

Analysis of crossover studies in patient narratives

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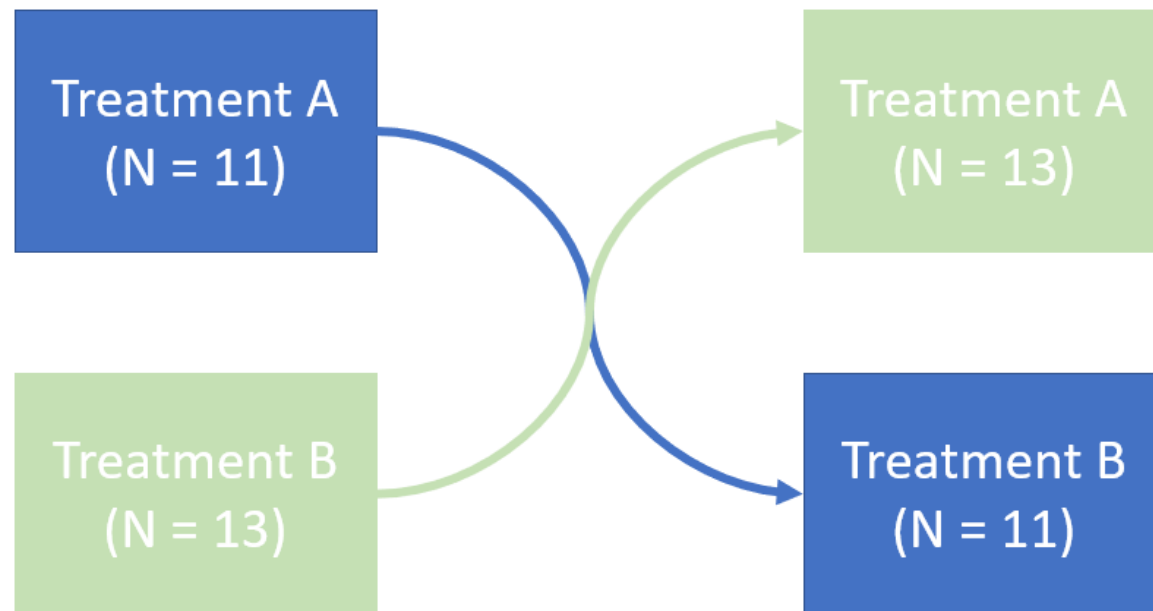
Geoffrey Mann

