

CHDR

Centre for Human Drug Research

Statistical appendix: Analysis of pharmacodynamic parameters CHDR1117

**Effects of paracetamol on nociceptive
pain in adolescents.**

PROTOCOL MANAGEMENT

CHDR protocol ID	CHDR1117
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Sponsor protocol ID	NA
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Investigator site

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Sponsor

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Description of the analysis

Changes in data

No changes in data before analysis.

Calculations

Delta electrical stairs PTT, PDT and AUC are calculated as the difference between the electrical stairs measurement before and after the cold test (after minus before). The measurement after the cold test is not used for the analysis of the electrical stairs variables, only to calculate the delta electrical stairs.

Analysis

All variables are listed by treatment, subject, gender, visit and time.

All variables are summarized by treatment and time. Time profiles are graphically represented.

PTT and PDT variables are log transformed prior to analysis to correct for the expected log-normal distribution of the data. Analysis is performed on log transformed data.

Repeated measured pharmacodynamic data are compared with a mixed model analysis of variance with fixed factors treatment, period, time and treatment by time, random factor subject, subject by treatment and subject by time and the average pre-value (average over all measurements at or before time=0) as covariate.

The following contrasts were calculated:

Paracetamol vs Placebo

A summary table of the analysis results was generated with estimates of the difference of the different contrasts and a back transformed estimate of the difference in percentage for log transformed parameters, 95% confidence intervals (in percentage for log-transformed parameters) and Least Square Means (geometric means for log transformed parameters), and the p-value of the contrasts. Least Square Means graphs were generated, with the Least Square Means of the analysis, and with the Least Square Means of the analysis of the data as change from baseline. This second analysis does not have different results than the first analysis, but the graph can be presented as change from baseline with a joint starting point at zero.

Finally the full ANOVA SAS output was added, as was the used SAS program.

All calculations were performed using SAS for windows V9.1.3 (SAS Institute, Inc., Cary, NC, USA).

Individual pharmacodynamic response data

Listing 1 Cold AAC (s*%)

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Listing 1 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Cold AAC (s*%)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:57	-0:17	-0:14	2113.8
				28DEC2011	12:33	1:16	1:22	2290.1
				28DEC2011	13:33	2:16	2:22	2271.1
				28DEC2011	14:43	3:16	3:32	3557.1
				28DEC2011	16:35	5:16	5:24	2876.8
	2	Paracetamol	Female	07JAN2012	10:47	-0:17	-0:09	3891.5
				07JAN2012	12:19	1:16	1:23	5419.2
				07JAN2012	13:17	2:16	2:21	3629.7
				07JAN2012	14:18	3:16	3:22	5117.7
				07JAN2012	16:17	5:16	5:21	4025.6
2	1	Paracetamol	Female	23NOV2012	10:44	-0:17	-0:07	788.8
				23NOV2012	12:05	1:16	1:14	860.3
				23NOV2012	13:06	2:16	2:15	776.1
				23NOV2012	14:04	3:16	3:13	772.7
				23NOV2012	16:07	5:16	5:16	757.3
	2	Placebo	Female	25NOV2012	10:24	-0:17	-0:19	715.0
				25NOV2012	11:59	1:16	1:16	795.8
				25NOV2012	12:57	2:16	2:14	715.6
				25NOV2012	13:57	3:16	3:14	830.8
				25NOV2012	15:57	5:16	5:14	655.4
	1	Paracetamol	Male	25NOV2012	11:45	-0:17	-0:16	5081.7
				25NOV2012	13:20	1:16	1:19	4496.5
				25NOV2012	14:23	2:16	2:22	4713.3
				25NOV2012	15:22	3:16	3:21	4186.1
				25NOV2012	17:22	5:16	5:21	5085.6
	2	Placebo	Male	16DEC2012	12:26	-0:17	-0:09	5093.1
				16DEC2012	13:56	1:16	1:21	4516.3
				16DEC2012	14:58	2:16	2:23	4609.3
				16DEC2012	15:55	3:16	3:20	4557.0
				16DEC2012	17:55	5:16	5:20	4100.1
4	1	Placebo	Male	25NOV2012	11:04	-0:17	-0:24	845.4
				25NOV2012	12:46	1:16	1:18	986.1
				25NOV2012	13:47	2:16	2:19	1165.7
				25NOV2012	14:47	3:16	3:19	1098.8
				25NOV2012	16:48	5:16	5:20	1049.6
	2	Paracetamol	Male	16DEC2012	12:48	-0:17	-0:17	1004.8
				16DEC2012	14:24	1:16	1:19	1141.0
				16DEC2012	15:25	2:16	2:20	1266.6
				16DEC2012	16:24	3:16	3:19	1509.6
				16DEC2012	18:26	5:16	5:21	1375.7
5	1	Paracetamol	Female	02JUN2014	10:59	-0:17	-0:13	1002.8
				02JUN2014	12:29	1:16	1:17	738.9
				02JUN2014	13:34	2:16	2:22	1055.6

M = Missing H = Maximum score reached

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Listing 1 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Cold AAC (s*%)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:32	3:16	3:20	1088.4
				02JUN2014	16:32	5:16	5:20	884.6
	2	Placebo	Female	03JUN2014	9:57	-0:17	-0:05	980.6
				03JUN2014	11:22	1:16	1:20	1132.1
				03JUN2014	12:19	2:16	2:17	912.2
				03JUN2014	13:20	3:16	3:18	884.2
				03JUN2014	15:20	5:16	5:18	1070.6
6	1	Placebo	Female	04JUL2014	10:34	-0:17	-0:04	1751.1
				04JUL2014	11:58	1:16	1:20	1429.7
				04JUL2014	13:00	2:16	2:22	1201.2
				04JUL2014	13:55	3:16	3:17	1072.1
				04JUL2014	15:57	5:16	5:19	1158.0
	2	Paracetamol	Female	05JUL2014	10:12	-0:17	-0:04	1071.0
				05JUL2014	11:36	1:16	1:20	1290.8
				05JUL2014	12:35	2:16	2:19	1287.6
				05JUL2014	13:38	3:16	3:22	1131.8
				05JUL2014	15:32	5:16	5:16	1090.3
7	1	Paracetamol	Female	05JUL2014	10:35	-0:17	-0:05	1039.5
				05JUL2014	11:59	1:16	1:19	989.8
				05JUL2014	12:58	2:16	2:18	1006.3
				05JUL2014	13:58	3:16	3:18	1196.1
				05JUL2014	15:58	5:16	5:18	1190.5
	2	Placebo	Female	18JUL2014	9:44	-0:17	-0:06	690.0
				18JUL2014	11:12	1:16	1:22	599.6
				18JUL2014	12:08	2:16	2:18	626.7
				18JUL2014	13:13	3:16	3:23	754.4
				18JUL2014	15:14	5:16	5:24	167.2
8	1	Placebo	Male	10JUL2014	11:24	-0:17	-0:08	2858.6
				10JUL2014	12:50	1:16	1:18	3521.6
				10JUL2014	13:56	2:16	2:24	2488.2
				10JUL2014	14:52	3:16	3:20	3157.1
				10JUL2014	16:51	5:16	5:19	2664.9
	2	Paracetamol	Male	11JUL2014	9:38	-0:17	-0:07	2244.3
				11JUL2014	11:04	1:16	1:19	2585.8
				11JUL2014	12:06	2:16	2:21	3418.9
				11JUL2014	13:08	3:16	3:23	3322.9
				11JUL2014	15:05	5:16	5:20	2751.0
9	1	Paracetamol	Female	11AUG2014	10:43	-0:17	-0:13	850.1
				11AUG2014	12:21	1:16	1:25	1082.7
				11AUG2014	13:23	2:16	2:27	955.7
				11AUG2014	14:16	3:16	3:20	1263.0
				11AUG2014	16:15	5:16	5:19	1091.0

M = Missing H = Maximum score reached

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Listing 1 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Cold AAC (s*%)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:16	-0:17	-0:21	1642.5
				12AUG2014	11:57	1:16	1:20	1373.4
				12AUG2014	12:57	2:16	2:20	1344.1
				12AUG2014	13:59	3:16	3:22	1356.3
				12AUG2014	15:58	5:16	5:21	1224.9
10	1	Placebo	Male	10JUL2014	10:56	-0:17	-0:12	6940.7
				10JUL2014	12:28	1:16	1:20	8155.8
				10JUL2014	13:35	2:16	2:27	9085.6
				10JUL2014	14:30	3:16	3:22	9960.4
				10JUL2014	16:29	5:16	5:21	4945.4
	2	Paracetamol	Male	11JUL2014	10:13	-0:17	-0:05	3267.6
				11JUL2014	12:39	2:16	2:21	2844.0
				11JUL2014	13:39	3:16	3:21	4445.9
				11JUL2014	15:41	5:16	5:23	4150.9
11	1	Placebo	Female	11AUG2014	10:23	-0:17	-0:08	3526.7
				11AUG2014	11:55	1:16	1:24	3506.6
				11AUG2014	12:57	2:16	2:26	3891.9
				11AUG2014	13:55	3:16	3:24	2657.4
				11AUG2014	15:51	5:16	5:20	3368.8
	2	Paracetamol	Female	12AUG2014	10:00	-0:17	-0:12	2705.6
				12AUG2014	11:33	1:16	1:21	3007.9
				12AUG2014	12:32	2:16	2:20	3333.9
				12AUG2014	13:38	3:16	3:26	2592.8
				12AUG2014	15:32	5:16	5:20	3041.8
12	1	Paracetamol	Male	12AUG2014	10:40	-0:17	-0:09	3896.9
				12AUG2014	12:08	1:16	1:19	2452.9
				12AUG2014	13:12	2:16	2:23	2287.1
				12AUG2014	14:10	3:16	3:21	2361.9
				12AUG2014	16:14	5:16	5:25	2316.6
	2	Placebo	Male	13AUG2014	9:48	-0:17	-0:12	1476.1
				13AUG2014	11:19	1:16	1:19	1580.8
				13AUG2014	12:18	2:16	2:18	2242.6
				13AUG2014	13:19	3:16	3:19	2903.1
				13AUG2014	15:22	5:16	5:22	1755.1

M = Missing H = Maximum score reached

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Listing 2 Cold PDT (s)

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Listing 2 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Cold PDT (s)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:57	-0:17	-0:14	0.7
				28DEC2011	12:33	1:16	1:22	0.3
				28DEC2011	13:33	2:16	2:22	1.8
				28DEC2011	14:43	3:16	3:32	1.7
				28DEC2011	16:35	5:16	5:24	3.2
	2	Paracetamol	Female	07JAN2012	10:47	-0:17	-0:09	1.1
				07JAN2012	12:19	1:16	1:23	2.3
				07JAN2012	13:17	2:16	2:21	2.5
				07JAN2012	14:18	3:16	3:22	3.2
				07JAN2012	16:17	5:16	5:21	5.5
2	1	Paracetamol	Female	23NOV2012	10:44	-0:17	-0:07	1.0
				23NOV2012	12:05	1:16	1:14	2.4
				23NOV2012	13:06	2:16	2:15	1.4
				23NOV2012	14:04	3:16	3:13	2.1
				23NOV2012	16:07	5:16	5:16	1.4
	2	Placebo	Female	25NOV2012	10:24	-0:17	-0:19	1.7
				25NOV2012	11:59	1:16	1:16	2.5
				25NOV2012	12:57	2:16	2:14	1.7
				25NOV2012	13:57	3:16	3:14	1.5
				25NOV2012	15:57	5:16	5:14	1.1
	3	Paracetamol	Male	25NOV2012	11:45	-0:17	-0:16	31.1
				25NOV2012	13:20	1:16	1:19	26.5
				25NOV2012	14:23	2:16	2:22	24.7
				25NOV2012	15:22	3:16	3:21	23.1
				25NOV2012	17:22	5:16	5:21	23.4
	2	Placebo	Male	16DEC2012	12:26	-0:17	-0:09	31.2
				16DEC2012	13:56	1:16	1:21	19.6
				16DEC2012	14:58	2:16	2:23	21.3
				16DEC2012	15:55	3:16	3:20	20.1
				16DEC2012	17:55	5:16	5:20	17.6
4	1	Placebo	Male	25NOV2012	11:04	-0:17	-0:24	0.0
				25NOV2012	12:46	1:16	1:18	1.9
				25NOV2012	13:47	2:16	2:19	2.0
				25NOV2012	14:47	3:16	3:19	2.3
				25NOV2012	16:48	5:16	5:20	3.2
	2	Paracetamol	Male	16DEC2012	12:48	-0:17	-0:17	1.6
				16DEC2012	14:24	1:16	1:19	2.7
				16DEC2012	15:25	2:16	2:20	3.0
				16DEC2012	16:24	3:16	3:19	3.5
				16DEC2012	18:26	5:16	5:21	4.5
	5	Paracetamol	Female	02JUN2014	10:59	-0:17	-0:13	6.6
				02JUN2014	12:29	1:16	1:17	3.8
				02JUN2014	13:34	2:16	2:22	7.5

M = Missing H = Maximum score reached

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Listing 2 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Cold PDT (s)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:32	3:16	3:20	5.6
					16:32	5:16	5:20	5.1
	2	Placebo	Female	03JUN2014	9:57	-0:17	-0:05	3.2
				03JUN2014	11:22	1:16	1:20	3.0
				03JUN2014	12:19	2:16	2:17	4.1
				03JUN2014	13:20	3:16	3:18	3.2
				03JUN2014	15:20	5:16	5:18	4.0
6	1	Placebo	Female	04JUL2014	10:34	-0:17	-0:04	4.5
				04JUL2014	11:58	1:16	1:20	2.2
				04JUL2014	13:00	2:16	2:22	2.7
				04JUL2014	13:55	3:16	3:17	1.7
				04JUL2014	15:57	5:16	5:19	2.5
	2	Paracetamol	Female	05JUL2014	10:12	-0:17	-0:04	3.8
				05JUL2014	11:36	1:16	1:20	5.0
				05JUL2014	12:35	2:16	2:19	5.3
				05JUL2014	13:38	3:16	3:22	4.3
				05JUL2014	15:32	5:16	5:16	4.9
7	1	Paracetamol	Female	05JUL2014	10:35	-0:17	-0:05	6.7
				05JUL2014	11:59	1:16	1:19	1.8
				05JUL2014	12:58	2:16	2:18	7.0
				05JUL2014	13:58	3:16	3:18	1.3
				05JUL2014	15:58	5:16	5:18	8.3
	2	Placebo	Female	18JUL2014	9:44	-0:17	-0:06	2.0
				18JUL2014	11:12	1:16	1:22	0.0
				18JUL2014	12:08	2:16	2:18	1.3
				18JUL2014	13:13	3:16	3:23	4.4
				18JUL2014	15:14	5:16	5:24	0.2
8	1	Placebo	Male	10JUL2014	11:24	-0:17	-0:08	6.6
				10JUL2014	12:50	1:16	1:18	12.5
				10JUL2014	13:56	2:16	2:24	8.0
				10JUL2014	14:52	3:16	3:20	9.4
				10JUL2014	16:51	5:16	5:19	7.9
	2	Paracetamol	Male	11JUL2014	9:38	-0:17	-0:07	3.4
				11JUL2014	11:04	1:16	1:19	9.8
				11JUL2014	12:06	2:16	2:21	15.6
				11JUL2014	13:08	3:16	3:23	14.5
				11JUL2014	15:05	5:16	5:20	7.4
9	1	Paracetamol	Female	11AUG2014	10:43	-0:17	-0:13	2.2
				11AUG2014	12:21	1:16	1:25	2.1
				11AUG2014	13:23	2:16	2:27	1.7
				11AUG2014	14:16	3:16	3:20	0.9
				11AUG2014	16:15	5:16	5:19	2.8

M = Missing H = Maximum score reached

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Listing 2 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Cold PDT (s)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:16	-0:17	-0:21	2.9
				12AUG2014	11:57	1:16	1:20	2.4
				12AUG2014	12:57	2:16	2:20	3.2
				12AUG2014	13:59	3:16	3:22	3.7
				12AUG2014	15:58	5:16	5:21	4.5
10	1	Placebo	Male	10JUL2014	10:56	-0:17	-0:12	17.2
				10JUL2014	12:28	1:16	1:20	24.8
				10JUL2014	13:35	2:16	2:27	17.4
				10JUL2014	14:30	3:16	3:22	26.7
				10JUL2014	16:29	5:16	5:21	14.5
	2	Paracetamol	Male	11JUL2014	10:13	-0:17	-0:05	13.4
				M	M	1:16	M	M
				11JUL2014	12:39	2:16	2:21	9.3
				11JUL2014	13:39	3:16	3:21	8.4
				11JUL2014	15:41	5:16	5:23	6.2
11	1	Placebo	Female	11AUG2014	10:23	-0:17	-0:08	13.3
				11AUG2014	11:55	1:16	1:24	14.9
				11AUG2014	12:57	2:16	2:26	9.7
				11AUG2014	13:55	3:16	3:24	7.5
				11AUG2014	15:51	5:16	5:20	10.8
	2	Paracetamol	Female	12AUG2014	10:00	-0:17	-0:12	10.6
				12AUG2014	11:33	1:16	1:21	8.6
				12AUG2014	12:32	2:16	2:20	6.9
				12AUG2014	13:38	3:16	3:26	7.4
				12AUG2014	15:32	5:16	5:20	17.8
12	1	Paracetamol	Male	12AUG2014	10:40	-0:17	-0:09	11.4
				12AUG2014	12:08	1:16	1:19	7.2
				12AUG2014	13:12	2:16	2:23	8.1
				12AUG2014	14:10	3:16	3:21	5.6
				12AUG2014	16:14	5:16	5:25	6.7
	2	Placebo	Male	13AUG2014	9:48	-0:17	-0:12	3.7
				13AUG2014	11:19	1:16	1:19	3.7
				13AUG2014	12:18	2:16	2:18	4.8
				13AUG2014	13:19	3:16	3:19	4.2
				13AUG2014	15:22	5:16	5:22	6.2

M = Missing H = Maximum score reached

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Listing 3 Cold PTT (s)

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Listing 3 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Cold PTT (s)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:57	-0:17	-0:14	64.6
				28DEC2011	12:33	1:16	1:22	62.9
				28DEC2011	13:33	2:16	2:22	120.0
				28DEC2011	14:43	3:16	3:32	75.8
				28DEC2011	16:35	5:16	5:24	67.5
	2	Paracetamol	Female	07JAN2012	10:47	-0:17	-0:09	120.0
				07JAN2012	12:19	1:16	1:23	120.0
				07JAN2012	13:17	2:16	2:21	88.8
				07JAN2012	14:18	3:16	3:22	104.2
				07JAN2012	16:17	5:16	5:21	120.0
2	1	Paracetamol	Female	23NOV2012	10:44	-0:17	-0:07	14.7
				23NOV2012	12:05	1:16	1:14	15.9
				23NOV2012	13:06	2:16	2:15	16.9
				23NOV2012	14:04	3:16	3:13	15.6
				23NOV2012	16:07	5:16	5:16	15.9
	2	Placebo	Female	25NOV2012	10:24	-0:17	-0:19	14.7
				25NOV2012	11:59	1:16	1:16	13.6
				25NOV2012	12:57	2:16	2:14	13.7
				25NOV2012	13:57	3:16	3:14	14.9
				25NOV2012	15:57	5:16	5:14	12.6
	3	Paracetamol	Male	25NOV2012	11:45	-0:17	-0:16	74.6
				25NOV2012	13:20	1:16	1:19	57.3
				25NOV2012	14:23	2:16	2:22	65.2
				25NOV2012	15:22	3:16	3:21	55.6
				25NOV2012	17:22	5:16	5:21	76.7
	2	Placebo	Male	16DEC2012	12:26	-0:17	-0:09	69.3
				16DEC2012	13:56	1:16	1:21	59.8
				16DEC2012	14:58	2:16	2:23	76.1
				16DEC2012	15:55	3:16	3:20	67.5
				16DEC2012	17:55	5:16	5:20	63.9
4	1	Placebo	Male	25NOV2012	11:04	-0:17	-0:24	15.6
				25NOV2012	12:46	1:16	1:18	19.5
				25NOV2012	13:47	2:16	2:19	20.0
				25NOV2012	14:47	3:16	3:19	20.1
				25NOV2012	16:48	5:16	5:20	20.3
	2	Paracetamol	Male	16DEC2012	12:48	-0:17	-0:17	16.8
				16DEC2012	14:24	1:16	1:19	19.0
				16DEC2012	15:25	2:16	2:20	22.6
				16DEC2012	16:24	3:16	3:19	25.9
				16DEC2012	18:26	5:16	5:21	24.1
5	1	Paracetamol	Female	02JUN2014	10:59	-0:17	-0:13	14.9
				02JUN2014	12:29	1:16	1:17	11.2
				02JUN2014	13:34	2:16	2:22	16.1

M = Missing H = Maximum score reached

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Listing 3 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Cold PTT (s)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:32	3:16	3:20	17.1
					16:32	5:16	5:20	15.3
	2	Placebo	Female	03JUN2014	9:57	-0:17	-0:05	16.7
				03JUN2014	11:22	1:16	1:20	17.9
				03JUN2014	12:19	2:16	2:17	16.0
				03JUN2014	13:20	3:16	3:18	16.4
				03JUN2014	15:20	5:16	5:18	18.6
6	1	Placebo	Female	04JUL2014	10:34	-0:17	-0:04	26.2
				04JUL2014	11:58	1:16	1:20	22.0
				04JUL2014	13:00	2:16	2:22	18.7
				04JUL2014	13:55	3:16	3:17	16.3
				04JUL2014	15:57	5:16	5:19	17.0
	2	Paracetamol	Female	05JUL2014	10:12	-0:17	-0:04	17.5
				05JUL2014	11:36	1:16	1:20	18.2
				05JUL2014	12:35	2:16	2:19	16.1
				05JUL2014	13:38	3:16	3:22	16.6
				05JUL2014	15:32	5:16	5:16	14.5
7	1	Paracetamol	Female	05JUL2014	10:35	-0:17	-0:05	12.4
				05JUL2014	11:59	1:16	1:19	13.2
				05JUL2014	12:58	2:16	2:18	13.6
				05JUL2014	13:58	3:16	3:18	15.2
				05JUL2014	15:58	5:16	5:18	15.5
	2	Placebo	Female	18JUL2014	9:44	-0:17	-0:06	11.3
				18JUL2014	11:12	1:16	1:22	10.0
				18JUL2014	12:08	2:16	2:18	10.1
				18JUL2014	13:13	3:16	3:23	10.3
				18JUL2014	15:14	5:16	5:24	3.5
8	1	Placebo	Male	10JUL2014	11:24	-0:17	-0:08	60.6
				10JUL2014	12:50	1:16	1:18	56.9
				10JUL2014	13:56	2:16	2:24	54.9
				10JUL2014	14:52	3:16	3:20	50.5
				10JUL2014	16:51	5:16	5:19	50.5
	2	Paracetamol	Male	11JUL2014	9:38	-0:17	-0:07	50.7
				11JUL2014	11:04	1:16	1:19	51.8
				11JUL2014	12:06	2:16	2:21	63.1
				11JUL2014	13:08	3:16	3:23	59.5
				11JUL2014	15:05	5:16	5:20	52.9
9	1	Paracetamol	Female	11AUG2014	10:43	-0:17	-0:13	14.0
				11AUG2014	12:21	1:16	1:25	15.1
				11AUG2014	13:23	2:16	2:27	16.3
				11AUG2014	14:16	3:16	3:20	17.8
				11AUG2014	16:15	5:16	5:19	19.9

M = Missing H = Maximum score reached

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Listing 3 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Cold PTT (s)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:16	-0:17	-0:21	26.0
				12AUG2014	11:57	1:16	1:20	21.2
				12AUG2014	12:57	2:16	2:20	20.3
				12AUG2014	13:59	3:16	3:22	20.0
				12AUG2014	15:58	5:16	5:21	22.9
10	1	Placebo	Male	10JUL2014	10:56	-0:17	-0:12	120.0
				10JUL2014	12:28	1:16	1:20	H
				10JUL2014	13:35	2:16	2:27	120.0
				10JUL2014	14:30	3:16	3:22	120.0
				10JUL2014	16:29	5:16	5:21	59.4
	2	Paracetamol	Male	11JUL2014	10:13	-0:17	-0:05	37.1
				M	M	1:16	M	M
				11JUL2014	12:39	2:16	2:21	33.1
				11JUL2014	13:39	3:16	3:21	54.9
				11JUL2014	15:41	5:16	5:23	54.1
11	1	Placebo	Female	11AUG2014	10:23	-0:17	-0:08	52.1
				11AUG2014	11:55	1:16	1:24	53.3
				11AUG2014	12:57	2:16	2:26	52.4
				11AUG2014	13:55	3:16	3:24	38.1
				11AUG2014	15:51	5:16	5:20	46.5
	2	Paracetamol	Female	12AUG2014	10:00	-0:17	-0:12	40.8
				12AUG2014	11:33	1:16	1:21	45.5
				12AUG2014	12:32	2:16	2:20	52.3
				12AUG2014	13:38	3:16	3:26	37.7
				12AUG2014	15:32	5:16	5:20	41.8
12	1	Paracetamol	Male	12AUG2014	10:40	-0:17	-0:09	74.8
				12AUG2014	12:08	1:16	1:19	46.6
				12AUG2014	13:12	2:16	2:23	51.4
				12AUG2014	14:10	3:16	3:21	56.7
				12AUG2014	16:14	5:16	5:25	42.8
	2	Placebo	Male	13AUG2014	9:48	-0:17	-0:12	32.0
				13AUG2014	11:19	1:16	1:19	37.9
				13AUG2014	12:18	2:16	2:18	40.9
				13AUG2014	13:19	3:16	3:19	55.2
				13AUG2014	15:22	5:16	5:22	39.4

M = Missing H = Maximum score reached

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Produced by M.L. de Kam

Listing 4 Electrical Stair AUC (mA*%)

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Listing 4 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Electrical Stair AUC (mA*%)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:48	-0:25	-0:23	3119.0
				28DEC2011	12:22	1:08	1:11	2920.6
				28DEC2011	13:25	2:08	2:14	2378.4
				28DEC2011	14:36	3:08	3:25	1737.8
				28DEC2011	16:26	5:08	5:15	1929.0
	2	Paracetamol	Female	07JAN2012	10:36	-0:25	-0:20	2616.3
				07JAN2012	12:08	1:08	1:12	2161.8
				07JAN2012	13:09	2:08	2:13	2118.6
				07JAN2012	14:10	3:08	3:14	1964.5
				07JAN2012	16:08	5:08	5:12	1924.4
2	1	Paracetamol	Female	23NOV2012	10:35	-0:25	-0:16	4093.6
				23NOV2012	11:59	1:08	1:08	3934.8
				23NOV2012	13:01	2:08	2:10	3924.0
				23NOV2012	13:59	3:08	3:08	3961.7
				23NOV2012	16:00	5:08	5:09	3772.0
	2	Placebo	Female	25NOV2012	10:18	-0:25	-0:25	4015.0
				25NOV2012	11:54	1:08	1:11	3762.2
				25NOV2012	12:51	2:08	2:08	3967.6
				25NOV2012	13:52	3:08	3:09	3692.0
				25NOV2012	15:52	5:08	5:09	3777.0
	3	Paracetamol	Male	25NOV2012	11:29	-0:25	-0:32	962.4
				25NOV2012	13:12	1:08	1:11	1560.3
				25NOV2012	14:11	2:08	2:10	1783.1
				25NOV2012	15:14	3:08	3:13	1345.1
				25NOV2012	17:13	5:08	5:12	1300.1
	2	Placebo	Male	16DEC2012	12:12	-0:25	-0:23	1887.5
				16DEC2012	13:48	1:08	1:13	1349.2
				16DEC2012	14:48	2:08	2:13	1213.0
				16DEC2012	15:47	3:08	3:12	918.3
				16DEC2012	17:46	5:08	5:11	599.7
4	1	Placebo	Male	25NOV2012	10:56	-0:25	-0:32	3702.5
				25NOV2012	12:40	1:08	1:12	3738.7
				25NOV2012	13:38	2:08	2:10	3605.6
				25NOV2012	14:39	3:08	3:11	3691.1
				25NOV2012	16:41	5:08	5:13	3534.4
	2	Paracetamol	Male	16DEC2012	12:40	-0:25	-0:25	3205.1
				16DEC2012	14:17	1:08	1:12	3092.5
				16DEC2012	15:17	2:08	2:12	2652.0
				16DEC2012	16:17	3:08	3:12	3009.9
				16DEC2012	18:17	5:08	5:12	2973.6
5	1	Paracetamol	Female	02JUN2014	10:52	-0:25	-0:20	4195.3
				02JUN2014	12:22	1:08	1:10	4023.6
				02JUN2014	13:24	2:08	2:12	3791.7

M = Missing H = Maximum score reached

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Listing 4 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Electrical Stair AUC (mA*%)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:25	3:08	3:13	3633.5
				02JUN2014	16:24	5:08	5:12	3570.9
	2	Placebo	Female	03JUN2014	9:49	-0:25	-0:13	4085.2
				03JUN2014	11:14	1:08	1:12	3862.6
				03JUN2014	12:12	2:08	2:10	3548.3
				03JUN2014	13:11	3:08	3:09	3894.0
				03JUN2014	15:11	5:08	5:09	3612.8
6	1	Placebo	Female	04JUL2014	10:21	-0:25	-0:17	4161.1
				04JUL2014	11:47	1:08	1:09	4186.1
				04JUL2014	12:52	2:08	2:14	4185.5
				04JUL2014	13:47	3:08	3:09	3974.0
				04JUL2014	15:48	5:08	5:10	4170.6
	2	Paracetamol	Female	05JUL2014	10:02	-0:25	-0:14	3821.6
				05JUL2014	11:27	1:08	1:11	3867.4
				05JUL2014	12:25	2:08	2:09	3774.8
				05JUL2014	13:25	3:08	3:09	3959.5
				05JUL2014	15:25	5:08	5:09	4048.6
7	1	Paracetamol	Female	05JUL2014	10:28	-0:25	-0:12	3671.0
				05JUL2014	11:50	1:08	1:10	3654.2
				05JUL2014	12:51	2:08	2:11	3455.1
				05JUL2014	13:49	3:08	3:09	3055.1
				05JUL2014	15:48	5:08	5:08	3435.9
	2	Placebo	Female	18JUL2014	9:33	-0:25	-0:17	3742.5
				18JUL2014	11:03	1:08	1:13	2784.1
				18JUL2014	12:00	2:08	2:10	2909.4
				18JUL2014	13:01	3:08	3:11	3125.4
				18JUL2014	15:06	5:08	5:16	2739.7
8	1	Placebo	Male	10JUL2014	11:16	-0:25	-0:16	3225.3
				10JUL2014	12:42	1:08	1:10	2639.7
				10JUL2014	13:47	2:08	2:15	2815.1
				10JUL2014	14:43	3:08	3:11	3174.5
				10JUL2014	16:42	5:08	5:10	3323.4
	2	Paracetamol	Male	11JUL2014	9:28	-0:25	-0:17	3653.2
				11JUL2014	10:54	1:08	1:09	3195.5
				11JUL2014	11:54	2:08	2:09	2841.9
				11JUL2014	12:57	3:08	3:12	2862.2
				11JUL2014	14:56	5:08	5:11	3175.9
9	1	Paracetamol	Female	11AUG2014	10:35	-0:25	-0:21	4077.2
				11AUG2014	12:08	1:08	1:12	3781.0
				11AUG2014	13:14	2:08	2:18	3755.0
				11AUG2014	14:07	3:08	3:11	3635.8
				11AUG2014	16:05	5:08	5:09	3576.2

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Listing 4 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Electrical Stair AUC (mA*%)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:07	-0:25	-0:30	3794.5
				12AUG2014	11:47	1:08	1:10	3572.9
				12AUG2014	12:46	2:08	2:09	3569.9
				12AUG2014	13:51	3:08	3:14	3623.4
				12AUG2014	15:50	5:08	5:13	3563.7
10	1	Placebo	Male	10JUL2014	10:44	-0:25	-0:24	2492.5
				10JUL2014	12:19	1:08	1:11	2206.3
				10JUL2014	13:22	2:08	2:14	2265.0
				10JUL2014	14:18	3:08	3:10	2210.1
				10JUL2014	16:18	5:08	5:10	2360.8
	2	Paracetamol	Male	11JUL2014	10:04	-0:25	-0:14	1795.3
				11JUL2014	11:28	1:08	1:10	1786.2
				11JUL2014	12:29	2:08	2:11	1723.1
				11JUL2014	13:29	3:08	3:11	1702.2
				11JUL2014	15:31	5:08	5:13	1705.3
11	1	Placebo	Female	11AUG2014	10:13	-0:25	-0:18	2233.9
				11AUG2014	11:43	1:08	1:12	2601.0
				11AUG2014	12:44	2:08	2:13	2961.2
				11AUG2014	13:47	3:08	3:16	2948.6
				11AUG2014	15:41	5:08	5:10	2782.1
	2	Paracetamol	Female	12AUG2014	9:40	-0:25	-0:32	2932.0
				12AUG2014	11:22	1:08	1:10	2814.5
				12AUG2014	12:22	2:08	2:10	2742.6
				12AUG2014	13:29	3:08	3:17	2550.1
				12AUG2014	15:25	5:08	5:13	2793.4
12	1	Paracetamol	Male	12AUG2014	10:25	-0:25	-0:24	3186.7
				12AUG2014	11:59	1:08	1:10	3442.3
				12AUG2014	13:00	2:08	2:11	2964.5
				12AUG2014	14:00	3:08	3:11	3045.9
				12AUG2014	16:05	5:08	5:16	3021.7
	2	Placebo	Male	13AUG2014	9:30	-0:25	-0:30	3513.6
				13AUG2014	11:09	1:08	1:09	3273.1
				13AUG2014	12:09	2:08	2:09	3147.6
				13AUG2014	13:10	3:08	3:10	2780.7
				13AUG2014	15:11	5:08	5:11	2841.4

M = Missing H = Maximum score reached

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Listing 5 Electrical Stair PDT (mA)

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Listing 5 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Electrical Stair PDT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:48	-0:25	-0:23	3.9
				28DEC2011	12:22	1:08	1:11	4.9
				28DEC2011	13:25	2:08	2:14	5.4
				28DEC2011	14:36	3:08	3:25	7.5
				28DEC2011	16:26	5:08	5:15	7.0
	2	Paracetamol	Female	07JAN2012	10:36	-0:25	-0:20	4.4
				07JAN2012	12:08	1:08	1:12	5.5
				07JAN2012	13:09	2:08	2:13	6.0
				07JAN2012	14:10	3:08	3:14	7.6
				07JAN2012	16:08	5:08	5:12	6.0
2	1	Paracetamol	Female	23NOV2012	10:35	-0:25	-0:16	3.8
				23NOV2012	11:59	1:08	1:08	4.9
				23NOV2012	13:01	2:08	2:10	5.4
				23NOV2012	13:59	3:08	3:08	4.9
				23NOV2012	16:00	5:08	5:09	5.4
	2	Placebo	Female	25NOV2012	10:18	-0:25	-0:25	3.8
				25NOV2012	11:54	1:08	1:11	6.9
				25NOV2012	12:51	2:08	2:08	5.9
				25NOV2012	13:52	3:08	3:09	6.4
				25NOV2012	15:52	5:08	5:09	5.9
	3	Paracetamol	Male	25NOV2012	11:29	-0:25	-0:32	26.4
				25NOV2012	13:12	1:08	1:11	22.4
				25NOV2012	14:11	2:08	2:10	14.3
				25NOV2012	15:14	3:08	3:13	19.3
				25NOV2012	17:13	5:08	5:12	14.3
	2	Placebo	Male	16DEC2012	12:12	-0:25	-0:23	12.0
				16DEC2012	13:48	1:08	1:13	12.6
				16DEC2012	14:48	2:08	2:13	16.1
				16DEC2012	15:47	3:08	3:12	19.2
				16DEC2012	17:46	5:08	5:11	25.9
4	1	Placebo	Male	25NOV2012	10:56	-0:25	-0:32	6.1
				25NOV2012	12:40	1:08	1:12	7.2
				25NOV2012	13:38	2:08	2:10	8.2
				25NOV2012	14:39	3:08	3:11	8.7
				25NOV2012	16:41	5:08	5:13	8.7
	2	Paracetamol	Male	16DEC2012	12:40	-0:25	-0:25	11.5
				16DEC2012	14:17	1:08	1:12	13.0
				16DEC2012	15:17	2:08	2:12	14.1
				16DEC2012	16:17	3:08	3:12	12.6
				16DEC2012	18:17	5:08	5:12	13.1
5	1	Paracetamol	Female	02JUN2014	10:52	-0:25	-0:20	1.9
				02JUN2014	12:22	1:08	1:10	3.4
				02JUN2014	13:24	2:08	2:12	4.9

M = Missing H = Maximum score reached

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Listing 5 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Electrical Stair PDT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:25	3:08	3:13	6.4
					16:24	5:08	5:12	1.9
	2	Placebo	Female	03JUN2014	9:49	-0:25	-0:13	2.0
					11:14	1:08	1:12	7.1
					12:12	2:08	2:10	10.2
					13:11	3:08	3:09	6.7
					15:11	5:08	5:09	7.2
6	1	Placebo	Female	04JUL2014	10:21	-0:25	-0:17	2.6
					11:47	1:08	1:09	2.6
					12:52	2:08	2:14	3.6
					13:47	3:08	3:09	3.1
					15:48	5:08	5:10	3.2
	2	Paracetamol	Female	05JUL2014	10:02	-0:25	-0:14	5.1
					11:27	1:08	1:11	5.6
					12:25	2:08	2:09	5.6
					13:25	3:08	3:09	5.1
					15:25	5:08	5:09	5.2
7	1	Paracetamol	Female	05JUL2014	10:28	-0:25	-0:12	4.1
					11:50	1:08	1:10	4.1
					12:51	2:08	2:11	3.6
					13:49	3:08	3:09	5.1
					15:48	5:08	5:08	3.6
	2	Placebo	Female	18JUL2014	9:33	-0:25	-0:17	6.3
					11:03	1:08	1:13	8.3
					12:00	2:08	2:10	10.4
					13:01	3:08	3:11	8.9
					15:06	5:08	5:16	8.3
8	1	Placebo	Male	10JUL2014	11:16	-0:25	-0:16	7.4
					12:42	1:08	1:10	11.9
					13:47	2:08	2:15	7.4
					14:43	3:08	3:11	6.8
					16:42	5:08	5:10	5.8
	2	Paracetamol	Male	11JUL2014	9:28	-0:25	-0:17	4.6
					10:54	1:08	1:09	8.3
					11:54	2:08	2:09	14.1
					12:57	3:08	3:12	12.5
					14:56	5:08	5:11	10.4
9	1	Paracetamol	Female	11AUG2014	10:35	-0:25	-0:21	1.3
					12:08	1:08	1:12	1.8
					13:14	2:08	2:18	1.4
					14:07	3:08	3:11	3.4
					16:05	5:08	5:09	4.4

M = Missing H = Maximum score reached

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Listing 5 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Electrical Stair PDT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:07	-0:25	-0:30	2.3
				12AUG2014	11:47	1:08	1:10	3.3
				12AUG2014	12:46	2:08	2:09	1.8
				12AUG2014	13:51	3:08	3:14	7.4
				12AUG2014	15:50	5:08	5:13	5.9
10	1	Placebo	Male	10JUL2014	10:44	-0:25	-0:24	12.5
				10JUL2014	12:19	1:08	1:11	13.9
				10JUL2014	13:22	2:08	2:14	11.9
				10JUL2014	14:18	3:08	3:10	15.9
				10JUL2014	16:18	5:08	5:10	13.9
	2	Paracetamol	Male	11JUL2014	10:04	-0:25	-0:14	20.8
				11JUL2014	11:28	1:08	1:10	15.6
				11JUL2014	12:29	2:08	2:11	15.1
				11JUL2014	13:29	3:08	3:11	14.6
				11JUL2014	15:31	5:08	5:13	17.7
11	1	Placebo	Female	11AUG2014	10:13	-0:25	-0:18	8.4
				11AUG2014	11:43	1:08	1:12	14.6
				11AUG2014	12:44	2:08	2:13	10.0
				11AUG2014	13:47	3:08	3:16	11.6
				11AUG2014	15:41	5:08	5:10	12.1
	2	Paracetamol	Female	12AUG2014	9:40	-0:25	-0:32	12.1
				12AUG2014	11:22	1:08	1:10	12.6
				12AUG2014	12:22	2:08	2:10	10.0
				12AUG2014	13:29	3:08	3:17	12.0
				12AUG2014	15:25	5:08	5:13	14.1
12	1	Paracetamol	Male	12AUG2014	10:25	-0:25	-0:24	8.5
				12AUG2014	11:59	1:08	1:10	5.9
				12AUG2014	13:00	2:08	2:11	10.4
				12AUG2014	14:00	3:08	3:11	10.4
				12AUG2014	16:05	5:08	5:16	11.9
	2	Placebo	Male	13AUG2014	9:30	-0:25	-0:30	6.3
				13AUG2014	11:09	1:08	1:09	6.4
				13AUG2014	12:09	2:08	2:09	6.9
				13AUG2014	13:10	3:08	3:10	8.5
				13AUG2014	15:11	5:08	5:11	9.0

M = Missing H = Maximum score reached

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Listing 6 Electrical Stair PTT (mA)

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Listing 6 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Electrical Stair PTT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:48	-0:25	-0:23	H
				28DEC2011	12:22	1:08	1:11	38.9
				28DEC2011	13:25	2:08	2:14	45.4
				28DEC2011	14:36	3:08	3:25	50.2
				28DEC2011	16:26	5:08	5:15	49.5
	2	Paracetamol	Female	07JAN2012	10:36	-0:25	-0:20	H
				07JAN2012	12:08	1:08	1:12	48.6
				07JAN2012	13:09	2:08	2:13	44.5
				07JAN2012	14:10	3:08	3:14	50.3
				07JAN2012	16:08	5:08	5:12	44.0
2	1	Paracetamol	Female	23NOV2012	10:35	-0:25	-0:16	13.1
				23NOV2012	11:59	1:08	1:08	15.1
				23NOV2012	13:01	2:08	2:10	14.1
				23NOV2012	13:59	3:08	3:08	14.6
				23NOV2012	16:00	5:08	5:09	16.7
	2	Placebo	Female	25NOV2012	10:18	-0:25	-0:25	14.6
				25NOV2012	11:54	1:08	1:11	16.1
				25NOV2012	12:51	2:08	2:08	15.1
				25NOV2012	13:52	3:08	3:09	17.7
				25NOV2012	15:52	5:08	5:09	17.2
3	1	Paracetamol	Male	25NOV2012	11:29	-0:25	-0:32	H
				25NOV2012	13:12	1:08	1:11	48.2
				25NOV2012	14:11	2:08	2:10	48.7
				25NOV2012	15:14	3:08	3:13	49.2
				25NOV2012	17:13	5:08	5:12	H
	2	Placebo	Male	16DEC2012	12:12	-0:25	-0:23	39.2
				16DEC2012	13:48	1:08	1:13	49.5
				16DEC2012	14:48	2:08	2:13	H
				16DEC2012	15:47	3:08	3:12	H
				16DEC2012	17:46	5:08	5:11	H
4	1	Placebo	Male	25NOV2012	10:56	-0:25	-0:32	15.8
				25NOV2012	12:40	1:08	1:12	15.3
				25NOV2012	13:38	2:08	2:10	16.8
				25NOV2012	14:39	3:08	3:11	16.3
				25NOV2012	16:41	5:08	5:13	17.8
	2	Paracetamol	Male	16DEC2012	12:40	-0:25	-0:25	21.3
				16DEC2012	14:17	1:08	1:12	25.4
				16DEC2012	15:17	2:08	2:12	28.5
				16DEC2012	16:17	3:08	3:12	25.9
				16DEC2012	18:17	5:08	5:12	27.9
5	1	Paracetamol	Female	02JUN2014	10:52	-0:25	-0:20	13.5
				02JUN2014	12:22	1:08	1:10	15.0
				02JUN2014	13:24	2:08	2:12	16.5

M = Missing H = Maximum score reached

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Listing 6 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Electrical Stair PTT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:25	3:08	3:13	18.0
					16:24	5:08	5:12	18.5
	2	Placebo	Female	03JUN2014	9:49	-0:25	-0:13	16.3
				03JUN2014	11:14	1:08	1:12	15.3
				03JUN2014	12:12	2:08	2:10	18.3
				03JUN2014	13:11	3:08	3:09	16.9
				03JUN2014	15:11	5:08	5:09	21.4
6	1	Placebo	Female	04JUL2014	10:21	-0:25	-0:17	11.7
				04JUL2014	11:47	1:08	1:09	11.7
				04JUL2014	12:52	2:08	2:14	12.2
				04JUL2014	13:47	3:08	3:09	14.2
				04JUL2014	15:48	5:08	5:10	11.3
	2	Paracetamol	Female	05JUL2014	10:02	-0:25	-0:14	16.3
				05JUL2014	11:27	1:08	1:11	13.7
				05JUL2014	12:25	2:08	2:09	14.3
				05JUL2014	13:25	3:08	3:09	13.3
				05JUL2014	15:25	5:08	5:09	11.7
	1	Paracetamol	Female	05JUL2014	10:28	-0:25	-0:12	19.3
				05JUL2014	11:50	1:08	1:10	21.4
				05JUL2014	12:51	2:08	2:11	21.9
				05JUL2014	13:49	3:08	3:09	23.5
				05JUL2014	15:48	5:08	5:08	21.3
	2	Placebo	Female	18JUL2014	9:33	-0:25	-0:17	22.8
				18JUL2014	11:03	1:08	1:13	28.5
				18JUL2014	12:00	2:08	2:10	28.0
				18JUL2014	13:01	3:08	3:11	24.9
				18JUL2014	15:06	5:08	5:16	26.4
8	1	Placebo	Male	10JUL2014	11:16	-0:25	-0:16	30.0
				10JUL2014	12:42	1:08	1:10	39.0
				10JUL2014	13:47	2:08	2:15	31.0
				10JUL2014	14:43	3:08	3:11	31.9
				10JUL2014	16:42	5:08	5:10	29.9
	2	Paracetamol	Male	11JUL2014	9:28	-0:25	-0:17	25.3
				11JUL2014	10:54	1:08	1:09	27.4
				11JUL2014	11:54	2:08	2:09	25.9
				11JUL2014	12:57	3:08	3:12	26.9
				11JUL2014	14:56	5:08	5:11	25.4
9	1	Paracetamol	Female	11AUG2014	10:35	-0:25	-0:21	13.1
				11AUG2014	12:08	1:08	1:12	14.6
				11AUG2014	13:14	2:08	2:18	15.7
				11AUG2014	14:07	3:08	3:11	16.7
				11AUG2014	16:05	5:08	5:09	16.7

M = Missing H = Maximum score reached

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Listing 6 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Electrical Stair PTT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:07	-0:25	-0:30	15.1
				12AUG2014	11:47	1:08	1:10	16.1
				12AUG2014	12:46	2:08	2:09	16.7
				12AUG2014	13:51	3:08	3:14	15.6
				12AUG2014	15:50	5:08	5:13	16.7
10	1	Placebo	Male	10JUL2014	10:44	-0:25	-0:24	30.1
				10JUL2014	12:19	1:08	1:11	31.0
				10JUL2014	13:22	2:08	2:14	32.0
				10JUL2014	14:18	3:08	3:10	29.9
				10JUL2014	16:18	5:08	5:10	30.4
	2	Paracetamol	Male	11JUL2014	10:04	-0:25	-0:14	37.3
				11JUL2014	11:28	1:08	1:10	37.4
				11JUL2014	12:29	2:08	2:11	37.4
				11JUL2014	13:29	3:08	3:11	41.0
				11JUL2014	15:31	5:08	5:13	40.5
11	1	Placebo	Female	11AUG2014	10:13	-0:25	-0:18	36.6
				11AUG2014	11:43	1:08	1:12	33.1
				11AUG2014	12:44	2:08	2:13	27.4
				11AUG2014	13:47	3:08	3:16	26.4
				11AUG2014	15:41	5:08	5:10	28.5
	2	Paracetamol	Female	12AUG2014	9:40	-0:25	-0:32	29.2
				12AUG2014	11:22	1:08	1:10	29.0
				12AUG2014	12:22	2:08	2:10	30.5
				12AUG2014	13:29	3:08	3:17	32.5
				12AUG2014	15:25	5:08	5:13	27.4
12	1	Paracetamol	Male	12AUG2014	10:25	-0:25	-0:24	24.6
				12AUG2014	11:59	1:08	1:10	25.0
				12AUG2014	13:00	2:08	2:11	29.5
				12AUG2014	14:00	3:08	3:11	28.5
				12AUG2014	16:05	5:08	5:16	28.0
	2	Placebo	Male	13AUG2014	9:30	-0:25	-0:30	22.7
				13AUG2014	11:09	1:08	1:09	26.9
				13AUG2014	12:09	2:08	2:09	32.0
				13AUG2014	13:10	3:08	3:10	33.6
				13AUG2014	15:11	5:08	5:11	33.0

M = Missing H = Maximum score reached

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Listing 7 Delta Electrical Stair AUC (mA*%)

