run-In	Randomized to Drug B		Run-In
9	EX1	TA	B	B	3	B	Drug B			Treatment

Crossover Trial Design

Figure 3

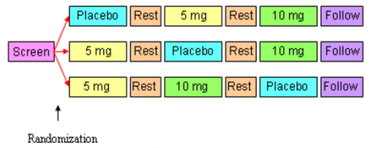

Figure 4

Row	STUDYID	DOMAIN	ARMCD	ARM	TAETORD	ETCD	ELEMENT	TABRANCH	TATRANS	EPOCH
1	EX2	TA	P-5-10	Placebo-5mg-10mg	1	SCRN	Screen	Randomized to Placebo - 5 mg - 10 mg		Screen Epoch
2	EX2	TA	P-5-10	Placebo-5mg-10mg	2	P	Placebo			First Treatment Epoch
3	EX2	TA	P-5-10	Placebo-5mg-10mg	3	REST	Rest			First Rest Epoch
4	EX2	TA	P-5-10	Placebo-5mg-10mg	4	5	5 mg			Second Treatment Epoch
5	EX2	TA	P-5-10	Placebo-5mg-10mg	5	REST	Rest			Second Rest Epoch
6	EX2	TA	P-5-10	Placebo-5mg-10mg	6	10	10 mg			Third Treatment Epoch
7	EX2	TA	P-5-10	Placebo-5mg-10mg	7	FU	Follow-up			Follow-up Epoch
8	EX2	TA	5-P-10	5mg-Placebo-10mg	1	SCRN	Screen	Randomized to 5 mg - Placebo - 10 mg		Screen Epoch
9	EX2	TA	5-P-10	5mg-Placebo-10mg	2	5	5 mg			First Treatment Epoch
10	EX2	TA	5-P-10	5mg-Placebo-10mg	3	REST	Rest			First Rest Epoch
11	EX2	TA	5-P-10	5mg-Placebo-10mg	4	P	Placebo			Second Treatment Epoch
12	EX2	TA	5-P-10	5mg-Placebo-10mg	5	REST	Rest			Second Rest Epoch
13	EX2	TA	5-P-10	5mg-Placebo-10mg	6	10	10 mg			Third Treatment Epoch
14	EX2	TA	5-P-10	5mg-Placebo-10mg	7	FU	Follow-up			Follow-up Epoch
15	EX2	TA	5-10-P	5mg-10mg-Placebo	1	SCRN	Screen	Randomized to 5 mg - 10 mg – Placebo		Screen Epoch
16	EX2	TA	5-10-P	5mg-10mg-Placebo	2	5	5 mg			First Treatment Epoch
17	EX2	TA	5-10-P	5mg-10mg-Placebo	3	REST	Rest			First Rest Epoch
18	EX2	TA	5-10-P	5mg-10mg-Placebo	4	10	10 mg			Second Treatment Epoch
19	EX2	TA	5-10-P	5mg-10mg-Placebo	5	REST	Rest			Second Rest Epoch
20	EX2	TA	5-10-P	5mg-10mg-Placebo	6	P	Placebo			Third Treatment Epoch
21	EX2	TA	5-10-P	5mg-10mg-Placebo	7	FU	Follow-up			Follow-up Epoch

Figures 1-7 Source: *CDISC, Study Data Tabulation Model Implementation Guide: Human Clinical Trials Version 3.2, November 2013.*

Trial Arms and Trial Elements

The Trial Elements and Trial Arms, along with the Trial Visits, datasets in the Trial Design model describe the planned design of the study. See Figures 2 and 4. Subject assignment to an Arm is reported in the ARM variable in Demographics (DM). Actual Elements and Visits data for each subject are described in two additional datasets: Subject Elements dataset and Subject Visits dataset. The values of ARM and ARMCD in DM must match entries in the Trial Arms (TA) dataset. The Subject Elements dataset is particularly useful for studies with multiple treatment periods, i.e. crossover studies. The Subject Elements dataset contains the dates/times at which a subject moved from one Element to another, so when the Trial Arms, Trial Elements, and Subject Elements datasets are included in a submission package, regulatory reviewers can relate all the observations made about a subject to that subject's progression through the clinical trial.