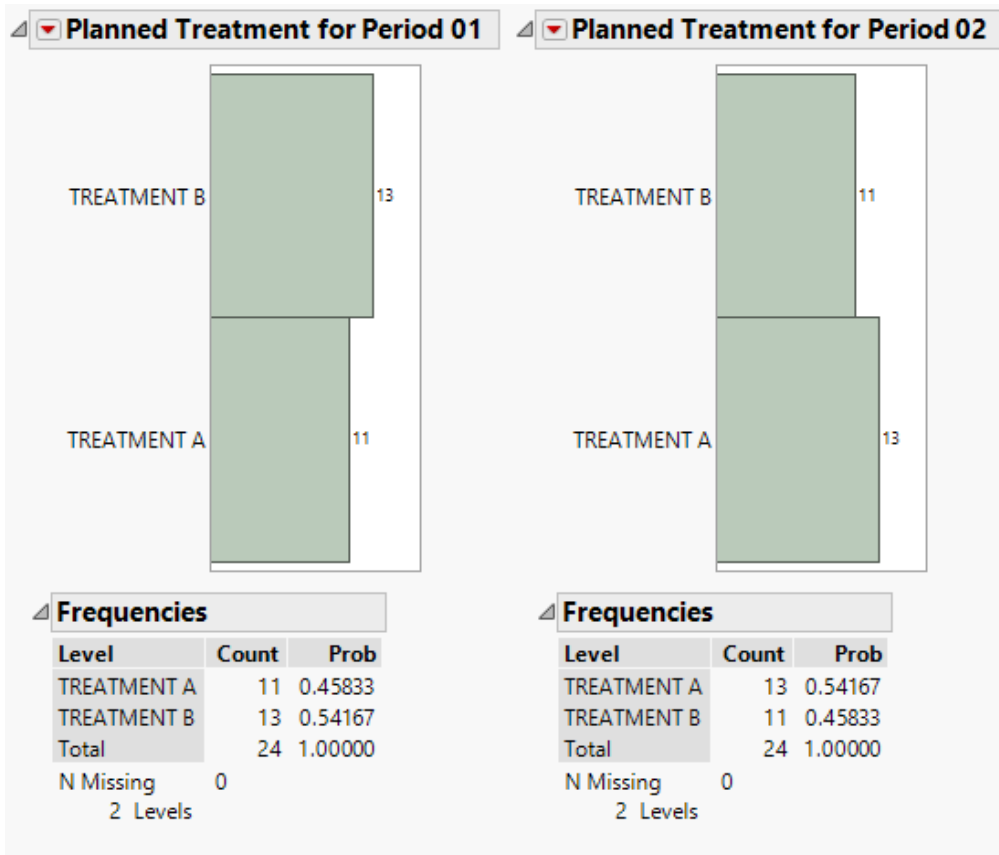
Crossover Design

- Two or more treatments over two or more periods
- Patients act as their own control
- Requires fewer patients to be enrolled
- “Carryover” effect can be minimized with a washout period
- Typically used for chronic diseases

2 x 2 Crossover Design

- Simplest crossover design
- Two treatment groups and two treatment periods
 - Treatment sequence 1: Treatment A in Period 1, Treatment B in Period 2
 - Treatment sequence 2: Treatment B in Period 1, Treatment A in Period 2





Subject Population by Treatment					
Period 1			Period 2		
Planned Treatment for Period 01	Count	% of Total	Planned Treatment for Period 02	Count	% of Total
TREATMENT A	11	45.8%	TREATMENT A	13	54.2%
TREATMENT B	13	54.2%	TREATMENT B	11	45.8%
All	24	100.0%	All	24	100.0%

Analysis of Crossover Data

- Assign treatment period to records based on treatment start and stop dates
- Period-matched baselines
- CDISC variables
 - TRTxP, TRxxSDT, TRxxEDT
 - APERIOD, TRTP, ASTDT
 - ABLFL, BASE, CHG

ADSL variables

- TRTxxP
 - Planned Treatment for Period xx
 - TRT01P for period 1, TRT02P for period 2
 - TRTxxA (Actual Treatment for Period xx) can also be used
- TRxxSDT
 - Date of First Exposure in Period xx
 - TR01SDT for period 1, TR02SDT for period 2
- TRxxEDT
 - Date of Last Exposure in Period xx
 - TR01EDT for period 1, TR02EDT for period 2

BDS or Occurrence Data Variables

- APERIOD
 - Period
 - Indicates the period the record occurs in
- TRTP
 - Planned Treatment
 - Identifies the treatment given at the time of the record
 - TRTA (Actual Treatment) can be used instead
- ASTDT
 - Analysis Start Date
 - Used to compare to treatment period start dates to determine period
 - ADT (Analysis Date) can be used instead

