Paper AS08

# Analysis of crossover studies in patient narratives

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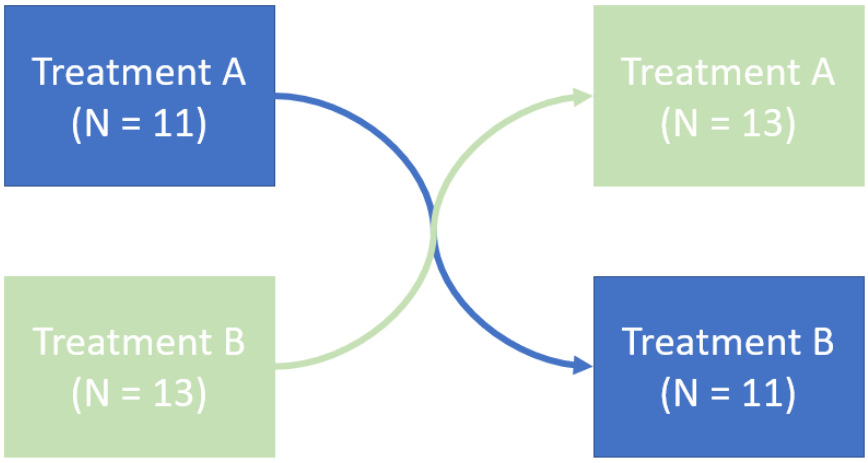
## ABSTRACT

Crossover design clinical trials allow for subjects to be their own control, which often means fewer patients need to be enrolled. However, multiple treatment periods create a more complicated statistical analysis, especially for patient narratives which pull data from multiple domains. By using treatment start date and planned or actual treatment variables, analysis periods and corresponding treatments can be assigned to adverse events and other record level data. By also adding in baseline flags, period-matched baselines can be created for each treatment period to conduct change from baseline analyses in findings data. With these components, the narratives can be written for a crossover design.