ADSL and BDS Data Structures

Figure 5 shows an example ADSL dataset from a parallel study. Each subject receives one drug as planned, but sometimes actual drug may differ from the planned. Subject 1003 has a planned treatment for Drug X 5mg, but received Placebo, therefore TRT01P and TRT01A do not match. This can occur in exceptional or accidental cases. Note that in Figure 6, several variables are used to differentiate treatment during Period 1 and Period 2 for the crossover study design. Subject 1003 has a TRTSEQP (Planned Sequence) of Drug X then Placebo, but TRTSEQA (Actual Sequence) indicates subject received Placebo for both periods. This can also be seen in the corresponding variables: TRT01P/TRT01A and TRT02P/TRT02A.

Figure 5

Row	USUBJID	ARM	TRT01P	TRT01A	TR01SDT	TR01EDT
1	1001	Drug X 5 mg	Drug X 5 mg	Drug X 5 mg	23OCT2007	17DEC2007
2	1002	Placebo	Placebo	Placebo	19JUL2006	20SEP2007
3	1003	Drug X 5 mg	Drug X 5 mg	Placebo	01NOV2007	20NOV2007

Figure 6

Row	USUBJID	TRTSEQP	TRT01P	TRT02P	TRTSEQA	TRT01A	TRT02A	TR01SDT	TR01EDT	TR02SDT	TR02EDT
1	1001	Placebo – Drug X	Placebo	Drug X	Placebo – Drug X	Placebo	Drug X	15FEB2006	03MAY2006	10MAY2006	15AUG2006
2	1002	Placebo – Drug X	Placebo	Drug X	Placebo – Placebo	Placebo	Placebo	01MAR2006	12JUN2006	20JUN2006	25SEP2006
3	1003	Drug X – Placebo	Drug X	Placebo	Placebo – Placebo	Placebo	Placebo	05FEB2006	25APR2006	01MAY2006	04AUG2006

Figure 7 is an example of ADLB data structure for a crossover study. The example subject received both 5mg and 10mg. All BDS datasets (ADVS, ADEG, ADAE, etc.) have similar structure. Note that for Period 1, baseline data is coming from Screening and for Period 2, baseline data is coming from Period 1, hence the reason BASETYPE for Period 1 is Screening and for Period 2 it is Period 1.

Figure 7

USUBJID	PARAMCD	APERIODC	ADT	AVAL	BASETYPE	TRTP
11-1001	BLOOD Basophils(10^9/L)	Period 1	10-May-19	10.8	Screening	5mg
11-1001	BLOOD Basophils(10^9/L)	Period 1	11-May-19	11.1	Screening	5mg
11-1001	BLOOD Basophils(10^9/L)	Period 1	12-May-19	10.7	Screening	5mg
11-1001	BLOOD Basophils(10^9/L)	Period 2	20-May-19	10.1	Period 1	10mg
11-1001	BLOOD Basophils(10^9/L)	Period 2	21-May-19	10.4	Period 1	10mg
11-1001	BLOOD Basophils(10^9/L)	Period 2	22-May-19	10.3	Period 1	10mg

Conclusion

The objective of this poster was to give an overview of parallel and crossover studies and trial design impact on dataset structure, particularly planned and actual treatment arms. SDTM and ADaM implementation will be guided by study design as seen in the examples provided. While a parallel design will have the same ARM/ARMCD for a subject throughout the trial, a crossover design will utilize additional variables such as EPOCH and PERIOD/PERIODC to indicate different epochs and treatment periods (e.g. Period 1, Period 2). Variables such as TRT01P/TRT01A and TRT02P/TRT02A will specify if a subject switched to a different treatment from Planned Treatment to Actual Treatment and in which period subject did so. Further details can be found via the corresponding CDISC documentation. See References and Acknowledgments.