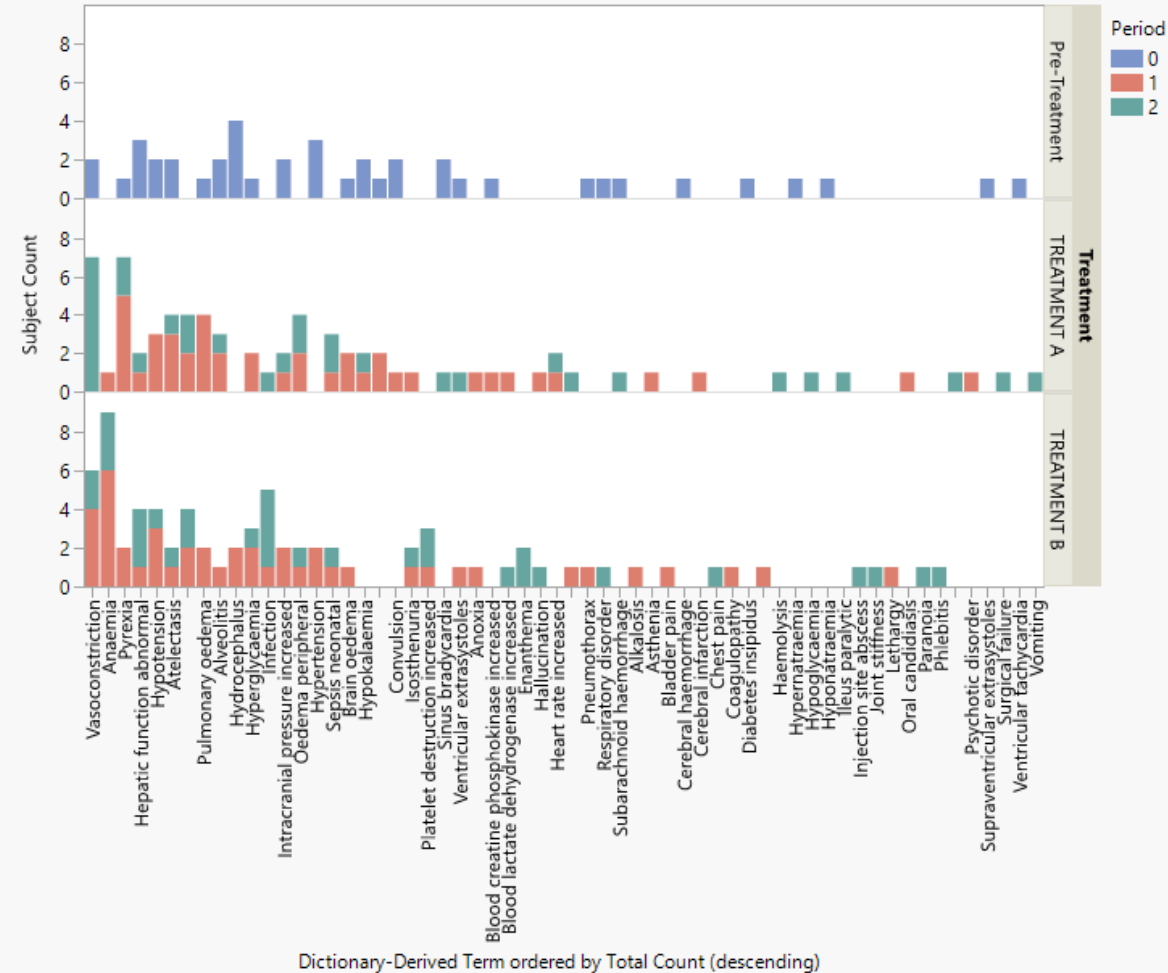
Assigning Period and Corresponding Treatment

- Compare ASTDT or ADT to TRxxSDT variables
- For ADAE in 2x2 design
 - If $ASTDT \geq TR02SDT$, then set to period 2.
 - Else if $ASTDT \geq TR01SDT$, then set to period 1.
 - If $ASTDT < TR01SDT$, then assign to Period 0 for Pre-Treatment

Counts Graph

- Multiple treatment periods have been detected and displayed.
- Pre-treatment has been assigned to period=0.
- Displayed counts indicate the number of subjects experiencing an event in each period.

Adverse Events Counts Graph



Period-Matched Baselines

- CDISC variables
 - ABLFL
 - Baseline Record Flag
 - Flag baseline for each period
 - BASE
 - Baseline Value
 - CHG
 - Change from Baseline

	USUBJID	PARAM	AVISITN	ADY	APERIOD	AVAL	AVALU	ABLFL	BASE	CHG
1	11009	Alanine Aminotransferase	•	-1	1	16	U/L	Y	16	•
2	11009	Alanine Aminotransferase	2	2	1	18	U/L		16	2
3	11009	Alanine Aminotransferase	4	4	1	16	U/L		16	0
4	11009	Alanine Aminotransferase	7	7	2	109	U/L	Y	109	•
5	11009	Alanine Aminotransferase	9	9	2	112	U/L		109	3

Laboratory Test Results Treatment Time Trends

Multiple treatment periods have been detected and displayed.