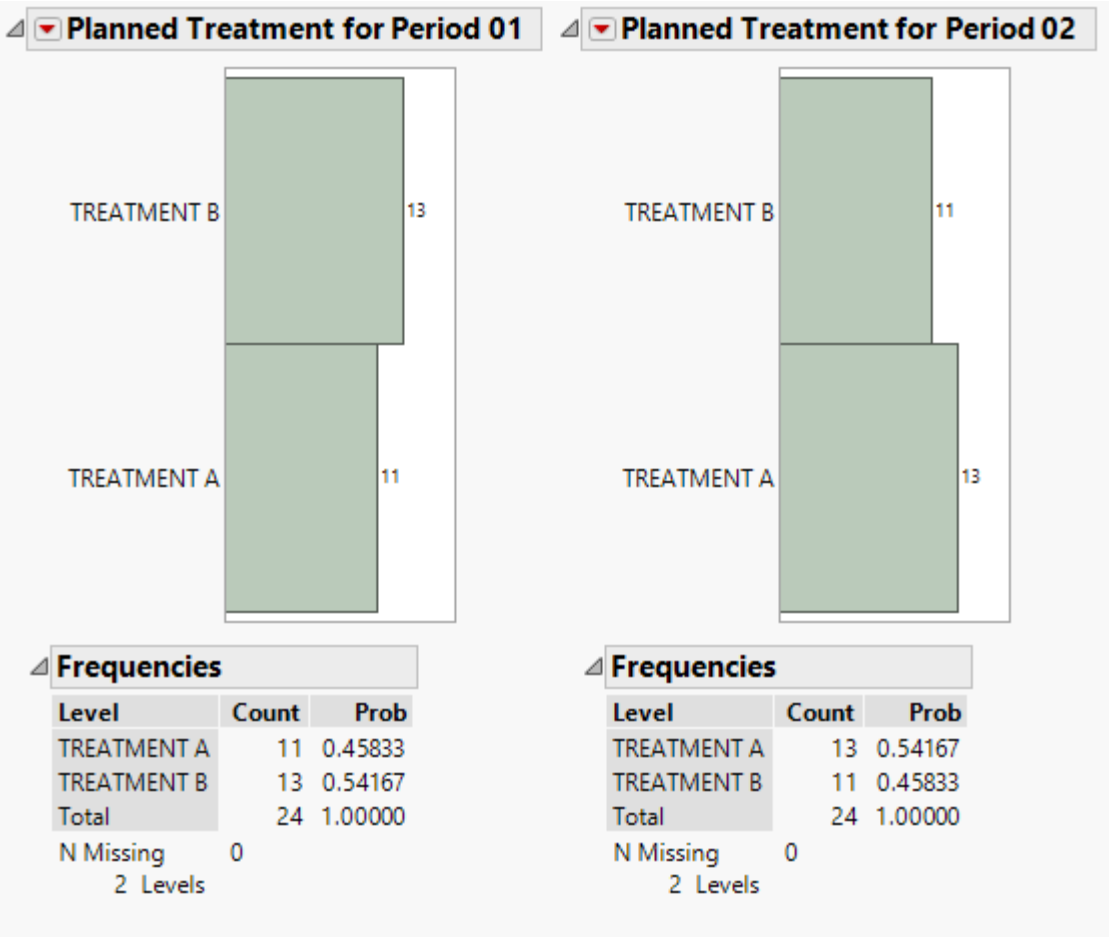
## INTRODUCTION

Crossover studies consist of patients receiving two or more treatments over the course of two or more treatment periods. In order to use a crossover design, the disease being treated typically needs to be chronic so that it persists over more than one treatment period to allow multiple treatments to be tested. In such cases, crossover designs can eliminate within-subject variability by allowing the subject to be compared to themselves. Often this allows for fewer patients to be enrolled than a similar parallel design study. The drawback is that a "carryover" effect between treatments needs to be considered. To minimize this effect, a washout period can be used between treatment periods[1,2].

With multiple treatment periods, analysis of crossover studies can lead to more complicated statistical analyses. Events, interventions, and findings data that occurs over the course of the study are assigned to a treatment period based on the start and end dates of each treatment period. In addition, any data compared to a baseline uses period-matched baselines to reset the baseline for each period. In patient narratives, both periods and period-matched baselines are used to display patient data by treatment period.




This paper will focus on the 2 x 2 design, consisting of two periods and two treatments. Patients are randomized to either receive treatment A in period 1 and treatment B in period 2 or treatment B in period 1 and treatment A in period 2. The example data used in this paper consists of 24 patients, 11 receiving treatment sequence AB and 13 receiving treatment sequence BA. All analyses are conducted using JMP® Clinical 7.1.




**Frequencies**

| Level | Count | Prob |
|---|---|---|
| TREATMENT A | 11 | 0.45833 |
| TREATMENT B | 13 | 0.54167 |
| Total | 24 | 1.00000 |

N Missing 0
2 Levels

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2 Levels

**Subject Population by Treatment**

**Period 1**

| Planned Treatment for Period 01 | Count | % of Total |
|---|---|---|
| TREATMENT A | 11 | 45.8% |
| TREATMENT B | 13 | 54.2% |
| All | 24 | 100.0% |