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Listing 7 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Delta Electrical Stair AUC (mA*%)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:48	-0:25	-0:23	0.00
				28DEC2011	12:22	1:08	1:11	-198.40
				28DEC2011	13:25	2:08	2:14	-740.60
				28DEC2011	14:36	3:08	3:25	-1381.20
				28DEC2011	16:26	5:08	5:15	-1190.00
	2	Paracetamol	Female	07JAN2012	10:36	-0:25	-0:20	0.00
				07JAN2012	12:08	1:08	1:12	-454.50
				07JAN2012	13:09	2:08	2:13	-497.70
				07JAN2012	14:10	3:08	3:14	-651.80
				07JAN2012	16:08	5:08	5:12	-691.90
2	1	Paracetamol	Female	23NOV2012	10:35	-0:25	-0:16	0.00
				23NOV2012	11:59	1:08	1:08	-158.80
				23NOV2012	13:01	2:08	2:10	-169.60
				23NOV2012	13:59	3:08	3:08	-131.90
				23NOV2012	16:00	5:08	5:09	-321.60
	2	Placebo	Female	25NOV2012	10:18	-0:25	-0:25	0.00
				25NOV2012	11:54	1:08	1:11	-252.80
				25NOV2012	12:51	2:08	2:08	-47.40
				25NOV2012	13:52	3:08	3:09	-323.00
				25NOV2012	15:52	5:08	5:09	-238.00
3	1	Paracetamol	Male	25NOV2012	11:29	-0:25	-0:32	0.00
				25NOV2012	13:12	1:08	1:11	597.90
				25NOV2012	14:11	2:08	2:10	820.70
				25NOV2012	15:14	3:08	3:13	382.70
				25NOV2012	17:13	5:08	5:12	337.70
	2	Placebo	Male	16DEC2012	12:12	-0:25	-0:23	0.00
				16DEC2012	13:48	1:08	1:13	-538.30
				16DEC2012	14:48	2:08	2:13	-674.50
				16DEC2012	15:47	3:08	3:12	-969.20
				16DEC2012	17:46	5:08	5:11	-1287.80
4	1	Placebo	Male	25NOV2012	10:56	-0:25	-0:32	0.00
				25NOV2012	12:40	1:08	1:12	36.20
				25NOV2012	13:38	2:08	2:10	-96.90
				25NOV2012	14:39	3:08	3:11	-11.40
				25NOV2012	16:41	5:08	5:13	-168.10
	2	Paracetamol	Male	16DEC2012	12:40	-0:25	-0:25	0.00
				16DEC2012	14:17	1:08	1:12	-112.60
				16DEC2012	15:17	2:08	2:12	-553.10
				16DEC2012	16:17	3:08	3:12	-195.20
				16DEC2012	18:17	5:08	5:12	-231.50
5	1	Paracetamol	Female	02JUN2014	10:52	-0:25	-0:20	0.00
				02JUN2014	12:22	1:08	1:10	-171.70
				02JUN2014	13:24	2:08	2:12	-403.60

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Listing 7 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Delta Electrical Stair AUC (mA*%)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:25	3:08	3:13	-561.80
				02JUN2014	16:24	5:08	5:12	-624.40
	2	Placebo	Female	03JUN2014	9:49	-0:25	-0:13	0.00
				03JUN2014	11:14	1:08	1:12	-222.60
				03JUN2014	12:12	2:08	2:10	-536.90
				03JUN2014	13:11	3:08	3:09	-191.20
				03JUN2014	15:11	5:08	5:09	-472.40
6	1	Placebo	Female	04JUL2014	10:21	-0:25	-0:17	0.00
				04JUL2014	11:47	1:08	1:09	25.00
				04JUL2014	12:52	2:08	2:14	24.40
				04JUL2014	13:47	3:08	3:09	-187.10
				04JUL2014	15:48	5:08	5:10	9.50
	2	Paracetamol	Female	05JUL2014	10:02	-0:25	-0:14	0.00
				05JUL2014	11:27	1:08	1:11	45.80
				05JUL2014	12:25	2:08	2:09	-46.80
				05JUL2014	13:25	3:08	3:09	137.90
				05JUL2014	15:25	5:08	5:09	227.00
7	1	Paracetamol	Female	05JUL2014	10:28	-0:25	-0:12	0.00
				05JUL2014	11:50	1:08	1:10	-16.80
				05JUL2014	12:51	2:08	2:11	-215.90
				05JUL2014	13:49	3:08	3:09	-615.90
				05JUL2014	15:48	5:08	5:08	-235.10
	2	Placebo	Female	18JUL2014	9:33	-0:25	-0:17	0.00
				18JUL2014	11:03	1:08	1:13	-958.40
				18JUL2014	12:00	2:08	2:10	-833.10
				18JUL2014	13:01	3:08	3:11	-617.10
				18JUL2014	15:06	5:08	5:16	-1002.80
8	1	Placebo	Male	10JUL2014	11:16	-0:25	-0:16	0.00
				10JUL2014	12:42	1:08	1:10	-585.60
				10JUL2014	13:47	2:08	2:15	-410.20
				10JUL2014	14:43	3:08	3:11	-50.80
				10JUL2014	16:42	5:08	5:10	98.10
	2	Paracetamol	Male	11JUL2014	9:28	-0:25	-0:17	0.00
				11JUL2014	10:54	1:08	1:09	-457.70
				11JUL2014	11:54	2:08	2:09	-811.30
				11JUL2014	12:57	3:08	3:12	-791.00
				11JUL2014	14:56	5:08	5:11	-477.30
9	1	Paracetamol	Female	11AUG2014	10:35	-0:25	-0:21	0.00
				11AUG2014	12:08	1:08	1:12	-296.20
				11AUG2014	13:14	2:08	2:18	-322.20
				11AUG2014	14:07	3:08	3:11	-441.40
				11AUG2014	16:05	5:08	5:09	-501.00

M = Missing H = Maximum score reached

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Listing 7 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Delta Electrical Stair AUC (mA*%)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:07	-0:25	-0:30	0.00
				12AUG2014	11:47	1:08	1:10	-221.60
				12AUG2014	12:46	2:08	2:09	-224.60
				12AUG2014	13:51	3:08	3:14	-171.10
				12AUG2014	15:50	5:08	5:13	-230.80
10	1	Placebo	Male	10JUL2014	10:44	-0:25	-0:24	0.00
				10JUL2014	12:19	1:08	1:11	-286.20
				10JUL2014	13:22	2:08	2:14	-227.50
				10JUL2014	14:18	3:08	3:10	-282.40
				10JUL2014	16:18	5:08	5:10	-131.70
	2	Paracetamol	Male	11JUL2014	10:04	-0:25	-0:14	0.00
				11JUL2014	11:28	1:08	1:10	-9.10
				11JUL2014	12:29	2:08	2:11	-72.20
				11JUL2014	13:29	3:08	3:11	-93.10
				11JUL2014	15:31	5:08	5:13	-90.00
11	1	Placebo	Female	11AUG2014	10:13	-0:25	-0:18	0.00
				11AUG2014	11:43	1:08	1:12	367.10
				11AUG2014	12:44	2:08	2:13	727.30
				11AUG2014	13:47	3:08	3:16	714.70
				11AUG2014	15:41	5:08	5:10	548.20
	2	Paracetamol	Female	12AUG2014	9:40	-0:25	-0:32	0.00
				12AUG2014	11:22	1:08	1:10	-117.50
				12AUG2014	12:22	2:08	2:10	-189.40
				12AUG2014	13:29	3:08	3:17	-381.90
				12AUG2014	15:25	5:08	5:13	-138.60
12	1	Paracetamol	Male	12AUG2014	10:25	-0:25	-0:24	0.00
				12AUG2014	11:59	1:08	1:10	255.60
				12AUG2014	13:00	2:08	2:11	-222.20
				12AUG2014	14:00	3:08	3:11	-140.80
				12AUG2014	16:05	5:08	5:16	-165.00
	2	Placebo	Male	13AUG2014	9:30	-0:25	-0:30	0.00
				13AUG2014	11:09	1:08	1:09	-240.50
				13AUG2014	12:09	2:08	2:09	-366.00
				13AUG2014	13:10	3:08	3:10	-732.90
				13AUG2014	15:11	5:08	5:11	-672.20

M = Missing H = Maximum score reached

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Listing 8 Delta Electrical Stair PDT (mA)

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Listing 8 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Delta Electrical Stair PDT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:48	-0:25	-0:23	0.00
				28DEC2011	12:22	1:08	1:11	1.00
				28DEC2011	13:25	2:08	2:14	1.50
				28DEC2011	14:36	3:08	3:25	3.60
				28DEC2011	16:26	5:08	5:15	3.10
	2	Paracetamol	Female	07JAN2012	10:36	-0:25	-0:20	0.00
				07JAN2012	12:08	1:08	1:12	1.10
				07JAN2012	13:09	2:08	2:13	1.60
				07JAN2012	14:10	3:08	3:14	3.20
				07JAN2012	16:08	5:08	5:12	1.60
2	1	Paracetamol	Female	23NOV2012	10:35	-0:25	-0:16	0.00
				23NOV2012	11:59	1:08	1:08	1.10
				23NOV2012	13:01	2:08	2:10	1.60
				23NOV2012	13:59	3:08	3:08	1.10
				23NOV2012	16:00	5:08	5:09	1.60
	2	Placebo	Female	25NOV2012	10:18	-0:25	-0:25	0.00
				25NOV2012	11:54	1:08	1:11	3.10
				25NOV2012	12:51	2:08	2:08	2.10
				25NOV2012	13:52	3:08	3:09	2.60
				25NOV2012	15:52	5:08	5:09	2.10
	3	Paracetamol	Male	25NOV2012	11:29	-0:25	-0:32	0.00
				25NOV2012	13:12	1:08	1:11	-4.00
				25NOV2012	14:11	2:08	2:10	-12.10
				25NOV2012	15:14	3:08	3:13	-7.10
				25NOV2012	17:13	5:08	5:12	-12.10
	2	Placebo	Male	16DEC2012	12:12	-0:25	-0:23	0.00
				16DEC2012	13:48	1:08	1:13	0.60
				16DEC2012	14:48	2:08	2:13	4.10
				16DEC2012	15:47	3:08	3:12	7.20
				16DEC2012	17:46	5:08	5:11	13.90
4	1	Placebo	Male	25NOV2012	10:56	-0:25	-0:32	0.00
				25NOV2012	12:40	1:08	1:12	1.10
				25NOV2012	13:38	2:08	2:10	2.10
				25NOV2012	14:39	3:08	3:11	2.60
				25NOV2012	16:41	5:08	5:13	2.60
	2	Paracetamol	Male	16DEC2012	12:40	-0:25	-0:25	0.00
				16DEC2012	14:17	1:08	1:12	1.50
				16DEC2012	15:17	2:08	2:12	2.60
				16DEC2012	16:17	3:08	3:12	1.10
				16DEC2012	18:17	5:08	5:12	1.60
5	1	Paracetamol	Female	02JUN2014	10:52	-0:25	-0:20	0.00
				02JUN2014	12:22	1:08	1:10	1.50
				02JUN2014	13:24	2:08	2:12	3.00

M = Missing H = Maximum score reached

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Listing 8 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Delta Electrical Stair PDT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:25	3:08	3:13	4.50
					16:24	5:08	5:12	0.00
	2	Placebo	Female	03JUN2014	9:49	-0:25	-0:13	0.00
				03JUN2014	11:14	1:08	1:12	5.10
				03JUN2014	12:12	2:08	2:10	8.20
				03JUN2014	13:11	3:08	3:09	4.70
				03JUN2014	15:11	5:08	5:09	5.20
6	1	Placebo	Female	04JUL2014	10:21	-0:25	-0:17	0.00
				04JUL2014	11:47	1:08	1:09	0.00
				04JUL2014	12:52	2:08	2:14	1.00
				04JUL2014	13:47	3:08	3:09	0.50
				04JUL2014	15:48	5:08	5:10	0.60
	2	Paracetamol	Female	05JUL2014	10:02	-0:25	-0:14	0.00
				05JUL2014	11:27	1:08	1:11	0.50
				05JUL2014	12:25	2:08	2:09	0.50
				05JUL2014	13:25	3:08	3:09	0.00
				05JUL2014	15:25	5:08	5:09	0.10
7	1	Paracetamol	Female	05JUL2014	10:28	-0:25	-0:12	0.00
				05JUL2014	11:50	1:08	1:10	0.00
				05JUL2014	12:51	2:08	2:11	-0.50
				05JUL2014	13:49	3:08	3:09	1.00
				05JUL2014	15:48	5:08	5:08	-0.50
	2	Placebo	Female	18JUL2014	9:33	-0:25	-0:17	0.00
				18JUL2014	11:03	1:08	1:13	2.00
				18JUL2014	12:00	2:08	2:10	4.10
				18JUL2014	13:01	3:08	3:11	2.60
				18JUL2014	15:06	5:08	5:16	2.00
8	1	Placebo	Male	10JUL2014	11:16	-0:25	-0:16	0.00
				10JUL2014	12:42	1:08	1:10	4.50
				10JUL2014	13:47	2:08	2:15	0.00
				10JUL2014	14:43	3:08	3:11	-0.60
				10JUL2014	16:42	5:08	5:10	-1.60
	2	Paracetamol	Male	11JUL2014	9:28	-0:25	-0:17	0.00
				11JUL2014	10:54	1:08	1:09	3.70
				11JUL2014	11:54	2:08	2:09	9.50
				11JUL2014	12:57	3:08	3:12	7.90
				11JUL2014	14:56	5:08	5:11	5.80
9	1	Paracetamol	Female	11AUG2014	10:35	-0:25	-0:21	0.00
				11AUG2014	12:08	1:08	1:12	0.50
				11AUG2014	13:14	2:08	2:18	0.10
				11AUG2014	14:07	3:08	3:11	2.10
				11AUG2014	16:05	5:08	5:09	3.10

M = Missing H = Maximum score reached

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Listing 8 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Delta Electrical Stair PDT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:07	-0:25	-0:30	0.00
				12AUG2014	11:47	1:08	1:10	1.00
				12AUG2014	12:46	2:08	2:09	-0.50
				12AUG2014	13:51	3:08	3:14	5.10
				12AUG2014	15:50	5:08	5:13	3.60
10	1	Placebo	Male	10JUL2014	10:44	-0:25	-0:24	0.00
				10JUL2014	12:19	1:08	1:11	1.40
				10JUL2014	13:22	2:08	2:14	-0.60
				10JUL2014	14:18	3:08	3:10	3.40
				10JUL2014	16:18	5:08	5:10	1.40
	2	Paracetamol	Male	11JUL2014	10:04	-0:25	-0:14	0.00
				11JUL2014	11:28	1:08	1:10	-5.20
				11JUL2014	12:29	2:08	2:11	-5.70
				11JUL2014	13:29	3:08	3:11	-6.20
				11JUL2014	15:31	5:08	5:13	-3.10
11	1	Placebo	Female	11AUG2014	10:13	-0:25	-0:18	0.00
				11AUG2014	11:43	1:08	1:12	6.20
				11AUG2014	12:44	2:08	2:13	1.60
				11AUG2014	13:47	3:08	3:16	3.20
				11AUG2014	15:41	5:08	5:10	3.70
	2	Paracetamol	Female	12AUG2014	9:40	-0:25	-0:32	0.00
				12AUG2014	11:22	1:08	1:10	0.50
				12AUG2014	12:22	2:08	2:10	-2.10
				12AUG2014	13:29	3:08	3:17	-0.10
				12AUG2014	15:25	5:08	5:13	2.00
12	1	Paracetamol	Male	12AUG2014	10:25	-0:25	-0:24	0.00
				12AUG2014	11:59	1:08	1:10	-2.60
				12AUG2014	13:00	2:08	2:11	1.90
				12AUG2014	14:00	3:08	3:11	1.90
				12AUG2014	16:05	5:08	5:16	3.40
	2	Placebo	Male	13AUG2014	9:30	-0:25	-0:30	0.00
				13AUG2014	11:09	1:08	1:09	0.10
				13AUG2014	12:09	2:08	2:09	0.60
				13AUG2014	13:10	3:08	3:10	2.20
				13AUG2014	15:11	5:08	5:11	2.70

M = Missing H = Maximum score reached

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Listing 9 Delta Electrical Stair PTT (mA)

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Listing 9 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Delta Electrical Stair PTT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
2	1	Paracetamol	Female	23NOV2012	10:35	-0:25	-0:16	0.00
				23NOV2012	11:59	1:08	1:08	2.00
				23NOV2012	13:01	2:08	2:10	1.00
				23NOV2012	13:59	3:08	3:08	1.50
				23NOV2012	16:00	5:08	5:09	3.60
	2	Placebo	Female	25NOV2012	10:18	-0:25	-0:25	0.00
				25NOV2012	11:54	1:08	1:11	1.50
				25NOV2012	12:51	2:08	2:08	0.50
				25NOV2012	13:52	3:08	3:09	3.10
				25NOV2012	15:52	5:08	5:09	2.60
3	2	Placebo	Male	16DEC2012	12:12	-0:25	-0:23	0.00
				16DEC2012	13:48	1:08	1:13	10.30
4	1	Placebo	Male	25NOV2012	10:56	-0:25	-0:32	0.00
				25NOV2012	12:40	1:08	1:12	-0.50
				25NOV2012	13:38	2:08	2:10	1.00
				25NOV2012	14:39	3:08	3:11	0.50
				25NOV2012	16:41	5:08	5:13	2.00
	2	Paracetamol	Male	16DEC2012	12:40	-0:25	-0:25	0.00
				16DEC2012	14:17	1:08	1:12	4.10
				16DEC2012	15:17	2:08	2:12	7.20
				16DEC2012	16:17	3:08	3:12	4.60
				16DEC2012	18:17	5:08	5:12	6.60
5	1	Paracetamol	Female	02JUN2014	10:52	-0:25	-0:20	0.00
				02JUN2014	12:22	1:08	1:10	1.50
				02JUN2014	13:24	2:08	2:12	3.00
				02JUN2014	14:25	3:08	3:13	4.50
				02JUN2014	16:24	5:08	5:12	5.00
	2	Placebo	Female	03JUN2014	9:49	-0:25	-0:13	0.00
				03JUN2014	11:14	1:08	1:12	-1.00
				03JUN2014	12:12	2:08	2:10	2.00
				03JUN2014	13:11	3:08	3:09	0.60
				03JUN2014	15:11	5:08	5:09	5.10
6	1	Placebo	Female	04JUL2014	10:21	-0:25	-0:17	0.00
				04JUL2014	11:47	1:08	1:09	0.00
				04JUL2014	12:52	2:08	2:14	0.50
				04JUL2014	13:47	3:08	3:09	2.50
				04JUL2014	15:48	5:08	5:10	-0.40
	2	Paracetamol	Female	05JUL2014	10:02	-0:25	-0:14	0.00
				05JUL2014	11:27	1:08	1:11	-2.60
				05JUL2014	12:25	2:08	2:09	-2.00
				05JUL2014	13:25	3:08	3:09	-3.00
				05JUL2014	15:25	5:08	5:09	-4.60

M = Missing H = Maximum score reached

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Listing 9 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Delta Electrical Stair PTT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
7	1	Paracetamol	Female	05JUL2014	10:28	-0:25	-0:12	0.00
				05JUL2014	11:50	1:08	1:10	2.10
				05JUL2014	12:51	2:08	2:11	2.60
				05JUL2014	13:49	3:08	3:09	4.20
				05JUL2014	15:48	5:08	5:08	2.00
	2	Placebo	Female	18JUL2014	9:33	-0:25	-0:17	0.00
				18JUL2014	11:03	1:08	1:13	5.70
				18JUL2014	12:00	2:08	2:10	5.20
				18JUL2014	13:01	3:08	3:11	2.10
				18JUL2014	15:06	5:08	5:16	3.60
8	1	Placebo	Male	10JUL2014	11:16	-0:25	-0:16	0.00
				10JUL2014	12:42	1:08	1:10	9.00
				10JUL2014	13:47	2:08	2:15	1.00
				10JUL2014	14:43	3:08	3:11	1.90
				10JUL2014	16:42	5:08	5:10	-0.10
	2	Paracetamol	Male	11JUL2014	9:28	-0:25	-0:17	0.00
				11JUL2014	10:54	1:08	1:09	2.10
				11JUL2014	11:54	2:08	2:09	0.60
				11JUL2014	12:57	3:08	3:12	1.60
				11JUL2014	14:56	5:08	5:11	0.10
9	1	Paracetamol	Female	11AUG2014	10:35	-0:25	-0:21	0.00
				11AUG2014	12:08	1:08	1:12	1.50
				11AUG2014	13:14	2:08	2:18	2.60
				11AUG2014	14:07	3:08	3:11	3.60
				11AUG2014	16:05	5:08	5:09	3.60
	2	Placebo	Female	12AUG2014	10:07	-0:25	-0:30	0.00
				12AUG2014	11:47	1:08	1:10	1.00
				12AUG2014	12:46	2:08	2:09	1.60
				12AUG2014	13:51	3:08	3:14	0.50
				12AUG2014	15:50	5:08	5:13	1.60
10	1	Placebo	Male	10JUL2014	10:44	-0:25	-0:24	0.00
				10JUL2014	12:19	1:08	1:11	0.90
				10JUL2014	13:22	2:08	2:14	1.90
				10JUL2014	14:18	3:08	3:10	-0.20
				10JUL2014	16:18	5:08	5:10	0.30
	2	Paracetamol	Male	11JUL2014	10:04	-0:25	-0:14	0.00
				11JUL2014	11:28	1:08	1:10	0.10
				11JUL2014	12:29	2:08	2:11	0.10
				11JUL2014	13:29	3:08	3:11	3.70
				11JUL2014	15:31	5:08	5:13	3.20
11	1	Placebo	Female	11AUG2014	10:13	-0:25	-0:18	0.00
				11AUG2014	11:43	1:08	1:12	-3.50
				11AUG2014	12:44	2:08	2:13	-9.20

M = Missing H = Maximum score reached

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Listing 9 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Delta Electrical Stair PTT (mA)
						Protocol (hh:mm)	Actual (hh:mm)	
11	1	Placebo	Female	11AUG2014	13:47	3:08	3:16	-10.20
				11AUG2014	15:41	5:08	5:10	-8.10
	2	Paracetamol	Female	12AUG2014	9:40	-0:25	-0:32	0.00
				12AUG2014	11:22	1:08	1:10	-0.20
				12AUG2014	12:22	2:08	2:10	1.30
				12AUG2014	13:29	3:08	3:17	3.30
				12AUG2014	15:25	5:08	5:13	-1.80
12	1	Paracetamol	Male	12AUG2014	10:25	-0:25	-0:24	0.00
				12AUG2014	11:59	1:08	1:10	0.40
				12AUG2014	13:00	2:08	2:11	4.90
				12AUG2014	14:00	3:08	3:11	3.90
				12AUG2014	16:05	5:08	5:16	3.40
	2	Placebo	Male	13AUG2014	9:30	-0:25	-0:30	0.00
				13AUG2014	11:09	1:08	1:09	4.20
				13AUG2014	12:09	2:08	2:09	9.30
				13AUG2014	13:10	3:08	3:10	10.90
				13AUG2014	15:11	5:08	5:11	10.30

M = Missing H = Maximum score reached

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Listing 10 Pressure AUC (kPa*%)

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Listing 10 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Pressure AUC (kPa*%)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:51	-0:20	-0:20	5592.6
				28DEC2011	12:26	1:13	1:15	6522.6
				28DEC2011	13:27	2:13	2:16	4588.8
				28DEC2011	14:39	3:13	3:28	4482.2
				28DEC2011	16:28	5:13	5:17	4869.4
	2	Paracetamol	Female	07JAN2012	10:39	-0:20	-0:17	4703.5
				07JAN2012	12:12	1:13	1:16	3990.0
				07JAN2012	13:12	2:13	2:16	5043.0
				07JAN2012	14:13	3:13	3:17	4325.7
				07JAN2012	16:12	5:13	5:16	2858.8
2	1	Paracetamol	Female	23NOV2012	10:40	-0:20	-0:11	8683.0
				23NOV2012	12:02	1:13	1:11	8551.2
				23NOV2012	13:02	2:13	2:11	8601.4
				23NOV2012	14:00	3:13	3:09	8474.8
				23NOV2012	16:02	5:13	5:11	8794.3
	2	Placebo	Female	25NOV2012	10:20	-0:20	-0:23	8972.3
				25NOV2012	11:55	1:13	1:12	8462.5
				25NOV2012	12:54	2:13	2:11	8705.1
				25NOV2012	13:54	3:13	3:11	8994.6
				25NOV2012	15:54	5:13	5:11	8913.1
	3	Paracetamol	Male	25NOV2012	11:33	-0:20	-0:28	4994.5
				25NOV2012	13:16	1:13	1:15	5812.3
				25NOV2012	14:18	2:13	2:17	5008.1
				25NOV2012	15:18	3:13	3:17	4685.5
				25NOV2012	17:16	5:13	5:15	5392.6
	2	Placebo	Male	16DEC2012	12:16	-0:20	-0:19	3961.7
				16DEC2012	13:51	1:13	1:16	3092.4
				16DEC2012	14:52	2:13	2:17	3630.5
				16DEC2012	15:51	3:13	3:16	2913.8
				16DEC2012	17:50	5:13	5:15	3371.0
4	1	Placebo	Male	25NOV2012	10:59	-0:20	-0:29	6798.2
				25NOV2012	12:42	1:13	1:14	7043.7
				25NOV2012	13:43	2:13	2:15	6218.0
				25NOV2012	14:42	3:13	3:14	7057.9
				25NOV2012	16:44	5:13	5:16	5886.3
	2	Paracetamol	Male	16DEC2012	12:44	-0:20	-0:21	5277.5
				16DEC2012	14:21	1:13	1:16	4721.4
				16DEC2012	15:21	2:13	2:16	3687.5
				16DEC2012	16:21	3:13	3:16	3929.0
				16DEC2012	18:22	5:13	5:17	3411.4
5	1	Paracetamol	Female	02JUN2014	10:55	-0:20	-0:17	8626.8
				02JUN2014	12:25	1:13	1:13	8487.9
				02JUN2014	13:29	2:13	2:17	8070.5

M = Missing H = Maximum score reached

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Listing 10 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Pressure AUC (kPa*%)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:27	3:13	3:15	8456.7
					16:26	5:13	5:14	7760.3
	2	Placebo	Female	03JUN2014	9:52	-0:20	-0:10	8332.8
				03JUN2014	11:18	1:13	1:16	7810.3
				03JUN2014	12:15	2:13	2:13	7871.3
				03JUN2014	13:15	3:13	3:13	7836.3
				03JUN2014	15:15	5:13	5:13	7106.3
6	1	Placebo	Female	04JUL2014	10:25	-0:20	-0:13	8133.4
				04JUL2014	11:52	1:13	1:14	7947.1
				04JUL2014	12:55	2:13	2:17	7946.3
				04JUL2014	13:51	3:13	3:13	8035.3
				04JUL2014	15:51	5:13	5:13	8069.8
	2	Paracetamol	Female	05JUL2014	10:05	-0:20	-0:11	8263.6
				05JUL2014	11:31	1:13	1:15	8255.6
				05JUL2014	12:29	2:13	2:13	8494.4
				05JUL2014	13:29	3:13	3:13	8380.2
				05JUL2014	15:28	5:13	5:12	8277.5
7	1	Paracetamol	Female	05JUL2014	10:31	-0:20	-0:09	8735.8
				05JUL2014	11:55	1:13	1:15	8011.7
				05JUL2014	12:54	2:13	2:14	8487.5
				05JUL2014	13:53	3:13	3:13	8288.1
				05JUL2014	15:53	5:13	5:13	8356.2
	2	Placebo	Female	18JUL2014	9:37	-0:20	-0:13	7235.6
				18JUL2014	11:07	1:13	1:17	7280.9
				18JUL2014	12:04	2:13	2:14	7308.3
				18JUL2014	13:08	3:13	3:18	6669.2
				18JUL2014	15:09	5:13	5:19	6589.2
8	1	Placebo	Male	10JUL2014	11:19	-0:20	-0:13	7782.7
				10JUL2014	12:45	1:13	1:13	7421.2
				10JUL2014	13:51	2:13	2:19	7585.1
				10JUL2014	14:47	3:13	3:15	6951.2
				10JUL2014	16:46	5:13	5:14	7062.9
	2	Paracetamol	Male	11JUL2014	9:32	-0:20	-0:13	7062.3
				11JUL2014	10:59	1:13	1:14	6362.2
				11JUL2014	11:58	2:13	2:13	5551.5
				11JUL2014	13:01	3:13	3:16	5990.9
				11JUL2014	15:00	5:13	5:15	5763.8
9	1	Paracetamol	Female	11AUG2014	10:38	-0:20	-0:18	7393.9
				11AUG2014	12:13	1:13	1:17	5988.3
				11AUG2014	13:18	2:13	2:22	6700.5
				11AUG2014	14:12	3:13	3:16	5583.2
				11AUG2014	16:10	5:13	5:14	6948.5

M = Missing H = Maximum score reached

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Listing 10 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Pressure AUC (kPa*%)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:11	-0:20	-0:26	6058.1
				12AUG2014	11:52	1:13	1:15	6633.0
				12AUG2014	12:52	2:13	2:15	6578.6
				12AUG2014	13:55	3:13	3:18	6515.8
				12AUG2014	15:53	5:13	5:16	6995.5
10	1	Placebo	Male	10JUL2014	10:49	-0:20	-0:19	5040.8
				10JUL2014	12:22	1:13	1:14	6002.5
				10JUL2014	13:28	2:13	2:20	4317.6
				10JUL2014	14:24	3:13	3:16	4523.4
				10JUL2014	16:24	5:13	5:16	6005.9
	2	Paracetamol	Male	11JUL2014	10:08	-0:20	-0:10	6911.3
				11JUL2014	11:32	1:13	1:14	6375.0
				11JUL2014	12:34	2:13	2:16	4365.9
				11JUL2014	13:33	3:13	3:15	5569.9
				11JUL2014	15:36	5:13	5:18	4978.2
11	1	Placebo	Female	11AUG2014	10:17	-0:20	-0:14	6683.5
				11AUG2014	11:48	1:13	1:17	7030.3
				11AUG2014	12:48	2:13	2:17	6776.7
				11AUG2014	13:50	3:13	3:19	7050.0
				11AUG2014	15:46	5:13	5:15	6994.0
	2	Paracetamol	Female	12AUG2014	9:51	-0:20	-0:21	7539.8
				12AUG2014	11:27	1:13	1:15	6654.5
				12AUG2014	12:27	2:13	2:15	6827.6
				12AUG2014	13:33	3:13	3:21	6889.0
				12AUG2014	15:27	5:13	5:15	6590.8
12	1	Paracetamol	Male	12AUG2014	10:33	-0:20	-0:16	6481.9
				12AUG2014	12:04	1:13	1:15	7065.3
				12AUG2014	13:04	2:13	2:15	6548.7
				12AUG2014	14:05	3:13	3:16	6059.5
				12AUG2014	16:10	5:13	5:21	6243.9
	2	Placebo	Male	13AUG2014	9:34	-0:20	-0:26	5332.8
				13AUG2014	11:15	1:13	1:15	6374.9
				13AUG2014	12:14	2:13	2:14	5852.7
				13AUG2014	13:14	3:13	3:14	6245.0
				13AUG2014	15:16	5:13	5:16	5678.2

M = Missing H = Maximum score reached

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Listing 11 Pressure PDT (kPa)

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Listing 11 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Pressure PDT (kPa)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:51	-0:20	-0:20	7.7
				28DEC2011	12:26	1:13	1:15	7.0
				28DEC2011	13:27	2:13	2:16	10.3
				28DEC2011	14:39	3:13	3:28	7.7
				28DEC2011	16:28	5:13	5:17	8.1
	2	Paracetamol	Female	07JAN2012	10:39	-0:20	-0:17	9.8
				07JAN2012	12:12	1:13	1:16	9.6
				07JAN2012	13:12	2:13	2:16	18.6
				07JAN2012	14:13	3:13	3:17	14.5
				07JAN2012	16:12	5:13	5:16	29.1
2	1	Paracetamol	Female	23NOV2012	10:40	-0:20	-0:11	7.5
				23NOV2012	12:02	1:13	1:11	10.3
				23NOV2012	13:02	2:13	2:11	7.7
				23NOV2012	14:00	3:13	3:09	11.1
				23NOV2012	16:02	5:13	5:11	6.6
	2	Placebo	Female	25NOV2012	10:20	-0:20	-0:23	5.0
				25NOV2012	11:55	1:13	1:12	9.6
				25NOV2012	12:54	2:13	2:11	7.0
				25NOV2012	13:54	3:13	3:11	5.5
				25NOV2012	15:54	5:13	5:11	6.7
3	1	Paracetamol	Male	25NOV2012	11:33	-0:20	-0:28	37.8
				25NOV2012	13:16	1:13	1:15	30.2
				25NOV2012	14:18	2:13	2:17	32.7
				25NOV2012	15:18	3:13	3:17	35.2
				25NOV2012	17:16	5:13	5:15	31.7
	2	Placebo	Male	16DEC2012	12:16	-0:20	-0:19	40.4
				16DEC2012	13:51	1:13	1:16	43.3
				16DEC2012	14:52	2:13	2:17	46.1
				16DEC2012	15:51	3:13	3:16	54.2
				16DEC2012	17:50	5:13	5:15	55.5
4	1	Placebo	Male	25NOV2012	10:59	-0:20	-0:29	12.0
				25NOV2012	12:42	1:13	1:14	17.3
				25NOV2012	13:43	2:13	2:15	15.3
				25NOV2012	14:42	3:13	3:14	15.6
				25NOV2012	16:44	5:13	5:16	21.1
	2	Paracetamol	Male	16DEC2012	12:44	-0:20	-0:21	18.4
				16DEC2012	14:21	1:13	1:16	28.9
				16DEC2012	15:21	2:13	2:16	28.4
				16DEC2012	16:21	3:13	3:16	32.3
				16DEC2012	18:22	5:13	5:17	38.7
5	1	Paracetamol	Female	02JUN2014	10:55	-0:20	-0:17	3.9
				02JUN2014	12:25	1:13	1:13	3.8
				02JUN2014	13:29	2:13	2:17	9.2

M = Missing H = Maximum score reached

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Listing 11 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Pressure PDT (kPa)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:27	3:13	3:15	4.2
					16:26	5:13	5:14	15.2
	2	Placebo	Female	03JUN2014	9:52	-0:20	-0:10	12.1
				03JUN2014	11:18	1:13	1:16	14.2
				03JUN2014	12:15	2:13	2:13	12.9
				03JUN2014	13:15	3:13	3:13	10.9
				03JUN2014	15:15	5:13	5:13	18.1
6	1	Placebo	Female	04JUL2014	10:25	-0:20	-0:13	8.6
				04JUL2014	11:52	1:13	1:14	9.8
				04JUL2014	12:55	2:13	2:17	9.2
				04JUL2014	13:51	3:13	3:13	9.8
				04JUL2014	15:51	5:13	5:13	11.9
	2	Paracetamol	Female	05JUL2014	10:05	-0:20	-0:11	10.6
				05JUL2014	11:31	1:13	1:15	10.1
				05JUL2014	12:29	2:13	2:13	7.9
				05JUL2014	13:29	3:13	3:13	10.5
				05JUL2014	15:28	5:13	5:12	12.9
7	1	Paracetamol	Female	05JUL2014	10:31	-0:20	-0:09	6.5
				05JUL2014	11:55	1:13	1:15	7.0
				05JUL2014	12:54	2:13	2:14	10.9
				05JUL2014	13:53	3:13	3:13	12.0
				05JUL2014	15:53	5:13	5:13	10.5
	2	Placebo	Female	18JUL2014	9:37	-0:20	-0:13	19.2
				18JUL2014	11:07	1:13	1:17	18.1
				18JUL2014	12:04	2:13	2:14	18.3
				18JUL2014	13:08	3:13	3:18	25.5
				18JUL2014	15:09	5:13	5:19	28.2
8	1	Placebo	Male	10JUL2014	11:19	-0:20	-0:13	12.2
				10JUL2014	12:45	1:13	1:13	13.6
				10JUL2014	13:51	2:13	2:19	8.5
				10JUL2014	14:47	3:13	3:15	12.6
				10JUL2014	16:46	5:13	5:14	9.7
	2	Paracetamol	Male	11JUL2014	9:32	-0:20	-0:13	18.6
				11JUL2014	10:59	1:13	1:14	17.4
				11JUL2014	11:58	2:13	2:13	32.3
				11JUL2014	13:01	3:13	3:16	21.4
				11JUL2014	15:00	5:13	5:15	30.9
9	1	Paracetamol	Female	11AUG2014	10:38	-0:20	-0:18	13.0
				11AUG2014	12:13	1:13	1:17	11.1
				11AUG2014	13:18	2:13	2:22	13.5
				11AUG2014	14:12	3:13	3:16	15.2
				11AUG2014	16:10	5:13	5:14	20.4

M = Missing H = Maximum score reached

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Listing 11 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Pressure PDT (kPa)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:11	-0:20	-0:26	23.1
				12AUG2014	11:52	1:13	1:15	21.7
				12AUG2014	12:52	2:13	2:15	21.4
				12AUG2014	13:55	3:13	3:18	16.9
				12AUG2014	15:53	5:13	5:16	11.4
10	1	Placebo	Male	10JUL2014	10:49	-0:20	-0:19	18.9
				10JUL2014	12:22	1:13	1:14	22.7
				10JUL2014	13:28	2:13	2:20	21.4
				10JUL2014	14:24	3:13	3:16	25.4
				10JUL2014	16:24	5:13	5:16	20.1
	2	Paracetamol	Male	11JUL2014	10:08	-0:20	-0:10	21.2
				11JUL2014	11:32	1:13	1:14	22.2
				11JUL2014	12:34	2:13	2:16	35.1
				11JUL2014	13:33	3:13	3:15	23.0
				11JUL2014	15:36	5:13	5:18	28.4
11	1	Placebo	Female	11AUG2014	10:17	-0:20	-0:14	16.5
				11AUG2014	11:48	1:13	1:17	19.8
				11AUG2014	12:48	2:13	2:17	14.7
				11AUG2014	13:50	3:13	3:19	13.3
				11AUG2014	15:46	5:13	5:15	19.6
	2	Paracetamol	Female	12AUG2014	9:51	-0:20	-0:21	15.7
				12AUG2014	11:27	1:13	1:15	24.8
				12AUG2014	12:27	2:13	2:15	18.0
				12AUG2014	13:33	3:13	3:21	17.2
				12AUG2014	15:27	5:13	5:15	27.4
12	1	Paracetamol	Male	12AUG2014	10:33	-0:20	-0:16	12.4
				12AUG2014	12:04	1:13	1:15	14.1
				12AUG2014	13:04	2:13	2:15	21.3
				12AUG2014	14:05	3:13	3:16	24.6
				12AUG2014	16:10	5:13	5:21	17.2
	2	Placebo	Male	13AUG2014	9:34	-0:20	-0:26	24.3
				13AUG2014	11:15	1:13	1:15	22.5
				13AUG2014	12:14	2:13	2:14	21.6
				13AUG2014	13:14	3:13	3:14	19.1
				13AUG2014	15:16	5:13	5:16	32.0

M = Missing H = Maximum score reached

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Listing 12 Pressure PTT (kPa)

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Listing 12 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Pressure PTT (kPa)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:51	-0:20	-0:20	81.0
				28DEC2011	12:26	1:13	1:15	69.5
				28DEC2011	13:27	2:13	2:16	89.4
				28DEC2011	14:39	3:13	3:28	89.2
				28DEC2011	16:28	5:13	5:17	77.8
	2	Paracetamol	Female	07JAN2012	10:39	-0:20	-0:17	96.9
				07JAN2012	12:12	1:13	1:16	97.2
				07JAN2012	13:12	2:13	2:16	82.2
				07JAN2012	14:13	3:13	3:17	88.5
				07JAN2012	16:12	5:13	5:16	94.6
2	1	Paracetamol	Female	23NOV2012	10:40	-0:20	-0:11	18.5
				23NOV2012	12:02	1:13	1:11	18.8
				23NOV2012	13:02	2:13	2:11	22.4
				23NOV2012	14:00	3:13	3:09	21.7
				23NOV2012	16:02	5:13	5:11	17.5
	2	Placebo	Female	25NOV2012	10:20	-0:20	-0:23	16.1
				25NOV2012	11:55	1:13	1:12	21.4
				25NOV2012	12:54	2:13	2:11	19.6
				25NOV2012	13:54	3:13	3:11	15.5
				25NOV2012	15:54	5:13	5:11	18.2
3	1	Paracetamol	Male	25NOV2012	11:33	-0:20	-0:28	65.2
				25NOV2012	13:16	1:13	1:15	57.2
				25NOV2012	14:18	2:13	2:17	66.5
				25NOV2012	15:18	3:13	3:17	66.4
				25NOV2012	17:16	5:13	5:15	59.9
	2	Placebo	Male	16DEC2012	12:16	-0:20	-0:19	74.2
				16DEC2012	13:51	1:13	1:16	80.8
				16DEC2012	14:52	2:13	2:17	76.4
				16DEC2012	15:51	3:13	3:16	85.4
				16DEC2012	17:50	5:13	5:15	76.3
4	1	Placebo	Male	25NOV2012	10:59	-0:20	-0:29	46.8
				25NOV2012	12:42	1:13	1:14	40.9
				25NOV2012	13:43	2:13	2:15	56.4
				25NOV2012	14:42	3:13	3:14	53.0
				25NOV2012	16:44	5:13	5:16	61.6
	2	Paracetamol	Male	16DEC2012	12:44	-0:20	-0:21	60.9
				16DEC2012	14:21	1:13	1:16	71.8
				16DEC2012	15:21	2:13	2:16	84.2
				16DEC2012	16:21	3:13	3:16	81.6
				16DEC2012	18:22	5:13	5:17	91.3
5	1	Paracetamol	Female	02JUN2014	10:55	-0:20	-0:17	23.2
				02JUN2014	12:25	1:13	1:13	23.3
				02JUN2014	13:29	2:13	2:17	29.0

M = Missing H = Maximum score reached

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Listing 12 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Pressure (kPa)	PTT
						Protocol (hh:mm)	Actual (hh:mm)		
5	1	Paracetamol	Female	02JUN2014	14:27	3:13	3:15	20.7	
					16:26	5:13	5:14	28.7	
	2	Placebo	Female	03JUN2014	9:52	-0:20	-0:10	22.1	
					11:18	1:13	1:16	28.0	
					12:15	2:13	2:13	30.7	
					13:15	3:13	3:13	32.6	
					15:15	5:13	5:13	39.5	
6	1	Placebo	Female	04JUL2014	10:25	-0:20	-0:13	29.2	
					11:52	1:13	1:14	31.9	
					12:55	2:13	2:17	28.4	
					13:51	3:13	3:13	25.5	
					15:51	5:13	5:13	25.7	
	2	Paracetamol	Female	05JUL2014	10:05	-0:20	-0:11	23.2	
					11:31	1:13	1:15	23.4	
					12:29	2:13	2:13	18.4	
					13:29	3:13	3:13	18.9	
					15:28	5:13	5:12	20.6	
7	1	Paracetamol	Female	05JUL2014	10:31	-0:20	-0:09	23.1	
					11:55	1:13	1:15	25.9	
					12:54	2:13	2:14	18.9	
					13:53	3:13	3:13	22.6	
					15:53	5:13	5:13	22.2	
	2	Placebo	Female	18JUL2014	9:37	-0:20	-0:13	36.8	
					11:07	1:13	1:17	43.6	
					12:04	2:13	2:14	33.2	
					13:08	3:13	3:18	38.9	
					15:09	5:13	5:19	41.0	
8	1	Placebo	Male	10JUL2014	11:19	-0:20	-0:13	34.6	
					12:45	1:13	1:13	42.7	
					13:51	2:13	2:19	42.9	
					14:47	3:13	3:15	50.8	
					16:46	5:13	5:14	51.6	
	2	Paracetamol	Male	11JUL2014	9:32	-0:20	-0:13	41.5	
					10:59	1:13	1:14	55.4	
					11:58	2:13	2:13	55.6	
					13:01	3:13	3:16	60.8	
					15:00	5:13	5:15	57.9	
9	1	Paracetamol	Female	11AUG2014	10:38	-0:20	-0:18	30.4	
					12:13	1:13	1:17	52.9	
					13:18	2:13	2:22	37.8	
					14:12	3:13	3:16	54.1	
					16:10	5:13	5:14	35.7	

M = Missing H = Maximum score reached

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Listing 12 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Pressure PTT (kPa)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:11	-0:20	-0:26	51.4
				12AUG2014	11:52	1:13	1:15	41.1
				12AUG2014	12:52	2:13	2:15	39.0
				12AUG2014	13:55	3:13	3:18	45.2
				12AUG2014	15:53	5:13	5:16	40.5
10	1	Placebo	Male	10JUL2014	10:49	-0:20	-0:19	60.1
				10JUL2014	12:22	1:13	1:14	50.9
				10JUL2014	13:28	2:13	2:20	71.2
				10JUL2014	14:24	3:13	3:16	64.9
				10JUL2014	16:24	5:13	5:16	52.4
	2	Paracetamol	Male	11JUL2014	10:08	-0:20	-0:10	38.0
				11JUL2014	11:32	1:13	1:14	46.2
				11JUL2014	12:34	2:13	2:16	64.8
				11JUL2014	13:33	3:13	3:15	54.0
				11JUL2014	15:36	5:13	5:18	67.4
11	1	Placebo	Female	11AUG2014	10:17	-0:20	-0:14	42.9
				11AUG2014	11:48	1:13	1:17	43.9
				11AUG2014	12:48	2:13	2:17	42.9
				11AUG2014	13:50	3:13	3:19	36.9
				11AUG2014	15:46	5:13	5:15	42.6
	2	Paracetamol	Female	12AUG2014	9:51	-0:20	-0:21	40.7
				12AUG2014	11:27	1:13	1:15	43.5
				12AUG2014	12:27	2:13	2:15	42.6
				12AUG2014	13:33	3:13	3:21	40.5
				12AUG2014	15:27	5:13	5:15	39.2
12	1	Paracetamol	Male	12AUG2014	10:33	-0:20	-0:16	54.8
				12AUG2014	12:04	1:13	1:15	40.5
				12AUG2014	13:04	2:13	2:15	47.0
				12AUG2014	14:05	3:13	3:16	54.1
				12AUG2014	16:10	5:13	5:21	54.6
	2	Placebo	Male	13AUG2014	9:34	-0:20	-0:26	64.1
				13AUG2014	11:15	1:13	1:15	49.7
				13AUG2014	12:14	2:13	2:14	60.9
				13AUG2014	13:14	3:13	3:14	59.2
				13AUG2014	15:16	5:13	5:16	61.9

M = Missing H = Maximum score reached

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Listing 13 Heat PDT (C)

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Listing 13 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Heat PDT (C)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:41	-0:30	-0:30	38.4
				28DEC2011	12:16	1:03	1:05	38.8
				28DEC2011	13:17	2:03	2:06	39.5
				28DEC2011	14:28	3:03	3:17	41.3
				28DEC2011	16:17	5:03	5:06	38.1
	2	Paracetamol	Female	07JAN2012	10:27	-0:30	-0:29	46.1
				07JAN2012	12:00	1:03	1:04	47.7
				07JAN2012	13:01	2:03	2:05	49.0
				07JAN2012	14:01	3:03	3:05	47.5
				07JAN2012	16:00	5:03	5:04	47.5
2	1	Paracetamol	Female	23NOV2012	10:34	-0:30	-0:17	36.6
				23NOV2012	11:56	1:03	1:05	37.6
				23NOV2012	12:58	2:03	2:07	38.4
				23NOV2012	13:59	3:03	3:08	37.4
				23NOV2012	15:58	5:03	5:07	41.5
	2	Placebo	Female	25NOV2012	10:15	-0:30	-0:28	38.6
				25NOV2012	11:52	1:03	1:09	40.7
				25NOV2012	12:50	2:03	2:07	40.9
				25NOV2012	13:50	3:03	3:07	39.8
				25NOV2012	15:50	5:03	5:07	39.1
3	1	Paracetamol	Male	25NOV2012	11:52	-0:30	-0:09	40.9
				25NOV2012	13:04	1:03	1:03	41.5
				25NOV2012	14:04	2:03	2:03	41.4
				25NOV2012	15:06	3:03	3:05	42.0
				25NOV2012	17:09	5:03	5:08	40.7
	2	Placebo	Male	16DEC2012	12:05	-0:30	-0:30	38.0
				16DEC2012	13:39	1:03	1:04	39.5
				16DEC2012	14:39	2:03	2:04	43.2
				16DEC2012	15:40	3:03	3:05	43.2
				16DEC2012	17:38	5:03	5:03	42.1
4	1	Placebo	Male	25NOV2012	11:08	-0:30	-0:20	45.0
				25NOV2012	12:32	1:03	1:04	45.8
				25NOV2012	13:31	2:03	2:03	45.2
				25NOV2012	14:32	3:03	3:04	45.3
				25NOV2012	16:32	5:03	5:04	46.3
	2	Paracetamol	Male	16DEC2012	12:33	-0:30	-0:32	48.5
				16DEC2012	14:10	1:03	1:05	47.6
				16DEC2012	15:10	2:03	2:05	47.1
				16DEC2012	16:10	3:03	3:05	47.1
				16DEC2012	18:10	5:03	5:05	47.7
5	1	Paracetamol	Female	02JUN2014	10:49	-0:30	-0:23	36.9
				02JUN2014	12:19	1:03	1:07	38.7
				02JUN2014	13:20	2:03	2:08	38.3