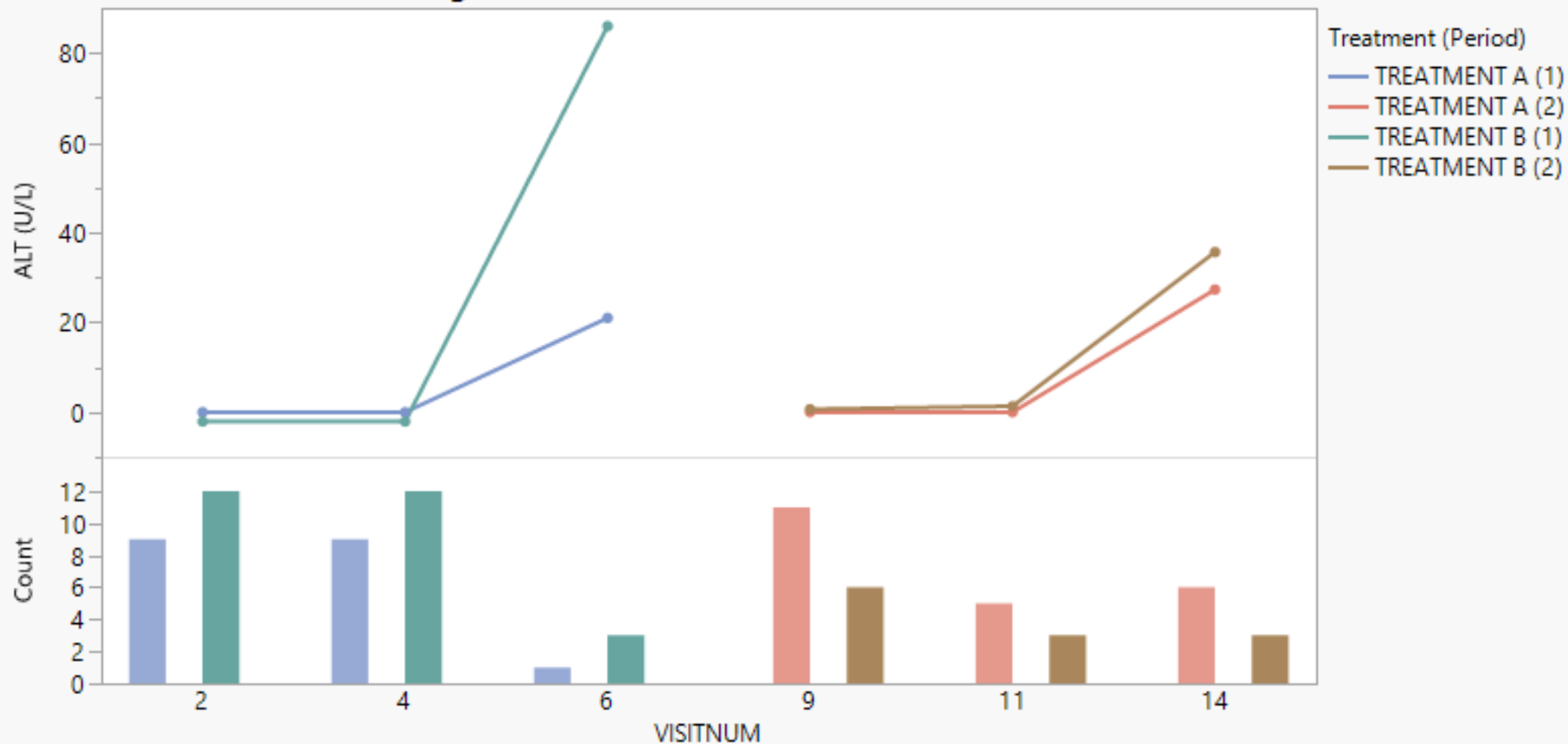
Pre-treatment has been assigned to period=0.

Period-matched baselines have been detected and used.

Frame Size

Change from Baseline for Alanine Aminotransferase

Average Measurements Across VISITNUM



Patient Narratives – Baseline Information

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).

Patient Narratives – Adverse Events

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.

Patient Narratives – Findings

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].

Conclusions

- With a few text changes patient narratives can be written for crossover studies
 - Treatment sequence
 - Assigning periods and corresponding treatment to adverse events
 - Period-matched baselines for findings data

Thank You!

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