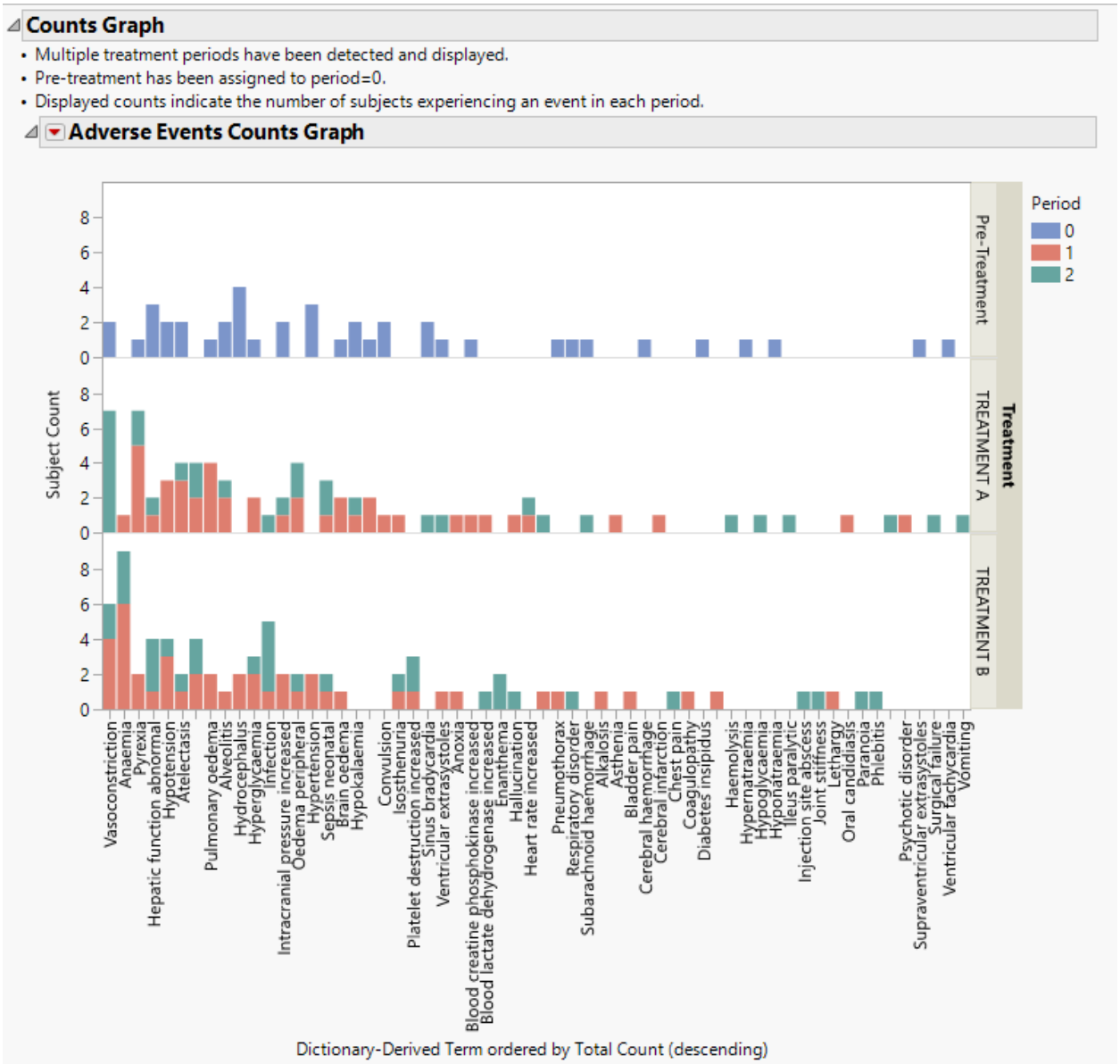
**Period 2**

| Planned Treatment for Period 02 | Count | % of Total |
|---|---|---|
| TREATMENT A | 13 | 54.2% |
| TREATMENT B | 11 | 45.8% |
| All | 24 | 100.0% |

## ASSIGNING PERIOD AND CORRESPONDING TREATMENT

Before data can be analyzed in a crossover study, periods and the treatment received in that period are assigned to each record in the dataset. This allows the data to be analyzed by treatment period. CDISC ADaM datasets include these variables as APERIOD (Period), TRTP (Planned Treatment), and TRTA (Actual Treatment)[3]. These three variables can be derived simultaneously by comparing the start date of the record to the treatment period start dates. For example, if the record starts on or after the first period treatment starts but before the second period treatment starts, then the event is assigned to period 1 and the treatment given in period 1. For these derivations, an ADSL dataset containing TRTxxP or TRTxxA variables along with the start dates of each treatment is required.