M = Missing H = Maximum score reached

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Listing 13 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Heat PDT (C)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:20	3:03	3:08	38.3
					16:19	5:03	5:07	38.1
	2	Placebo	Female	03JUN2014	9:45	-0:30	-0:17	41.8
				03JUN2014	11:12	1:03	1:10	37.4
				03JUN2014	12:09	2:03	2:07	37.7
				03JUN2014	13:09	3:03	3:07	37.2
				03JUN2014	15:09	5:03	5:07	37.2
	1	Placebo	Female	04JUL2014	10:15	-0:30	-0:23	43.1
				04JUL2014	11:41	1:03	1:03	42.1
				04JUL2014	12:45	2:03	2:07	42.0
				04JUL2014	13:42	3:03	3:04	40.3
				04JUL2014	15:42	5:03	5:04	42.1
7	2	Paracetamol	Female	05JUL2014	9:56	-0:30	-0:20	40.4
				05JUL2014	11:19	1:03	1:03	41.3
				05JUL2014	12:19	2:03	2:03	41.1
				05JUL2014	13:19	3:03	3:03	40.9
				05JUL2014	15:19	5:03	5:03	41.5
	1	Paracetamol	Female	05JUL2014	10:18	-0:30	-0:22	38.9
				05JUL2014	11:43	1:03	1:03	39.7
				05JUL2014	12:43	2:03	2:03	40.0
				05JUL2014	13:43	3:03	3:03	37.3
				05JUL2014	15:43	5:03	5:03	38.4
	2	Placebo	Female	18JUL2014	M	-0:30		43.1
				18JUL2014	11:01	1:03	1:11	39.0
				18JUL2014	11:58	2:03	2:08	40.9
				18JUL2014	12:58	3:03	3:08	39.7
				18JUL2014	15:01	5:03	5:11	40.0
8	1	Placebo	Male	10JUL2014	11:08	-0:30	-0:24	41.1
				10JUL2014	12:35	1:03	1:03	40.2
				10JUL2014	13:41	2:03	2:09	37.5
				10JUL2014	14:36	3:03	3:04	39.3
				10JUL2014	16:36	5:03	5:04	38.8
	2	Paracetamol	Male	11JUL2014	9:22	-0:30	-0:23	43.0
				11JUL2014	10:48	1:03	1:03	40.6
				11JUL2014	11:48	2:03	2:03	40.4
				11JUL2014	12:50	3:03	3:05	40.4
				11JUL2014	14:50	5:03	5:05	41.6
9	1	Paracetamol	Female	11AUG2014	10:29	-0:30	-0:27	40.9
				11AUG2014	12:01	1:03	1:05	45.3
				11AUG2014	13:03	2:03	2:07	42.4
				11AUG2014	14:01	3:03	3:05	39.3
				11AUG2014	16:00	5:03	5:04	39.1

M = Missing H = Maximum score reached

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Listing 13 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Heat PDT (C)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	9:46	-0:30	-0:51	42.1
				12AUG2014	11:40	1:03	1:03	39.1
				12AUG2014	12:40	2:03	2:03	40.3
				12AUG2014	13:41	3:03	3:04	38.5
				12AUG2014	15:47	5:03	5:10	41.6
10	1	Placebo	Male	10JUL2014	10:37	-0:30	-0:31	41.2
				10JUL2014	12:12	1:03	1:04	42.6
				10JUL2014	13:15	2:03	2:07	42.5
				10JUL2014	14:12	3:03	3:04	44.0
				10JUL2014	16:11	5:03	5:03	40.9
	2	Paracetamol	Male	11JUL2014	9:56	-0:30	-0:22	45.1
				11JUL2014	11:21	1:03	1:03	45.6
				11JUL2014	12:21	2:03	2:03	44.7
				11JUL2014	13:21	3:03	3:03	44.7
				11JUL2014	15:24	5:03	5:06	44.9
11	1	Placebo	Female	11AUG2014	10:06	-0:30	-0:25	39.5
				11AUG2014	11:35	1:03	1:04	42.3
				11AUG2014	12:36	2:03	2:05	38.5
				11AUG2014	13:40	3:03	3:09	38.6
				11AUG2014	15:35	5:03	5:04	38.5
	2	Paracetamol	Female	12AUG2014	9:35	-0:30	-0:37	36.6
				12AUG2014	11:15	1:03	1:03	36.9
				12AUG2014	12:15	2:03	2:03	38.1
				12AUG2014	13:18	3:03	3:06	39.9
				12AUG2014	15:15	5:03	5:03	36.5
12	1	Paracetamol	Male	12AUG2014	10:18	-0:30	-0:31	43.7
				12AUG2014	11:52	1:03	1:03	43.0
				12AUG2014	12:53	2:03	2:04	43.7
				12AUG2014	13:54	3:03	3:05	43.8
				12AUG2014	15:57	5:03	5:08	42.9
	2	Placebo	Male	13AUG2014	9:22	-0:30	-0:38	43.6
				13AUG2014	11:03	1:03	1:03	41.9
				13AUG2014	12:03	2:03	2:03	42.2
				13AUG2014	13:03	3:03	3:03	42.3
				13AUG2014	15:03	5:03	5:03	41.4

M = Missing H = Maximum score reached

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Listing 14 Heat PTT (C)

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Listing 14 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Heat PTT (C)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:41	-0:30	-0:30	44.1
				28DEC2011	12:16	1:03	1:05	47.1
				28DEC2011	13:17	2:03	2:06	48.8
				28DEC2011	14:28	3:03	3:17	48.3
				28DEC2011	16:17	5:03	5:06	47.5
	2	Paracetamol	Female	07JAN2012	10:27	-0:30	-0:29	50.0
				07JAN2012	12:00	1:03	1:04	50.0
				07JAN2012	13:01	2:03	2:05	50.0
				07JAN2012	14:01	3:03	3:05	49.4
				07JAN2012	16:00	5:03	5:04	50.0
2	1	Paracetamol	Female	23NOV2012	10:34	-0:30	-0:17	44.4
				23NOV2012	11:56	1:03	1:05	43.7
				23NOV2012	12:58	2:03	2:07	45.0
				23NOV2012	13:59	3:03	3:08	44.0
				23NOV2012	15:58	5:03	5:07	45.6
	2	Placebo	Female	25NOV2012	10:15	-0:30	-0:28	46.6
				25NOV2012	11:52	1:03	1:09	46.6
				25NOV2012	12:50	2:03	2:07	45.6
				25NOV2012	13:50	3:03	3:07	44.9
				25NOV2012	15:50	5:03	5:07	42.7
3	1	Paracetamol	Male	25NOV2012	11:52	-0:30	-0:09	46.6
				25NOV2012	13:04	1:03	1:03	45.1
				25NOV2012	14:04	2:03	2:03	46.7
				25NOV2012	15:06	3:03	3:05	47.3
				25NOV2012	17:09	5:03	5:08	47.1
	2	Placebo	Male	16DEC2012	12:05	-0:30	-0:30	46.4
				16DEC2012	13:39	1:03	1:04	47.4
				16DEC2012	14:39	2:03	2:04	49.0
				16DEC2012	15:40	3:03	3:05	47.9
				16DEC2012	17:38	5:03	5:03	47.8
4	1	Placebo	Male	25NOV2012	11:08	-0:30	-0:20	49.4
				25NOV2012	12:32	1:03	1:04	49.4
				25NOV2012	13:31	2:03	2:03	49.4
				25NOV2012	14:32	3:03	3:04	50.1
				25NOV2012	16:32	5:03	5:04	49.4
	2	Paracetamol	Male	16DEC2012	12:33	-0:30	-0:32	50.5
				16DEC2012	14:10	1:03	1:05	50.5
				16DEC2012	15:10	2:03	2:05	50.2
				16DEC2012	16:10	3:03	3:05	50.5
				16DEC2012	18:10	5:03	5:05	50.5
5	1	Paracetamol	Female	02JUN2014	10:49	-0:30	-0:23	44.1
				02JUN2014	12:19	1:03	1:07	45.8
				02JUN2014	13:20	2:03	2:08	45.3

M = Missing H = Maximum score reached

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Listing 14 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Heat PTT (C)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:20	3:03	3:08	44.6
					16:19	5:03	5:07	45.1
	2	Placebo	Female	03JUN2014	9:45	-0:30	-0:17	45.9
				03JUN2014	11:12	1:03	1:10	44.2
				03JUN2014	12:09	2:03	2:07	43.9
				03JUN2014	13:09	3:03	3:07	44.7
				03JUN2014	15:09	5:03	5:07	43.2
6	1	Placebo	Female	04JUL2014	10:15	-0:30	-0:23	46.6
				04JUL2014	11:41	1:03	1:03	45.9
				04JUL2014	12:45	2:03	2:07	47.6
				04JUL2014	13:42	3:03	3:04	46.2
				04JUL2014	15:42	5:03	5:04	46.6
	2	Paracetamol	Female	05JUL2014	9:56	-0:30	-0:20	44.7
				05JUL2014	11:19	1:03	1:03	45.6
				05JUL2014	12:19	2:03	2:03	45.3
				05JUL2014	13:19	3:03	3:03	45.5
				05JUL2014	15:19	5:03	5:03	45.9
	1	Paracetamol	Female	05JUL2014	10:18	-0:30	-0:22	42.4
				05JUL2014	11:43	1:03	1:03	43.2
				05JUL2014	12:43	2:03	2:03	43.5
				05JUL2014	13:43	3:03	3:03	41.7
				05JUL2014	15:43	5:03	5:03	42.3
	2	Placebo	Female	18JUL2014	M	-0:30		47.1
				18JUL2014	11:01	1:03	1:11	45.2
				18JUL2014	11:58	2:03	2:08	47.1
				18JUL2014	12:58	3:03	3:08	45.9
				18JUL2014	15:01	5:03	5:11	45.4
8	1	Placebo	Male	10JUL2014	11:08	-0:30	-0:24	48.8
				10JUL2014	12:35	1:03	1:03	48.3
				10JUL2014	13:41	2:03	2:09	47.5
				10JUL2014	14:36	3:03	3:04	46.9
				10JUL2014	16:36	5:03	5:04	47.1
	2	Paracetamol	Male	11JUL2014	9:22	-0:30	-0:23	47.2
				11JUL2014	10:48	1:03	1:03	48.1
				11JUL2014	11:48	2:03	2:03	47.3
				11JUL2014	12:50	3:03	3:05	47.5
				11JUL2014	14:50	5:03	5:05	47.3
	1	Paracetamol	Female	11AUG2014	10:29	-0:30	-0:27	46.4
				11AUG2014	12:01	1:03	1:05	48.2
				11AUG2014	13:03	2:03	2:07	46.0
				11AUG2014	14:01	3:03	3:05	46.0
				11AUG2014	16:00	5:03	5:04	45.9

M = Missing H = Maximum score reached

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Listing 14 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Heat PTT (C)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	9:46	-0:30	-0:51	47.1
				12AUG2014	11:40	1:03	1:03	48.0
				12AUG2014	12:40	2:03	2:03	47.1
				12AUG2014	13:41	3:03	3:04	46.8
				12AUG2014	15:47	5:03	5:10	46.7
10	1	Placebo	Male	10JUL2014	10:37	-0:30	-0:31	46.7
				10JUL2014	12:12	1:03	1:04	47.2
				10JUL2014	13:15	2:03	2:07	47.4
				10JUL2014	14:12	3:03	3:04	47.8
				10JUL2014	16:11	5:03	5:03	46.8
	2	Paracetamol	Male	11JUL2014	9:56	-0:30	-0:22	48.5
				11JUL2014	11:21	1:03	1:03	48.6
				11JUL2014	12:21	2:03	2:03	48.0
				11JUL2014	13:21	3:03	3:03	48.3
				11JUL2014	15:24	5:03	5:06	48.1
11	1	Placebo	Female	11AUG2014	10:06	-0:30	-0:25	46.6
				11AUG2014	11:35	1:03	1:04	48.2
				11AUG2014	12:36	2:03	2:05	48.0
				11AUG2014	13:40	3:03	3:09	47.0
				11AUG2014	15:35	5:03	5:04	46.8
	2	Paracetamol	Female	12AUG2014	9:35	-0:30	-0:37	47.5
				12AUG2014	11:15	1:03	1:03	46.4
				12AUG2014	12:15	2:03	2:03	48.6
				12AUG2014	13:18	3:03	3:06	47.9
				12AUG2014	15:15	5:03	5:03	47.0
12	1	Paracetamol	Male	12AUG2014	10:18	-0:30	-0:31	49.1
				12AUG2014	11:52	1:03	1:03	48.0
				12AUG2014	12:53	2:03	2:04	48.7
				12AUG2014	13:54	3:03	3:05	48.2
				12AUG2014	15:57	5:03	5:08	48.2
	2	Placebo	Male	13AUG2014	9:22	-0:30	-0:38	47.8
				13AUG2014	11:03	1:03	1:03	47.7
				13AUG2014	12:03	2:03	2:03	48.5
				13AUG2014	13:03	3:03	3:03	48.4
				13AUG2014	15:03	5:03	5:03	48.8

M = Missing H = Maximum score reached

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Listing 15 Sensory after Cold

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Listing 15 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Sensory after Cold
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:57	-0:17	-0:14	M
				28DEC2011	12:33	1:16	1:22	M
				28DEC2011	13:33	2:16	2:22	M
				28DEC2011	14:43	3:16	3:32	M
				28DEC2011	16:35	5:16	5:24	M
	2	Paracetamol	Female	07JAN2012	10:47	-0:17	-0:09	M
				07JAN2012	12:19	1:16	1:23	M
				07JAN2012	13:17	2:16	2:21	M
				07JAN2012	14:18	3:16	3:22	M
				07JAN2012	16:17	5:16	5:21	M
2	1	Paracetamol	Female	23NOV2012	10:44	-0:17	-0:07	1.8
				23NOV2012	12:05	1:16	1:14	1.6
				23NOV2012	13:06	2:16	2:15	1.7
				23NOV2012	14:04	3:16	3:13	1.8
				23NOV2012	16:07	5:16	5:16	1.8
	2	Placebo	Female	25NOV2012	10:24	-0:17	-0:19	1.8
				25NOV2012	11:59	1:16	1:16	2.0
				25NOV2012	12:57	2:16	2:14	1.8
				25NOV2012	13:57	3:16	3:14	2.1
				25NOV2012	15:57	5:16	5:14	1.7
	3	Paracetamol	Male	25NOV2012	11:45	-0:17	-0:16	0.5
				25NOV2012	13:20	1:16	1:19	0.5
				25NOV2012	14:23	2:16	2:22	0.5
				25NOV2012	15:22	3:16	3:21	0.5
				25NOV2012	17:22	5:16	5:21	0.7
	2	Placebo	Male	16DEC2012	12:26	-0:17	-0:09	0.5
				16DEC2012	13:56	1:16	1:21	0.4
				16DEC2012	14:58	2:16	2:23	0.5
				16DEC2012	15:55	3:16	3:20	0.6
				16DEC2012	17:55	5:16	5:20	0.5
4	1	Placebo	Male	25NOV2012	11:04	-0:17	-0:24	0.5
				25NOV2012	12:46	1:16	1:18	0.5
				25NOV2012	13:47	2:16	2:19	0.5
				25NOV2012	14:47	3:16	3:19	0.4
				25NOV2012	16:48	5:16	5:20	0.3
	2	Paracetamol	Male	16DEC2012	12:48	-0:17	-0:17	0.5
				16DEC2012	14:24	1:16	1:19	0.4
				16DEC2012	15:25	2:16	2:20	0.4
				16DEC2012	16:24	3:16	3:19	0.3
				16DEC2012	18:26	5:16	5:21	0.5
5	1	Paracetamol	Female	02JUN2014	10:59	-0:17	-0:13	1.0
				02JUN2014	12:29	1:16	1:17	0.9
				02JUN2014	13:34	2:16	2:22	1.0

M = Missing

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Listing 15 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Sensory after Cold
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:32	3:16	3:20	1.0
					16:32	5:16	5:20	1.0
	2	Placebo	Female	03JUN2014	9:57	-0:17	-0:05	1.1
				03JUN2014	11:22	1:16	1:20	1.0
				03JUN2014	12:19	2:16	2:17	1.0
				03JUN2014	13:20	3:16	3:18	1.3
				03JUN2014	15:20	5:16	5:18	0.8
6	1	Placebo	Female	04JUL2014	10:34	-0:17	-0:04	1.5
				04JUL2014	11:58	1:16	1:20	1.7
				04JUL2014	13:00	2:16	2:22	1.7
				04JUL2014	13:55	3:16	3:17	1.6
				04JUL2014	15:57	5:16	5:19	1.5
	2	Paracetamol	Female	05JUL2014	10:12	-0:17	-0:04	1.7
				05JUL2014	11:36	1:16	1:20	1.5
				05JUL2014	12:35	2:16	2:19	1.4
				05JUL2014	13:38	3:16	3:22	1.7
				05JUL2014	15:32	5:16	5:16	1.5
7	1	Paracetamol	Female	05JUL2014	10:35	-0:17	-0:05	1.5
				05JUL2014	11:59	1:16	1:19	1.8
				05JUL2014	12:58	2:16	2:18	1.5
				05JUL2014	13:58	3:16	3:18	1.2
				05JUL2014	15:58	5:16	5:18	1.3
	2	Placebo	Female	18JUL2014	9:44	-0:17	-0:06	1.2
				18JUL2014	11:12	1:16	1:22	1.3
				18JUL2014	12:08	2:16	2:18	1.1
				18JUL2014	13:13	3:16	3:23	1.0
				18JUL2014	15:14	5:16	5:24	1.2
8	1	Placebo	Male	10JUL2014	11:24	-0:17	-0:08	0.8
				10JUL2014	12:50	1:16	1:18	0.5
				10JUL2014	13:56	2:16	2:24	0.5
				10JUL2014	14:52	3:16	3:20	0.5
				10JUL2014	16:51	5:16	5:19	0.3
	2	Paracetamol	Male	11JUL2014	9:38	-0:17	-0:07	0.4
				11JUL2014	11:04	1:16	1:19	0.5
				11JUL2014	12:06	2:16	2:21	0.5
				11JUL2014	13:08	3:16	3:23	0.4
				11JUL2014	15:05	5:16	5:20	0.4
9	1	Paracetamol	Female	11AUG2014	10:43	-0:17	-0:13	0.9
				11AUG2014	12:21	1:16	1:25	0.6
				11AUG2014	13:23	2:16	2:27	0.7
				11AUG2014	14:16	3:16	3:20	0.5
				11AUG2014	16:15	5:16	5:19	0.5

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Listing 15 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Sensory after Cold
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:16	-0:17	-0:21	0.5
				12AUG2014	11:57	1:16	1:20	0.5
				12AUG2014	12:57	2:16	2:20	0.5
				12AUG2014	13:59	3:16	3:22	0.5
				12AUG2014	15:58	5:16	5:21	0.5
10	1	Placebo	Male	10JUL2014	10:56	-0:17	-0:12	0.7
				10JUL2014	12:28	1:16	1:20	0.5
				10JUL2014	13:35	2:16	2:27	0.6
				10JUL2014	14:30	3:16	3:22	0.5
				10JUL2014	16:29	5:16	5:21	0.8
	2	Paracetamol	Male	11JUL2014	10:13	-0:17	-0:05	0.6
				M	M	1:16	M	M
				11JUL2014	12:39	2:16	2:21	0.7
				11JUL2014	13:39	3:16	3:21	0.6
				11JUL2014	15:41	5:16	5:23	0.5
11	1	Placebo	Female	11AUG2014	10:23	-0:17	-0:08	1.0
				11AUG2014	11:55	1:16	1:24	1.0
				11AUG2014	12:57	2:16	2:26	1.2
				11AUG2014	13:55	3:16	3:24	1.3
				11AUG2014	15:51	5:16	5:20	1.0
	2	Paracetamol	Female	12AUG2014	10:00	-0:17	-0:12	1.1
				12AUG2014	11:33	1:16	1:21	1.0
				12AUG2014	12:32	2:16	2:20	0.7
				12AUG2014	13:38	3:16	3:26	0.8
				12AUG2014	15:32	5:16	5:20	0.8
12	1	Paracetamol	Male	12AUG2014	10:40	-0:17	-0:09	1.4
				12AUG2014	12:08	1:16	1:19	1.4
				12AUG2014	13:12	2:16	2:23	1.3
				12AUG2014	14:10	3:16	3:21	1.4
				12AUG2014	16:14	5:16	5:25	1.3
	2	Placebo	Male	13AUG2014	9:48	-0:17	-0:12	1.0
				13AUG2014	11:19	1:16	1:19	1.4
				13AUG2014	12:18	2:16	2:18	1.4
				13AUG2014	13:19	3:16	3:19	1.6
				13AUG2014	15:22	5:16	5:22	1.6

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Listing 16 Affective after Cold

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Listing 16 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Affective after Cold
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:57	-0:17	-0:14	M
				28DEC2011	12:33	1:16	1:22	M
				28DEC2011	13:33	2:16	2:22	M
				28DEC2011	14:43	3:16	3:32	M
				28DEC2011	16:35	5:16	5:24	M
	2	Paracetamol	Female	07JAN2012	10:47	-0:17	-0:09	M
				07JAN2012	12:19	1:16	1:23	M
				07JAN2012	13:17	2:16	2:21	M
				07JAN2012	14:18	3:16	3:22	M
				07JAN2012	16:17	5:16	5:21	M
2	1	Paracetamol	Female	23NOV2012	10:44	-0:17	-0:07	0.5
				23NOV2012	12:05	1:16	1:14	0.3
				23NOV2012	13:06	2:16	2:15	0.3
				23NOV2012	14:04	3:16	3:13	0.3
				23NOV2012	16:07	5:16	5:16	0.3
	2	Placebo	Female	25NOV2012	10:24	-0:17	-0:19	0.3
				25NOV2012	11:59	1:16	1:16	0.3
				25NOV2012	12:57	2:16	2:14	0.3
				25NOV2012	13:57	3:16	3:14	0.3
				25NOV2012	15:57	5:16	5:14	0.3
	3	Paracetamol	Male	25NOV2012	11:45	-0:17	-0:16	0.0
				25NOV2012	13:20	1:16	1:19	0.0
				25NOV2012	14:23	2:16	2:22	0.0
				25NOV2012	15:22	3:16	3:21	0.0
				25NOV2012	17:22	5:16	5:21	0.0
	2	Placebo	Male	16DEC2012	12:26	-0:17	-0:09	0.0
				16DEC2012	13:56	1:16	1:21	0.0
				16DEC2012	14:58	2:16	2:23	0.0
				16DEC2012	15:55	3:16	3:20	0.0
				16DEC2012	17:55	5:16	5:20	0.0
4	1	Placebo	Male	25NOV2012	11:04	-0:17	-0:24	0.5
				25NOV2012	12:46	1:16	1:18	0.8
				25NOV2012	13:47	2:16	2:19	0.5
				25NOV2012	14:47	3:16	3:19	0.0
				25NOV2012	16:48	5:16	5:20	0.5
	2	Paracetamol	Male	16DEC2012	12:48	-0:17	-0:17	0.3
				16DEC2012	14:24	1:16	1:19	0.3
				16DEC2012	15:25	2:16	2:20	0.5
				16DEC2012	16:24	3:16	3:19	0.3
				16DEC2012	18:26	5:16	5:21	0.0
5	1	Paracetamol	Female	02JUN2014	10:59	-0:17	-0:13	0.3
				02JUN2014	12:29	1:16	1:17	0.3
				02JUN2014	13:34	2:16	2:22	0.3

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Listing 16 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Affective after Cold
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:32	3:16	3:20	0.3
					16:32	5:16	5:20	0.3
	2	Placebo	Female	03JUN2014	9:57	-0:17	-0:05	0.3
				03JUN2014	11:22	1:16	1:20	0.3
				03JUN2014	12:19	2:16	2:17	0.3
				03JUN2014	13:20	3:16	3:18	0.3
				03JUN2014	15:20	5:16	5:18	0.3
6	1	Placebo	Female	04JUL2014	10:34	-0:17	-0:04	1.5
				04JUL2014	11:58	1:16	1:20	1.5
				04JUL2014	13:00	2:16	2:22	1.0
				04JUL2014	13:55	3:16	3:17	1.5
				04JUL2014	15:57	5:16	5:19	1.0
	2	Paracetamol	Female	05JUL2014	10:12	-0:17	-0:04	1.0
				05JUL2014	11:36	1:16	1:20	1.0
				05JUL2014	12:35	2:16	2:19	1.0
				05JUL2014	13:38	3:16	3:22	1.0
				05JUL2014	15:32	5:16	5:16	1.0
7	1	Paracetamol	Female	05JUL2014	10:35	-0:17	-0:05	1.3
				05JUL2014	11:59	1:16	1:19	1.3
				05JUL2014	12:58	2:16	2:18	1.3
				05JUL2014	13:58	3:16	3:18	1.3
				05JUL2014	15:58	5:16	5:18	1.3
	2	Placebo	Female	18JUL2014	9:44	-0:17	-0:06	1.3
				18JUL2014	11:12	1:16	1:22	0.8
				18JUL2014	12:08	2:16	2:18	1.3
				18JUL2014	13:13	3:16	3:23	1.3
				18JUL2014	15:14	5:16	5:24	1.3
8	1	Placebo	Male	10JUL2014	11:24	-0:17	-0:08	0.0
				10JUL2014	12:50	1:16	1:18	0.0
				10JUL2014	13:56	2:16	2:24	0.0
				10JUL2014	14:52	3:16	3:20	0.0
				10JUL2014	16:51	5:16	5:19	0.0
	2	Paracetamol	Male	11JUL2014	9:38	-0:17	-0:07	0.0
				11JUL2014	11:04	1:16	1:19	0.0
				11JUL2014	12:06	2:16	2:21	0.0
				11JUL2014	13:08	3:16	3:23	0.0
				11JUL2014	15:05	5:16	5:20	0.0
9	1	Paracetamol	Female	11AUG2014	10:43	-0:17	-0:13	0.0
				11AUG2014	12:21	1:16	1:25	0.0
				11AUG2014	13:23	2:16	2:27	0.0
				11AUG2014	14:16	3:16	3:20	0.0
				11AUG2014	16:15	5:16	5:19	0.0

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Listing 16 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Affective after Cold
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:16	-0:17	-0:21	0.0
				12AUG2014	11:57	1:16	1:20	0.0
				12AUG2014	12:57	2:16	2:20	0.0
				12AUG2014	13:59	3:16	3:22	0.0
				12AUG2014	15:58	5:16	5:21	0.0
10	1	Placebo	Male	10JUL2014	10:56	-0:17	-0:12	0.0
				10JUL2014	12:28	1:16	1:20	0.0
				10JUL2014	13:35	2:16	2:27	0.0
				10JUL2014	14:30	3:16	3:22	0.0
				10JUL2014	16:29	5:16	5:21	0.0
	2	Paracetamol	Male	11JUL2014	10:13	-0:17	-0:05	0.0
				M	M	1:16	M	M
				11JUL2014	12:39	2:16	2:21	0.0
				11JUL2014	13:39	3:16	3:21	0.0
				11JUL2014	15:41	5:16	5:23	0.0
11	1	Placebo	Female	11AUG2014	10:23	-0:17	-0:08	0.3
				11AUG2014	11:55	1:16	1:24	0.0
				11AUG2014	12:57	2:16	2:26	0.0
				11AUG2014	13:55	3:16	3:24	0.0
				11AUG2014	15:51	5:16	5:20	0.3
	2	Paracetamol	Female	12AUG2014	10:00	-0:17	-0:12	0.3
				12AUG2014	11:33	1:16	1:21	0.3
				12AUG2014	12:32	2:16	2:20	0.3
				12AUG2014	13:38	3:16	3:26	0.3
				12AUG2014	15:32	5:16	5:20	0.3
12	1	Paracetamol	Male	12AUG2014	10:40	-0:17	-0:09	0.0
				12AUG2014	12:08	1:16	1:19	0.0
				12AUG2014	13:12	2:16	2:23	0.0
				12AUG2014	14:10	3:16	3:21	0.0
				12AUG2014	16:14	5:16	5:25	0.0
	2	Placebo	Male	13AUG2014	9:48	-0:17	-0:12	0.0
				13AUG2014	11:19	1:16	1:19	0.0
				13AUG2014	12:18	2:16	2:18	0.0
				13AUG2014	13:19	3:16	3:19	0.0
				13AUG2014	15:22	5:16	5:22	0.0

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Listing 17 MPQ VAS after Cold (mm)

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Listing 17 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		MPQ VAS after Cold (mm)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:57	-0:17	-0:14	55.4
				28DEC2011	12:33	1:16	1:22	59.4
				28DEC2011	13:33	2:16	2:22	42.2
				28DEC2011	14:43	3:16	3:32	57
				28DEC2011	16:35	5:16	5:24	54.2
	2	Paracetamol	Female	07JAN2012	10:47	-0:17	-0:09	46.6
				07JAN2012	12:19	1:16	1:23	37.2
				07JAN2012	13:17	2:16	2:21	48.9
				07JAN2012	14:18	3:16	3:22	42.9
				07JAN2012	16:17	5:16	5:21	45.7
2	1	Paracetamol	Female	23NOV2012	10:44	-0:17	-0:07	76.5
				23NOV2012	12:05	1:16	1:14	79.2
				23NOV2012	13:06	2:16	2:15	79.5
				23NOV2012	14:04	3:16	3:13	78.5
				23NOV2012	16:07	5:16	5:16	75.9
	2	Placebo	Female	25NOV2012	10:24	-0:17	-0:19	71.9
				25NOV2012	11:59	1:16	1:16	74
				25NOV2012	12:57	2:16	2:14	66.8
				25NOV2012	13:57	3:16	3:14	74.3
				25NOV2012	15:57	5:16	5:14	75
	3	Paracetamol	Male	25NOV2012	11:45	-0:17	-0:16	56.7
				25NOV2012	13:20	1:16	1:19	56.8
				25NOV2012	14:23	2:16	2:22	55.2
				25NOV2012	15:22	3:16	3:21	55.8
				25NOV2012	17:22	5:16	5:21	61.4
	2	Placebo	Male	16DEC2012	12:26	-0:17	-0:09	47.5
				16DEC2012	13:56	1:16	1:21	45
				16DEC2012	14:58	2:16	2:23	50.4
				16DEC2012	15:55	3:16	3:20	48
				16DEC2012	17:55	5:16	5:20	54.8
4	1	Placebo	Male	25NOV2012	11:04	-0:17	-0:24	16.5
				25NOV2012	12:46	1:16	1:18	27.4
				25NOV2012	13:47	2:16	2:19	7.9
				25NOV2012	14:47	3:16	3:19	8
				25NOV2012	16:48	5:16	5:20	13.5
	2	Paracetamol	Male	16DEC2012	12:48	-0:17	-0:17	0
				16DEC2012	14:24	1:16	1:19	0
				16DEC2012	15:25	2:16	2:20	0
				16DEC2012	16:24	3:16	3:19	11.6
				16DEC2012	18:26	5:16	5:21	0
5	1	Paracetamol	Female	02JUN2014	10:59	-0:17	-0:13	64.3
				02JUN2014	12:29	1:16	1:17	62
				02JUN2014	13:34	2:16	2:22	65.2

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Listing 17 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		MPQ VAS after Cold (mm)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:32	3:16	3:20	68.6
				02JUN2014	16:32	5:16	5:20	67.9
	2	Placebo	Female	03JUN2014	9:57	-0:17	-0:05	66.6
				03JUN2014	11:22	1:16	1:20	68.1
				03JUN2014	12:19	2:16	2:17	65.8
				03JUN2014	13:20	3:16	3:18	67
				03JUN2014	15:20	5:16	5:18	62.9
6	1	Placebo	Female	04JUL2014	10:34	-0:17	-0:04	82.8
				04JUL2014	11:58	1:16	1:20	89.7
				04JUL2014	13:00	2:16	2:22	89.3
				04JUL2014	13:55	3:16	3:17	77.8
				04JUL2014	15:57	5:16	5:19	89.3
	2	Paracetamol	Female	05JUL2014	10:12	-0:17	-0:04	77.7
				05JUL2014	11:36	1:16	1:20	83.7
				05JUL2014	12:35	2:16	2:19	87.3
				05JUL2014	13:38	3:16	3:22	79.9
				05JUL2014	15:32	5:16	5:16	78.4
7	1	Paracetamol	Female	05JUL2014	10:35	-0:17	-0:05	46
				05JUL2014	11:59	1:16	1:19	52.6
				05JUL2014	12:58	2:16	2:18	49.4
				05JUL2014	13:58	3:16	3:18	43.7
				05JUL2014	15:58	5:16	5:18	41.2
	2	Placebo	Female	18JUL2014	9:44	-0:17	-0:06	50.9
				18JUL2014	11:12	1:16	1:22	35.7
				18JUL2014	12:08	2:16	2:18	30.5
				18JUL2014	13:13	3:16	3:23	28.9
				18JUL2014	15:14	5:16	5:24	45.1
8	1	Placebo	Male	10JUL2014	11:24	-0:17	-0:08	42.7
				10JUL2014	12:50	1:16	1:18	30.3
				10JUL2014	13:56	2:16	2:24	37.1
				10JUL2014	14:52	3:16	3:20	30.1
				10JUL2014	16:51	5:16	5:19	35.6
	2	Paracetamol	Male	11JUL2014	9:38	-0:17	-0:07	35.2
				11JUL2014	11:04	1:16	1:19	29.5
				11JUL2014	12:06	2:16	2:21	37.3
				11JUL2014	13:08	3:16	3:23	34.1
				11JUL2014	15:05	5:16	5:20	35.9
9	1	Paracetamol	Female	11AUG2014	10:43	-0:17	-0:13	20.9
				11AUG2014	12:21	1:16	1:25	15.4
				11AUG2014	13:23	2:16	2:27	13
				11AUG2014	14:16	3:16	3:20	12.7
				11AUG2014	16:15	5:16	5:19	15.1

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Listing 17 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		MPQ VAS after Cold (mm)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:16	-0:17	-0:21	9.6
				12AUG2014	11:57	1:16	1:20	12.5
				12AUG2014	12:57	2:16	2:20	13.5
				12AUG2014	13:59	3:16	3:22	15.6
				12AUG2014	15:58	5:16	5:21	13.5
10	1	Placebo	Male	10JUL2014	10:56	-0:17	-0:12	17.7
				10JUL2014	12:28	1:16	1:20	9
				10JUL2014	13:35	2:16	2:27	7.3
				10JUL2014	14:30	3:16	3:22	6.2
				10JUL2014	16:29	5:16	5:21	27.3
	2	Paracetamol	Male	11JUL2014	10:13	-0:17	-0:05	22.7
				M	M	1:16	M	M
				11JUL2014	12:39	2:16	2:21	31.9
				11JUL2014	13:39	3:16	3:21	26.7
				11JUL2014	15:41	5:16	5:23	19.7
11	1	Placebo	Female	11AUG2014	10:23	-0:17	-0:08	19.5
				11AUG2014	11:55	1:16	1:24	15.8
				11AUG2014	12:57	2:16	2:26	19.7
				11AUG2014	13:55	3:16	3:24	12.2
				11AUG2014	15:51	5:16	5:20	13.6
	2	Paracetamol	Female	12AUG2014	10:00	-0:17	-0:12	13
				12AUG2014	11:33	1:16	1:21	16
				12AUG2014	12:32	2:16	2:20	16.5
				12AUG2014	13:38	3:16	3:26	11.8
				12AUG2014	15:32	5:16	5:20	13.4
12	1	Paracetamol	Male	12AUG2014	10:40	-0:17	-0:09	71.1
				12AUG2014	12:08	1:16	1:19	69.7
				12AUG2014	13:12	2:16	2:23	68.2
				12AUG2014	14:10	3:16	3:21	69.9
				12AUG2014	16:14	5:16	5:25	64.6
	2	Placebo	Male	13AUG2014	9:48	-0:17	-0:12	68.1
				13AUG2014	11:19	1:16	1:19	70.1
				13AUG2014	12:18	2:16	2:18	71.7
				13AUG2014	13:19	3:16	3:19	69.5
				13AUG2014	15:22	5:16	5:22	67.5

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Listing 18 Sensory after ES

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Listing 18 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Sensory after ES
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:48	-0:25	-0:23	M
				28DEC2011	12:22	1:08	1:11	M
				28DEC2011	13:25	2:08	2:14	M
				28DEC2011	14:36	3:08	3:25	M
				28DEC2011	16:26	5:08	5:15	M
	2	Paracetamol	Female	07JAN2012	10:36	-0:25	-0:20	M
				07JAN2012	12:08	1:08	1:12	M
				07JAN2012	13:09	2:08	2:13	M
				07JAN2012	14:10	3:08	3:14	M
				07JAN2012	16:08	5:08	5:12	M
2	1	Paracetamol	Female	23NOV2012	10:35	-0:25	-0:16	1.5
				23NOV2012	11:59	1:08	1:08	1.8
				23NOV2012	13:01	2:08	2:10	1.8
				23NOV2012	13:59	3:08	3:08	1.8
				23NOV2012	16:00	5:08	5:09	1.8
	2	Placebo	Female	25NOV2012	10:18	-0:25	-0:25	1.7
				25NOV2012	11:54	1:08	1:11	1.8
				25NOV2012	12:51	2:08	2:08	1.9
				25NOV2012	13:52	3:08	3:09	2.0
				25NOV2012	15:52	5:08	5:09	1.9
3	1	Paracetamol	Male	25NOV2012	11:29	-0:25	-0:32	1.0
				25NOV2012	13:12	1:08	1:11	0.8
				25NOV2012	14:11	2:08	2:10	0.8
				25NOV2012	15:14	3:08	3:13	0.8
				25NOV2012	17:13	5:08	5:12	0.8
	2	Placebo	Male	16DEC2012	12:12	-0:25	-0:23	0.8
				16DEC2012	13:48	1:08	1:13	1.1
				16DEC2012	14:48	2:08	2:13	0.8
				16DEC2012	15:47	3:08	3:12	0.7
				16DEC2012	17:46	5:08	5:11	0.7
4	1	Placebo	Male	25NOV2012	10:56	-0:25	-0:32	1.1
				25NOV2012	12:40	1:08	1:12	1.0
				25NOV2012	13:38	2:08	2:10	0.8
				25NOV2012	14:39	3:08	3:11	0.6
				25NOV2012	16:41	5:08	5:13	0.6
	2	Paracetamol	Male	16DEC2012	12:40	-0:25	-0:25	0.9
				16DEC2012	14:17	1:08	1:12	0.5
				16DEC2012	15:17	2:08	2:12	0.5
				16DEC2012	16:17	3:08	3:12	0.5
				16DEC2012	18:17	5:08	5:12	0.5
5	1	Paracetamol	Female	02JUN2014	10:52	-0:25	-0:20	1.1
				02JUN2014	12:22	1:08	1:10	0.8
				02JUN2014	13:24	2:08	2:12	0.9

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Listing 18 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Sensory after ES
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:25	3:08	3:13	1.0
					16:24	5:08	5:12	1.0
	2	Placebo	Female	03JUN2014	9:49	-0:25	-0:13	1.2
				03JUN2014	11:14	1:08	1:12	1.2
				03JUN2014	12:12	2:08	2:10	1.2
				03JUN2014	13:11	3:08	3:09	1.0
				03JUN2014	15:11	5:08	5:09	1.1
6	1	Placebo	Female	04JUL2014	10:21	-0:25	-0:17	1.8
				04JUL2014	11:47	1:08	1:09	1.5
				04JUL2014	12:52	2:08	2:14	1.7
				04JUL2014	13:47	3:08	3:09	1.7
				04JUL2014	15:48	5:08	5:10	1.7
	2	Paracetamol	Female	05JUL2014	10:02	-0:25	-0:14	1.5
				05JUL2014	11:27	1:08	1:11	1.6
				05JUL2014	12:25	2:08	2:09	1.6
				05JUL2014	13:25	3:08	3:09	1.6
				05JUL2014	15:25	5:08	5:09	1.6
7	1	Paracetamol	Female	05JUL2014	10:28	-0:25	-0:12	2.2
				05JUL2014	11:50	1:08	1:10	2.0
				05JUL2014	12:51	2:08	2:11	2.0
				05JUL2014	13:49	3:08	3:09	1.7
				05JUL2014	15:48	5:08	5:08	1.7
	2	Placebo	Female	18JUL2014	9:33	-0:25	-0:17	1.5
				18JUL2014	11:03	1:08	1:13	1.5
				18JUL2014	12:00	2:08	2:10	1.4
				18JUL2014	13:01	3:08	3:11	1.3
				18JUL2014	15:06	5:08	5:16	0.7
8	1	Placebo	Male	10JUL2014	11:16	-0:25	-0:16	1.1
				10JUL2014	12:42	1:08	1:10	0.6
				10JUL2014	13:47	2:08	2:15	0.7
				10JUL2014	14:43	3:08	3:11	0.6
				10JUL2014	16:42	5:08	5:10	0.7
	2	Paracetamol	Male	11JUL2014	9:28	-0:25	-0:17	0.7
				11JUL2014	10:54	1:08	1:09	0.7
				11JUL2014	11:54	2:08	2:09	0.7
				11JUL2014	12:57	3:08	3:12	0.7
				11JUL2014	14:56	5:08	5:11	0.7
9	1	Paracetamol	Female	11AUG2014	10:35	-0:25	-0:21	0.9
				11AUG2014	12:08	1:08	1:12	0.6
				11AUG2014	13:14	2:08	2:18	0.8
				11AUG2014	14:07	3:08	3:11	0.5
				11AUG2014	16:05	5:08	5:09	0.7

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Listing 18 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Sensory after ES
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:07	-0:25	-0:30	0.7
				12AUG2014	11:47	1:08	1:10	0.6
				12AUG2014	12:46	2:08	2:09	0.7
				12AUG2014	13:51	3:08	3:14	0.5
				12AUG2014	15:50	5:08	5:13	0.5
10	1	Placebo	Male	10JUL2014	10:44	-0:25	-0:24	0.8
				10JUL2014	12:19	1:08	1:11	0.7
				10JUL2014	13:22	2:08	2:14	0.7
				10JUL2014	14:18	3:08	3:10	0.6
				10JUL2014	16:18	5:08	5:10	0.5
	2	Paracetamol	Male	11JUL2014	10:04	-0:25	-0:14	0.7
				11JUL2014	11:28	1:08	1:10	0.7
				11JUL2014	12:29	2:08	2:11	0.7
				11JUL2014	13:29	3:08	3:11	0.7
				11JUL2014	15:31	5:08	5:13	0.6
11	1	Placebo	Female	11AUG2014	10:13	-0:25	-0:18	1.1
				11AUG2014	11:43	1:08	1:12	1.5
				11AUG2014	12:44	2:08	2:13	1.6
				11AUG2014	13:47	3:08	3:16	1.5
				11AUG2014	15:41	5:08	5:10	1.4
	2	Paracetamol	Female	12AUG2014	9:40	-0:25	-0:32	1.5
				12AUG2014	11:22	1:08	1:10	1.5
				12AUG2014	12:22	2:08	2:10	1.4
				12AUG2014	13:29	3:08	3:17	1.1
				12AUG2014	15:25	5:08	5:13	1.2
12	1	Paracetamol	Male	12AUG2014	10:25	-0:25	-0:24	1.8
				12AUG2014	11:59	1:08	1:10	1.5
				12AUG2014	13:00	2:08	2:11	1.5
				12AUG2014	14:00	3:08	3:11	1.5
				12AUG2014	16:05	5:08	5:16	1.7
	2	Placebo	Male	13AUG2014	9:30	-0:25	-0:30	1.6
				13AUG2014	11:09	1:08	1:09	1.5
				13AUG2014	12:09	2:08	2:09	1.9
				13AUG2014	13:10	3:08	3:10	1.9
				13AUG2014	15:11	5:08	5:11	1.6

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Listing 19 Affective after ES

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Listing 19 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Affective after ES
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:48	-0:25	-0:23	M
				28DEC2011	12:22	1:08	1:11	M
				28DEC2011	13:25	2:08	2:14	M
				28DEC2011	14:36	3:08	3:25	M
				28DEC2011	16:26	5:08	5:15	M
	2	Paracetamol	Female	07JAN2012	10:36	-0:25	-0:20	M
				07JAN2012	12:08	1:08	1:12	M
				07JAN2012	13:09	2:08	2:13	M
				07JAN2012	14:10	3:08	3:14	M
				07JAN2012	16:08	5:08	5:12	M
2	1	Paracetamol	Female	23NOV2012	10:35	-0:25	-0:16	0.0
				23NOV2012	11:59	1:08	1:08	0.0
				23NOV2012	13:01	2:08	2:10	0.0
				23NOV2012	13:59	3:08	3:08	0.0
				23NOV2012	16:00	5:08	5:09	0.0
	2	Placebo	Female	25NOV2012	10:18	-0:25	-0:25	0.0
				25NOV2012	11:54	1:08	1:11	0.0
				25NOV2012	12:51	2:08	2:08	0.0
				25NOV2012	13:52	3:08	3:09	0.0
				25NOV2012	15:52	5:08	5:09	0.0
	3	Paracetamol	Male	25NOV2012	11:29	-0:25	-0:32	0.0
				25NOV2012	13:12	1:08	1:11	0.0
				25NOV2012	14:11	2:08	2:10	0.0
				25NOV2012	15:14	3:08	3:13	0.0
				25NOV2012	17:13	5:08	5:12	0.0
	2	Placebo	Male	16DEC2012	12:12	-0:25	-0:23	0.3
				16DEC2012	13:48	1:08	1:13	0.3
				16DEC2012	14:48	2:08	2:13	0.3
				16DEC2012	15:47	3:08	3:12	0.3
				16DEC2012	17:46	5:08	5:11	0.3
4	1	Placebo	Male	25NOV2012	10:56	-0:25	-0:32	0.8
				25NOV2012	12:40	1:08	1:12	0.8
				25NOV2012	13:38	2:08	2:10	0.5
				25NOV2012	14:39	3:08	3:11	0.5
				25NOV2012	16:41	5:08	5:13	0.3
	2	Paracetamol	Male	16DEC2012	12:40	-0:25	-0:25	1.0
				16DEC2012	14:17	1:08	1:12	0.8
				16DEC2012	15:17	2:08	2:12	0.3
				16DEC2012	16:17	3:08	3:12	0.3
				16DEC2012	18:17	5:08	5:12	0.3
5	1	Paracetamol	Female	02JUN2014	10:52	-0:25	-0:20	0.3
				02JUN2014	12:22	1:08	1:10	0.0
				02JUN2014	13:24	2:08	2:12	0.8

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Listing 19 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Affective after ES
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:25	3:08	3:13	0.3
					16:24	5:08	5:12	0.3
	2	Placebo	Female	03JUN2014	9:49	-0:25	-0:13	0.3
				03JUN2014	11:14	1:08	1:12	0.3
				03JUN2014	12:12	2:08	2:10	0.3
				03JUN2014	13:11	3:08	3:09	0.3
				03JUN2014	15:11	5:08	5:09	0.3
	1	Placebo	Female	04JUL2014	10:21	-0:25	-0:17	1.3
				04JUL2014	11:47	1:08	1:09	1.8
				04JUL2014	12:52	2:08	2:14	1.3
				04JUL2014	13:47	3:08	3:09	1.0
				04JUL2014	15:48	5:08	5:10	1.0
7	2	Paracetamol	Female	05JUL2014	10:02	-0:25	-0:14	1.0
				05JUL2014	11:27	1:08	1:11	1.0
				05JUL2014	12:25	2:08	2:09	1.0
				05JUL2014	13:25	3:08	3:09	1.0
				05JUL2014	15:25	5:08	5:09	1.0
	1	Paracetamol	Female	05JUL2014	10:28	-0:25	-0:12	0.8
				05JUL2014	11:50	1:08	1:10	1.3
				05JUL2014	12:51	2:08	2:11	1.0
				05JUL2014	13:49	3:08	3:09	1.0
				05JUL2014	15:48	5:08	5:08	1.0
	2	Placebo	Female	18JUL2014	9:33	-0:25	-0:17	1.0
				18JUL2014	11:03	1:08	1:13	1.0
				18JUL2014	12:00	2:08	2:10	1.0
				18JUL2014	13:01	3:08	3:11	1.0
				18JUL2014	15:06	5:08	5:16	1.0
8	1	Placebo	Male	10JUL2014	11:16	-0:25	-0:16	0.0
				10JUL2014	12:42	1:08	1:10	0.0
				10JUL2014	13:47	2:08	2:15	0.0
				10JUL2014	14:43	3:08	3:11	0.0
				10JUL2014	16:42	5:08	5:10	0.0
	2	Paracetamol	Male	11JUL2014	9:28	-0:25	-0:17	0.0
				11JUL2014	10:54	1:08	1:09	0.0
				11JUL2014	11:54	2:08	2:09	0.0
				11JUL2014	12:57	3:08	3:12	0.0
				11JUL2014	14:56	5:08	5:11	0.0
9	1	Paracetamol	Female	11AUG2014	10:35	-0:25	-0:21	0.0
				11AUG2014	12:08	1:08	1:12	0.0
				11AUG2014	13:14	2:08	2:18	0.0
				11AUG2014	14:07	3:08	3:11	0.0
				11AUG2014	16:05	5:08	5:09	0.0