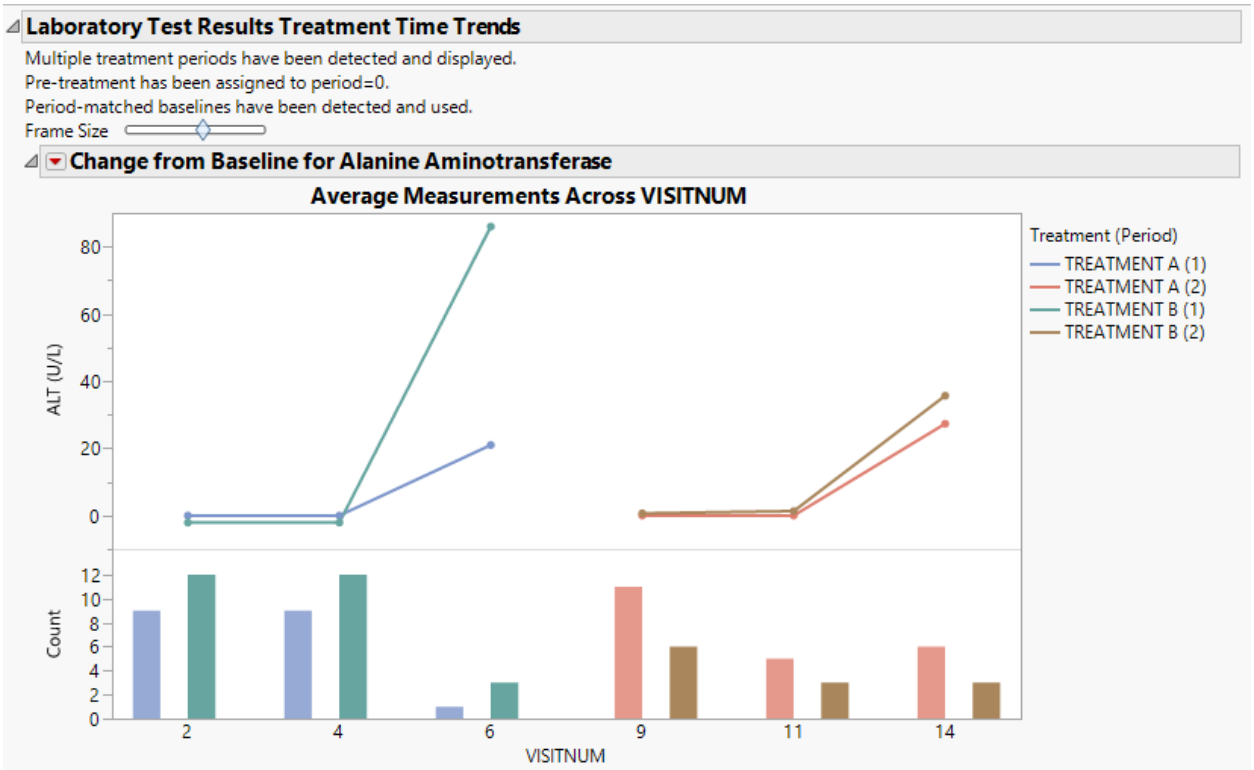
In patient narratives, multiple datasets may need to be assigned treatment periods, including adverse events, exposure, and findings datasets. For adverse events data, the start date of the adverse event is compared to each of the treatment period start dates. In the 2 x 2 design, the AE start date, usually ASTDT in ADaM data, is first compared to the period 2 treatment start date, TR02SDT. If ASTDT is greater than or equal to TR02SDT, then the adverse event is assigned to period 2. If the adverse event does not fall into period 2, then ASTDT is next compared to the period 1 treatment start date, TR01SDT. If ASTDT is greater than or equal to TR01SDT, then the adverse event is assigned to period 1. For this example, adverse events occurring before treatment period 1 starts (ASTDT < TR01SDT) are assigned to period 0 and treatment is assigned as “Pre-Treatment”. Similar derivations can be used for other datasets.




**PERIOD-MATCHED BASELINES**

For data used in change from baseline analyses, period-matched baselines are derived. Each period is assigned a baseline using the appropriate baseline flag, in ADaM data the variable ABLFL. If a record is flagged as a baseline record, then the period and corresponding treatment are assigned to the period in which it will be used as baseline. For example, if the baseline record occurs on or before the first period treatment starts, then the baseline record is assigned to period 1 and the treatment given in period 1. This record can then be compared against all other records in period 1 to calculate change from baseline. In this example, the baseline for each period is based on the last record on or before the treatment period begins.

In patient narratives, change from baseline results may be included for laboratory tests. In this case, each lab test is assigned a baseline for each period. For Alanine Aminotransferase in the example data, the period 1 baseline occurred on or before visit number 1 and the period 2 baseline occurred on either visit number 7 or visit number 8 depending on the patient. The value of each baseline is placed in one variable, in ADaM data the variable BASE. Laboratory test results drawn on visits 2, 4, and 6 are compared against the period 1 baseline and results drawn on visits 9, 11, and 14 are compared against the period 2 baseline. The change from baseline values can be placed in the ADaM variable CHG. The change from baseline results over time can be visualized by plotting time trends.




## CROSSOVER DATA IN PATIENT NARRATIVES

### BASELINE INFORMATION

The patient narratives in this example are displayed by subject with a patient header for each patient followed by a summary of baseline information for the patient and a section for each adverse event. In the header for each patient in the narrative, the randomized arm displays the treatment sequence the patient received. For patient 11009, the treatment received is treatment A in period 1 and treatment B in period 2. The section following the header includes baseline information for the patient, including baseline values for any findings data selected. Period-matched baselines are displayed by splitting the values into one row for period 1 and a separate row for period 2. In this example, laboratory results and vital signs data are included.

**Participant: 11009**
**Randomized Arm: TREATMENT A,TREATMENT B**
**Investigator Name: 011A**

Participant 11009 was a 65-year-old white female. Her medical history included focal deficit, headache, vomiting, other medical condition, hematological disease, allergies, and hypertension. She began dosing with 41 mg/h of TREATMENT A on 24FEB1988 (Day 1), and ended dosing with 41 mg/h of TREATMENT B on 09MAR1988 (Day 15).

The participant had the following abnormal laboratory test results at baseline: (Period 1) high activated partial thromboplastin time [35.900002 sec, range = (20 - 30)], and low carbon dioxide [91.308 mg/dL, range = (100.004 - 130.44)]
(Period 2) high activated partial thromboplastin time [34.900002 sec, range = (20 - 30)], high alanine aminotransferase [109 U/L, range = (10 - 40)], high blood urea nitrogen [12.138 mmol/L, range = (2.499 - 7.497)], high chloride [110 mmol/L, range = (97 - 107)], high lactate dehydrogenase [506 U/L, range = (105 - 333)], high prothrombin time [12.6 sec, range = (11 - 12.5)], and high sodium [147 mmol/L, range = (136 - 144)].

The participant had the following vital signs at baseline: (Period 1) diastolic blood pressure (53 mmHg), heart rate (75 BEATS/MIN), and systolic blood pressure (163 mmHg)
(Period 2) diastolic blood pressure (70 mmHg), heart rate (89 BEATS/MIN), and systolic blood pressure (150 mmHg).

**ADVERSE EVENTS**

Following the baseline information, a section for each adverse event is included. The treatment received at the start of the adverse event along with the treatment period are displayed in the header of the adverse event. The text following the header gives dosing information on the treatment received at the start of the event, including the total amount of treatment received in the period the event occurred. This patient had a cerebral infarction adverse event in period 1 while receiving Treatment A. At the time of the event, the patient had been treated with a cumulative dose of 82 mg/h of Treatment A.

**Serious Adverse Event (coded term): CEREBRAL INFARCTION**
**Drugs and Doses on Day of Event: On Treatment, 41 mg/h of TREATMENT A taken that day**
**Treatment (Period): TREATMENT A (1)**

On 25FEB1988 (Day 2) the participant experienced a cerebral infarction (severe) which was considered a serious adverse event (SAE). Though the event was considered serious, no reasons were provided on the case report form. On the day of the event, the participant was taking 41 mg/h of TREATMENT A and had been at this dose for 2 days. The SAE occurred 1 day after the first dose of any study medication. Up to and including the day of the event, the participant was treated with 82 mg/h of TREATMENT A. Trial medication had an action of dose not changed as a result of the event. It is not known from the case report form if therapeutic measures were administered to treat the event.

The closest prior and subsequent findings results to the start of the event are also displayed. The period the results were taken in is shown for each set of findings results. In this example, laboratory results that are different than baseline are displayed. Each laboratory result includes the period-matched baseline corresponding to the period of the result to allow for easy comparison of the laboratory result to the correct baseline value. For this participant, the closest laboratory results subsequent to the start of the event occurred in period 2, so the baseline values displayed for each laboratory test are the period 2 baseline value.

On the closest laboratory test results day on or prior to the start of the event, the participant had no on-study laboratory test results with results different than baseline. On the closest laboratory test results day subsequent to the start of the event (07MAR1988, Day 13, Period 2), the participant had the following on-study laboratory test results with results different than baseline: normal blood urea nitrogen [5.712 mmol/L, range = (2.499 - 7.497), BL =high], normal chloride [106 mmol/L, range = (97 - 107), BL =high], normal sodium [142 mmol/L, range = (136 - 144), BL =high], and low urate [0.1003 mmol/L, range = (0.1239 - 0.5015), BL =normal].

## CONCLUSION

Crossover designs can be useful in chronic disease studies by reducing the number of patients needed to evaluate endpoints. Adding variables for periods and corresponding treatment allows the analysis to be conducted by treatment period. These derivations can be done easily by comparing treatment period start dates with the date of an event, intervention, or finding. With datasets divided by period, period-matched baselines can be derived to conduct change from baseline analyses. By using periods and period-matched baselines, the narratives can clearly distinguish which events occurred in each treatment period with a few additions to the text.

## REFERENCES


1. Jones B and Kenward MG. Design and analysis of cross-over trials. 3rd ed. Boca Raton: Chapman & Hall, 2015.
2. Sibbald B and Roberts C. Understanding controlled trials Crossover trials. BMJ. 1998 Jun 6; 316(7146): 1719-1720.
3. Clinical Data Interchange Standards Consortium, ADaM Implementation Guide v1.1 (12 February 2016). https://www.cdisc.org/system/files/members/standard/foundational/adam/ADaMIG_v1.1.pdf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