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Listing 19 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Affective after ES
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:07	-0:25	-0:30	0.0
				12AUG2014	11:47	1:08	1:10	0.0
				12AUG2014	12:46	2:08	2:09	0.0
				12AUG2014	13:51	3:08	3:14	0.0
				12AUG2014	15:50	5:08	5:13	0.0
10	1	Placebo	Male	10JUL2014	10:44	-0:25	-0:24	0.0
				10JUL2014	12:19	1:08	1:11	0.0
				10JUL2014	13:22	2:08	2:14	0.0
				10JUL2014	14:18	3:08	3:10	0.0
				10JUL2014	16:18	5:08	5:10	0.0
	2	Paracetamol	Male	11JUL2014	10:04	-0:25	-0:14	0.0
				11JUL2014	11:28	1:08	1:10	0.0
				11JUL2014	12:29	2:08	2:11	0.0
				11JUL2014	13:29	3:08	3:11	0.0
				11JUL2014	15:31	5:08	5:13	0.0
11	1	Placebo	Female	11AUG2014	10:13	-0:25	-0:18	0.3
				11AUG2014	11:43	1:08	1:12	0.5
				11AUG2014	12:44	2:08	2:13	0.5
				11AUG2014	13:47	3:08	3:16	0.3
				11AUG2014	15:41	5:08	5:10	0.5
	2	Paracetamol	Female	12AUG2014	9:40	-0:25	-0:32	0.5
				12AUG2014	11:22	1:08	1:10	0.5
				12AUG2014	12:22	2:08	2:10	0.5
				12AUG2014	13:29	3:08	3:17	0.5
				12AUG2014	15:25	5:08	5:13	0.5
12	1	Paracetamol	Male	12AUG2014	10:25	-0:25	-0:24	0.0
				12AUG2014	11:59	1:08	1:10	0.0
				12AUG2014	13:00	2:08	2:11	0.0
				12AUG2014	14:00	3:08	3:11	0.0
				12AUG2014	16:05	5:08	5:16	0.0
	2	Placebo	Male	13AUG2014	9:30	-0:25	-0:30	0.0
				13AUG2014	11:09	1:08	1:09	0.0
				13AUG2014	12:09	2:08	2:09	0.0
				13AUG2014	13:10	3:08	3:10	0.0
				13AUG2014	15:11	5:08	5:11	0.0

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Listing 20 MPQ VAS after ES (mm)

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Listing 20 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		MPQ VAS after ES (mm)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:48	-0:25	-0:23	45.9
				28DEC2011	12:22	1:08	1:11	49.2
				28DEC2011	13:25	2:08	2:14	39.7
				28DEC2011	14:36	3:08	3:25	32.9
				28DEC2011	16:26	5:08	5:15	46.9
	2	Paracetamol	Female	07JAN2012	10:36	-0:25	-0:20	42.3
				07JAN2012	12:08	1:08	1:12	37.7
				07JAN2012	13:09	2:08	2:13	38.9
				07JAN2012	14:10	3:08	3:14	35.3
				07JAN2012	16:08	5:08	5:12	38.9
2	1	Paracetamol	Female	23NOV2012	10:35	-0:25	-0:16	43.5
				23NOV2012	11:59	1:08	1:08	46.3
				23NOV2012	13:01	2:08	2:10	56.9
				23NOV2012	13:59	3:08	3:08	53.3
				23NOV2012	16:00	5:08	5:09	54.9
	2	Placebo	Female	25NOV2012	10:18	-0:25	-0:25	54.6
				25NOV2012	11:54	1:08	1:11	50.4
				25NOV2012	12:51	2:08	2:08	54.6
				25NOV2012	13:52	3:08	3:09	54.7
				25NOV2012	15:52	5:08	5:09	54.7
	3	Paracetamol	Male	25NOV2012	11:29	-0:25	-0:32	57.7
				25NOV2012	13:12	1:08	1:11	58
				25NOV2012	14:11	2:08	2:10	54
				25NOV2012	15:14	3:08	3:13	48.3
				25NOV2012	17:13	5:08	5:12	47.7
	2	Placebo	Male	16DEC2012	12:12	-0:25	-0:23	55.1
				16DEC2012	13:48	1:08	1:13	55.9
				16DEC2012	14:48	2:08	2:13	41.6
				16DEC2012	15:47	3:08	3:12	39.2
				16DEC2012	17:46	5:08	5:11	26.7
4	1	Placebo	Male	25NOV2012	10:56	-0:25	-0:32	23.2
				25NOV2012	12:40	1:08	1:12	26.8
				25NOV2012	13:38	2:08	2:10	8.2
				25NOV2012	14:39	3:08	3:11	25.6
				25NOV2012	16:41	5:08	5:13	23
	2	Paracetamol	Male	16DEC2012	12:40	-0:25	-0:25	12.1
				16DEC2012	14:17	1:08	1:12	11.4
				16DEC2012	15:17	2:08	2:12	0
				16DEC2012	16:17	3:08	3:12	0
				16DEC2012	18:17	5:08	5:12	0
5	1	Paracetamol	Female	02JUN2014	10:52	-0:25	-0:20	60.7
				02JUN2014	12:22	1:08	1:10	62.6
				02JUN2014	13:24	2:08	2:12	65.6

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Listing 20 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		MPQ VAS after ES (mm)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:25	3:08	3:13	64.3
					16:24	5:08	5:12	66.3
	2	Placebo	Female	03JUN2014	9:49	-0:25	-0:13	63.6
				03JUN2014	11:14	1:08	1:12	65.5
				03JUN2014	12:12	2:08	2:10	65.3
				03JUN2014	13:11	3:08	3:09	65.6
				03JUN2014	15:11	5:08	5:09	64.8
6	1	Placebo	Female	04JUL2014	10:21	-0:25	-0:17	75.2
				04JUL2014	11:47	1:08	1:09	68.8
				04JUL2014	12:52	2:08	2:14	77.5
				04JUL2014	13:47	3:08	3:09	80.2
				04JUL2014	15:48	5:08	5:10	77
	2	Paracetamol	Female	05JUL2014	10:02	-0:25	-0:14	76.7
				05JUL2014	11:27	1:08	1:11	79.1
				05JUL2014	12:25	2:08	2:09	88.6
				05JUL2014	13:25	3:08	3:09	81.2
				05JUL2014	15:25	5:08	5:09	78.3
	1	Paracetamol	Female	05JUL2014	10:28	-0:25	-0:12	20
				05JUL2014	11:50	1:08	1:10	44.7
				05JUL2014	12:51	2:08	2:11	25.9
				05JUL2014	13:49	3:08	3:09	22
				05JUL2014	15:48	5:08	5:08	25.5
	2	Placebo	Female	18JUL2014	9:33	-0:25	-0:17	32.7
				18JUL2014	11:03	1:08	1:13	23.2
				18JUL2014	12:00	2:08	2:10	28.6
				18JUL2014	13:01	3:08	3:11	23.2
				18JUL2014	15:06	5:08	5:16	27.6
8	1	Placebo	Male	10JUL2014	11:16	-0:25	-0:16	30.4
				10JUL2014	12:42	1:08	1:10	13.8
				10JUL2014	13:47	2:08	2:15	27.6
				10JUL2014	14:43	3:08	3:11	25.7
				10JUL2014	16:42	5:08	5:10	22.8
	2	Paracetamol	Male	11JUL2014	9:28	-0:25	-0:17	24
				11JUL2014	10:54	1:08	1:09	23.2
				11JUL2014	11:54	2:08	2:09	26.4
				11JUL2014	12:57	3:08	3:12	19.6
				11JUL2014	14:56	5:08	5:11	26.7
9	1	Paracetamol	Female	11AUG2014	10:35	-0:25	-0:21	13.4
				11AUG2014	12:08	1:08	1:12	18.6
				11AUG2014	13:14	2:08	2:18	12.9
				11AUG2014	14:07	3:08	3:11	9.2
				11AUG2014	16:05	5:08	5:09	11.9

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Listing 20 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		MPQ VAS after ES (mm)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:07	-0:25	-0:30	11.5
				12AUG2014	11:47	1:08	1:10	16.3
				12AUG2014	12:46	2:08	2:09	15.8
				12AUG2014	13:51	3:08	3:14	14.9
				12AUG2014	15:50	5:08	5:13	15.5
10	1	Placebo	Male	10JUL2014	10:44	-0:25	-0:24	27.6
				10JUL2014	12:19	1:08	1:11	15.4
				10JUL2014	13:22	2:08	2:14	19.5
				10JUL2014	14:18	3:08	3:10	8.7
				10JUL2014	16:18	5:08	5:10	16.3
	2	Paracetamol	Male	11JUL2014	10:04	-0:25	-0:14	27.8
				11JUL2014	11:28	1:08	1:10	20.1
				11JUL2014	12:29	2:08	2:11	25.7
				11JUL2014	13:29	3:08	3:11	33.1
				11JUL2014	15:31	5:08	5:13	26.6
11	1	Placebo	Female	11AUG2014	10:13	-0:25	-0:18	26.8
				11AUG2014	11:43	1:08	1:12	37.6
				11AUG2014	12:44	2:08	2:13	46.4
				11AUG2014	13:47	3:08	3:16	26
				11AUG2014	15:41	5:08	5:10	25.3
	2	Paracetamol	Female	12AUG2014	9:40	-0:25	-0:32	23.6
				12AUG2014	11:22	1:08	1:10	23.1
				12AUG2014	12:22	2:08	2:10	22.4
				12AUG2014	13:29	3:08	3:17	20
				12AUG2014	15:25	5:08	5:13	21.6
12	1	Paracetamol	Male	12AUG2014	10:25	-0:25	-0:24	58.1
				12AUG2014	11:59	1:08	1:10	53.3
				12AUG2014	13:00	2:08	2:11	57.6
				12AUG2014	14:00	3:08	3:11	57.9
				12AUG2014	16:05	5:08	5:16	58.9
	2	Placebo	Male	13AUG2014	9:30	-0:25	-0:30	60.3
				13AUG2014	11:09	1:08	1:09	59.4
				13AUG2014	12:09	2:08	2:09	57.2
				13AUG2014	13:10	3:08	3:10	57.9
				13AUG2014	15:11	5:08	5:11	56

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Listing 21 Sensory after Pressure

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Listing 21 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Sensory after Pressure
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:51	-0:20	-0:20	M
				28DEC2011	12:26	1:13	1:15	M
				28DEC2011	13:27	2:13	2:16	M
				28DEC2011	14:39	3:13	3:28	M
				28DEC2011	16:28	5:13	5:17	M
	2	Paracetamol	Female	07JAN2012	10:39	-0:20	-0:17	M
				07JAN2012	12:12	1:13	1:16	M
				07JAN2012	13:12	2:13	2:16	M
				07JAN2012	14:13	3:13	3:17	M
				07JAN2012	16:12	5:13	5:16	M
2	1	Paracetamol	Female	23NOV2012	10:40	-0:20	-0:11	1.7
				23NOV2012	12:02	1:13	1:11	2.2
				23NOV2012	13:02	2:13	2:11	2.2
				23NOV2012	14:00	3:13	3:09	2.0
				23NOV2012	16:02	5:13	5:11	2.0
	2	Placebo	Female	25NOV2012	10:20	-0:20	-0:23	1.7
				25NOV2012	11:55	1:13	1:12	2.0
				25NOV2012	12:54	2:13	2:11	2.0
				25NOV2012	13:54	3:13	3:11	1.9
				25NOV2012	15:54	5:13	5:11	1.7
	3	Paracetamol	Male	25NOV2012	11:33	-0:20	-0:28	0.7
				25NOV2012	13:16	1:13	1:15	0.4
				25NOV2012	14:18	2:13	2:17	0.5
				25NOV2012	15:18	3:13	3:17	0.5
				25NOV2012	17:16	5:13	5:15	0.5
	2	Placebo	Male	16DEC2012	12:16	-0:20	-0:19	0.5
				16DEC2012	13:51	1:13	1:16	0.5
				16DEC2012	14:52	2:13	2:17	0.5
				16DEC2012	15:51	3:13	3:16	0.5
				16DEC2012	17:50	5:13	5:15	0.5
4	1	Placebo	Male	25NOV2012	10:59	-0:20	-0:29	0.8
				25NOV2012	12:42	1:13	1:14	0.7
				25NOV2012	13:43	2:13	2:15	0.5
				25NOV2012	14:42	3:13	3:14	0.5
				25NOV2012	16:44	5:13	5:16	0.5
	2	Paracetamol	Male	16DEC2012	12:44	-0:20	-0:21	0.7
				16DEC2012	14:21	1:13	1:16	0.5
				16DEC2012	15:21	2:13	2:16	0.5
				16DEC2012	16:21	3:13	3:16	0.5
				16DEC2012	18:22	5:13	5:17	0.5
5	1	Paracetamol	Female	02JUN2014	10:55	-0:20	-0:17	0.9
				02JUN2014	12:25	1:13	1:13	0.6
				02JUN2014	13:29	2:13	2:17	0.6

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Listing 21 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Sensory after Pressure
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:27	3:13	3:15	0.6
					16:26	5:13	5:14	0.8
	2	Placebo	Female	03JUN2014	9:52	-0:20	-0:10	0.5
				03JUN2014	11:18	1:13	1:16	0.7
				03JUN2014	12:15	2:13	2:13	0.9
				03JUN2014	13:15	3:13	3:13	0.5
				03JUN2014	15:15	5:13	5:13	0.6
6	1	Placebo	Female	04JUL2014	10:25	-0:20	-0:13	1.5
				04JUL2014	11:52	1:13	1:14	1.5
				04JUL2014	12:55	2:13	2:17	1.5
				04JUL2014	13:51	3:13	3:13	1.4
				04JUL2014	15:51	5:13	5:13	1.4
	2	Paracetamol	Female	05JUL2014	10:05	-0:20	-0:11	1.3
				05JUL2014	11:31	1:13	1:15	1.5
				05JUL2014	12:29	2:13	2:13	1.5
				05JUL2014	13:29	3:13	3:13	1.4
				05JUL2014	15:28	5:13	5:12	1.5
	1	Paracetamol	Female	05JUL2014	10:31	-0:20	-0:09	1.0
				05JUL2014	11:55	1:13	1:15	1.2
				05JUL2014	12:54	2:13	2:14	1.5
				05JUL2014	13:53	3:13	3:13	0.7
				05JUL2014	15:53	5:13	5:13	0.7
7	2	Placebo	Female	18JUL2014	9:37	-0:20	-0:13	0.9
				18JUL2014	11:07	1:13	1:17	1.1
				18JUL2014	12:04	2:13	2:14	0.8
				18JUL2014	13:08	3:13	3:18	0.6
				18JUL2014	15:09	5:13	5:19	0.8
	1	Placebo	Male	10JUL2014	11:19	-0:20	-0:13	0.9
				10JUL2014	12:45	1:13	1:13	0.5
				10JUL2014	13:51	2:13	2:19	0.5
				10JUL2014	14:47	3:13	3:15	0.5
				10JUL2014	16:46	5:13	5:14	0.5
	2	Paracetamol	Male	11JUL2014	9:32	-0:20	-0:13	0.5
				11JUL2014	10:59	1:13	1:14	0.3
				11JUL2014	11:58	2:13	2:13	0.5
				11JUL2014	13:01	3:13	3:16	0.4
				11JUL2014	15:00	5:13	5:15	0.3
9	1	Paracetamol	Female	11AUG2014	10:38	-0:20	-0:18	0.7
				11AUG2014	12:13	1:13	1:17	0.7
				11AUG2014	13:18	2:13	2:22	0.5
				11AUG2014	14:12	3:13	3:16	0.9
				11AUG2014	16:10	5:13	5:14	0.3

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Listing 21 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Sensory after Pressure
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:11	-0:20	-0:26	0.6
				12AUG2014	11:52	1:13	1:15	0.6
				12AUG2014	12:52	2:13	2:15	0.5
				12AUG2014	13:55	3:13	3:18	0.5
				12AUG2014	15:53	5:13	5:16	0.6
10	1	Placebo	Male	10JUL2014	10:49	-0:20	-0:19	0.6
				10JUL2014	12:22	1:13	1:14	0.8
				10JUL2014	13:28	2:13	2:20	0.5
				10JUL2014	14:24	3:13	3:16	0.5
				10JUL2014	16:24	5:13	5:16	0.6
	2	Paracetamol	Male	11JUL2014	10:08	-0:20	-0:10	0.7
				11JUL2014	11:32	1:13	1:14	0.5
				11JUL2014	12:34	2:13	2:16	0.6
				11JUL2014	13:33	3:13	3:15	0.7
				11JUL2014	15:36	5:13	5:18	0.7
11	1	Placebo	Female	11AUG2014	10:17	-0:20	-0:14	1.0
				11AUG2014	11:48	1:13	1:17	1.1
				11AUG2014	12:48	2:13	2:17	1.3
				11AUG2014	13:50	3:13	3:19	0.9
				11AUG2014	15:46	5:13	5:15	0.5
	2	Paracetamol	Female	12AUG2014	9:51	-0:20	-0:21	0.7
				12AUG2014	11:27	1:13	1:15	0.5
				12AUG2014	12:27	2:13	2:15	0.5
				12AUG2014	13:33	3:13	3:21	0.6
				12AUG2014	15:27	5:13	5:15	0.6
12	1	Paracetamol	Male	12AUG2014	10:33	-0:20	-0:16	1.7
				12AUG2014	12:04	1:13	1:15	1.5
				12AUG2014	13:04	2:13	2:15	1.5
				12AUG2014	14:05	3:13	3:16	1.8
				12AUG2014	16:10	5:13	5:21	1.7
	2	Placebo	Male	13AUG2014	9:34	-0:20	-0:26	1.5
				13AUG2014	11:15	1:13	1:15	1.5
				13AUG2014	12:14	2:13	2:14	1.4
				13AUG2014	13:14	3:13	3:14	1.5
				13AUG2014	15:16	5:13	5:16	1.6

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Listing 22 Affective after Pressure

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Listing 22 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Affective after Pressure
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:51	-0:20	-0:20	M
				28DEC2011	12:26	1:13	1:15	M
				28DEC2011	13:27	2:13	2:16	M
				28DEC2011	14:39	3:13	3:28	M
				28DEC2011	16:28	5:13	5:17	M
	2	Paracetamol	Female	07JAN2012	10:39	-0:20	-0:17	M
				07JAN2012	12:12	1:13	1:16	M
				07JAN2012	13:12	2:13	2:16	M
				07JAN2012	14:13	3:13	3:17	M
				07JAN2012	16:12	5:13	5:16	M
2	1	Paracetamol	Female	23NOV2012	10:40	-0:20	-0:11	0.0
				23NOV2012	12:02	1:13	1:11	0.0
				23NOV2012	13:02	2:13	2:11	0.0
				23NOV2012	14:00	3:13	3:09	0.0
				23NOV2012	16:02	5:13	5:11	0.0
	2	Placebo	Female	25NOV2012	10:20	-0:20	-0:23	0.0
				25NOV2012	11:55	1:13	1:12	0.0
				25NOV2012	12:54	2:13	2:11	0.0
				25NOV2012	13:54	3:13	3:11	0.0
				25NOV2012	15:54	5:13	5:11	0.0
	3	Paracetamol	Male	25NOV2012	11:33	-0:20	-0:28	0.0
				25NOV2012	13:16	1:13	1:15	0.0
				25NOV2012	14:18	2:13	2:17	0.0
				25NOV2012	15:18	3:13	3:17	0.0
				25NOV2012	17:16	5:13	5:15	0.0
	2	Placebo	Male	16DEC2012	12:16	-0:20	-0:19	0.0
				16DEC2012	13:51	1:13	1:16	0.0
				16DEC2012	14:52	2:13	2:17	0.0
				16DEC2012	15:51	3:13	3:16	0.0
				16DEC2012	17:50	5:13	5:15	0.0
4	1	Placebo	Male	25NOV2012	10:59	-0:20	-0:29	0.5
				25NOV2012	12:42	1:13	1:14	0.3
				25NOV2012	13:43	2:13	2:15	0.3
				25NOV2012	14:42	3:13	3:14	0.0
				25NOV2012	16:44	5:13	5:16	0.5
	2	Paracetamol	Male	16DEC2012	12:44	-0:20	-0:21	0.5
				16DEC2012	14:21	1:13	1:16	0.3
				16DEC2012	15:21	2:13	2:16	0.0
				16DEC2012	16:21	3:13	3:16	0.3
				16DEC2012	18:22	5:13	5:17	0.5
5	1	Paracetamol	Female	02JUN2014	10:55	-0:20	-0:17	0.3
				02JUN2014	12:25	1:13	1:13	0.3
				02JUN2014	13:29	2:13	2:17	0.0

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Listing 22 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Affective after Pressure
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:27	3:13	3:15	0.3
					16:26	5:13	5:14	0.3
	2	Placebo	Female	03JUN2014	9:52	-0:20	-0:10	0.5
				03JUN2014	11:18	1:13	1:16	0.5
				03JUN2014	12:15	2:13	2:13	0.3
				03JUN2014	13:15	3:13	3:13	0.3
				03JUN2014	15:15	5:13	5:13	0.5
6	1	Placebo	Female	04JUL2014	10:25	-0:20	-0:13	1.5
				04JUL2014	11:52	1:13	1:14	1.5
				04JUL2014	12:55	2:13	2:17	1.5
				04JUL2014	13:51	3:13	3:13	1.3
				04JUL2014	15:51	5:13	5:13	1.0
	2	Paracetamol	Female	05JUL2014	10:05	-0:20	-0:11	1.0
				05JUL2014	11:31	1:13	1:15	1.3
				05JUL2014	12:29	2:13	2:13	1.0
				05JUL2014	13:29	3:13	3:13	1.0
				05JUL2014	15:28	5:13	5:12	0.8
	1	Paracetamol	Female	05JUL2014	10:31	-0:20	-0:09	0.5
				05JUL2014	11:55	1:13	1:15	0.3
				05JUL2014	12:54	2:13	2:14	0.0
				05JUL2014	13:53	3:13	3:13	0.0
				05JUL2014	15:53	5:13	5:13	0.3
	2	Placebo	Female	18JUL2014	9:37	-0:20	-0:13	0.3
				18JUL2014	11:07	1:13	1:17	0.0
				18JUL2014	12:04	2:13	2:14	0.0
				18JUL2014	13:08	3:13	3:18	0.0
				18JUL2014	15:09	5:13	5:19	0.3
8	1	Placebo	Male	10JUL2014	11:19	-0:20	-0:13	0.0
				10JUL2014	12:45	1:13	1:13	0.0
				10JUL2014	13:51	2:13	2:19	0.0
				10JUL2014	14:47	3:13	3:15	0.0
				10JUL2014	16:46	5:13	5:14	0.0
	2	Paracetamol	Male	11JUL2014	9:32	-0:20	-0:13	0.0
				11JUL2014	10:59	1:13	1:14	0.0
				11JUL2014	11:58	2:13	2:13	0.0
				11JUL2014	13:01	3:13	3:16	0.0
				11JUL2014	15:00	5:13	5:15	0.0
	1	Paracetamol	Female	11AUG2014	10:38	-0:20	-0:18	0.0
				11AUG2014	12:13	1:13	1:17	0.0
				11AUG2014	13:18	2:13	2:22	0.0
				11AUG2014	14:12	3:13	3:16	0.0
				11AUG2014	16:10	5:13	5:14	0.0

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Listing 22 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		Affective after Pressure
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:11	-0:20	-0:26	0.0
				12AUG2014	11:52	1:13	1:15	0.0
				12AUG2014	12:52	2:13	2:15	0.0
				12AUG2014	13:55	3:13	3:18	0.0
				12AUG2014	15:53	5:13	5:16	0.0
10	1	Placebo	Male	10JUL2014	10:49	-0:20	-0:19	0.0
				10JUL2014	12:22	1:13	1:14	0.0
				10JUL2014	13:28	2:13	2:20	0.0
				10JUL2014	14:24	3:13	3:16	0.0
				10JUL2014	16:24	5:13	5:16	0.0
	2	Paracetamol	Male	11JUL2014	10:08	-0:20	-0:10	0.0
				11JUL2014	11:32	1:13	1:14	0.0
				11JUL2014	12:34	2:13	2:16	0.0
				11JUL2014	13:33	3:13	3:15	0.0
				11JUL2014	15:36	5:13	5:18	0.0
11	1	Placebo	Female	11AUG2014	10:17	-0:20	-0:14	0.3
				11AUG2014	11:48	1:13	1:17	0.0
				11AUG2014	12:48	2:13	2:17	0.0
				11AUG2014	13:50	3:13	3:19	0.0
				11AUG2014	15:46	5:13	5:15	0.0
	2	Paracetamol	Female	12AUG2014	9:51	-0:20	-0:21	0.0
				12AUG2014	11:27	1:13	1:15	0.0
				12AUG2014	12:27	2:13	2:15	0.0
				12AUG2014	13:33	3:13	3:21	0.0
				12AUG2014	15:27	5:13	5:15	0.0
12	1	Paracetamol	Male	12AUG2014	10:33	-0:20	-0:16	0.0
				12AUG2014	12:04	1:13	1:15	0.0
				12AUG2014	13:04	2:13	2:15	0.0
				12AUG2014	14:05	3:13	3:16	0.0
				12AUG2014	16:10	5:13	5:21	0.0
	2	Placebo	Male	13AUG2014	9:34	-0:20	-0:26	0.0
				13AUG2014	11:15	1:13	1:15	0.0
				13AUG2014	12:14	2:13	2:14	0.0
				13AUG2014	13:14	3:13	3:14	0.0
				13AUG2014	15:16	5:13	5:16	0.0

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Listing 23 MPQ VAS after Pressure (mm)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataL.sas

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Listing 23 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		MPQ VAS after Pressure (mm)
						Protocol (hh:mm)	Actual (hh:mm)	
1	1	Placebo	Female	28DEC2011	10:51	-0:20	-0:20	47.1
				28DEC2011	12:26	1:13	1:15	53.6
				28DEC2011	13:27	2:13	2:16	33.9
				28DEC2011	14:39	3:13	3:28	41.8
				28DEC2011	16:28	5:13	5:17	47.6
	2	Paracetamol	Female	07JAN2012	10:39	-0:20	-0:17	38
				07JAN2012	12:12	1:13	1:16	37.4
				07JAN2012	13:12	2:13	2:16	47.3
				07JAN2012	14:13	3:13	3:17	44.8
				07JAN2012	16:12	5:13	5:16	33.8
2	1	Paracetamol	Female	23NOV2012	10:40	-0:20	-0:11	59.9
				23NOV2012	12:02	1:13	1:11	58.1
				23NOV2012	13:02	2:13	2:11	52.7
				23NOV2012	14:00	3:13	3:09	49.9
				23NOV2012	16:02	5:13	5:11	49.6
	2	Placebo	Female	25NOV2012	10:20	-0:20	-0:23	47.2
				25NOV2012	11:55	1:13	1:12	55
				25NOV2012	12:54	2:13	2:11	53.9
				25NOV2012	13:54	3:13	3:11	55.5
				25NOV2012	15:54	5:13	5:11	56.5
	3	Paracetamol	Male	25NOV2012	11:33	-0:20	-0:28	48
				25NOV2012	13:16	1:13	1:15	58.5
				25NOV2012	14:18	2:13	2:17	56.6
				25NOV2012	15:18	3:13	3:17	52.8
				25NOV2012	17:16	5:13	5:15	51.5
	2	Placebo	Male	16DEC2012	12:16	-0:20	-0:19	57.1
				16DEC2012	13:51	1:13	1:16	44.4
				16DEC2012	14:52	2:13	2:17	40.3
				16DEC2012	15:51	3:13	3:16	44.8
				16DEC2012	17:50	5:13	5:15	46.3
4	1	Placebo	Male	25NOV2012	10:59	-0:20	-0:29	23.9
				25NOV2012	12:42	1:13	1:14	16.7
				25NOV2012	13:43	2:13	2:15	19.6
				25NOV2012	14:42	3:13	3:14	9.1
				25NOV2012	16:44	5:13	5:16	20.1
	2	Paracetamol	Male	16DEC2012	12:44	-0:20	-0:21	0.1
				16DEC2012	14:21	1:13	1:16	0.1
				16DEC2012	15:21	2:13	2:16	0.1
				16DEC2012	16:21	3:13	3:16	0.1
				16DEC2012	18:22	5:13	5:17	0.1
5	1	Paracetamol	Female	02JUN2014	10:55	-0:20	-0:17	66.1
				02JUN2014	12:25	1:13	1:13	64.4
				02JUN2014	13:29	2:13	2:17	62.9

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Listing 23 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		MPQ VAS after Pressure (mm)
						Protocol (hh:mm)	Actual (hh:mm)	
5	1	Paracetamol	Female	02JUN2014	14:27	3:13	3:15	59.8
				02JUN2014	16:26	5:13	5:14	62.8
	2	Placebo	Female	03JUN2014	9:52	-0:20	-0:10	62.1
				03JUN2014	11:18	1:13	1:16	64.7
				03JUN2014	12:15	2:13	2:13	59.1
				03JUN2014	13:15	3:13	3:13	61.7
				03JUN2014	15:15	5:13	5:13	65.3
6	1	Placebo	Female	04JUL2014	10:25	-0:20	-0:13	81
				04JUL2014	11:52	1:13	1:14	76.6
				04JUL2014	12:55	2:13	2:17	78.6
				04JUL2014	13:51	3:13	3:13	80.4
				04JUL2014	15:51	5:13	5:13	70.8
	2	Paracetamol	Female	05JUL2014	10:05	-0:20	-0:11	66.7
				05JUL2014	11:31	1:13	1:15	78.6
				05JUL2014	12:29	2:13	2:13	82.6
				05JUL2014	13:29	3:13	3:13	73.4
				05JUL2014	15:28	5:13	5:12	66.5
7	1	Paracetamol	Female	05JUL2014	10:31	-0:20	-0:09	19.8
				05JUL2014	11:55	1:13	1:15	28.4
				05JUL2014	12:54	2:13	2:14	25
				05JUL2014	13:53	3:13	3:13	10.2
				05JUL2014	15:53	5:13	5:13	18.3
	2	Placebo	Female	18JUL2014	9:37	-0:20	-0:13	25.1
				18JUL2014	11:07	1:13	1:17	10.5
				18JUL2014	12:04	2:13	2:14	21.6
				18JUL2014	13:08	3:13	3:18	14.5
				18JUL2014	15:09	5:13	5:19	25.7
8	1	Placebo	Male	10JUL2014	11:19	-0:20	-0:13	33.9
				10JUL2014	12:45	1:13	1:13	18.2
				10JUL2014	13:51	2:13	2:19	14.3
				10JUL2014	14:47	3:13	3:15	13.5
				10JUL2014	16:46	5:13	5:14	10.8
	2	Paracetamol	Male	11JUL2014	9:32	-0:20	-0:13	10.7
				11JUL2014	10:59	1:13	1:14	13
				11JUL2014	11:58	2:13	2:13	15.7
				11JUL2014	13:01	3:13	3:16	13.8
				11JUL2014	15:00	5:13	5:15	16
9	1	Paracetamol	Female	11AUG2014	10:38	-0:20	-0:18	10.8
				11AUG2014	12:13	1:13	1:17	10.7
				11AUG2014	13:18	2:13	2:22	7.8
				11AUG2014	14:12	3:13	3:16	10.3
				11AUG2014	16:10	5:13	5:14	10.9

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Listing 23 of dynamic measurements

Safety population

Subject	Visit	Treatment	Gender	Date	Time (hh:mm)	Time from dosing		MPQ VAS after Pressure (mm)
						Protocol (hh:mm)	Actual (hh:mm)	
9	2	Placebo	Female	12AUG2014	10:11	-0:20	-0:26	13
				12AUG2014	11:52	1:13	1:15	12.4
				12AUG2014	12:52	2:13	2:15	14
				12AUG2014	13:55	3:13	3:18	13.3
				12AUG2014	15:53	5:13	5:16	13.7
10	1	Placebo	Male	10JUL2014	10:49	-0:20	-0:19	16
				10JUL2014	12:22	1:13	1:14	15.3
				10JUL2014	13:28	2:13	2:20	12.9
				10JUL2014	14:24	3:13	3:16	14.2
				10JUL2014	16:24	5:13	5:16	21.3
	2	Paracetamol	Male	11JUL2014	10:08	-0:20	-0:10	25.9
				11JUL2014	11:32	1:13	1:14	25.2
				11JUL2014	12:34	2:13	2:16	23.2
				11JUL2014	13:33	3:13	3:15	20.2
				11JUL2014	15:36	5:13	5:18	16.7
11	1	Placebo	Female	11AUG2014	10:17	-0:20	-0:14	12.1
				11AUG2014	11:48	1:13	1:17	8.2
				11AUG2014	12:48	2:13	2:17	13.6
				11AUG2014	13:50	3:13	3:19	8.4
				11AUG2014	15:46	5:13	5:15	5
	2	Paracetamol	Female	12AUG2014	9:51	-0:20	-0:21	7.7
				12AUG2014	11:27	1:13	1:15	5.6
				12AUG2014	12:27	2:13	2:15	6.6
				12AUG2014	13:33	3:13	3:21	8
				12AUG2014	15:27	5:13	5:15	7.8
12	1	Paracetamol	Male	12AUG2014	10:33	-0:20	-0:16	48.6
				12AUG2014	12:04	1:13	1:15	54.1
				12AUG2014	13:04	2:13	2:15	54.8
				12AUG2014	14:05	3:13	3:16	53.5
				12AUG2014	16:10	5:13	5:21	53.1
	2	Placebo	Male	13AUG2014	9:34	-0:20	-0:26	55.6
				13AUG2014	11:15	1:13	1:15	58.4
				13AUG2014	12:14	2:13	2:14	56
				13AUG2014	13:14	3:13	3:14	53.4
				13AUG2014	15:16	5:13	5:16	55.7

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Individual pharmacodynamic response plots

Individual plots 1 Cold AAC (s*%)

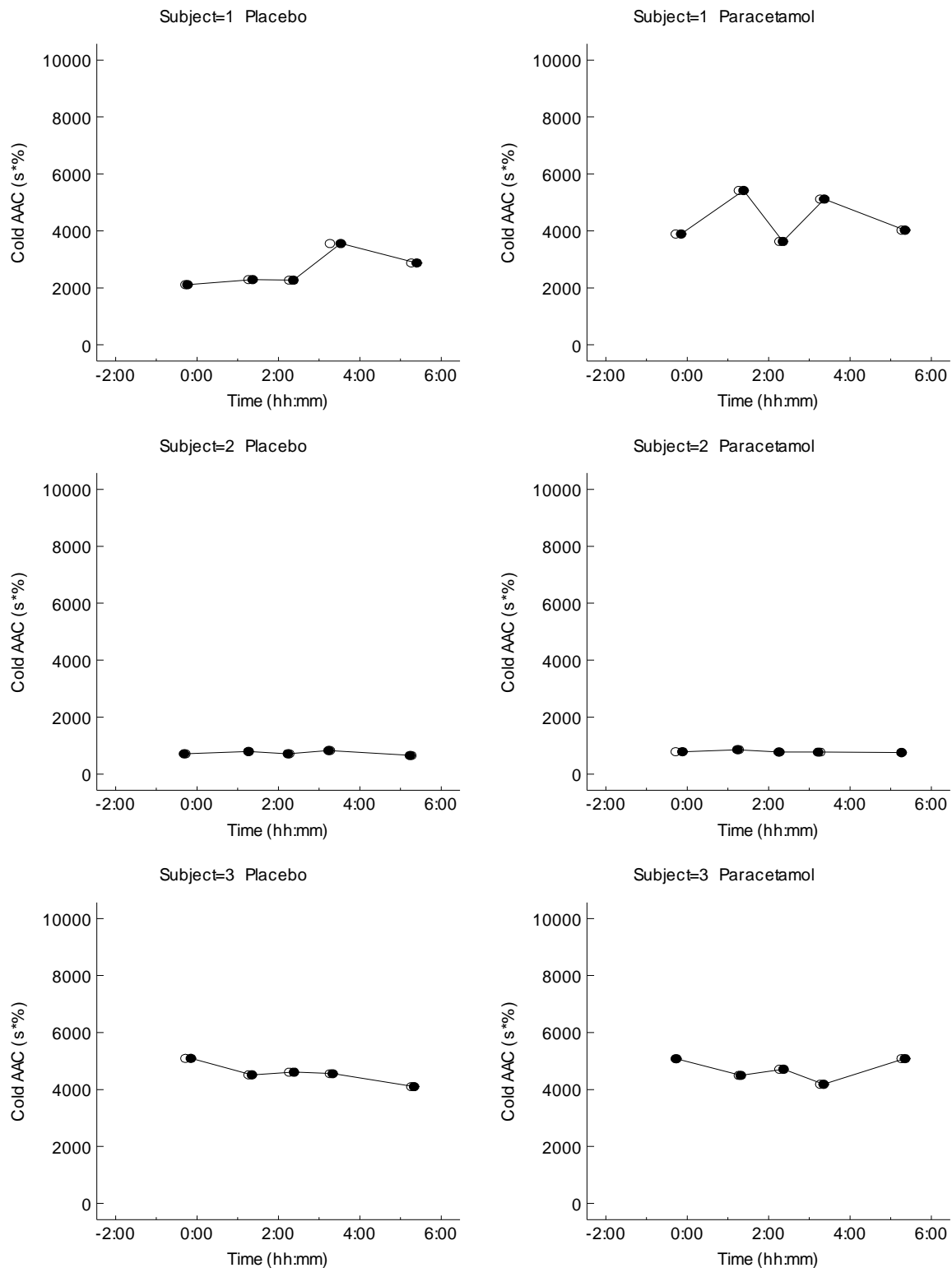
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30SEP2014 10:28 Page: 1

Individual Plots 1 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



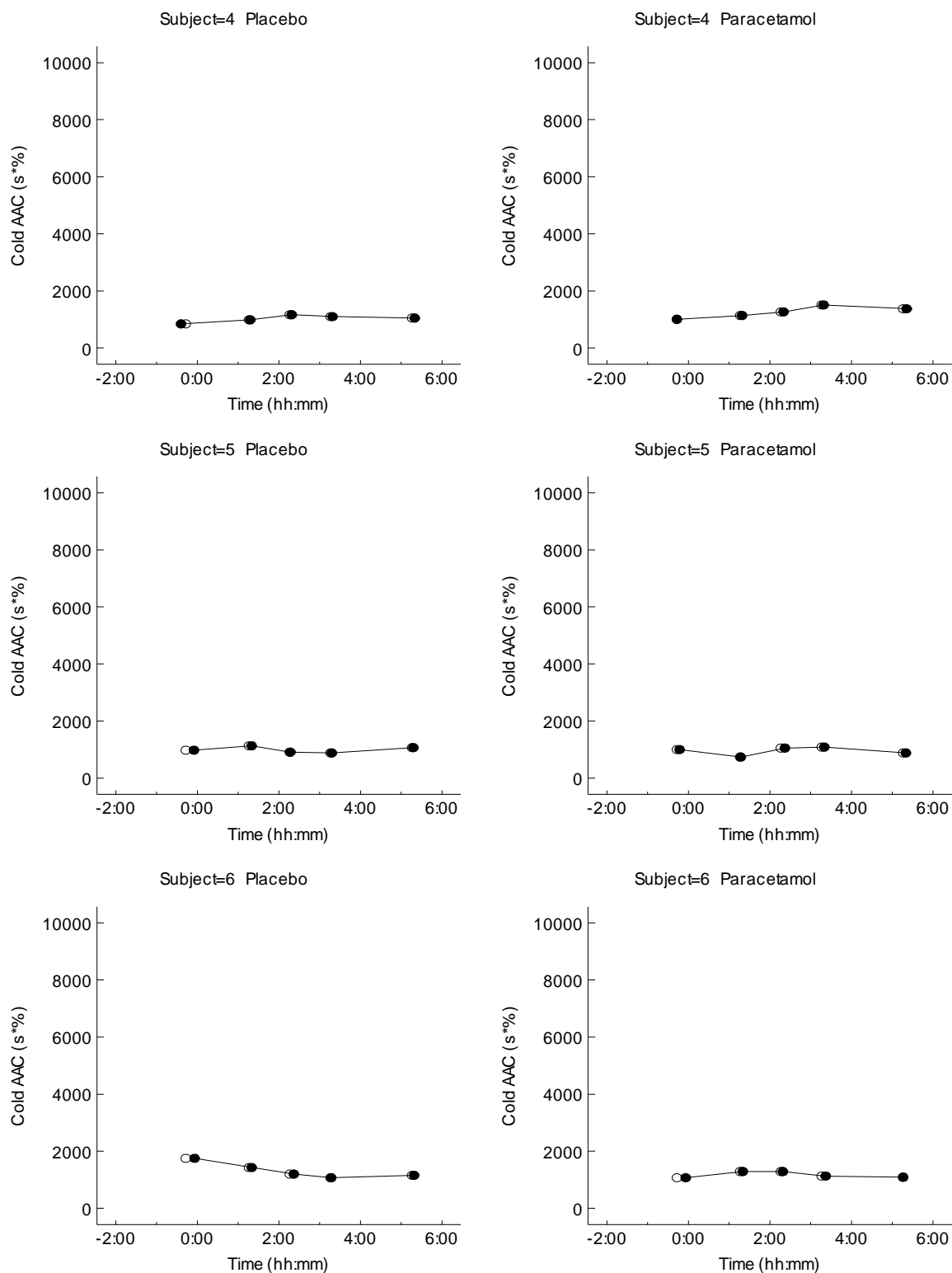
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Individual Plots 1 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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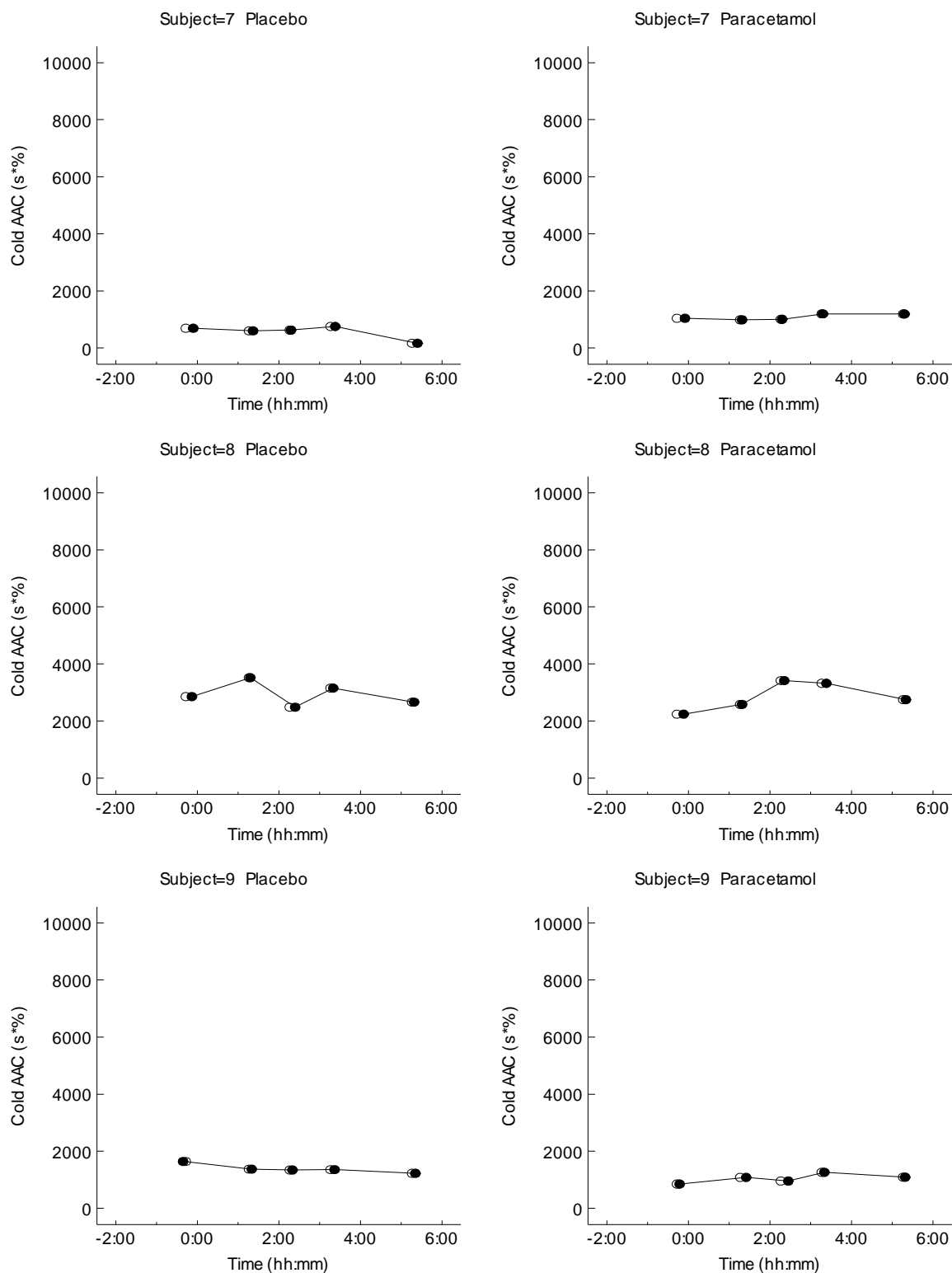
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Individual Plots 1 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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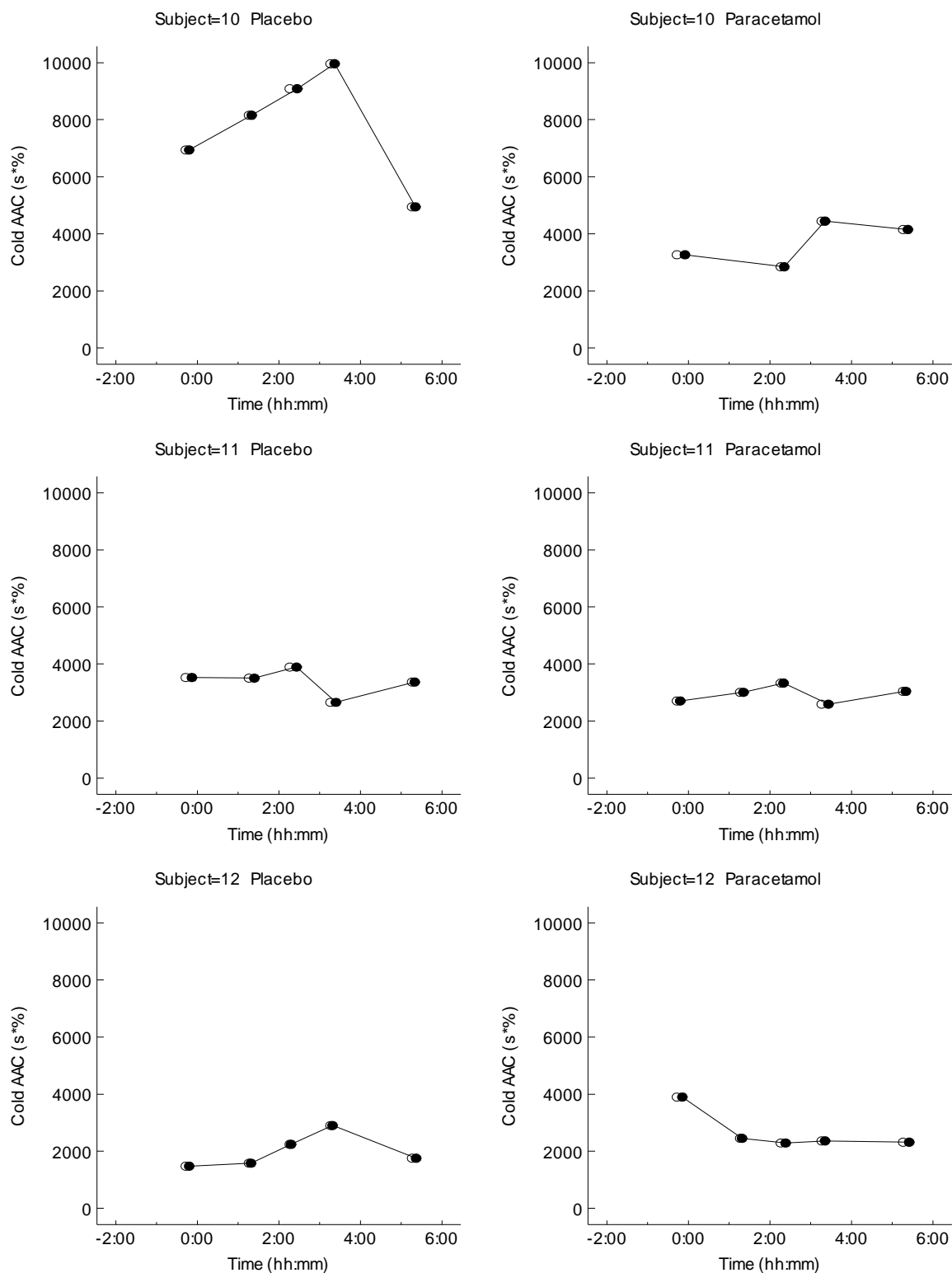
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Individual Plots 1 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 2 Cold PDT (s)

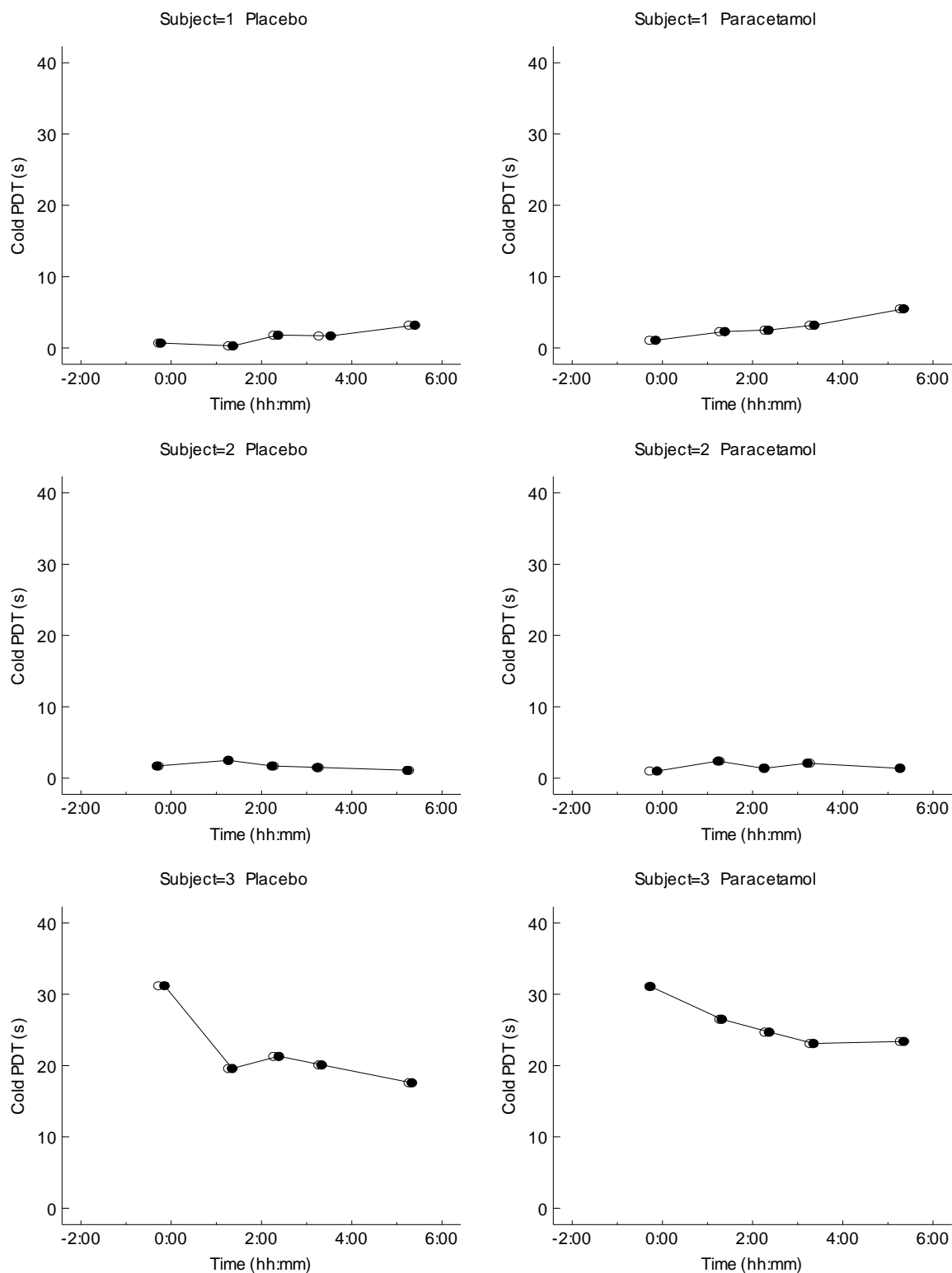
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Individual Plots 2 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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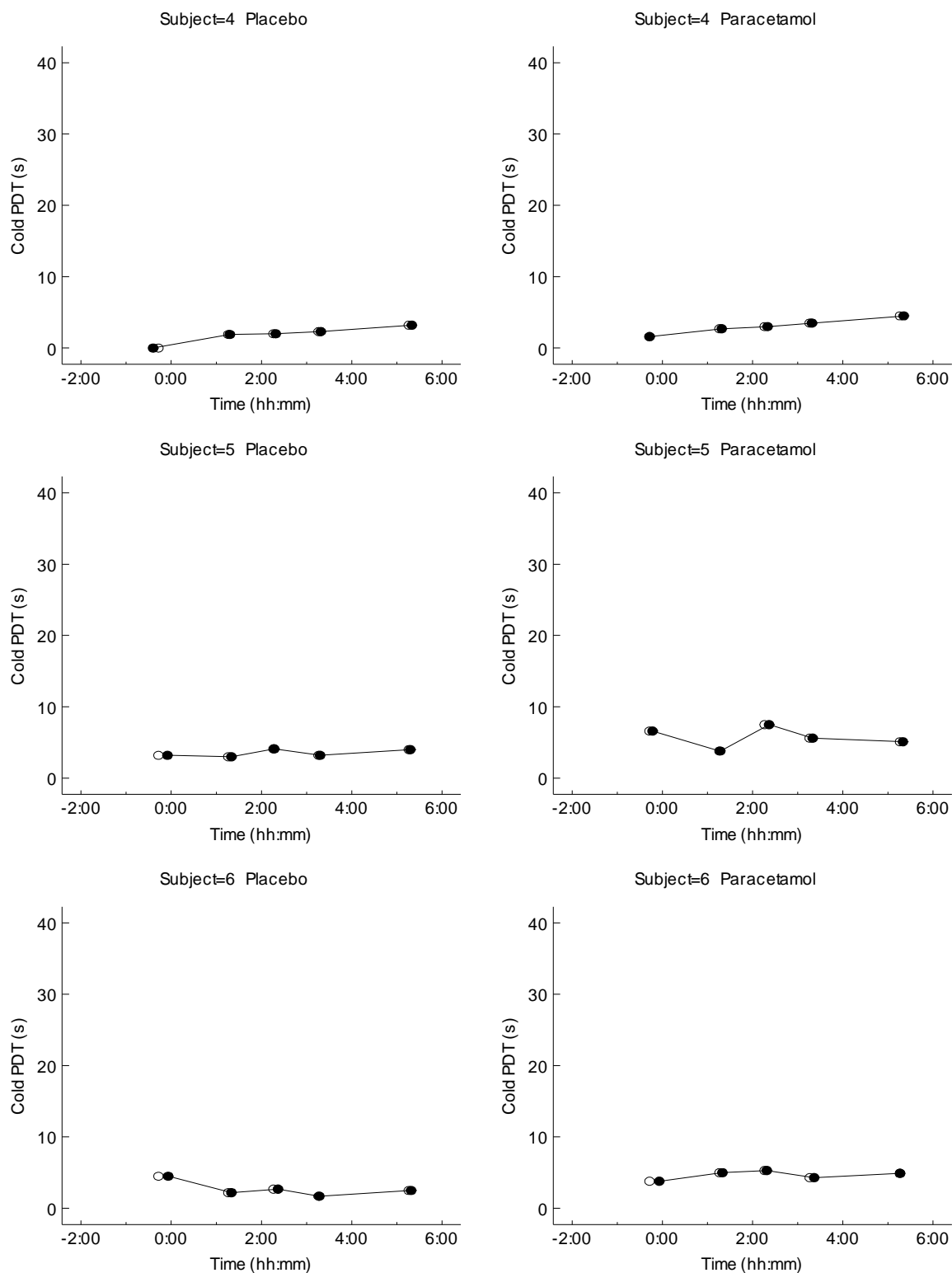
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Individual Plots 2 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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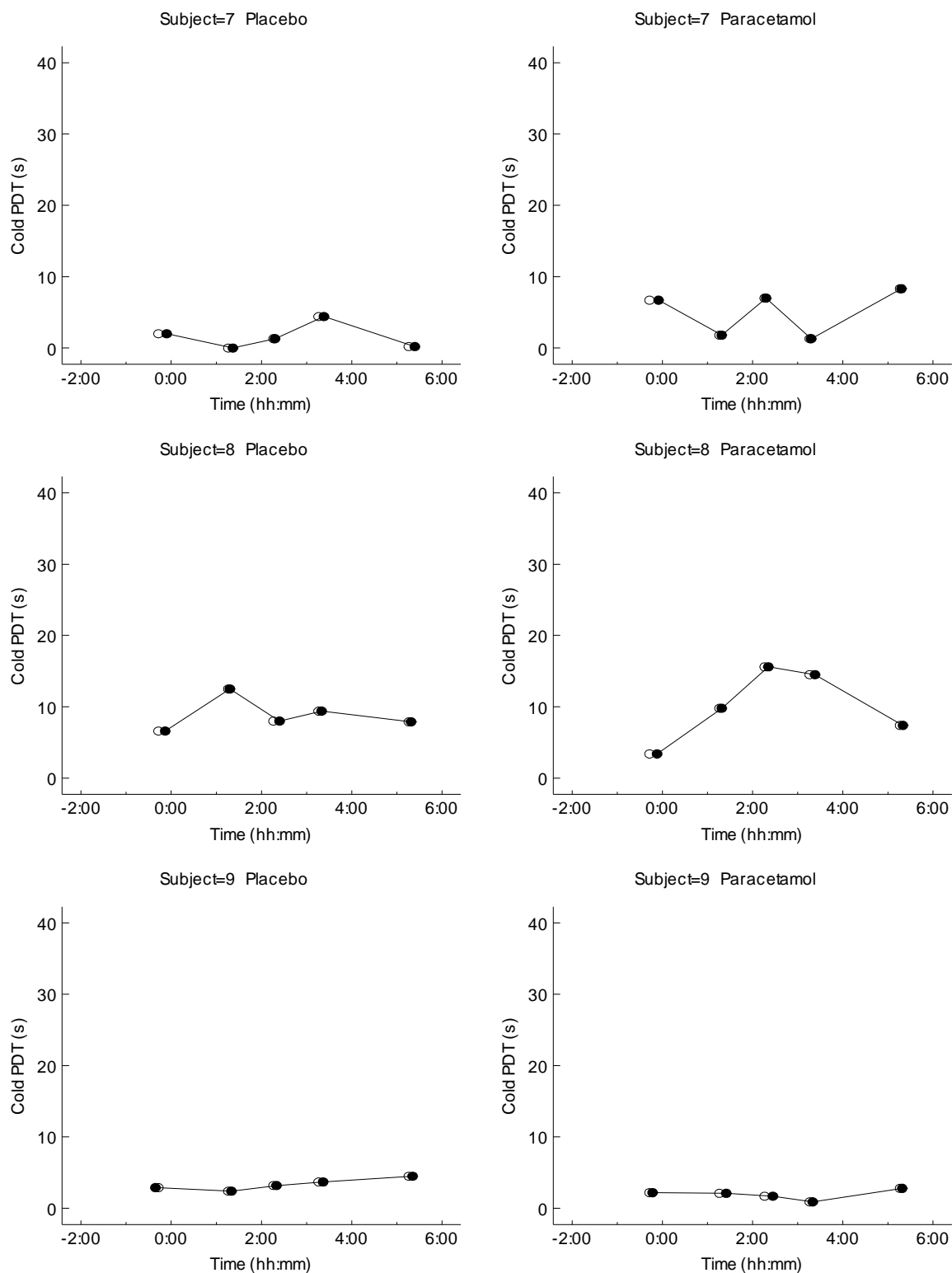
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Individual Plots 2 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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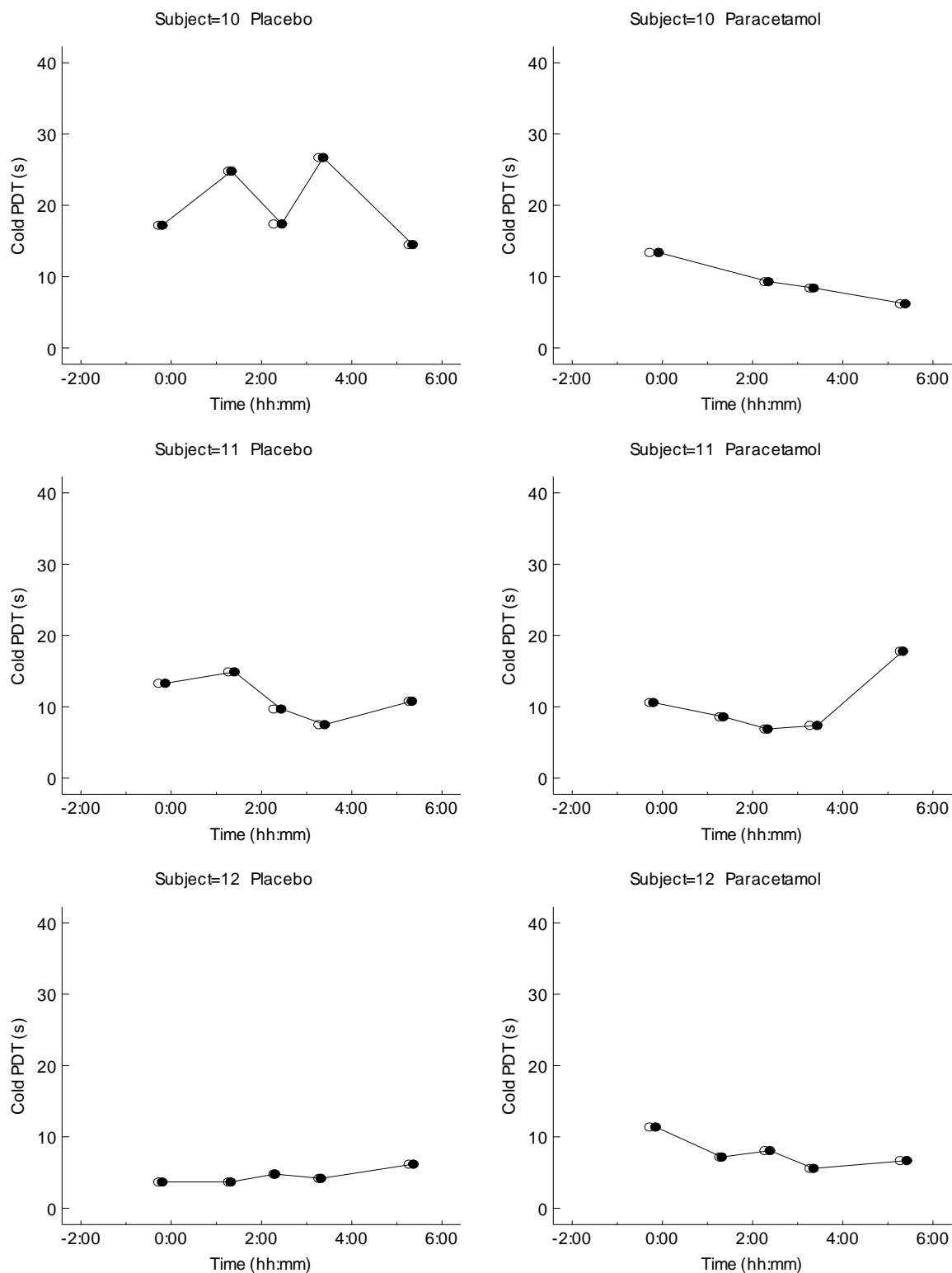
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Individual Plots 2 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 3 Cold PTT (s)

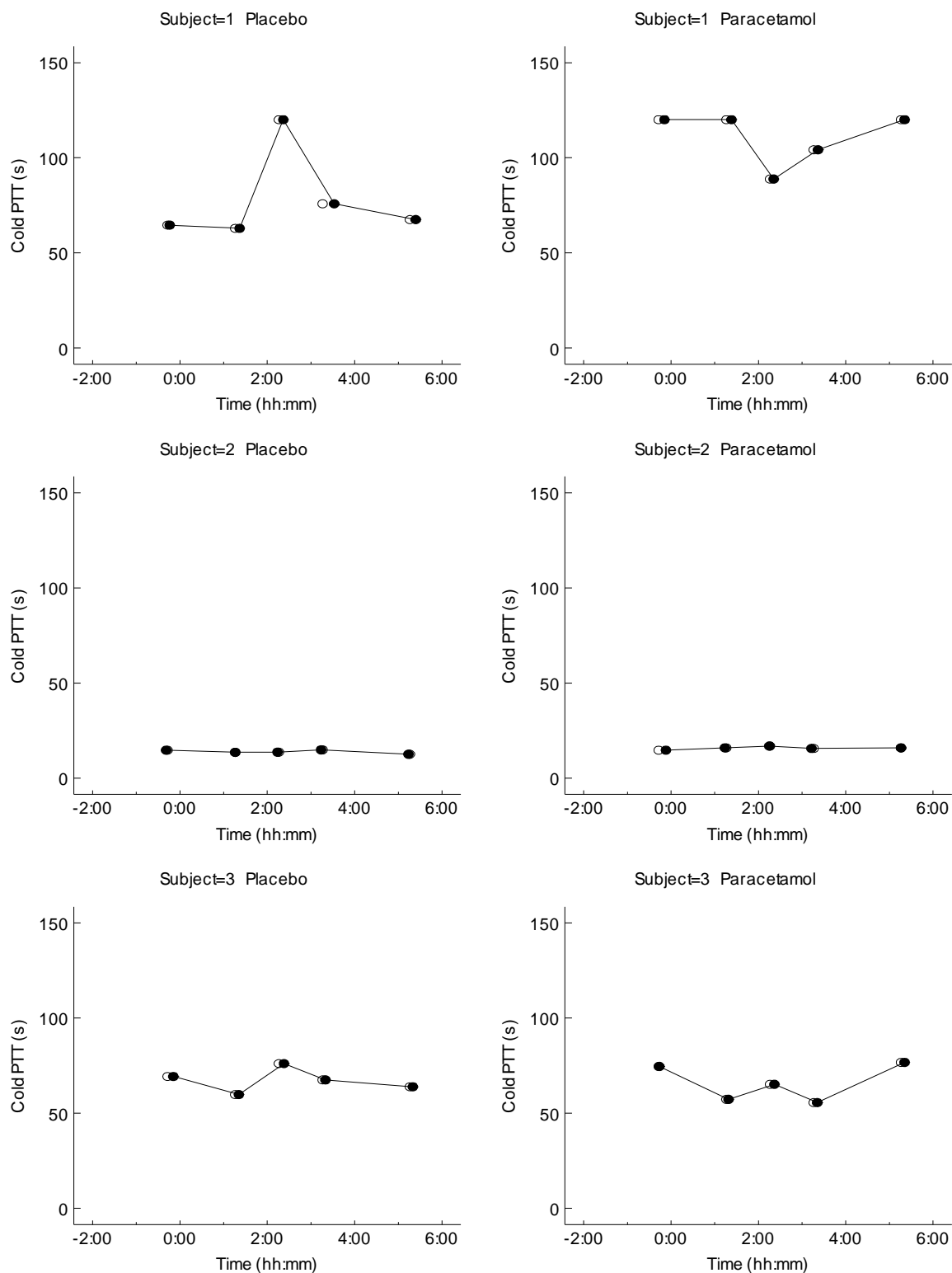
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Individual Plots 3 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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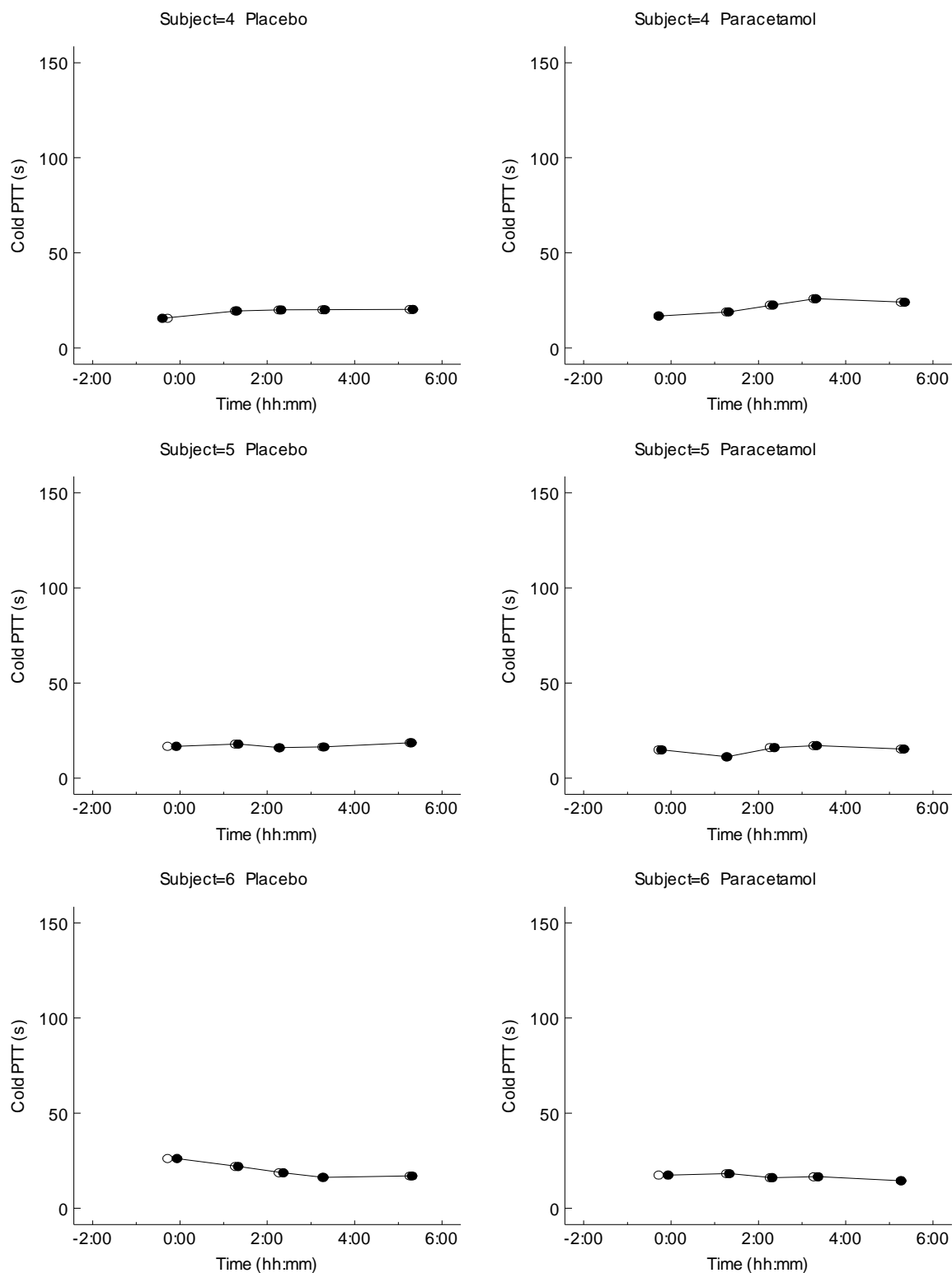
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Individual Plots 3 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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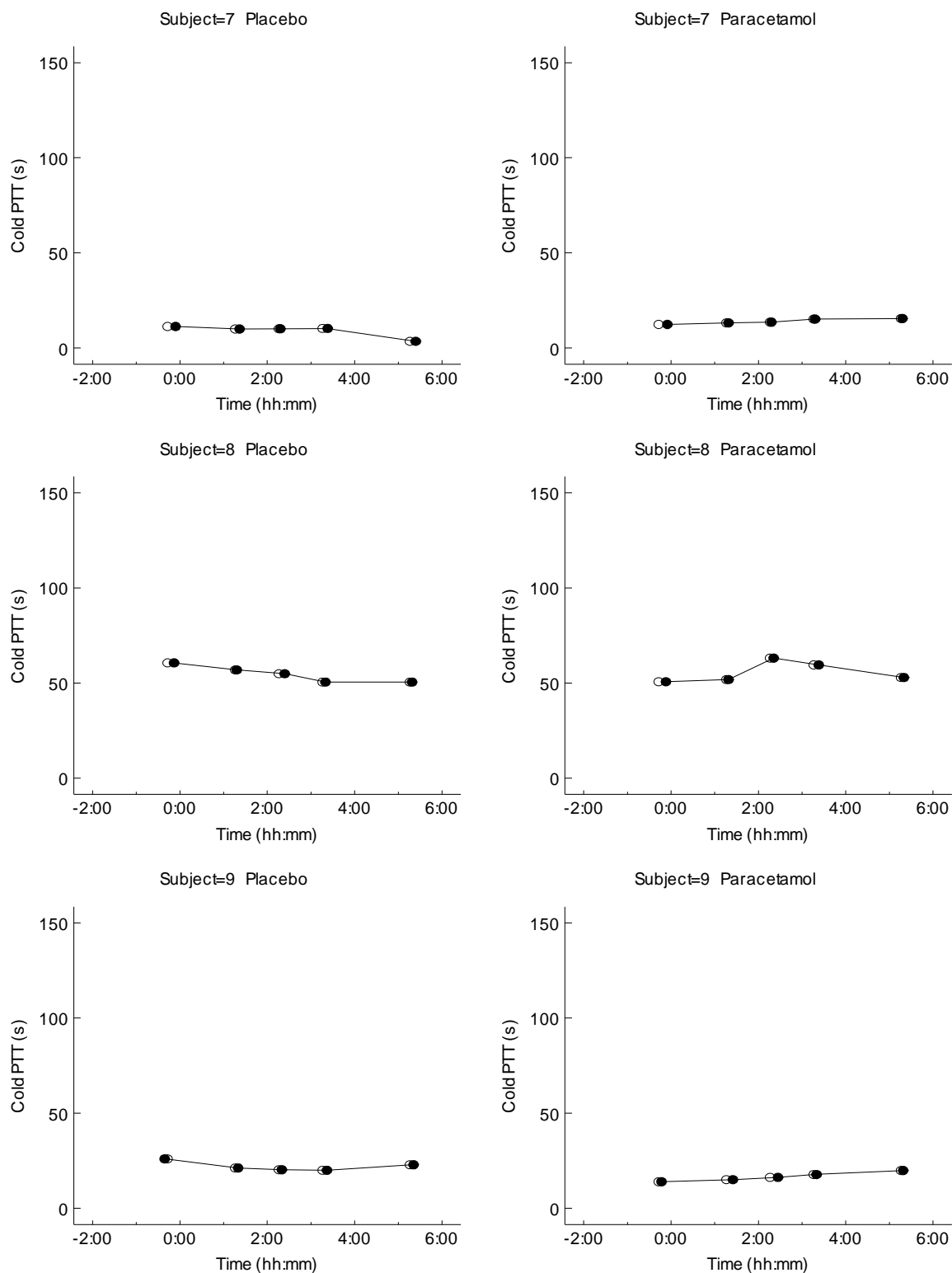
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Individual Plots 3 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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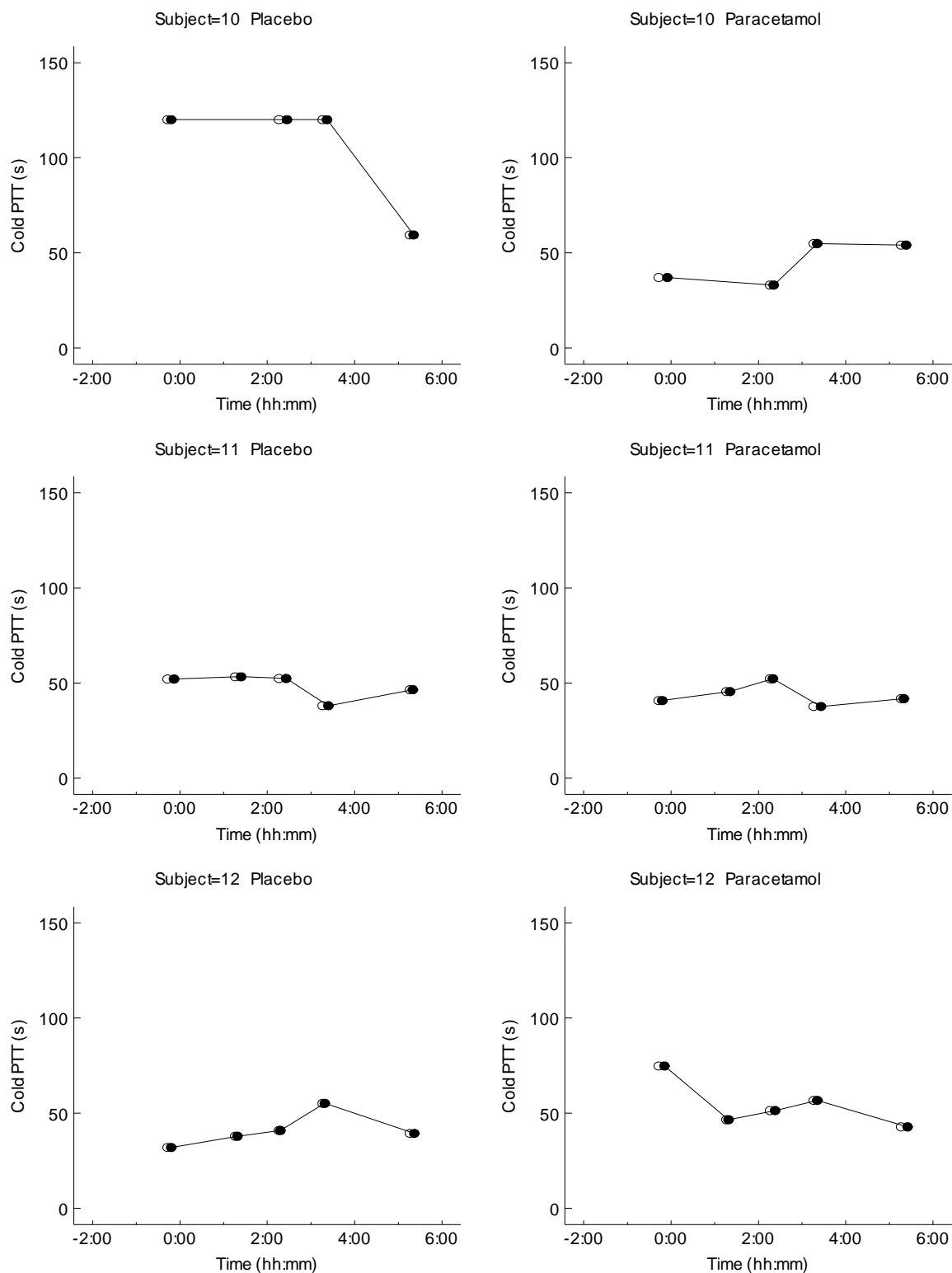
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Individual Plots 3 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 4 Electrical Stair AUC (mA*%)

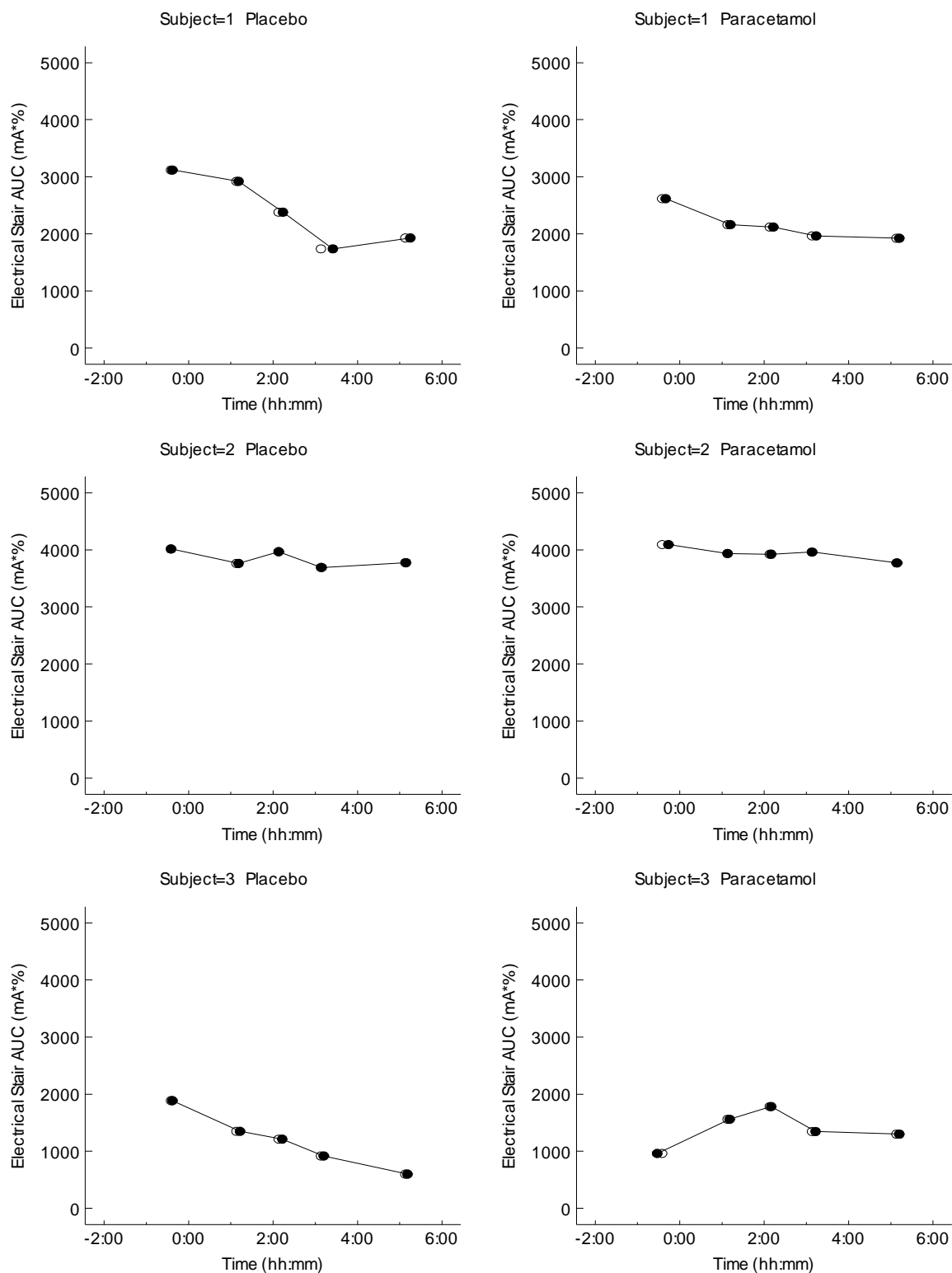
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Individual Plots 4 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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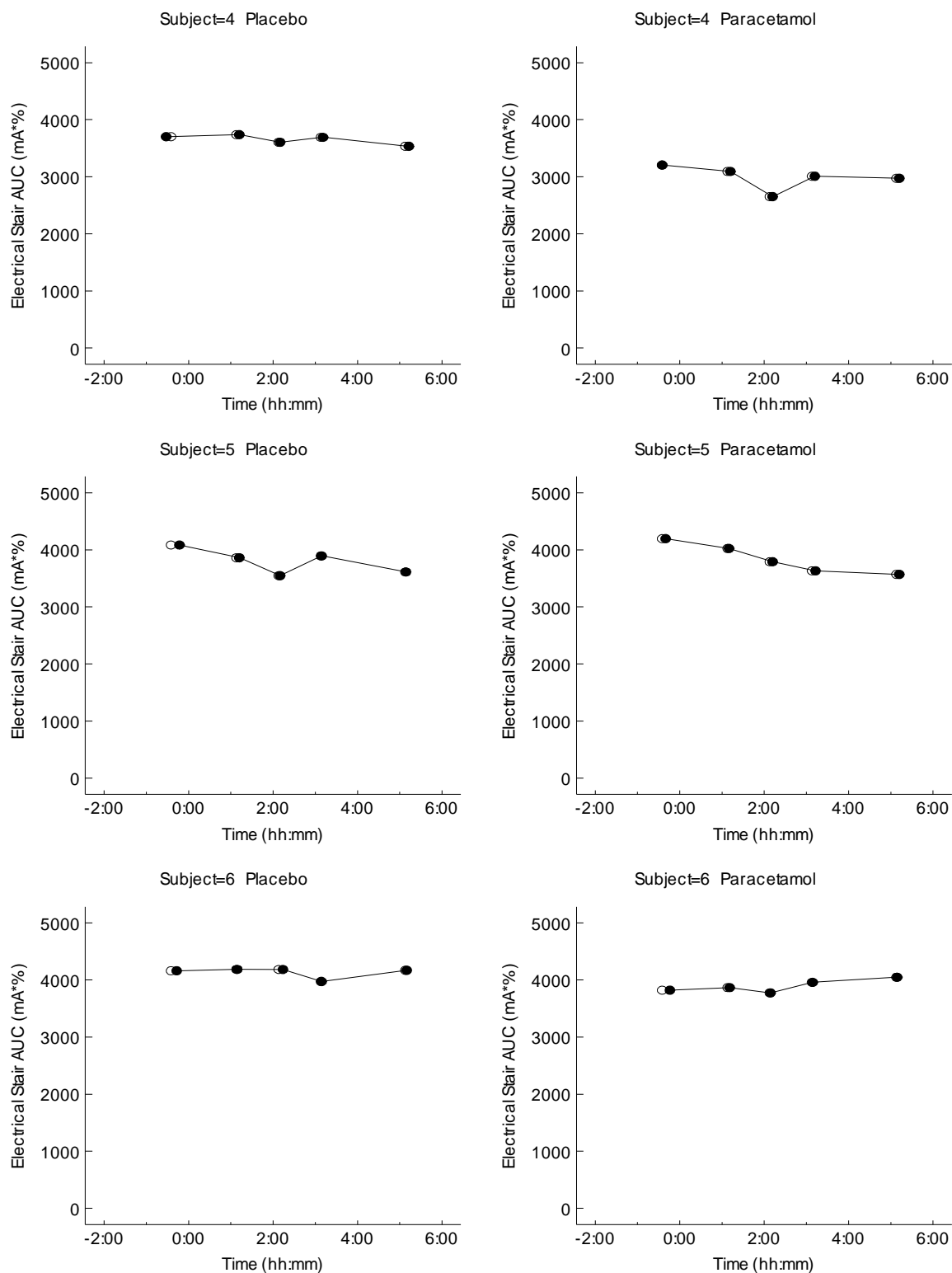
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Individual Plots 4 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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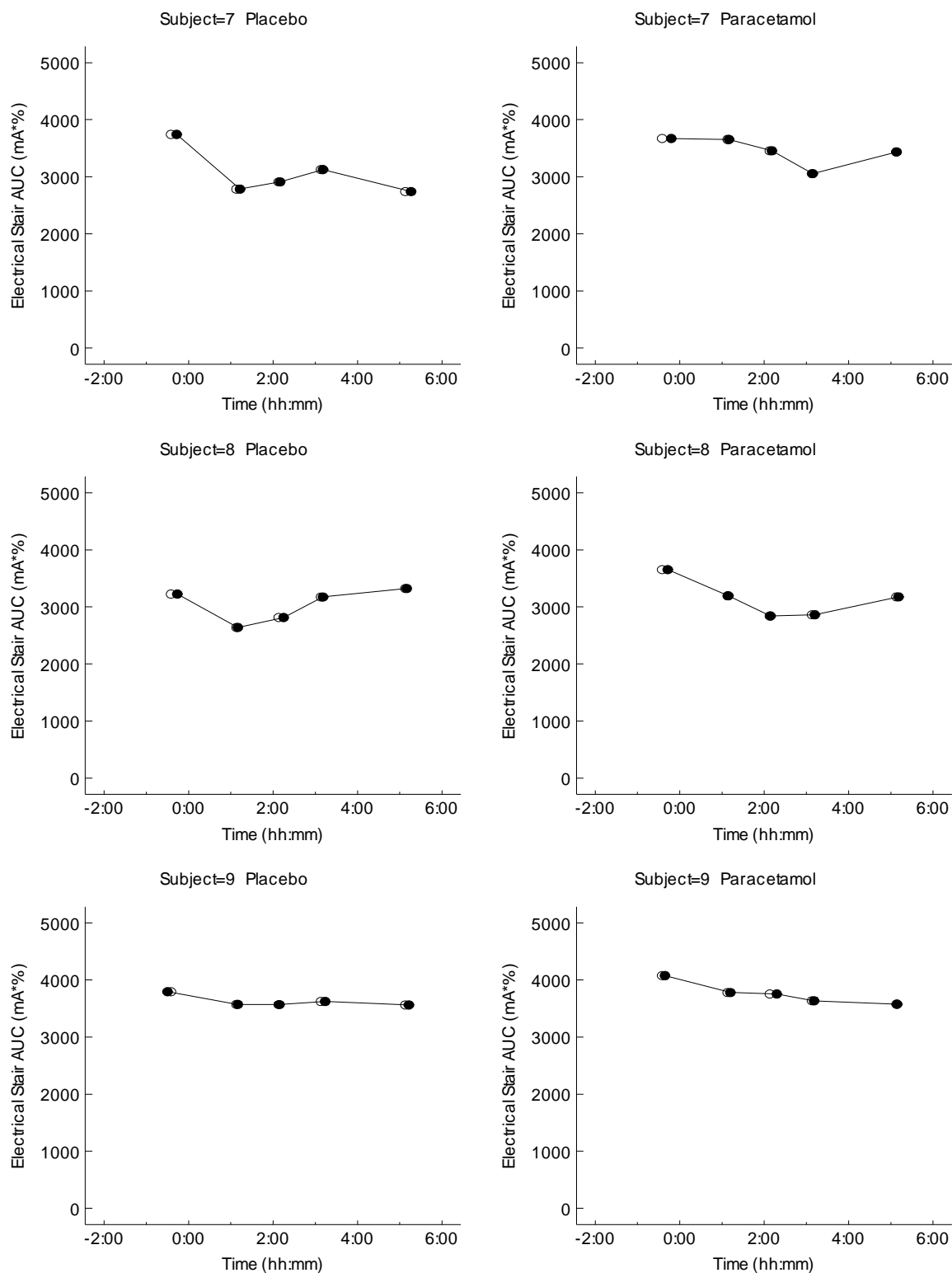
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Individual Plots 4 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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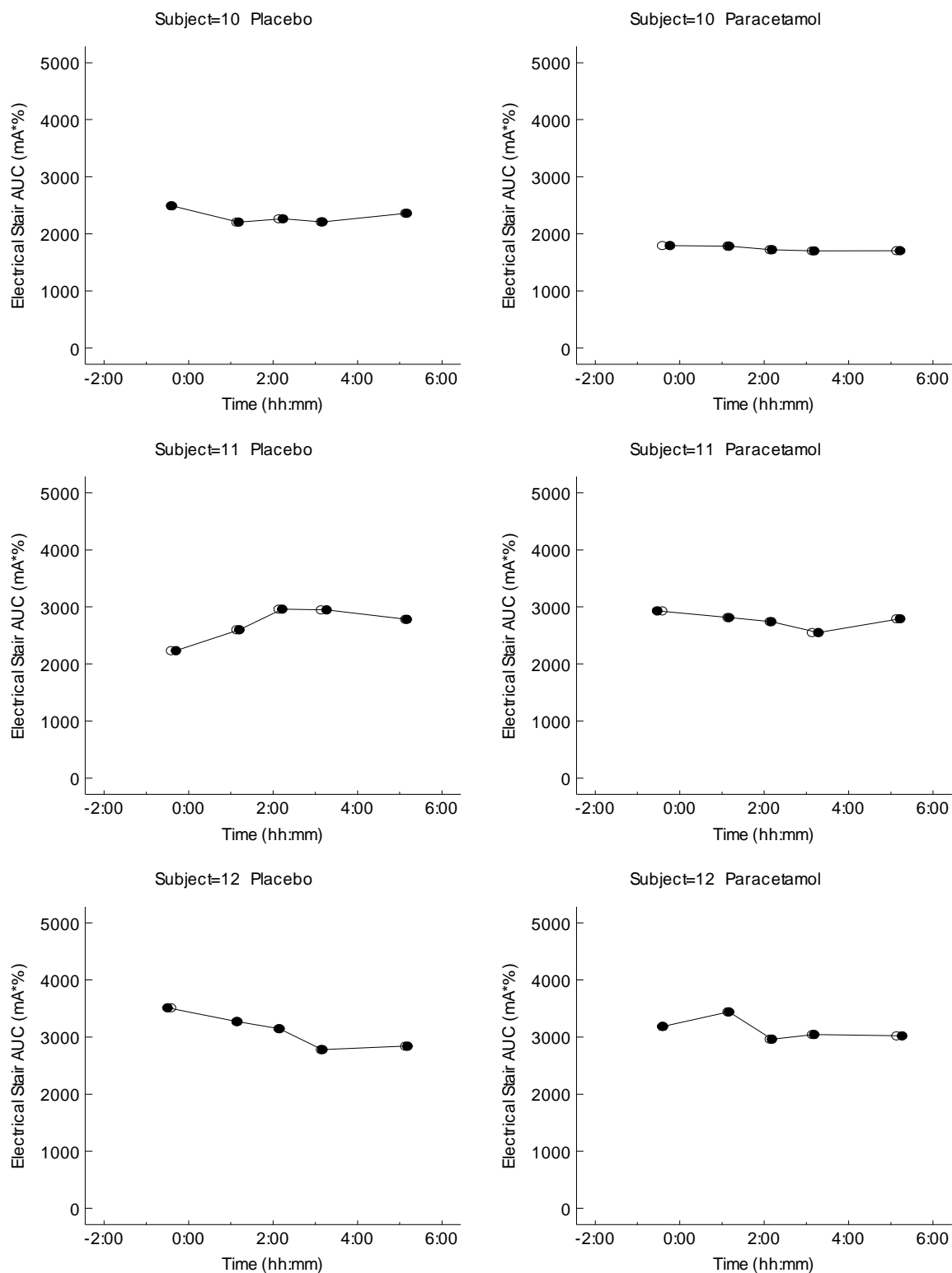
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Individual Plots 4 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 5 Electrical Stair PDT (mA)

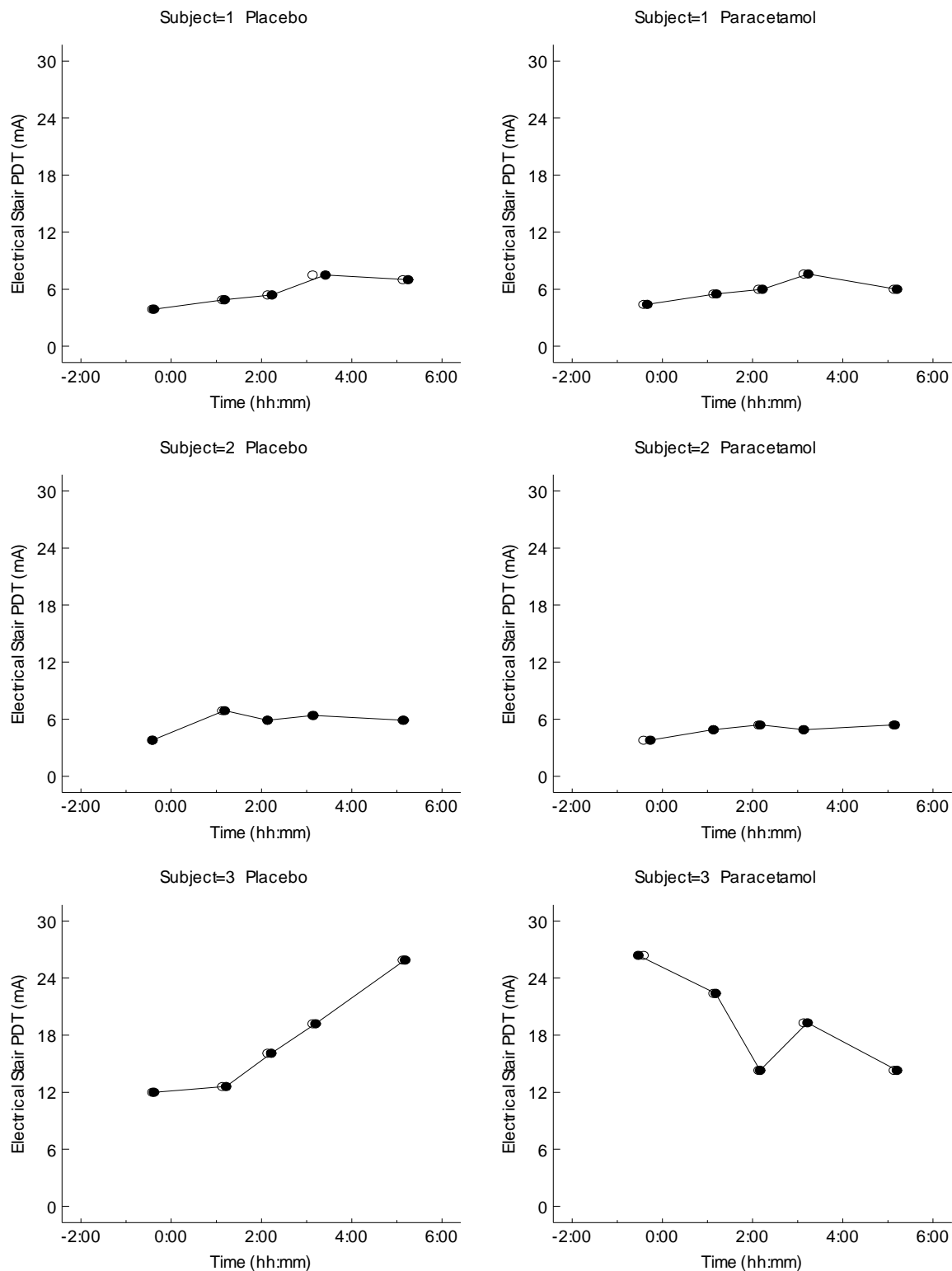
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Individual Plots 5 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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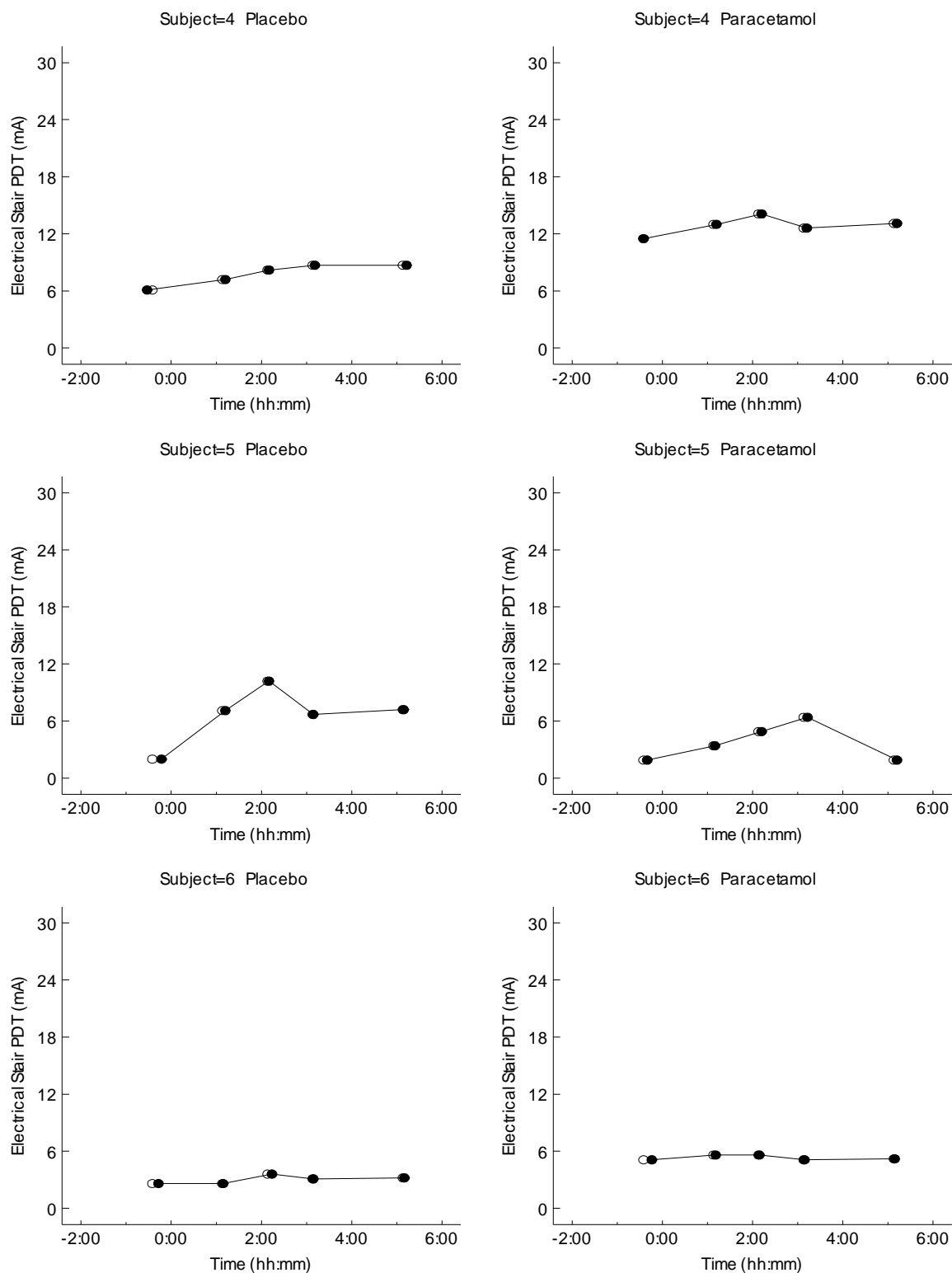
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Individual Plots 5 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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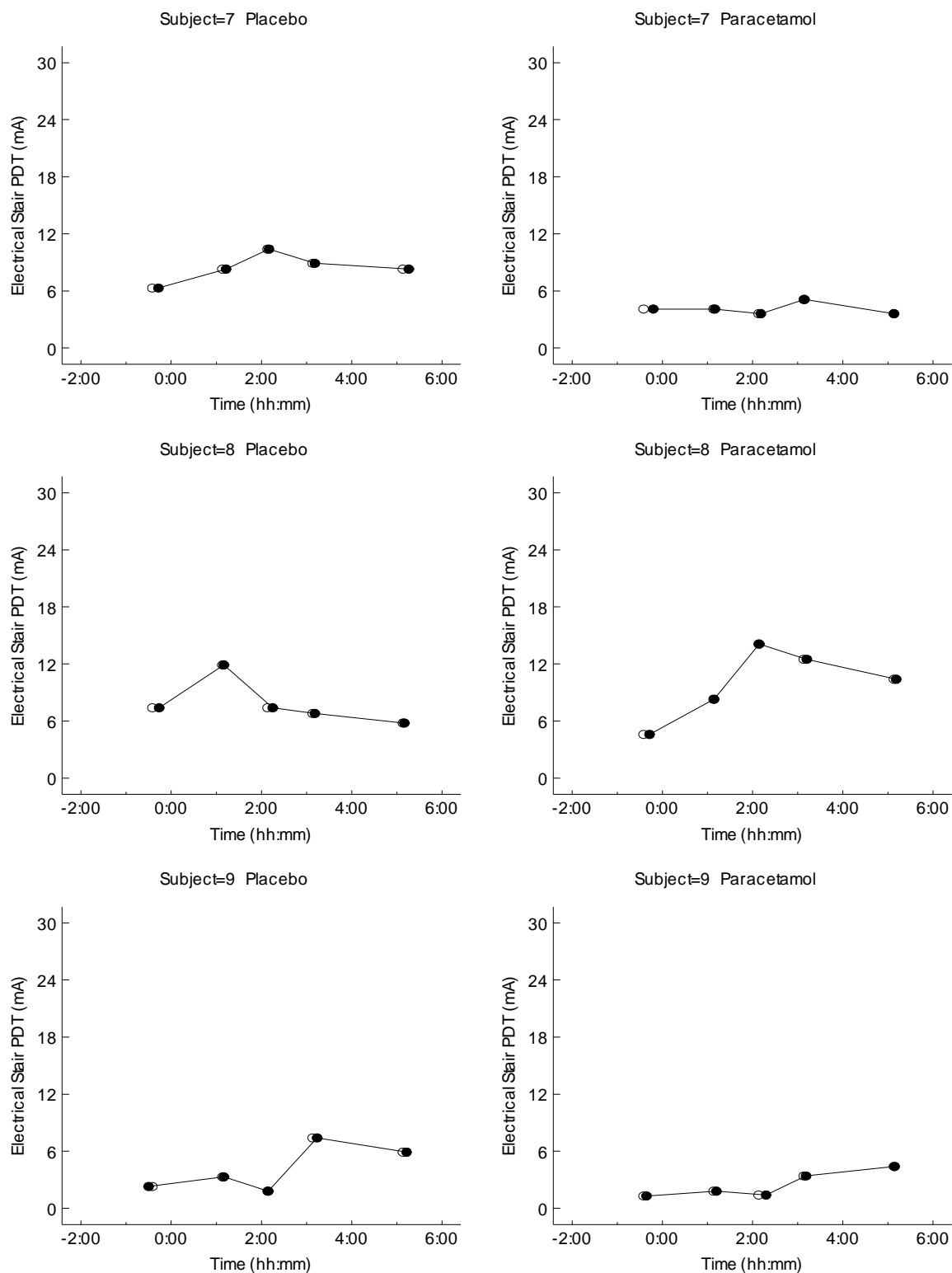
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Individual Plots 5 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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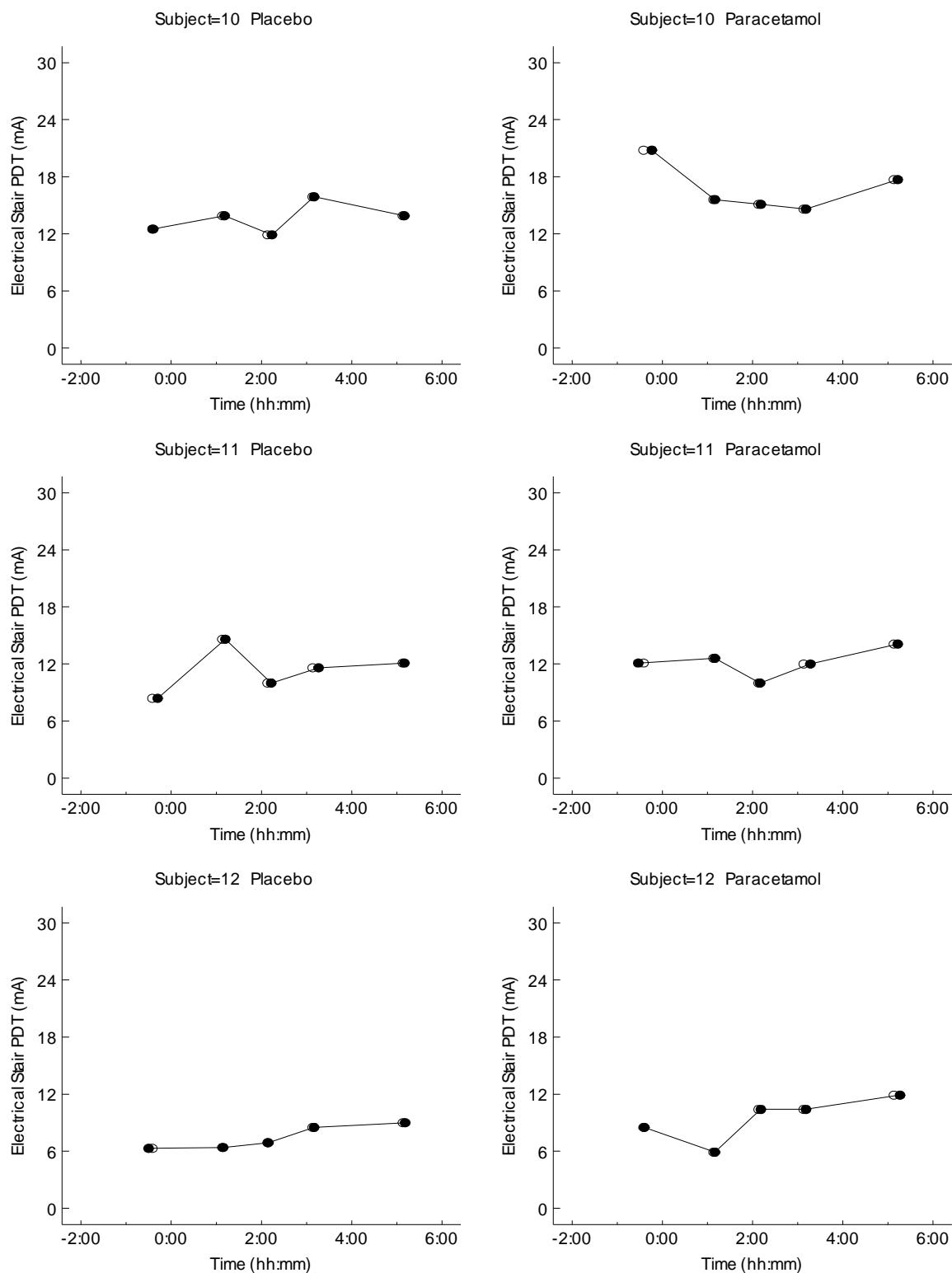
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Individual Plots 5 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 6 Electrical Stair PTT (mA)

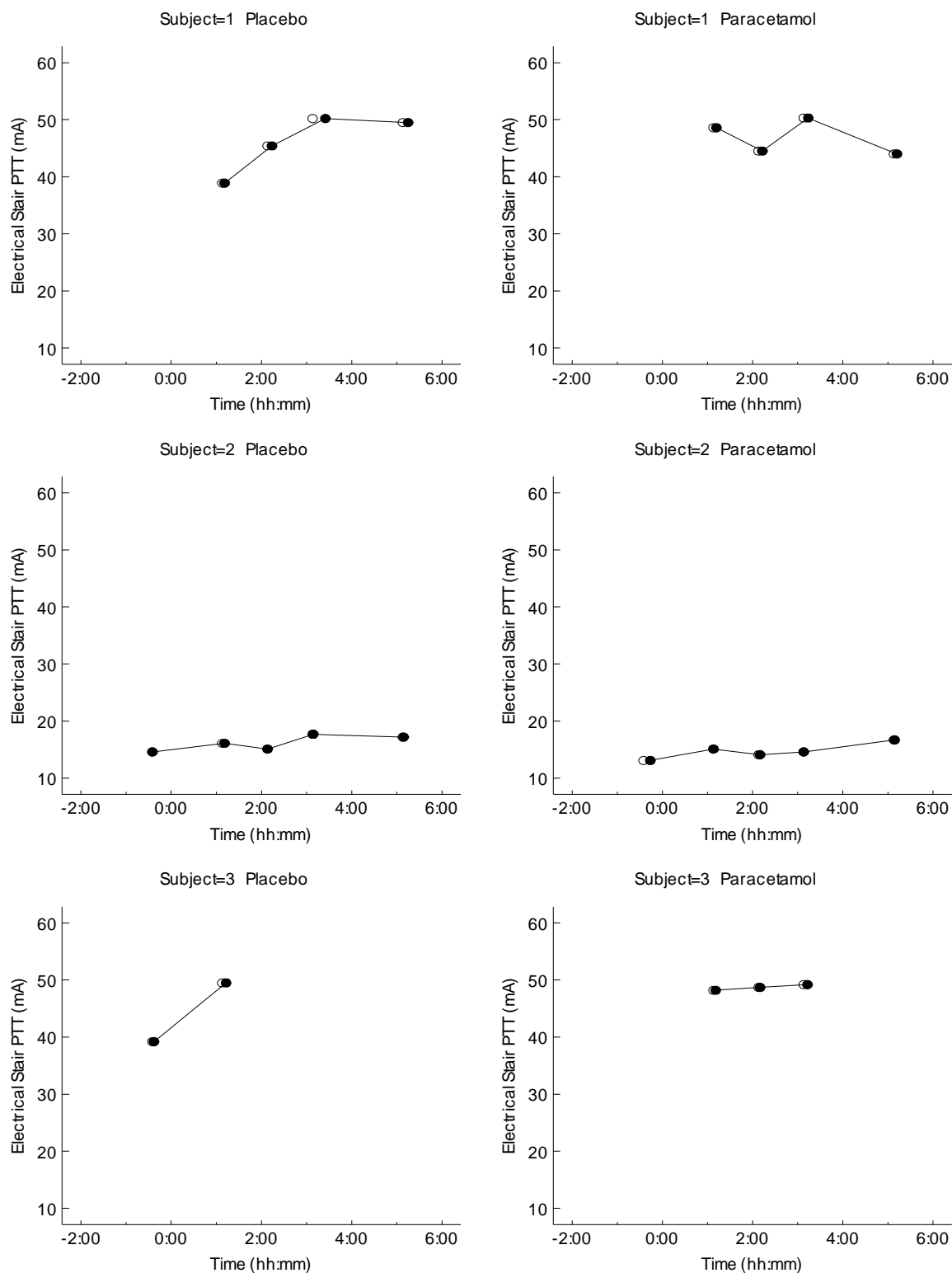
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Individual Plots 6 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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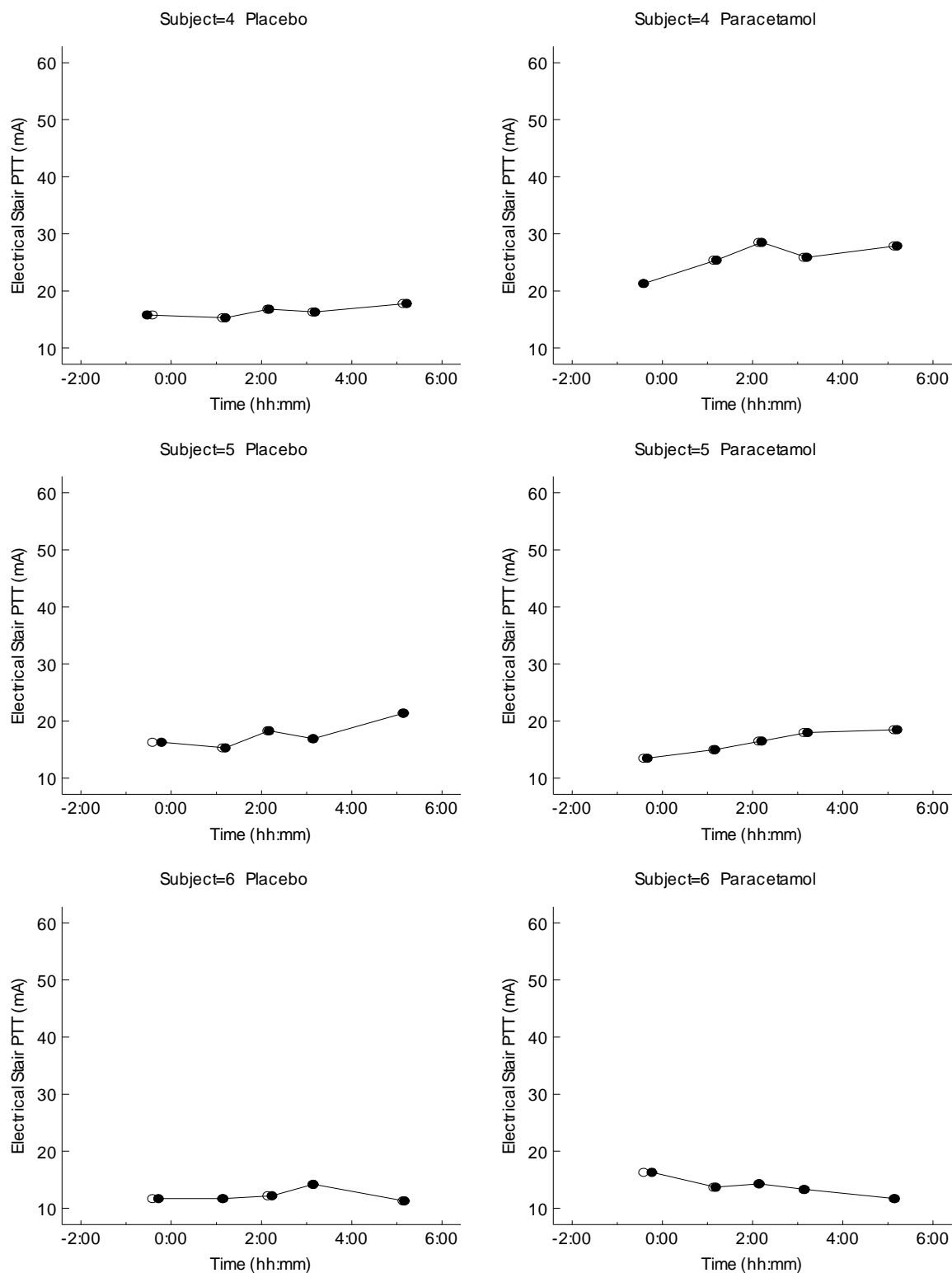
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Individual Plots 6 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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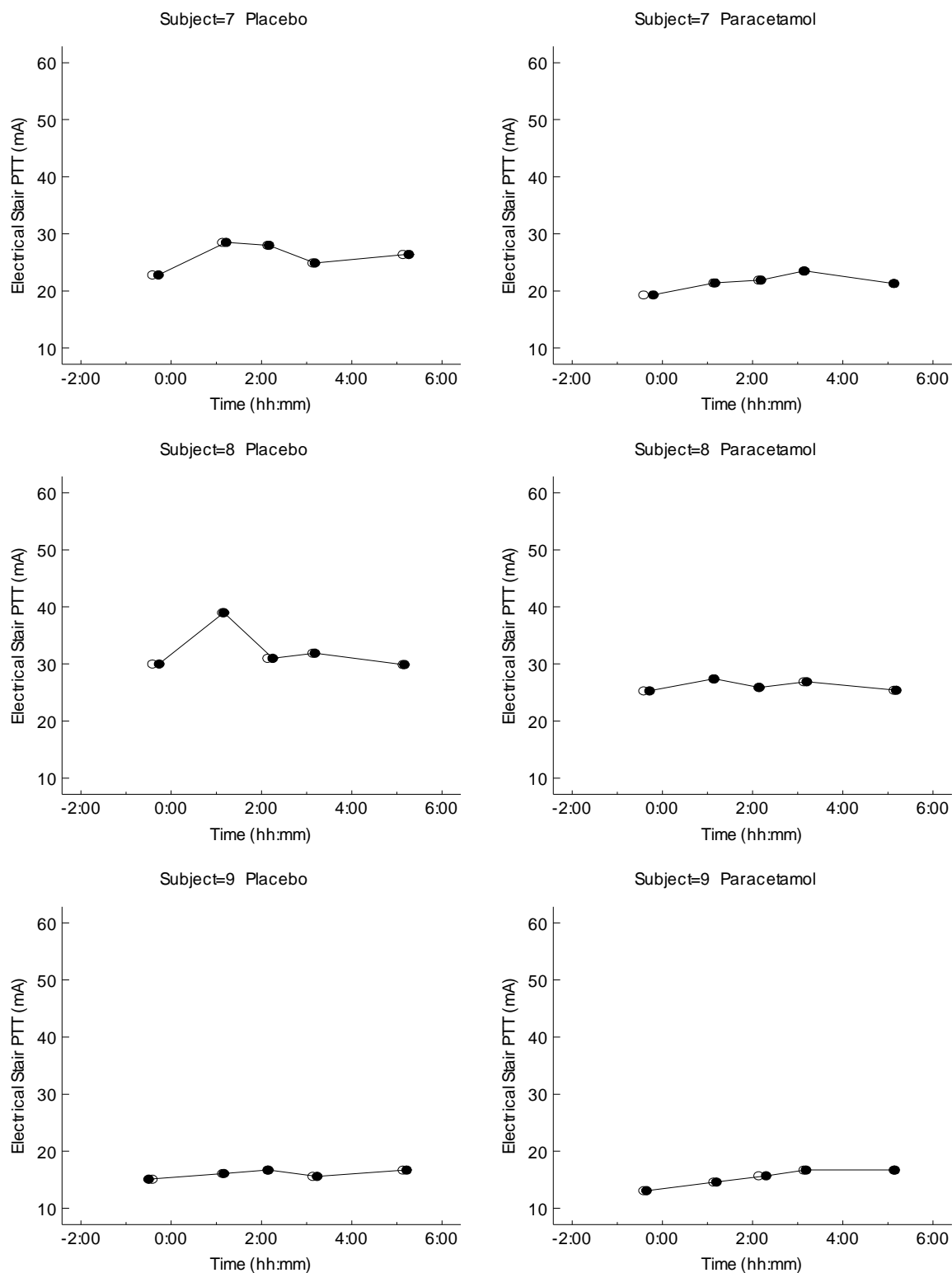
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Individual Plots 6 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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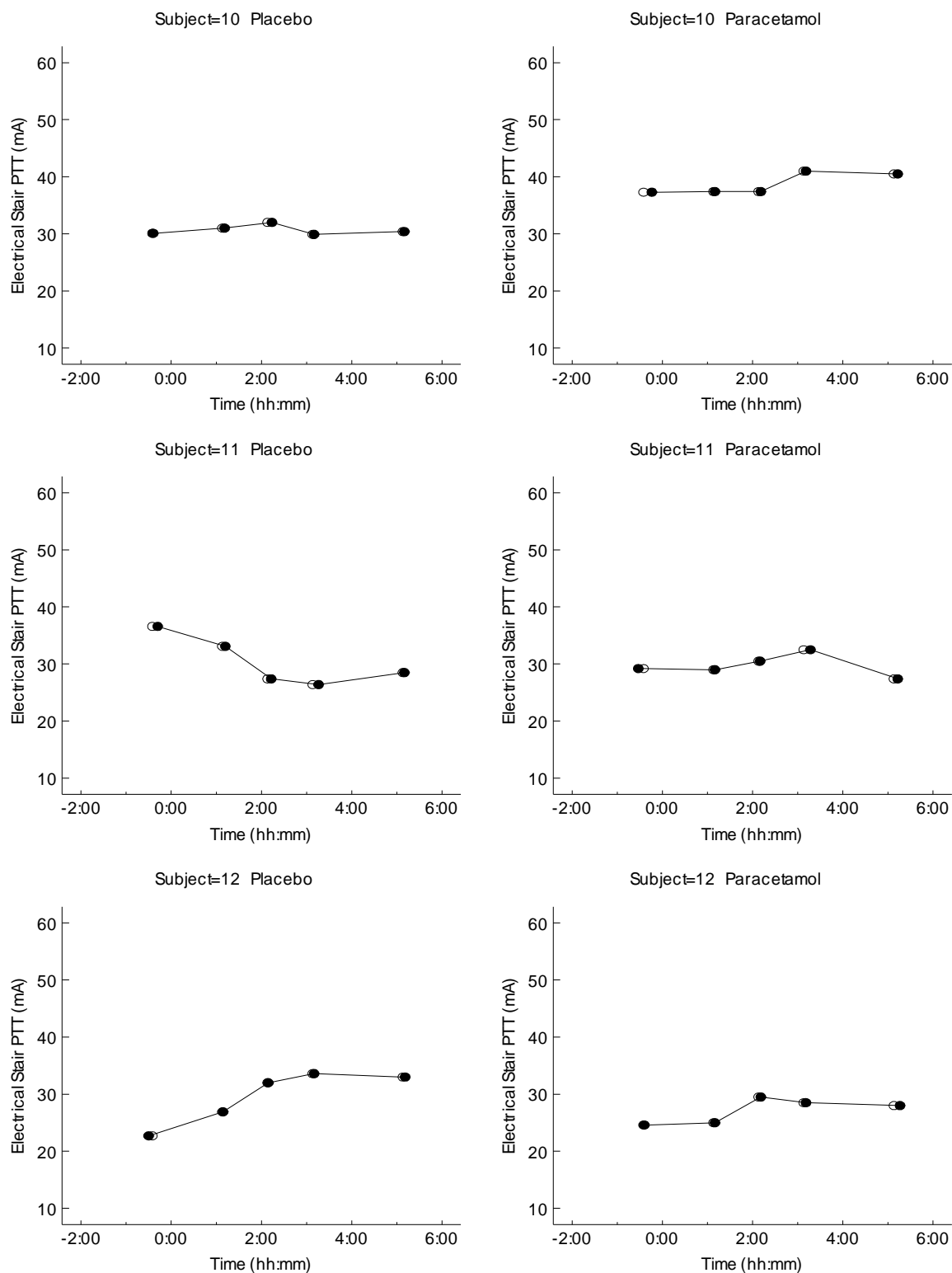
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Individual Plots 6 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 7 Delta Electrical Stair AUC (mA*%)

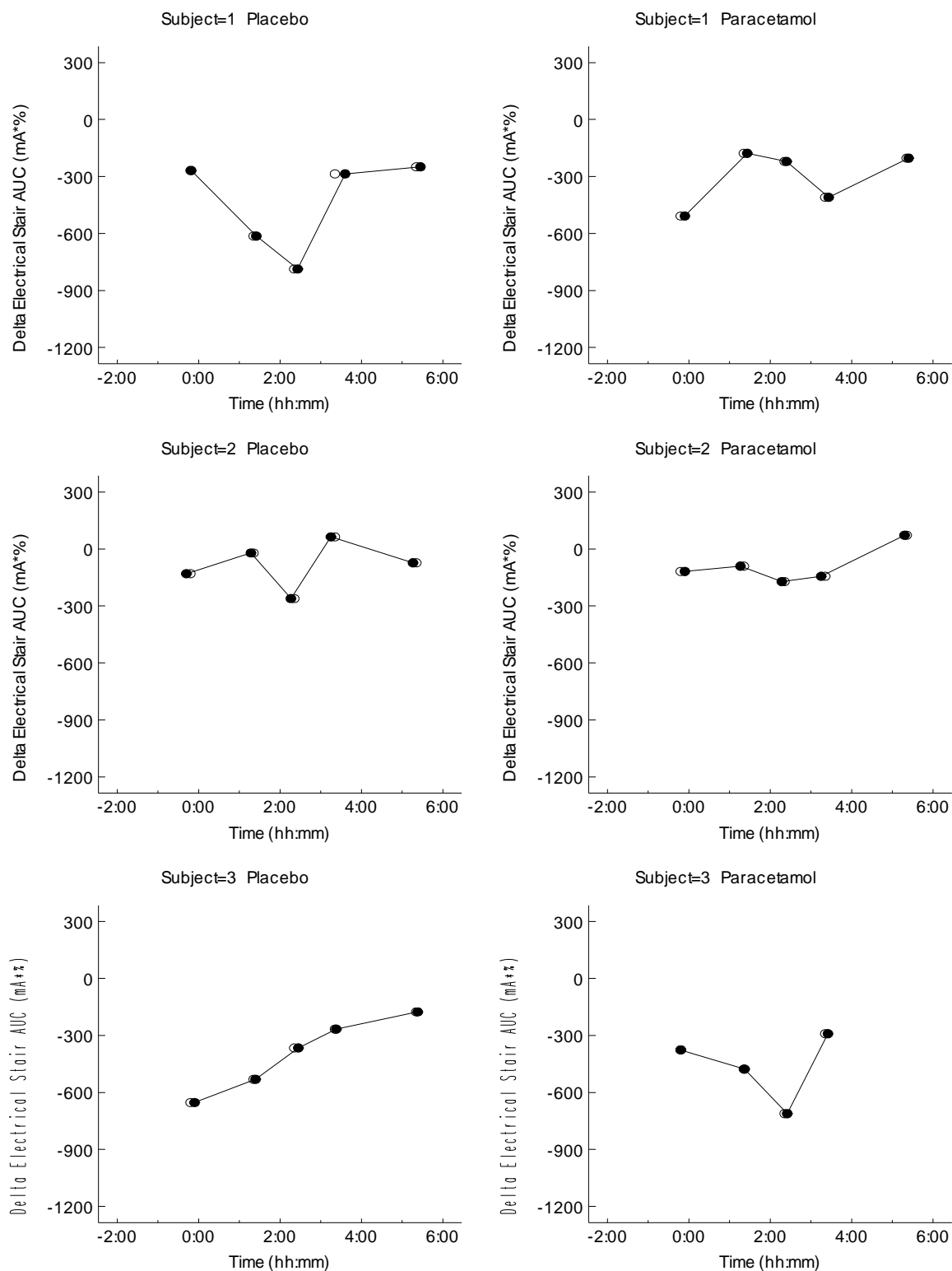
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Individual Plots 7 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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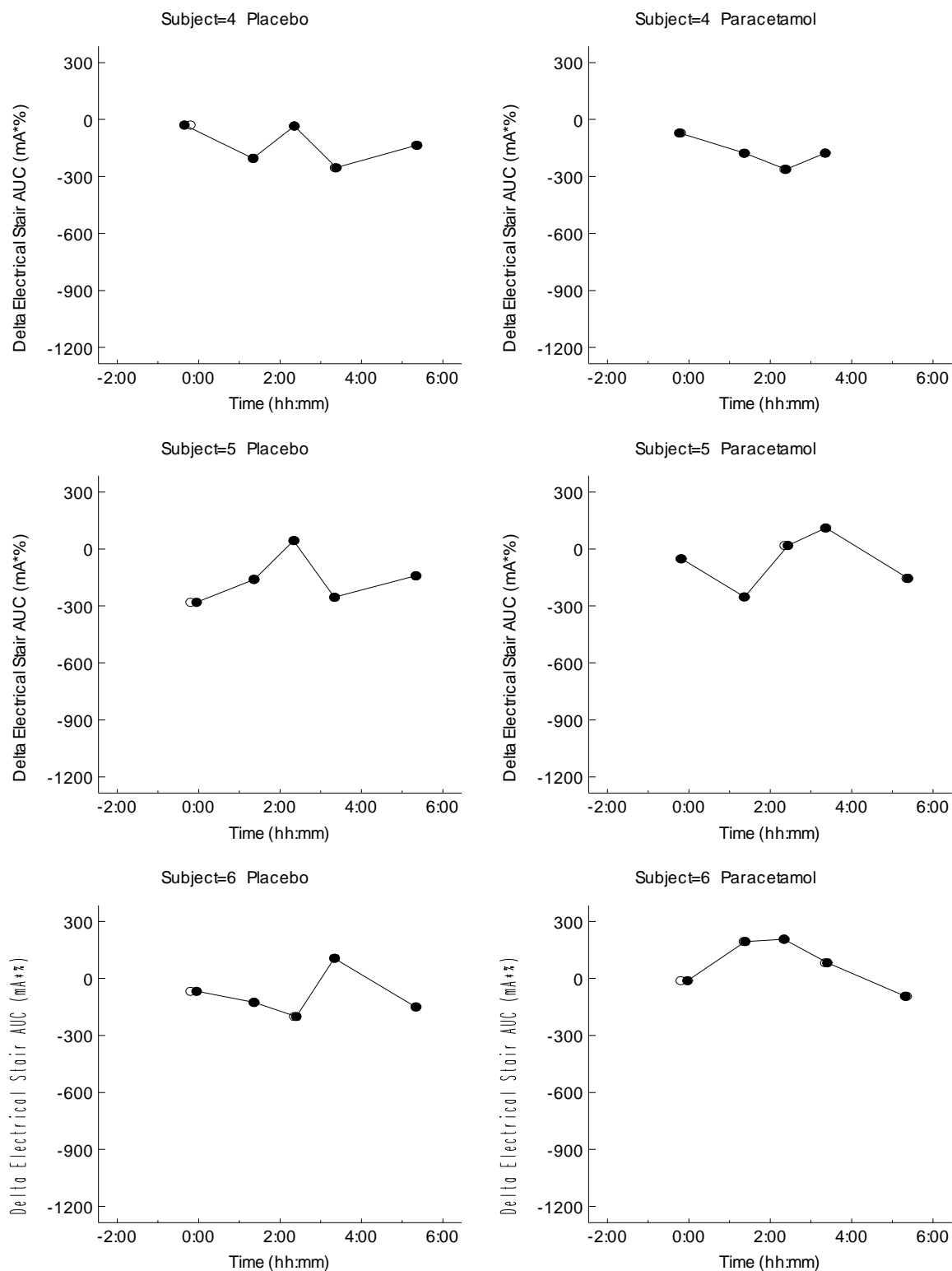
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Individual Plots 7 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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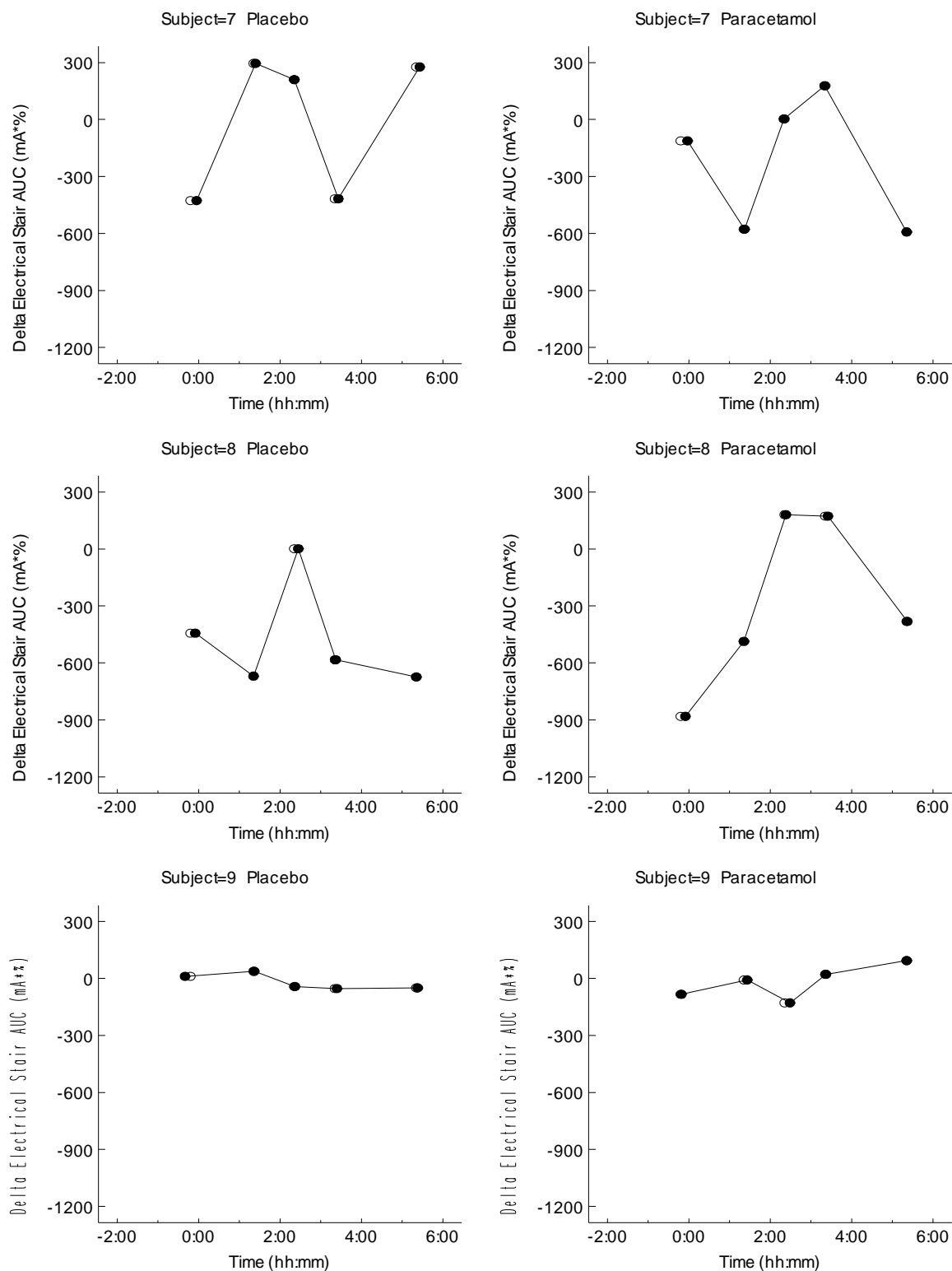
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Individual Plots 7 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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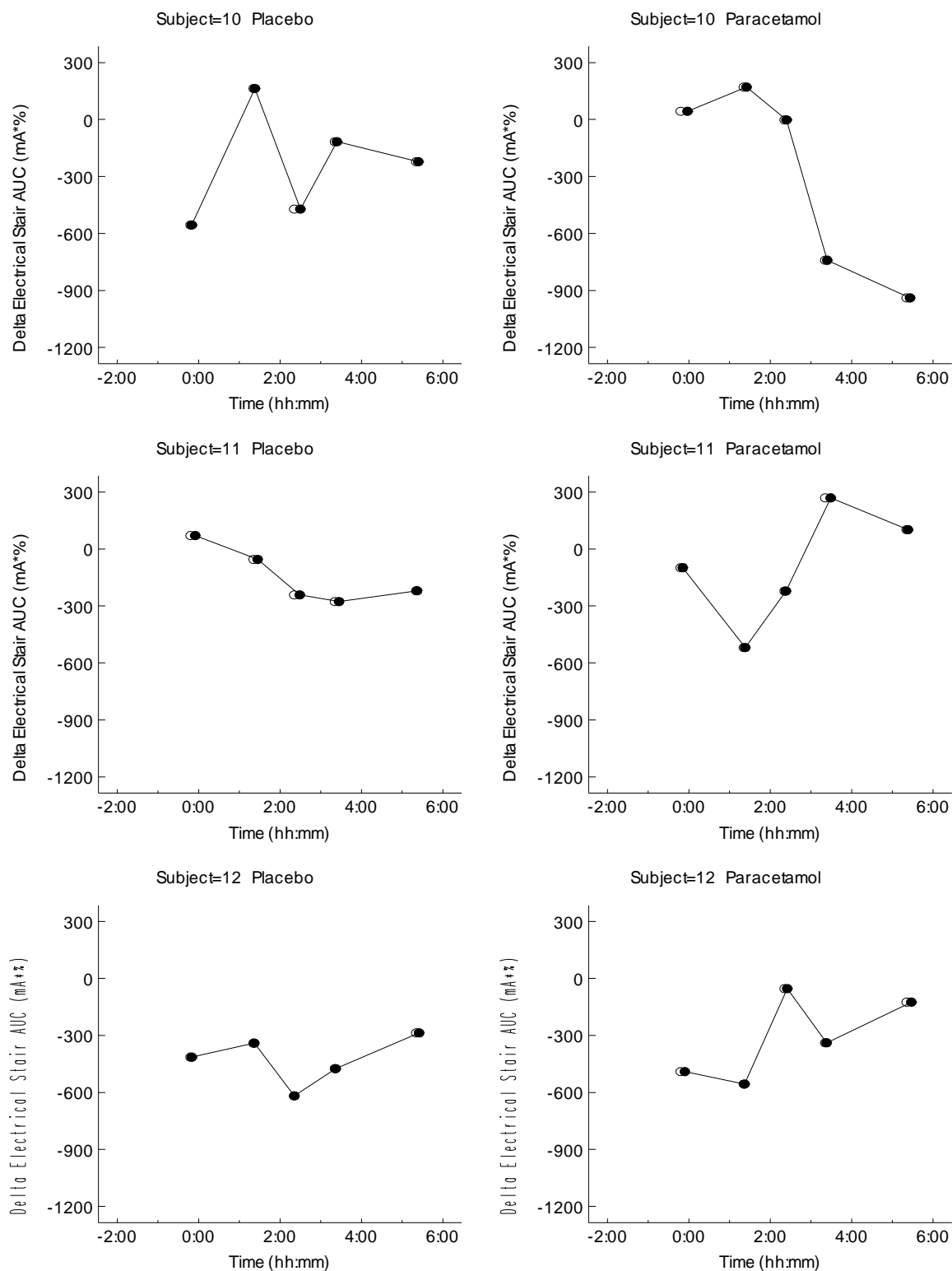
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Individual Plots 7 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 8 Delta Electrical Stair PDT (mA)

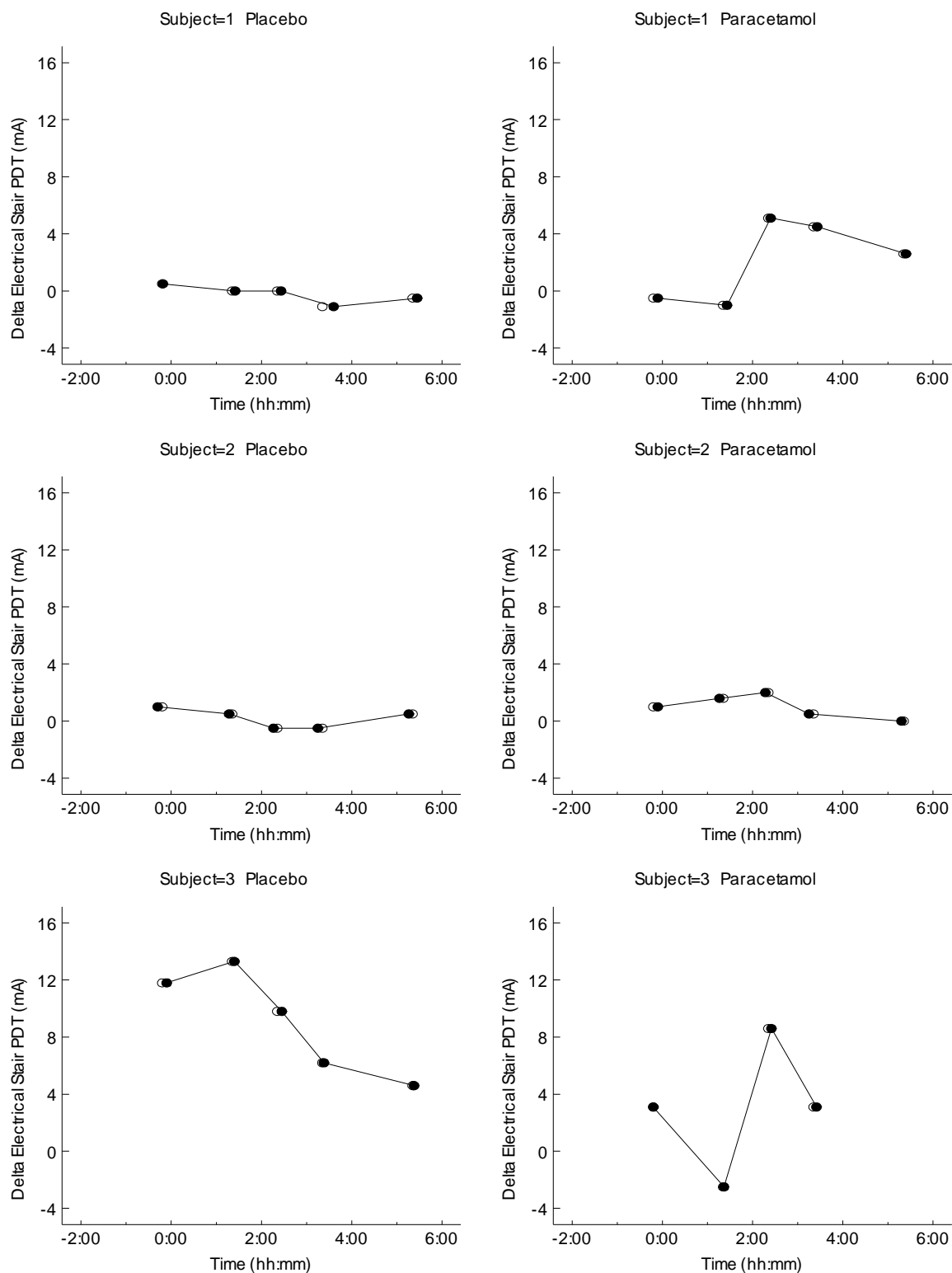
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Individual Plots 8 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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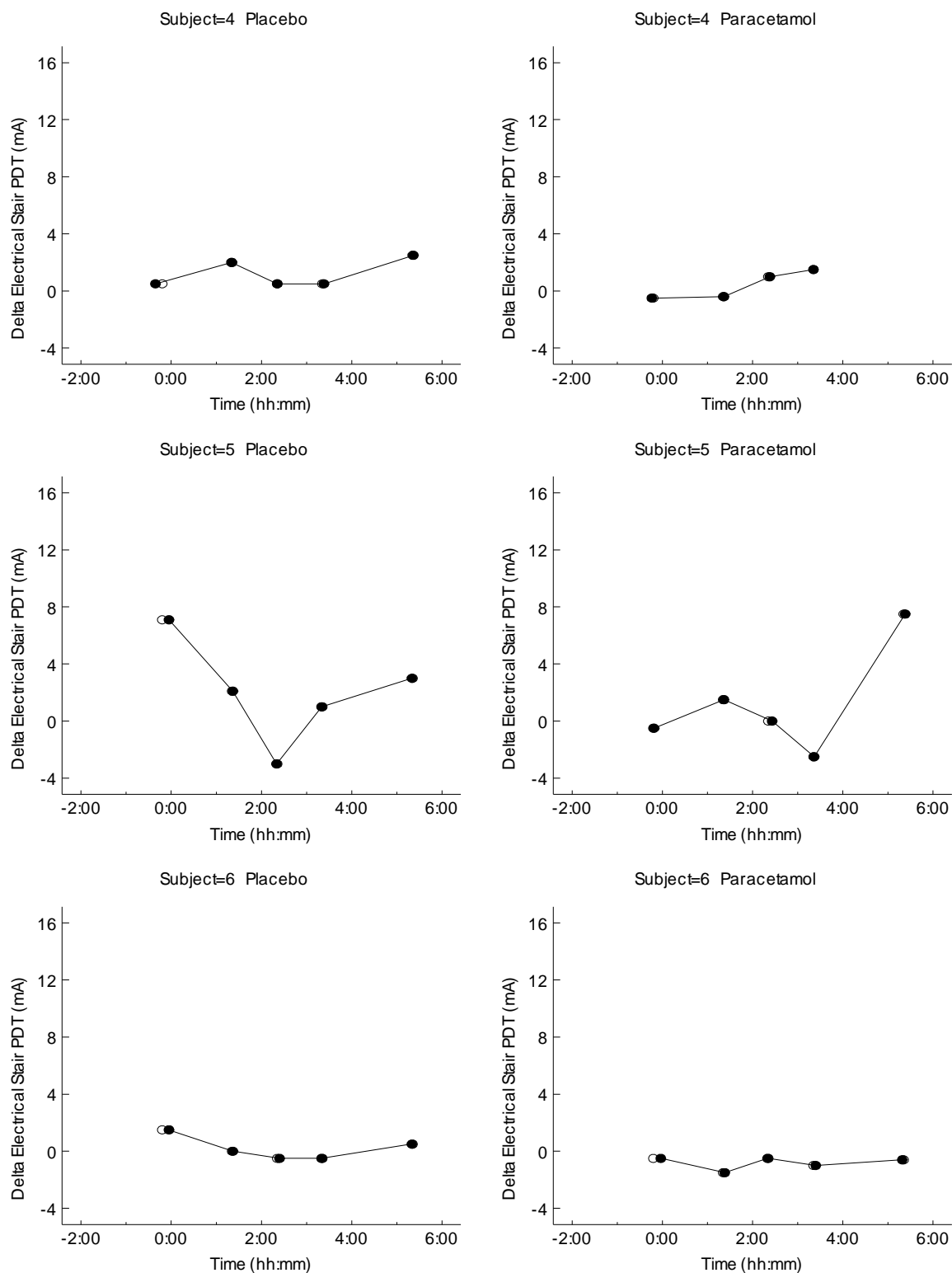
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Individual Plots 8 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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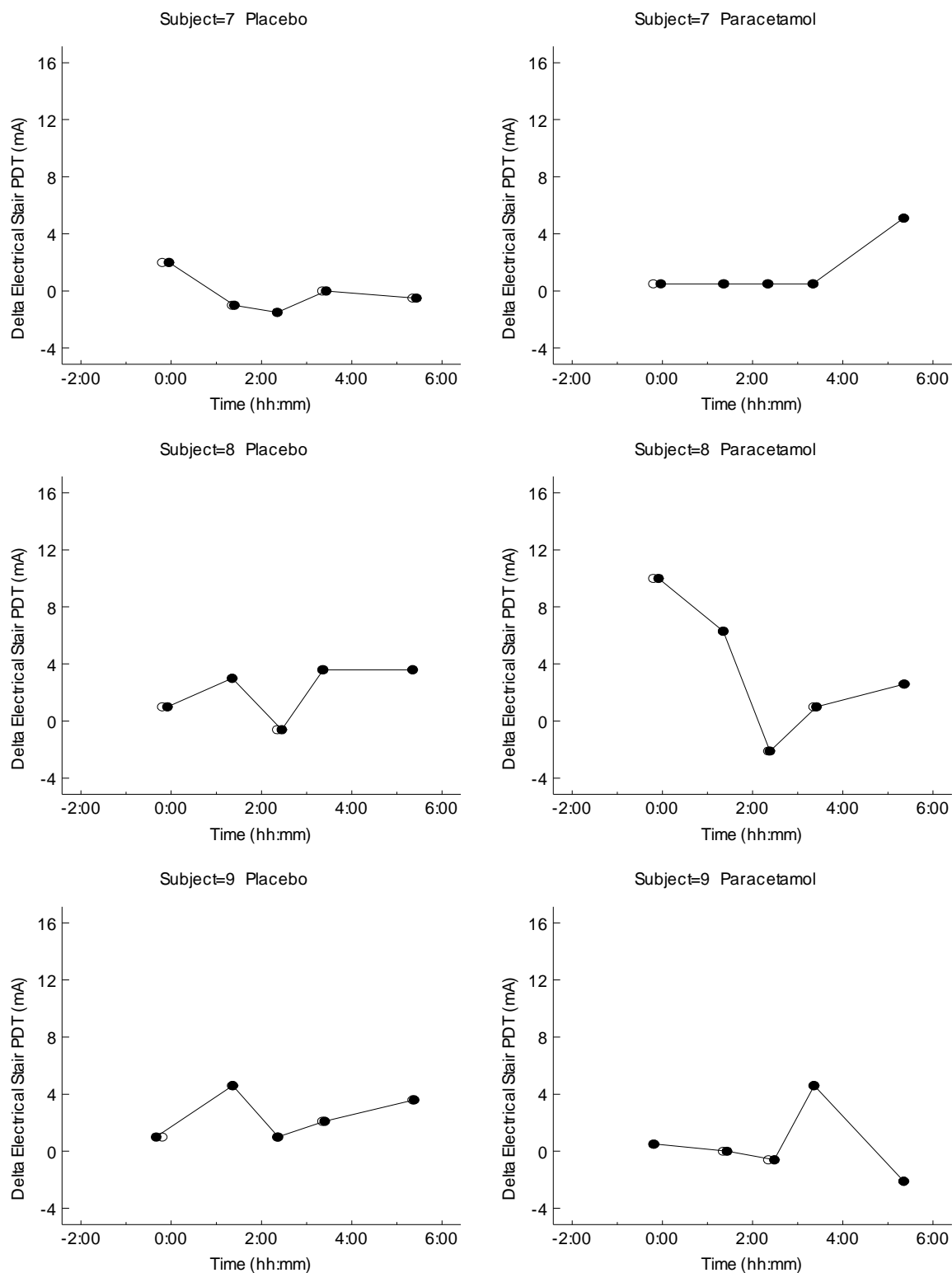
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Individual Plots 8 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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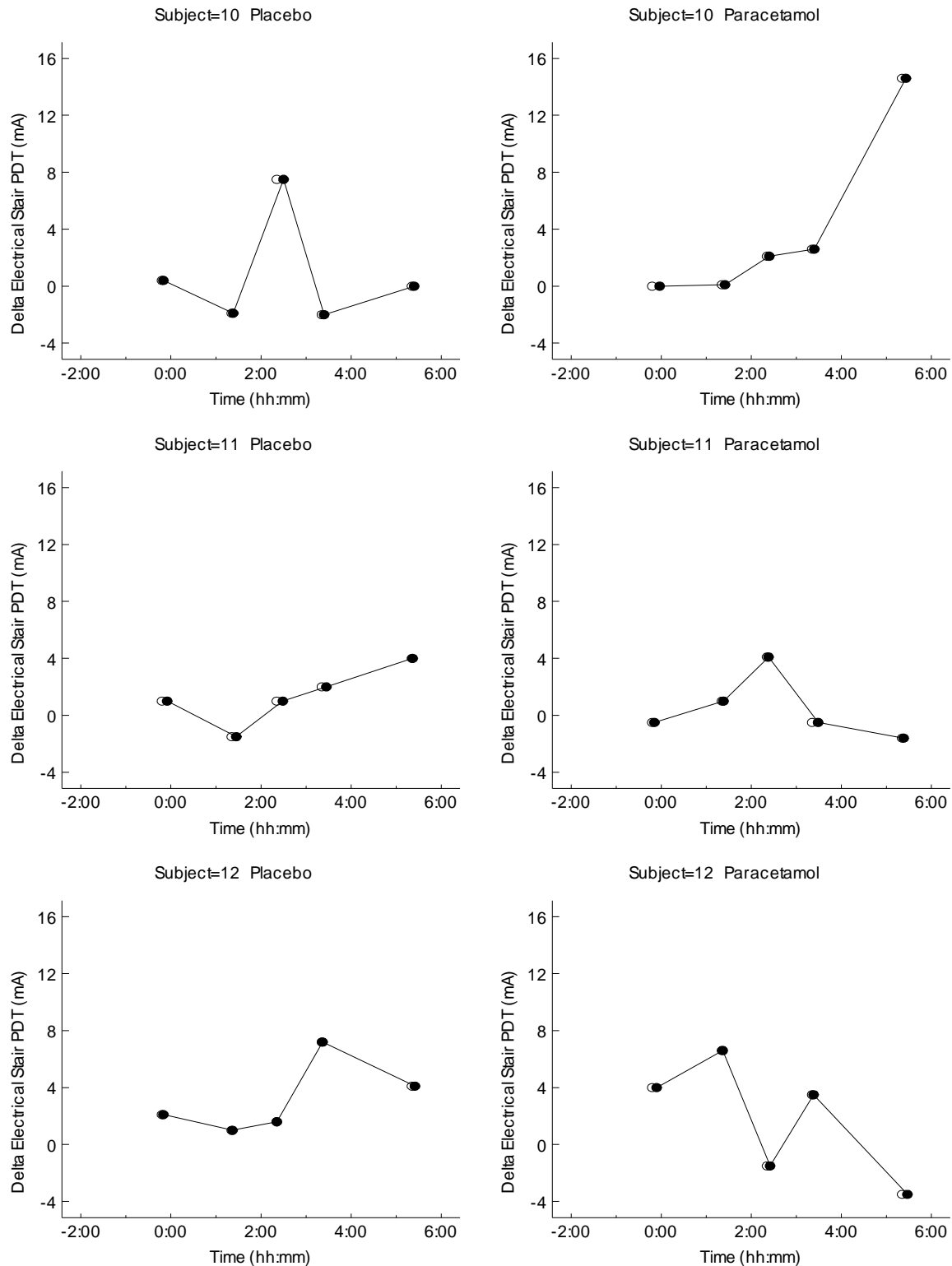
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Individual Plots 8 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 9 Delta Electrical Stair PTT (mA)

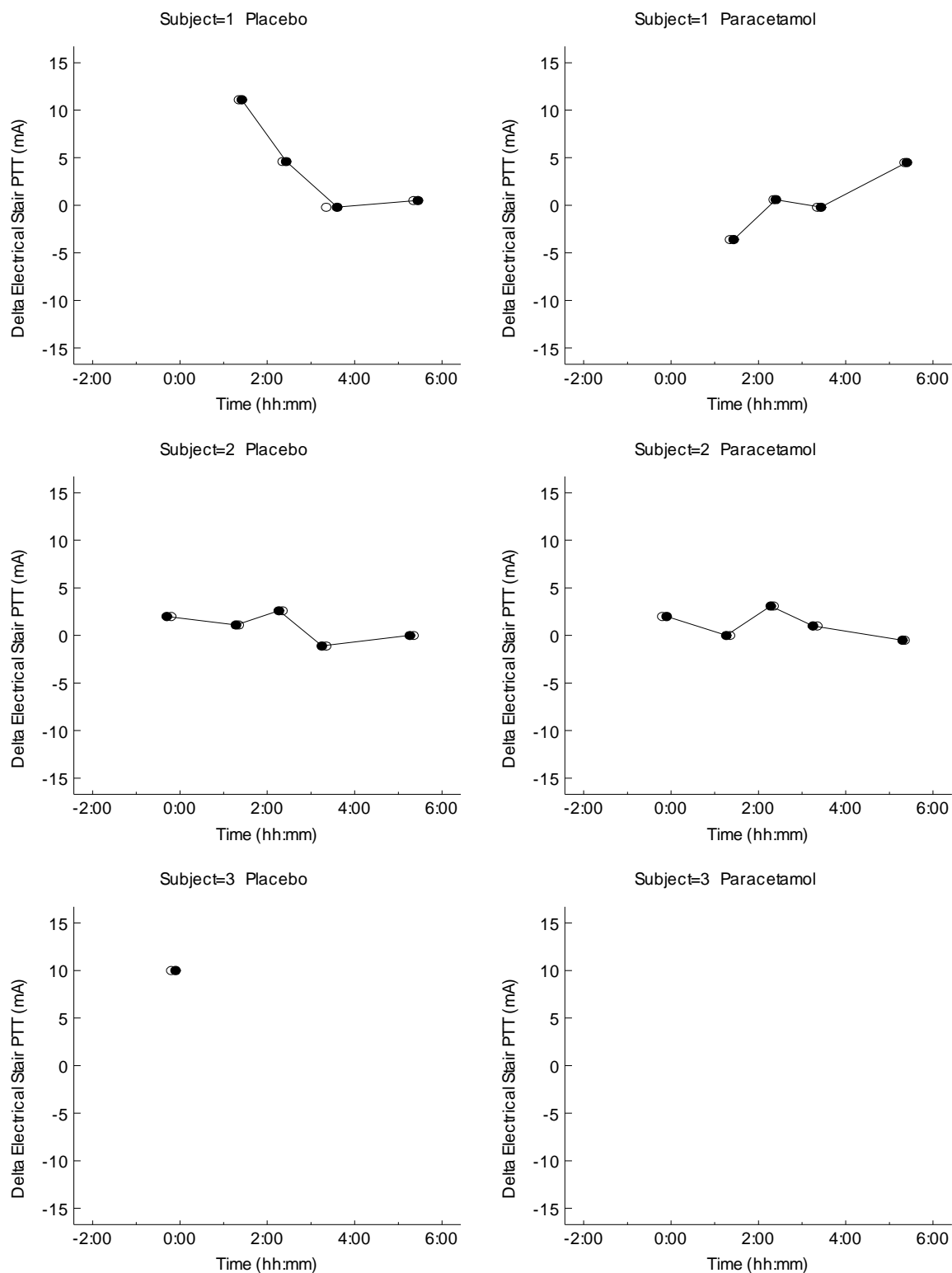
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Individual Plots 9 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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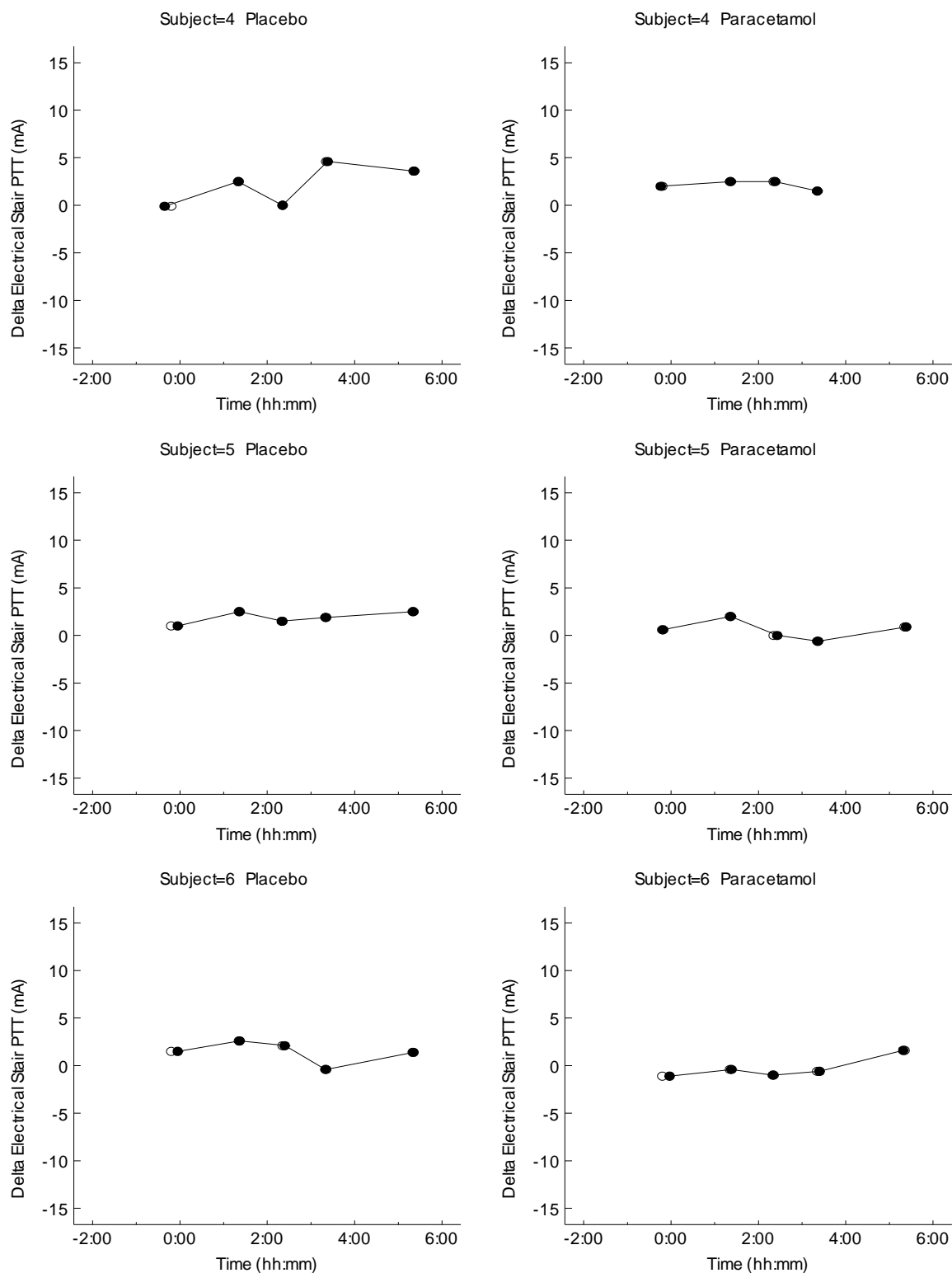
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Individual Plots 9 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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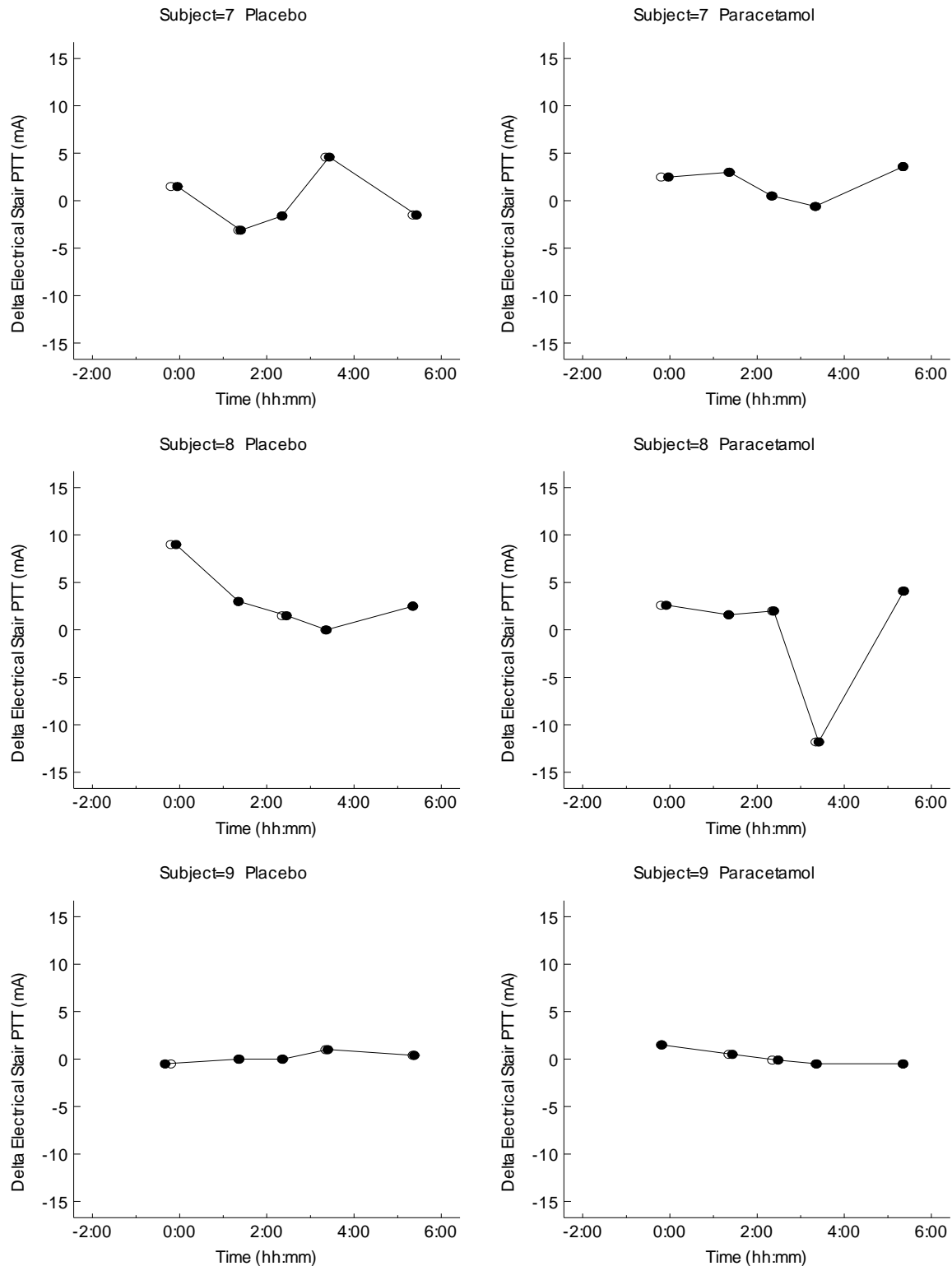
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Individual Plots 9 of dynamic measurements

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Dot: actual time Circle: protocol time



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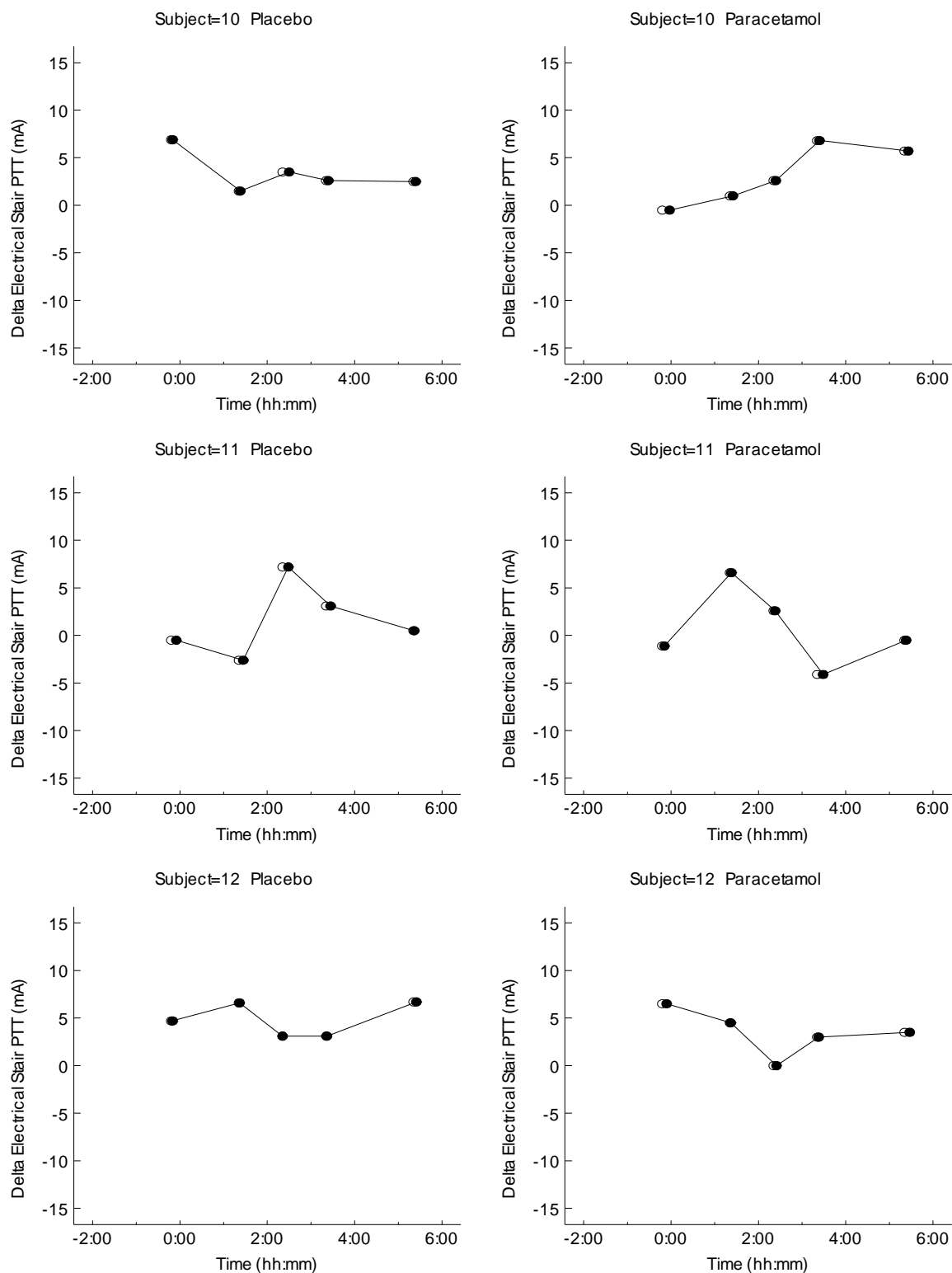
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Individual Plots 9 of dynamic measurements

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Dot: actual time Circle: protocol time



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Individual plots 10 Pressure AUC (kPa*%)

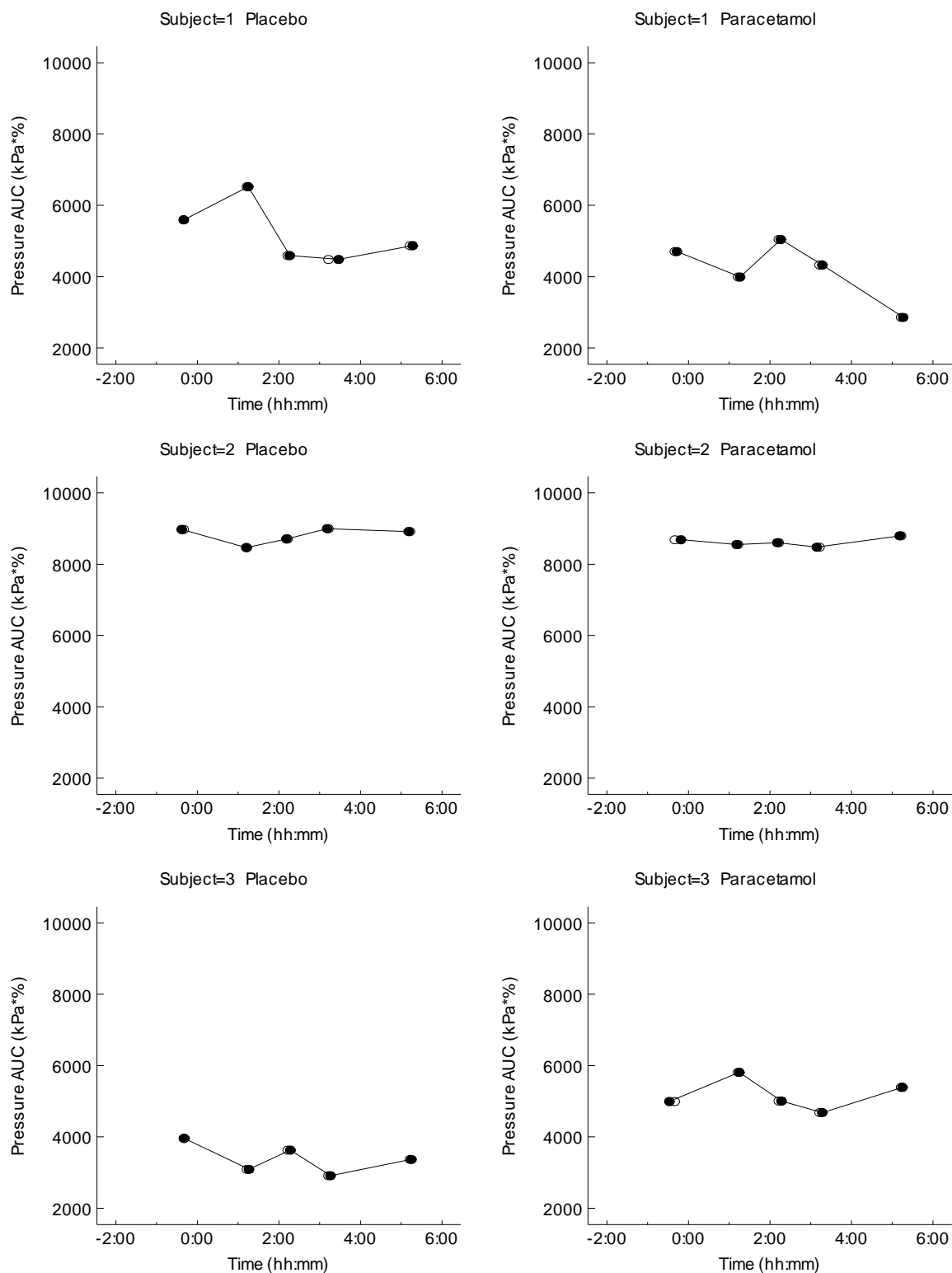
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Individual Plots 10 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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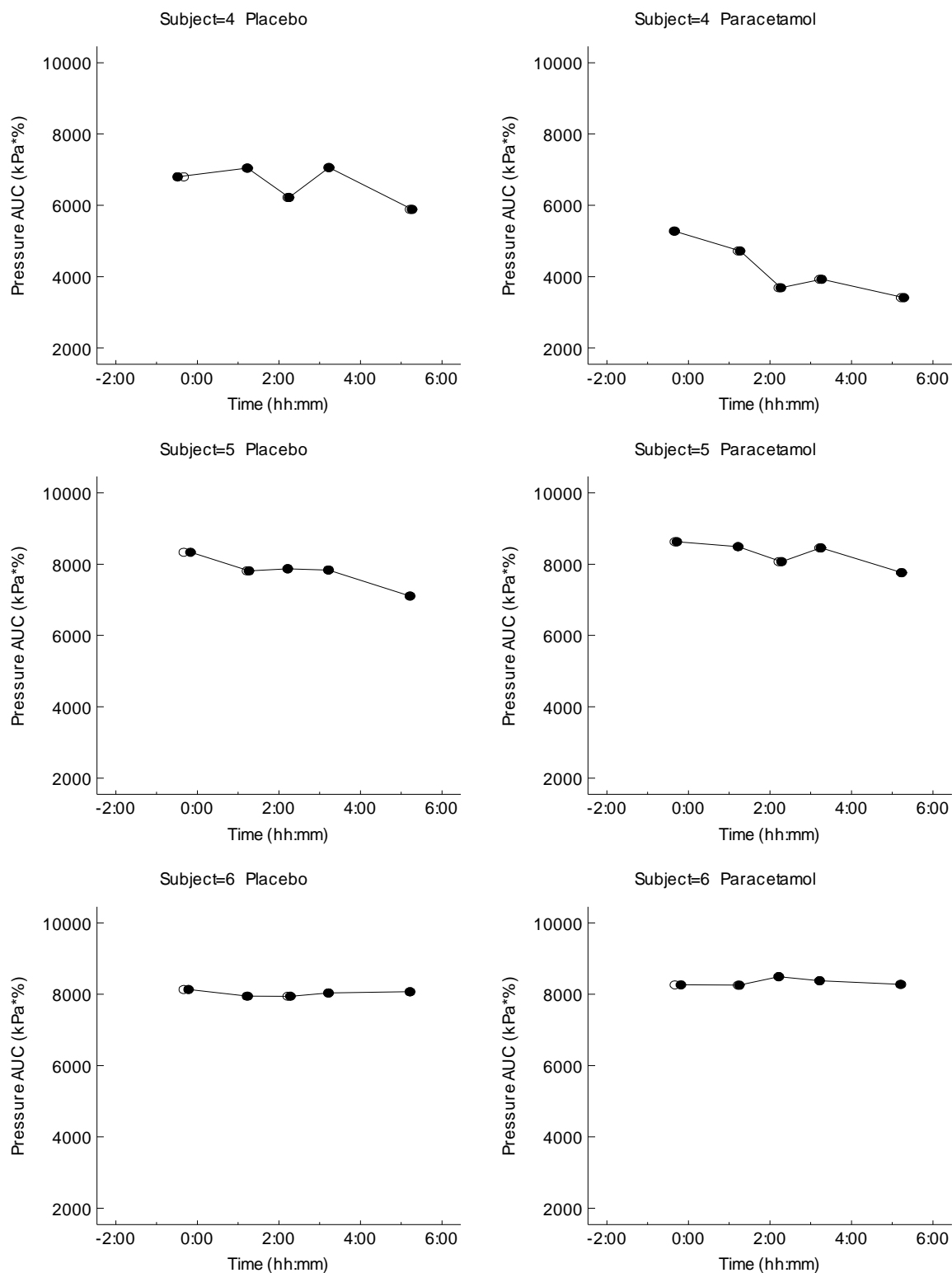
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Individual Plots 10 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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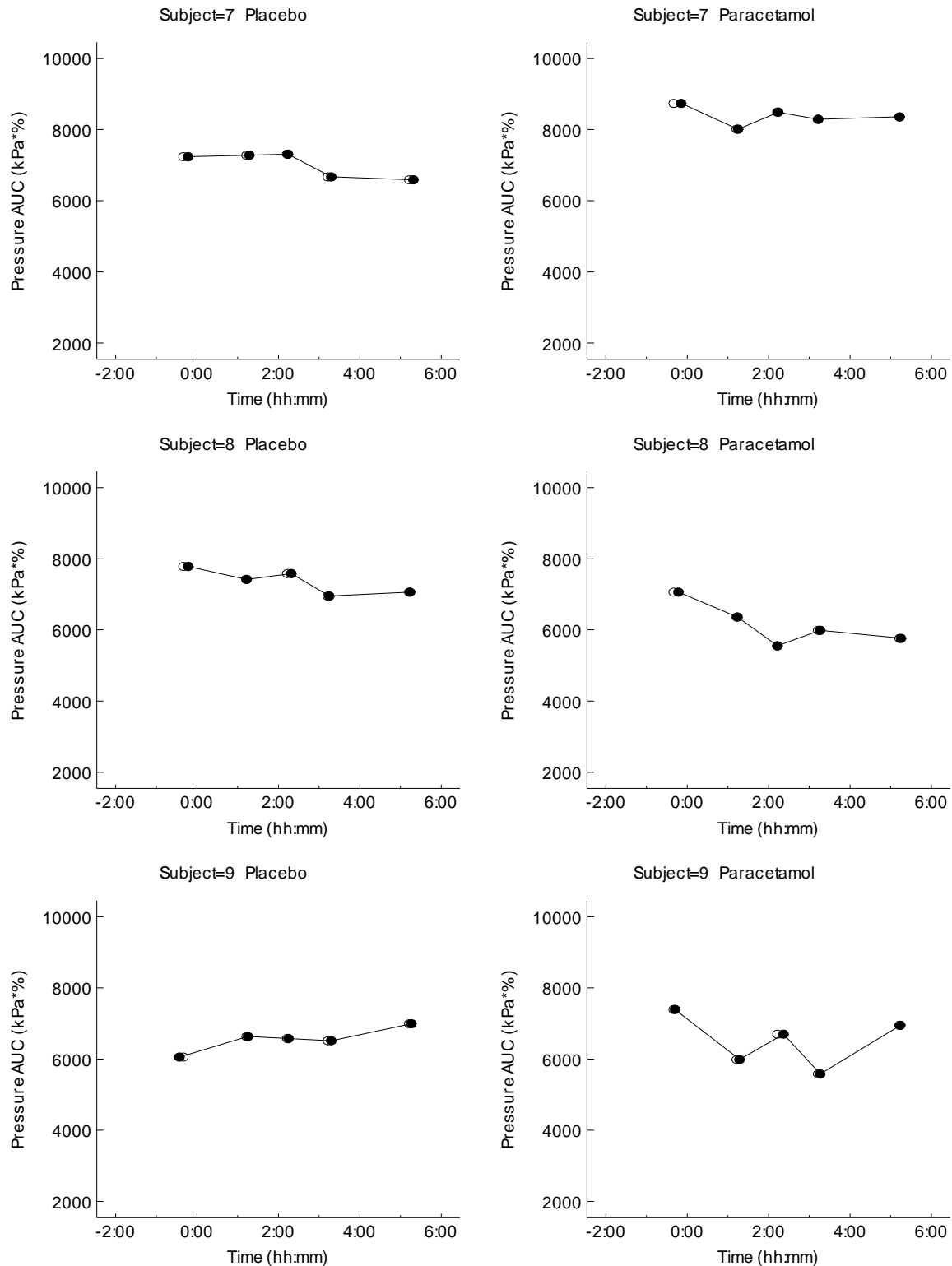
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Individual Plots 10 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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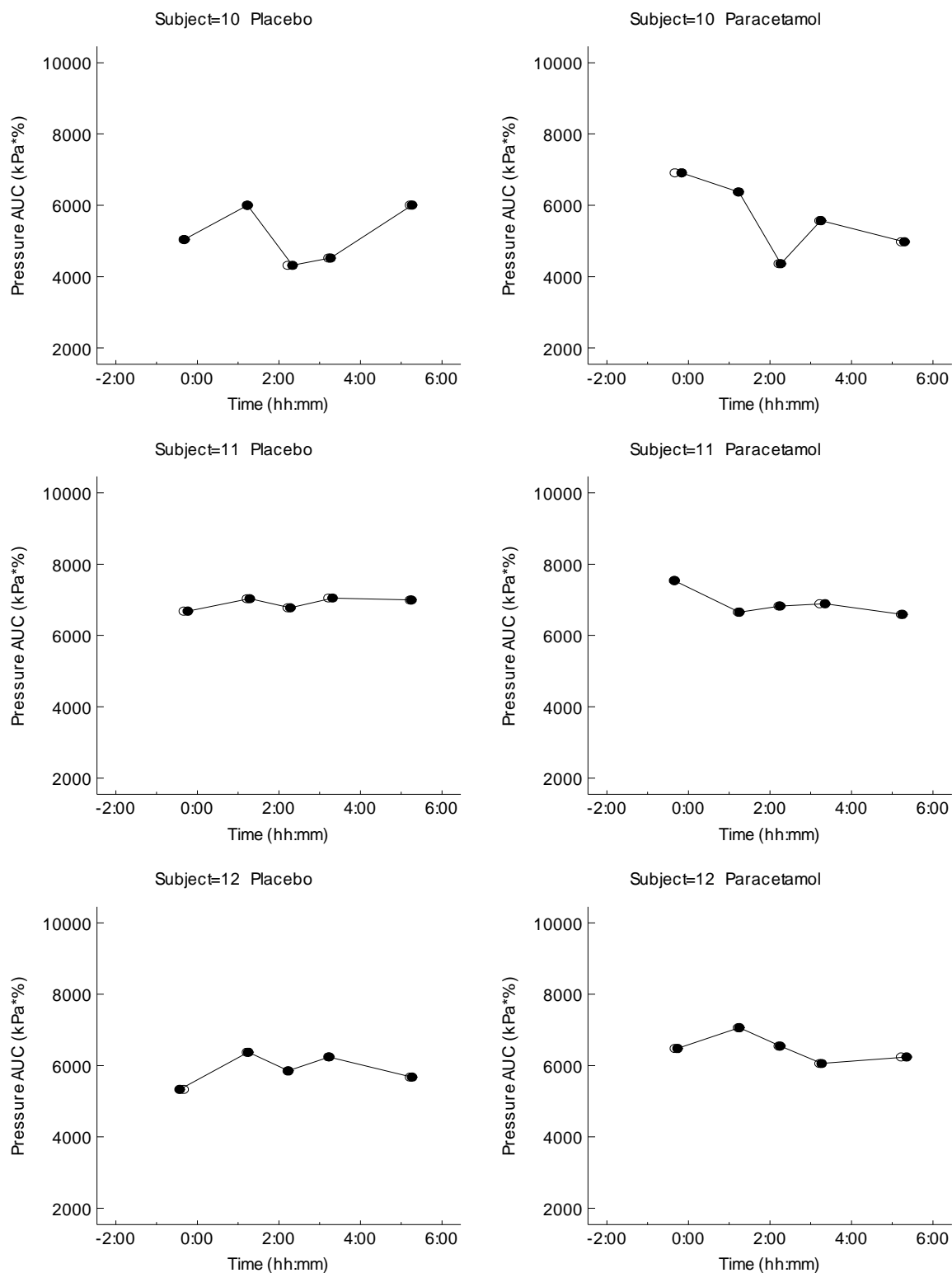
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Individual Plots 10 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 11 Pressure PDT (kPa)

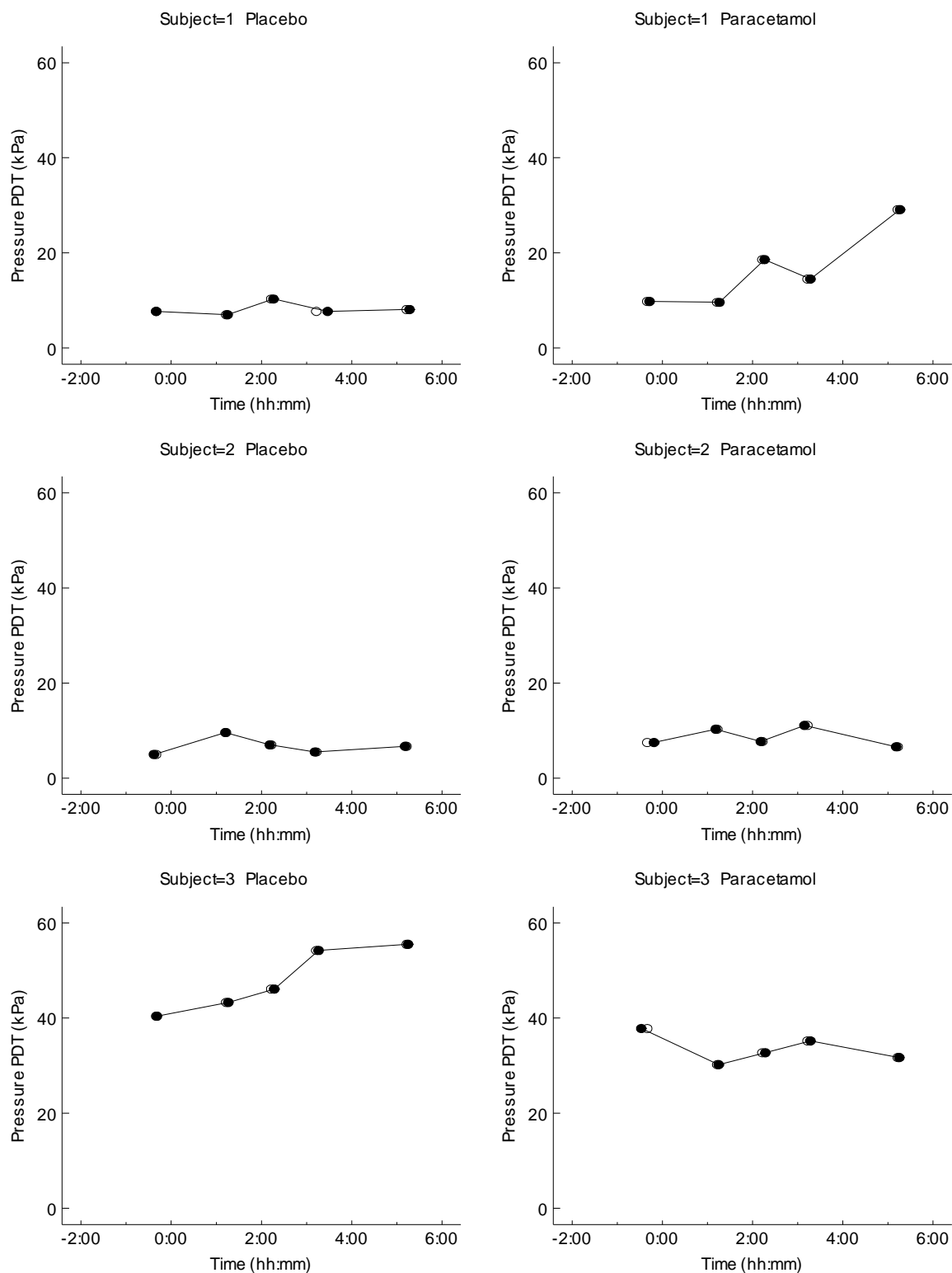
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Individual Plots 11 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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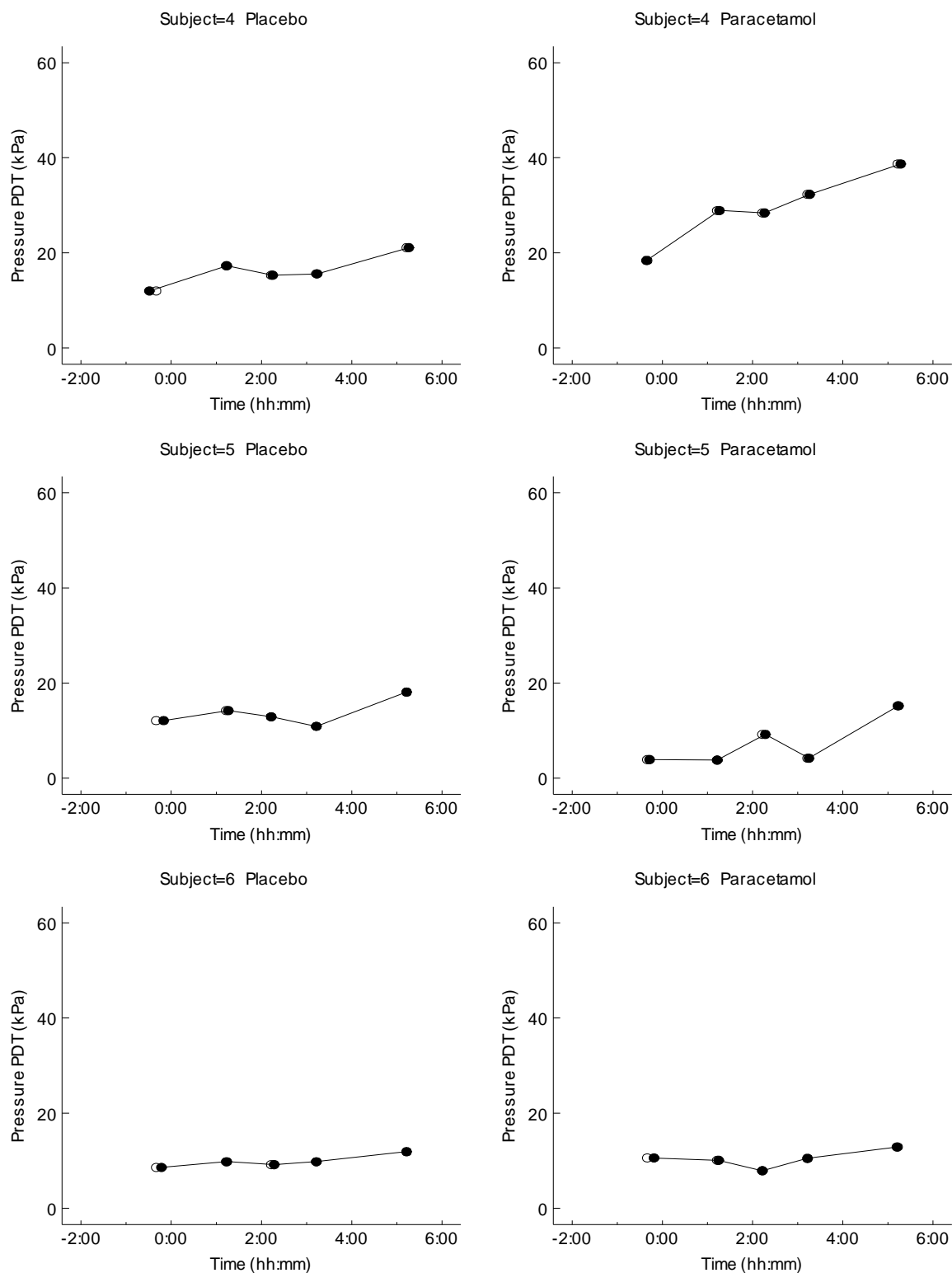
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Individual Plots 11 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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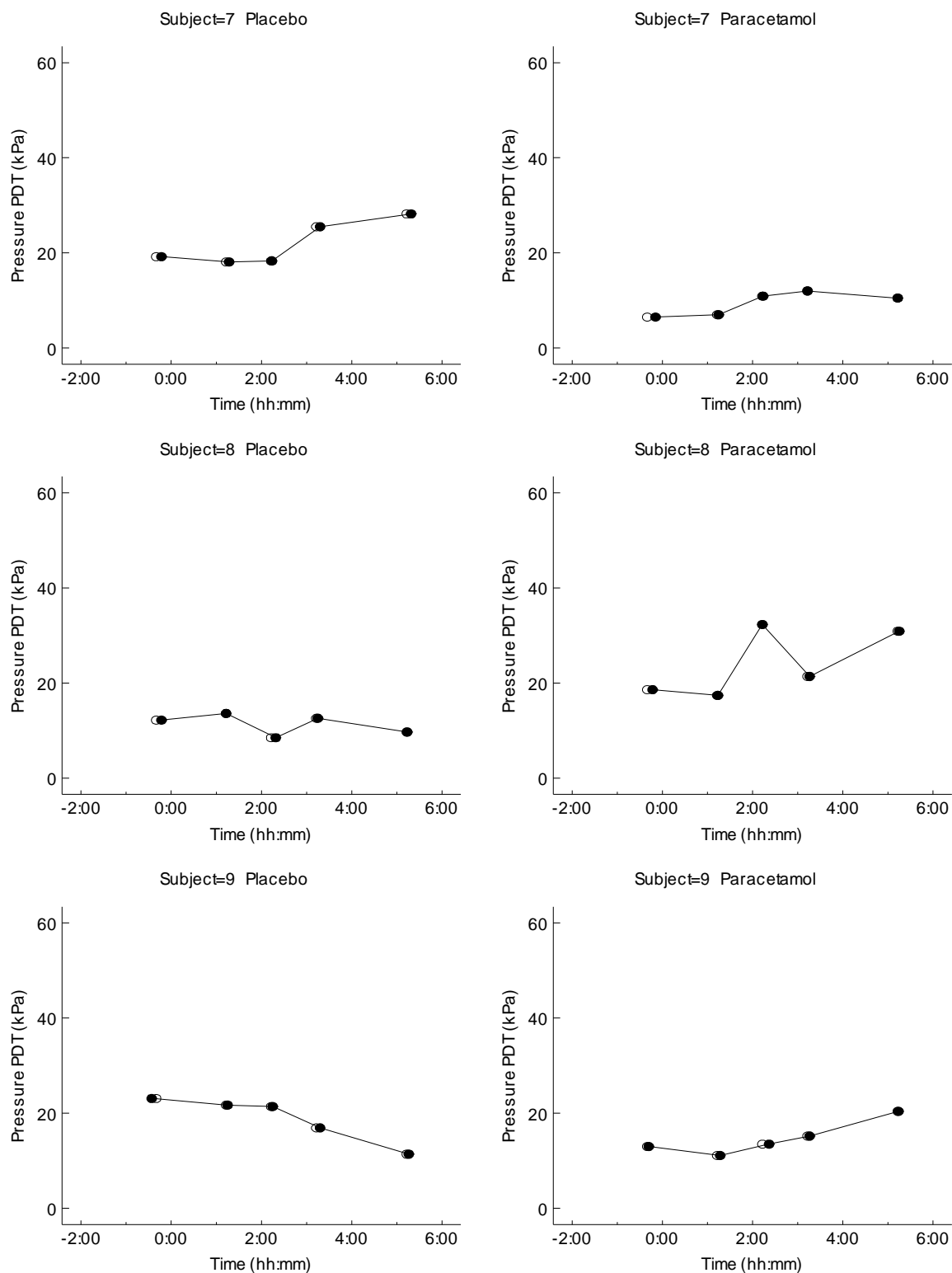
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Individual Plots 11 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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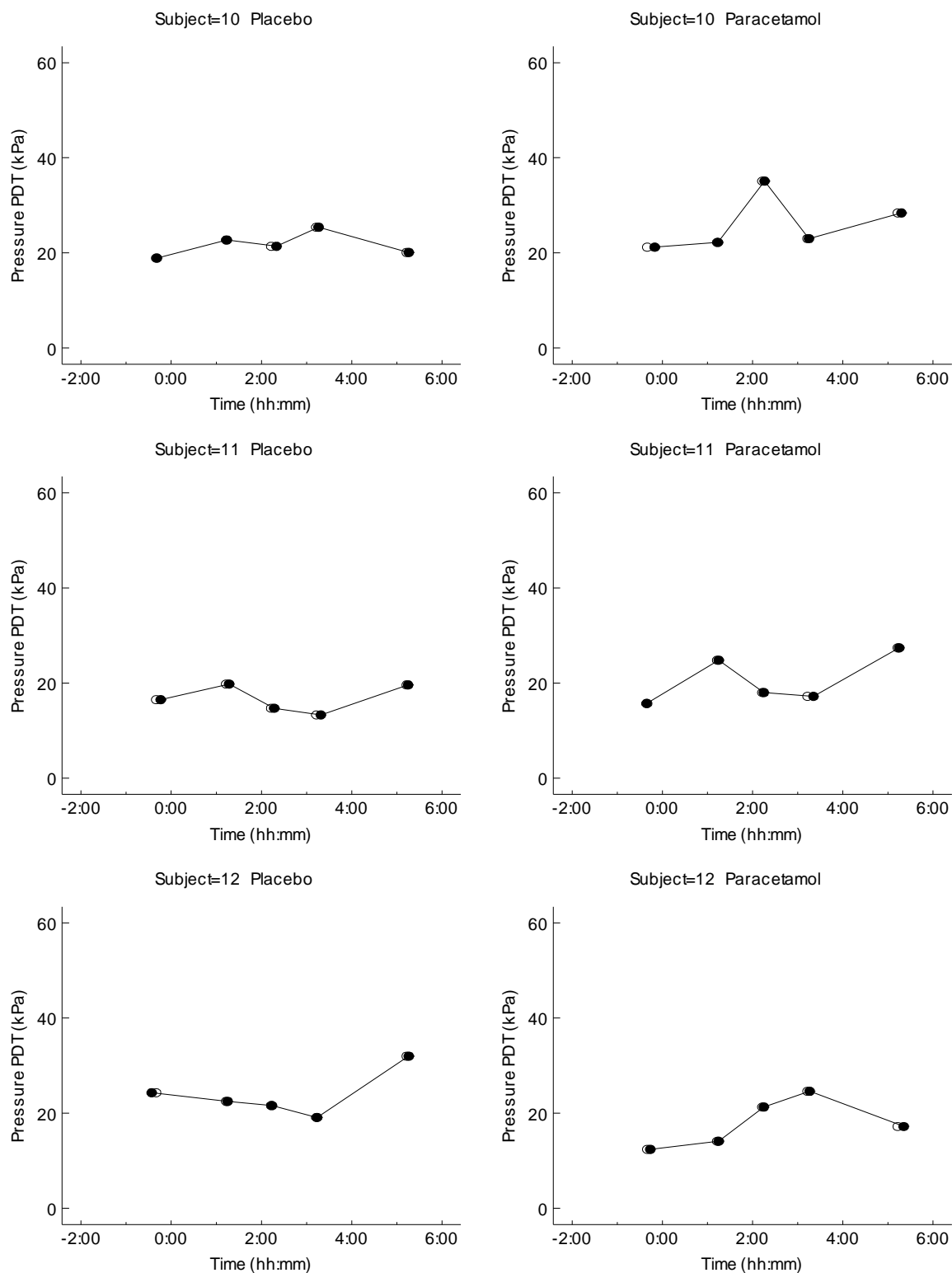
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Individual Plots 11 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 12 Pressure PTT (kPa)

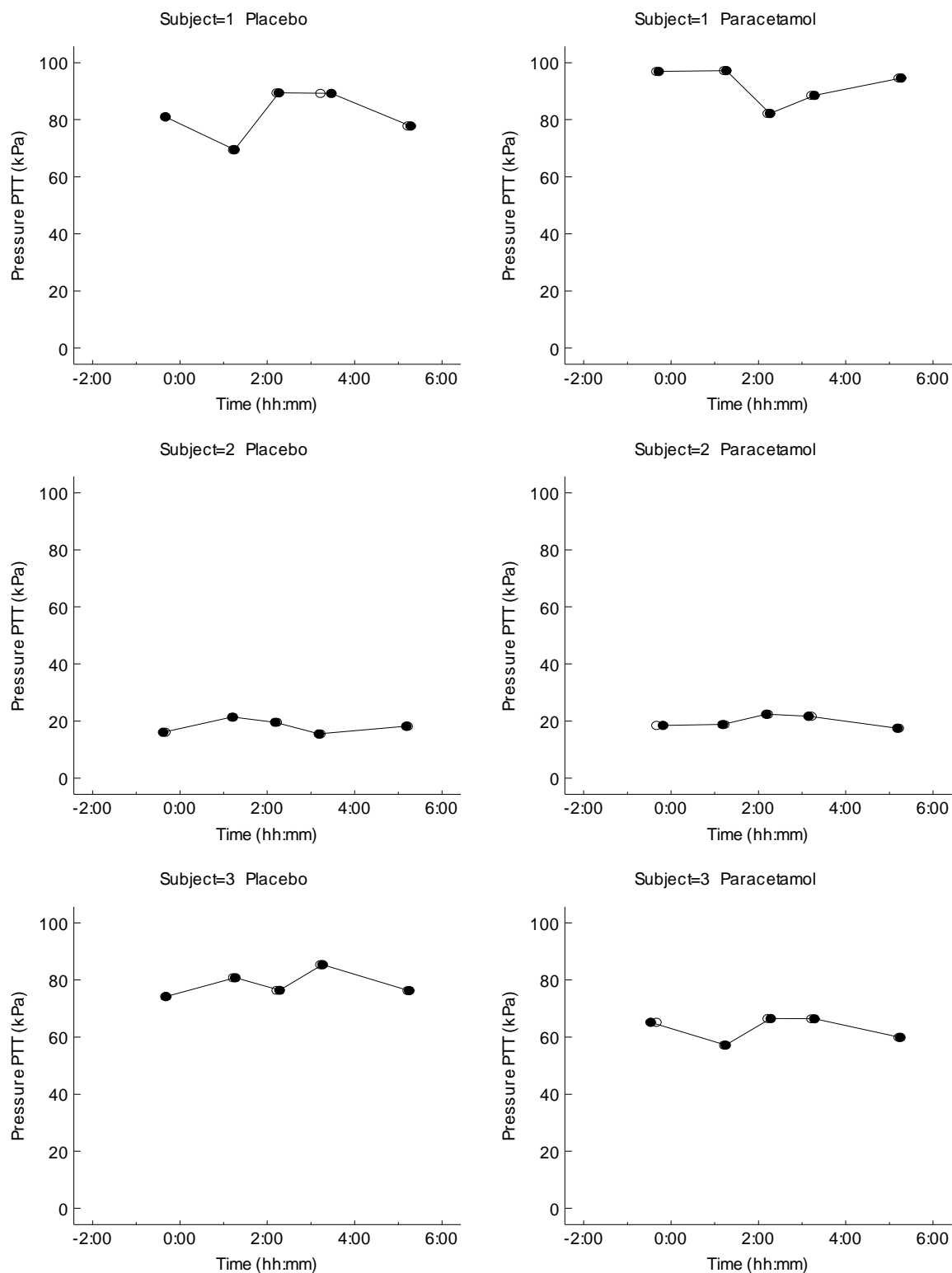
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Individual Plots 12 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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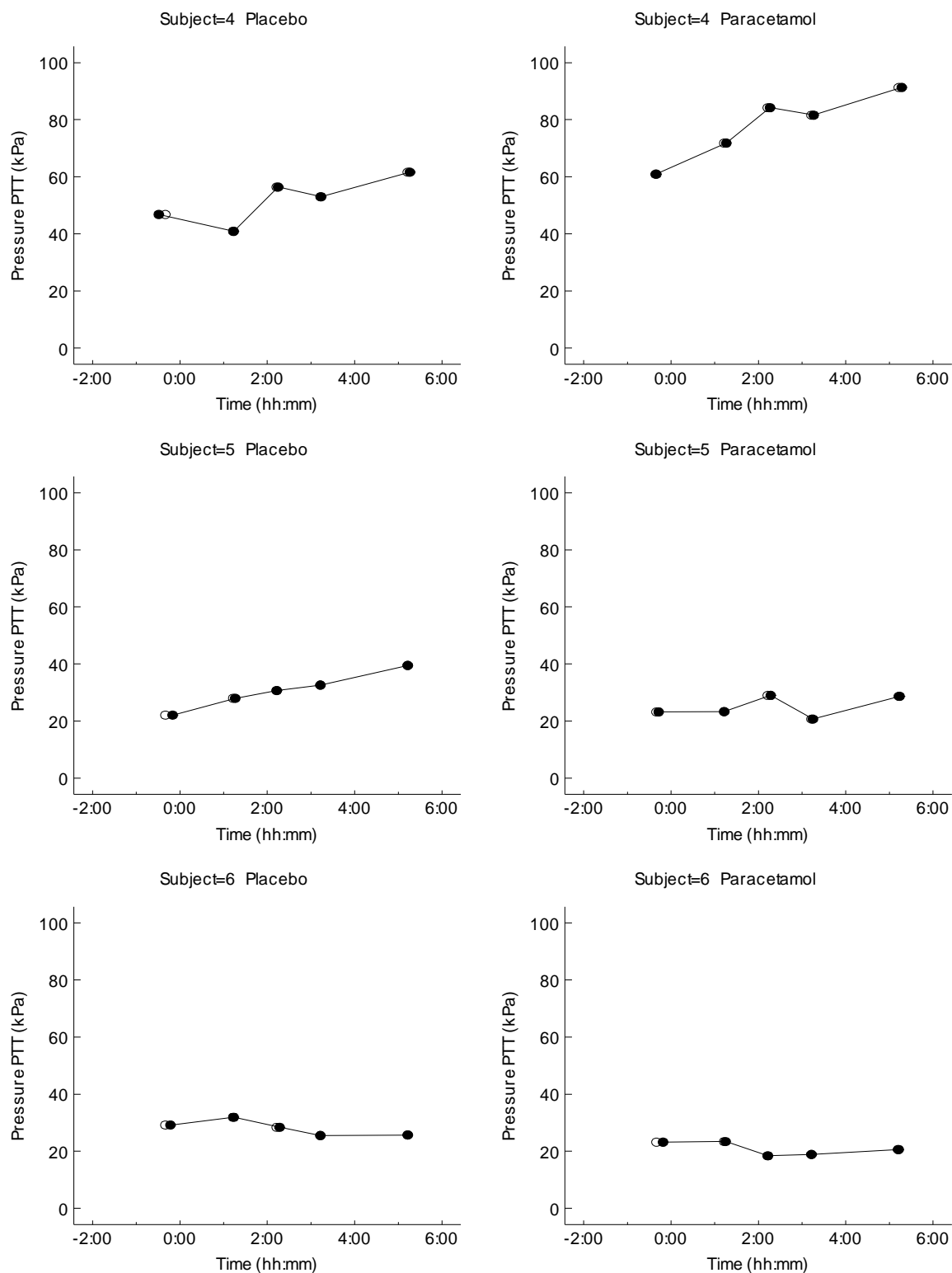
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Individual Plots 12 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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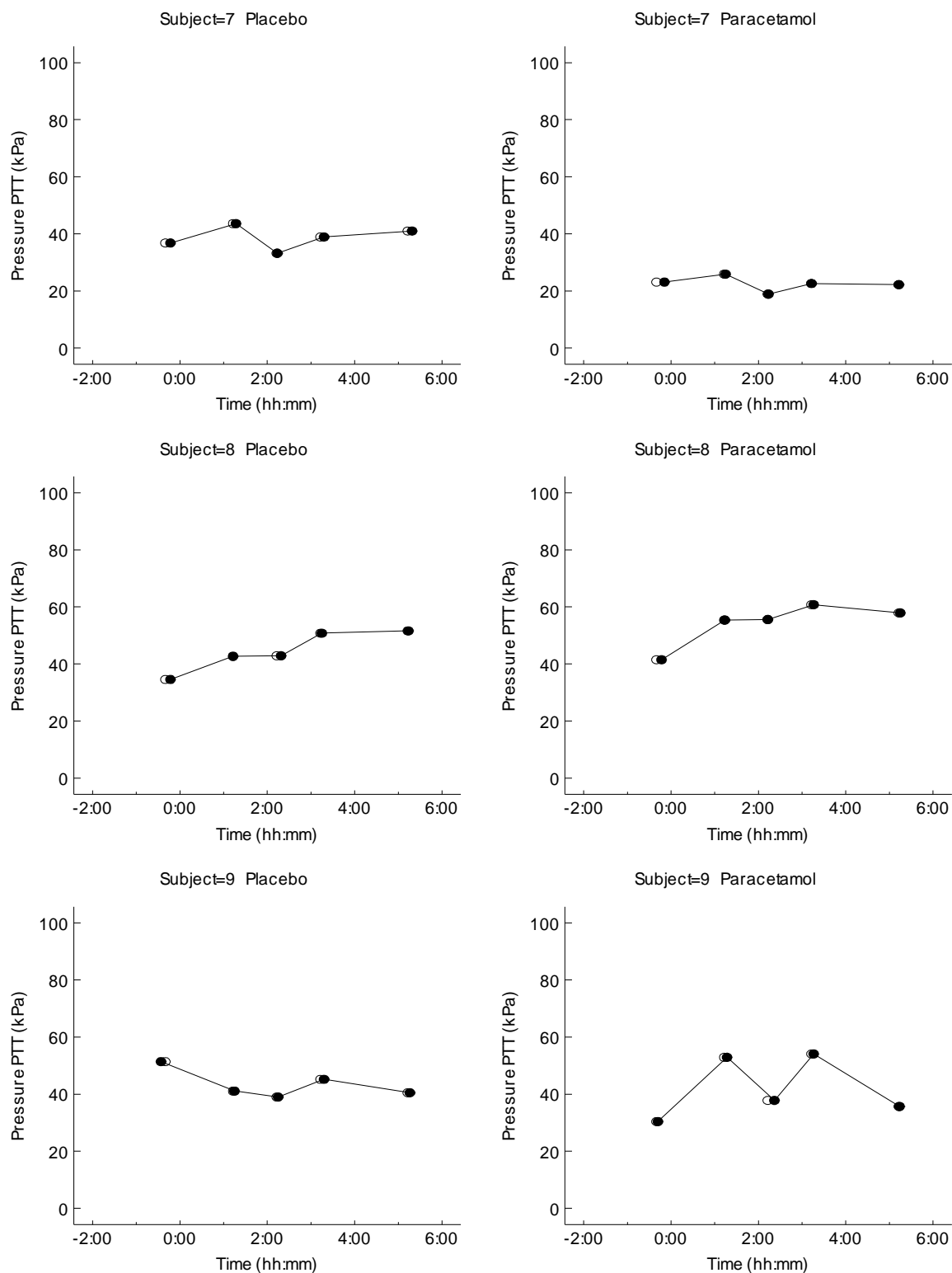
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Individual Plots 12 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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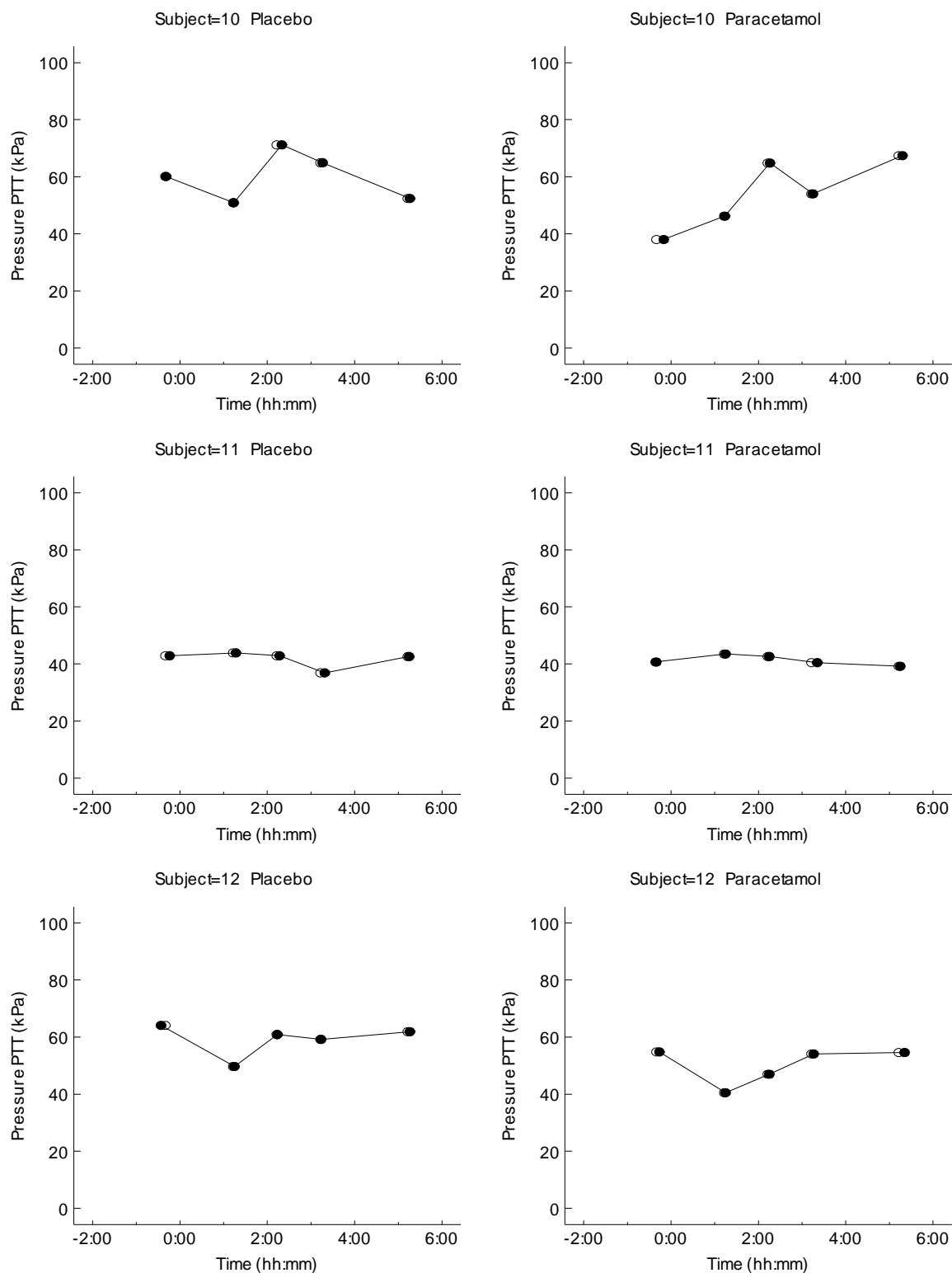
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Individual Plots 12 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 13 Heat PDT (C)

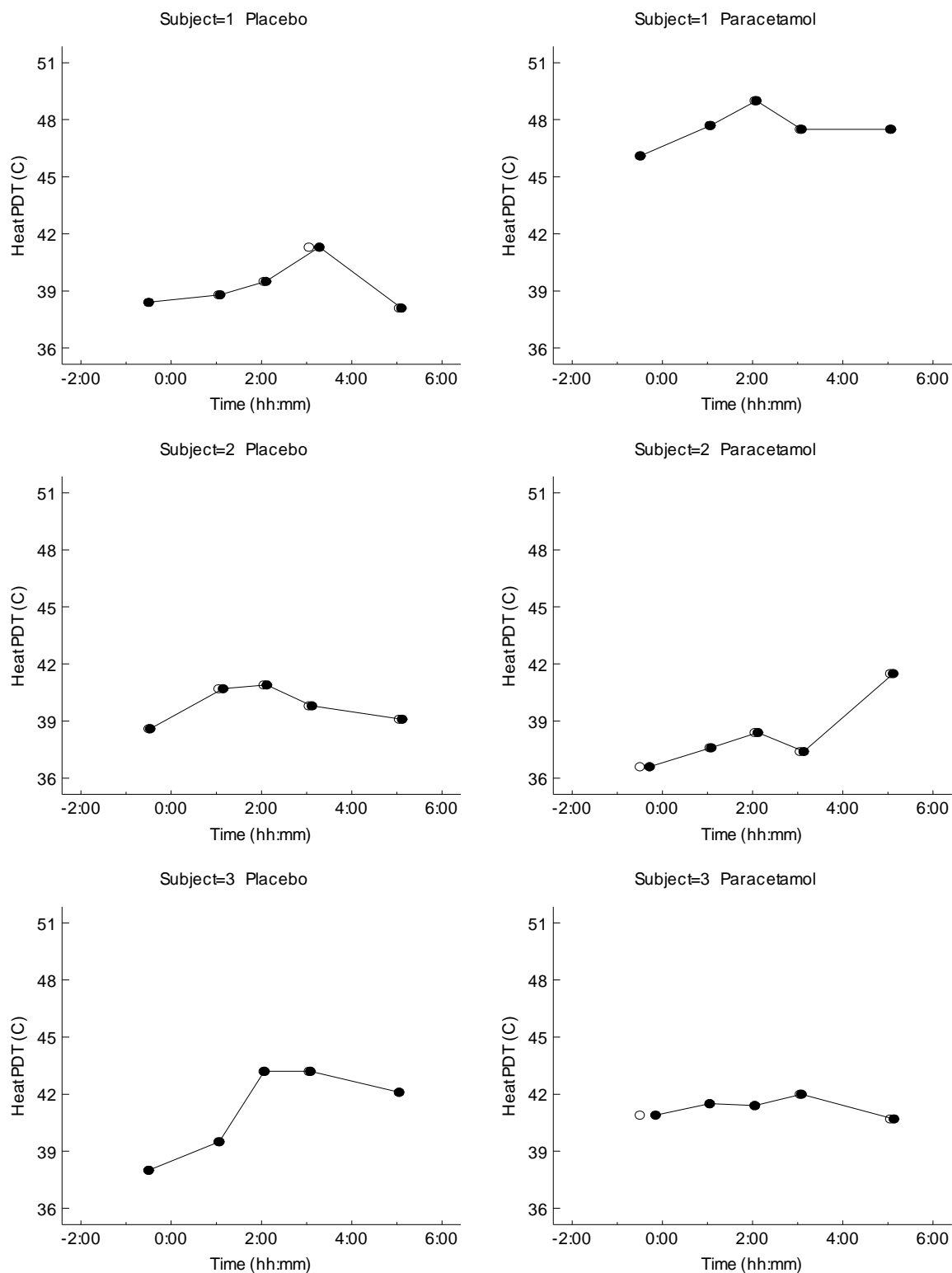
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Individual Plots 13 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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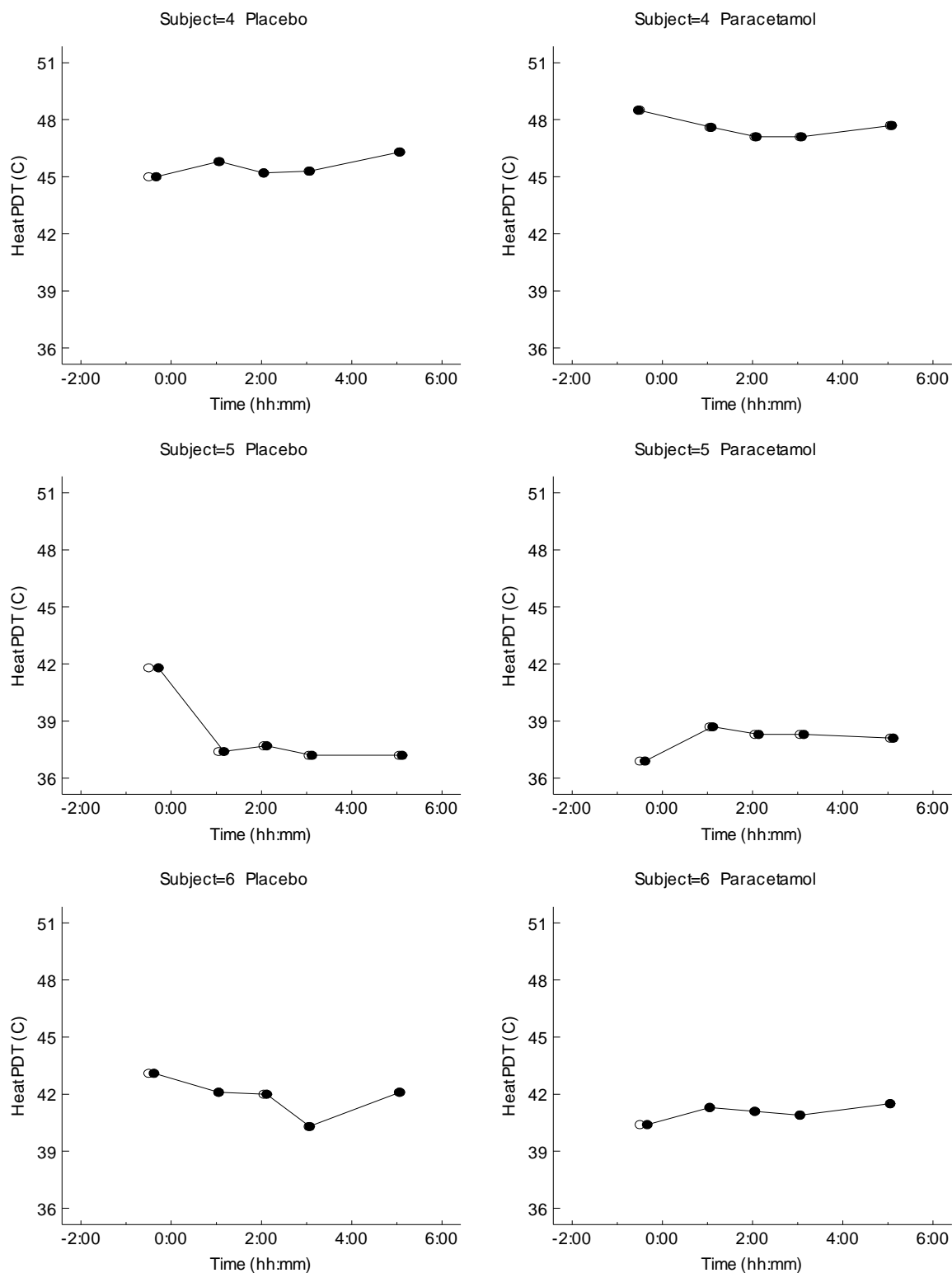
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Individual Plots 13 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



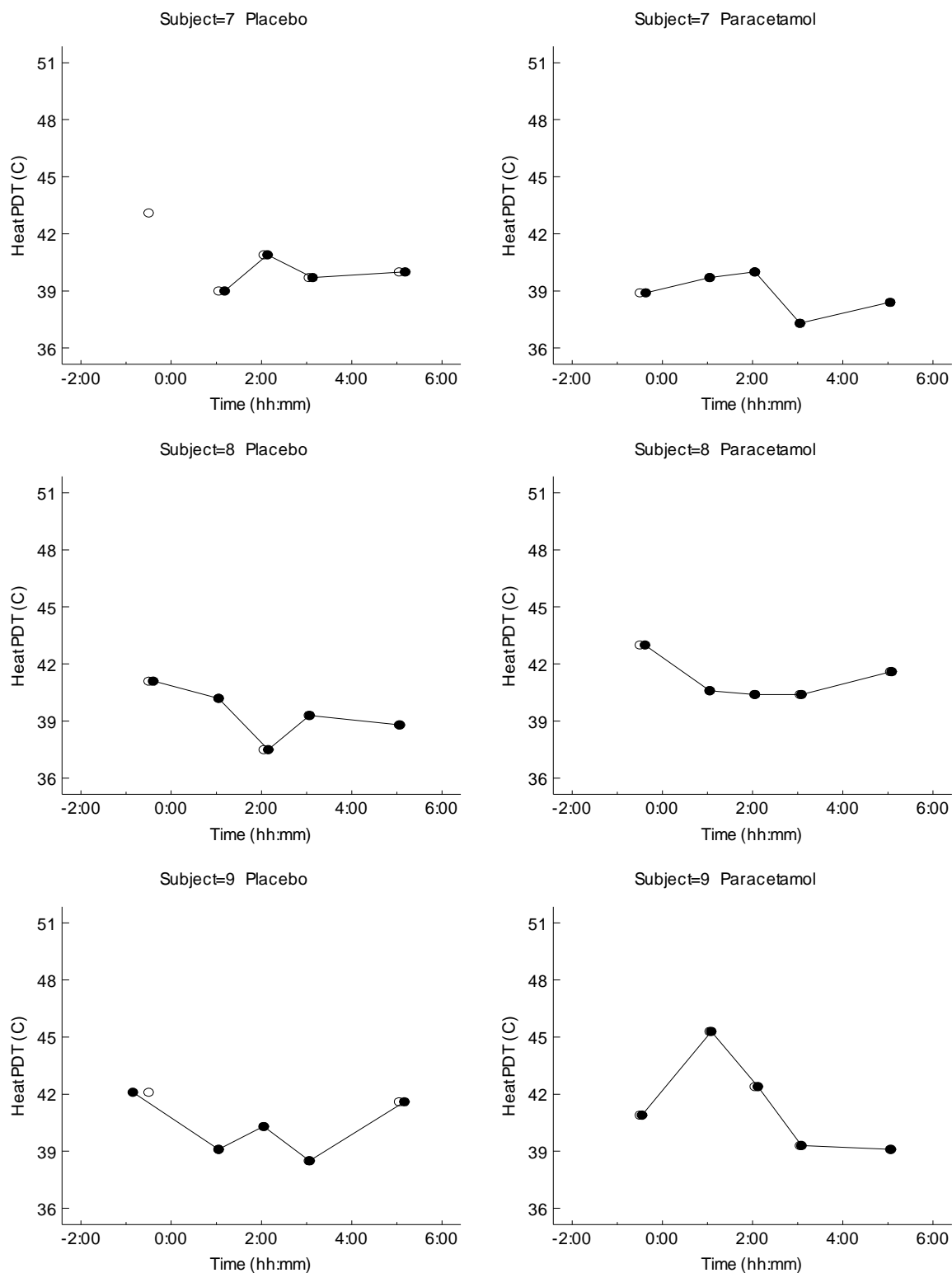
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Individual Plots 13 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



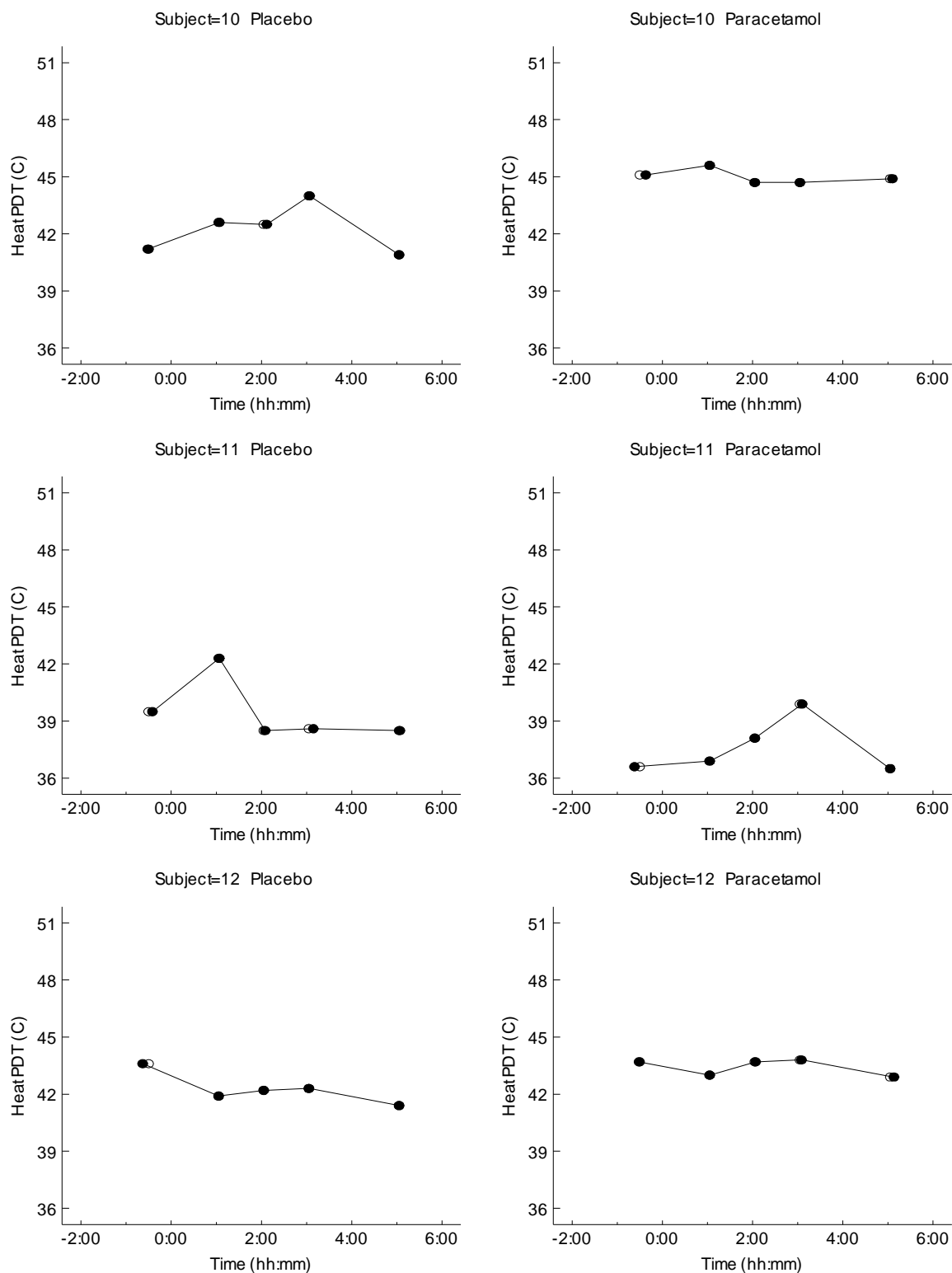
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Individual Plots 13 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 14 Heat PTT (C)

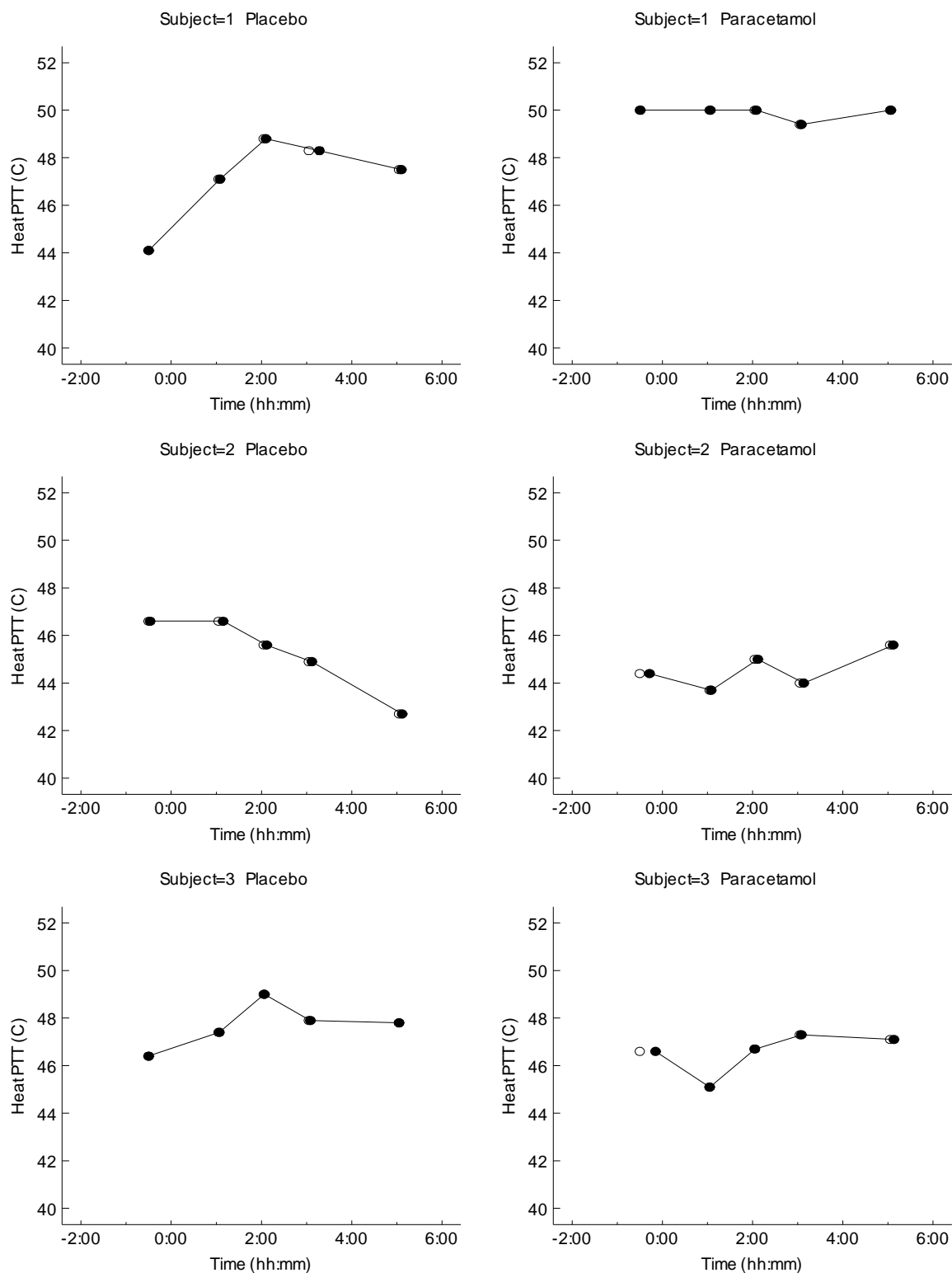
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Individual Plots 14 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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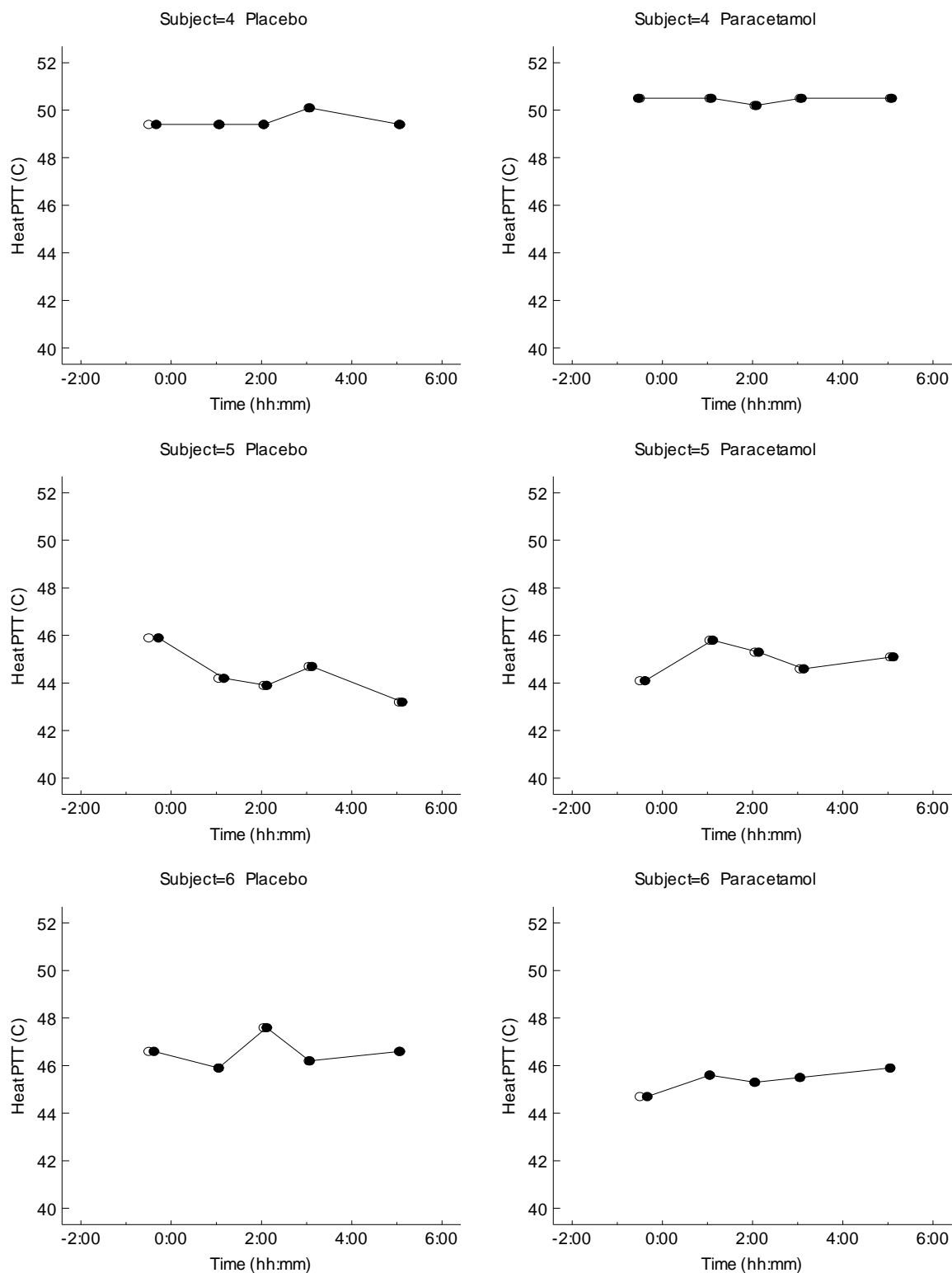
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Individual Plots 14 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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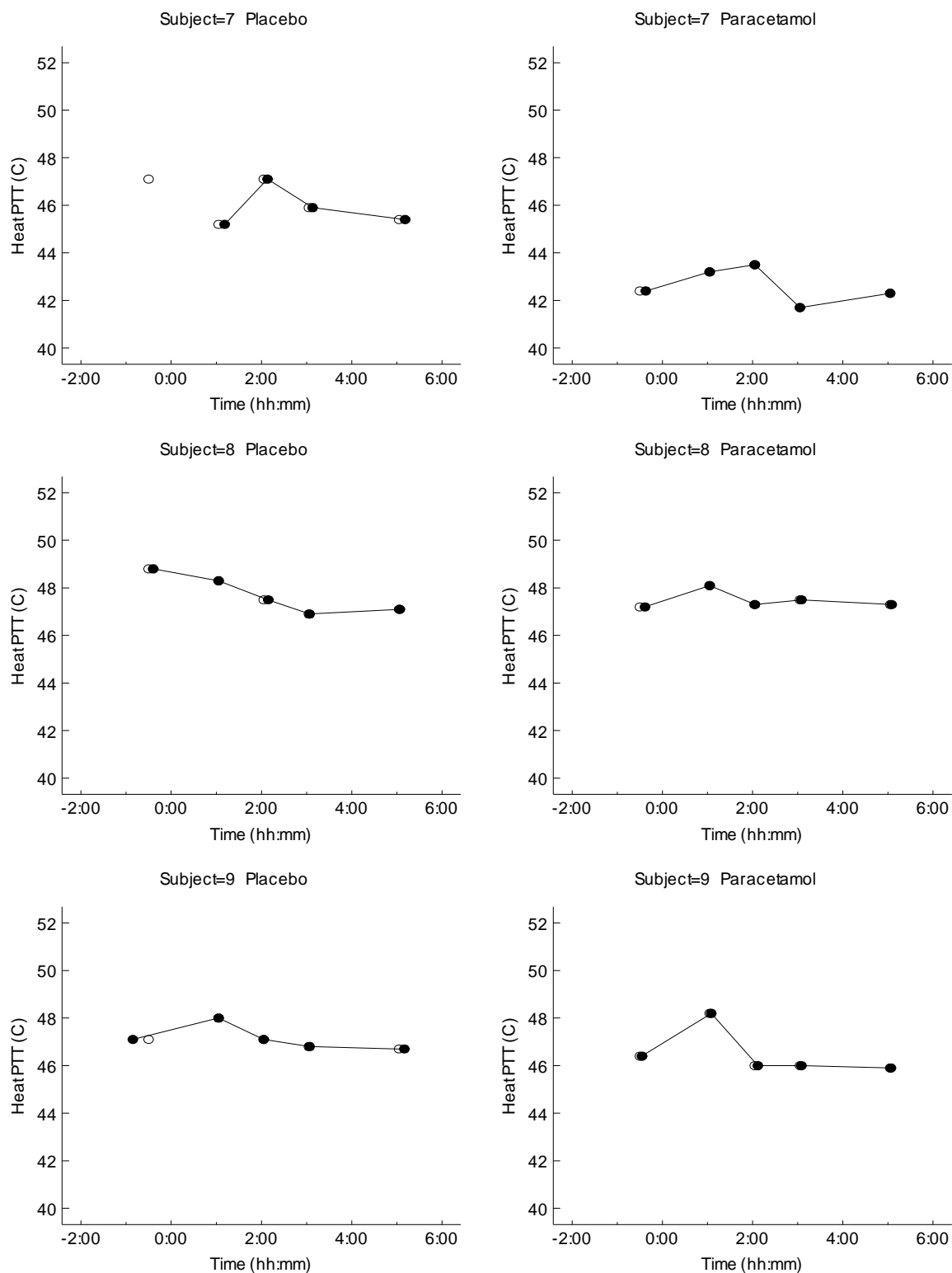
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Individual Plots 14 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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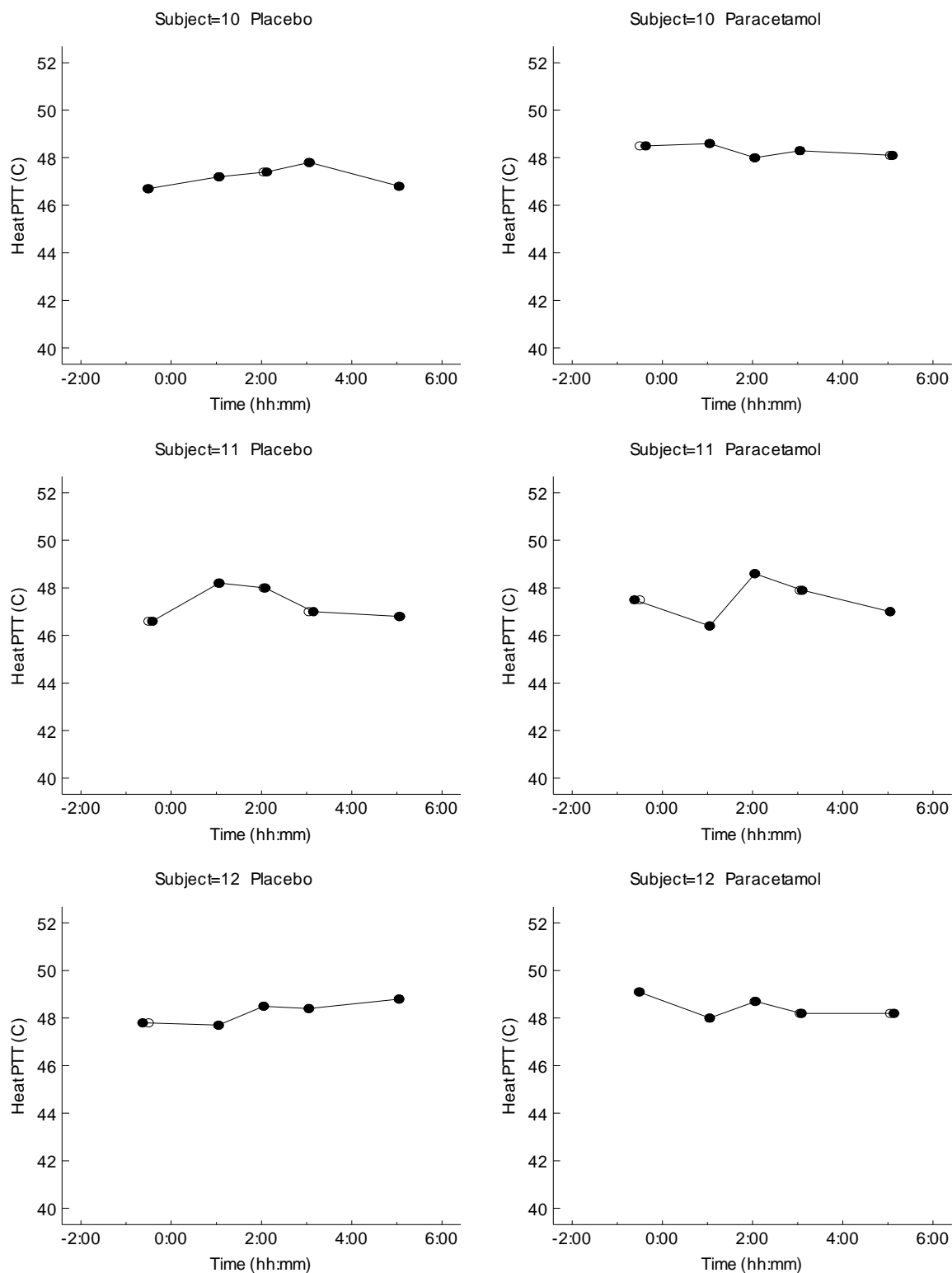
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Individual Plots 14 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 15 Sensory after Cold

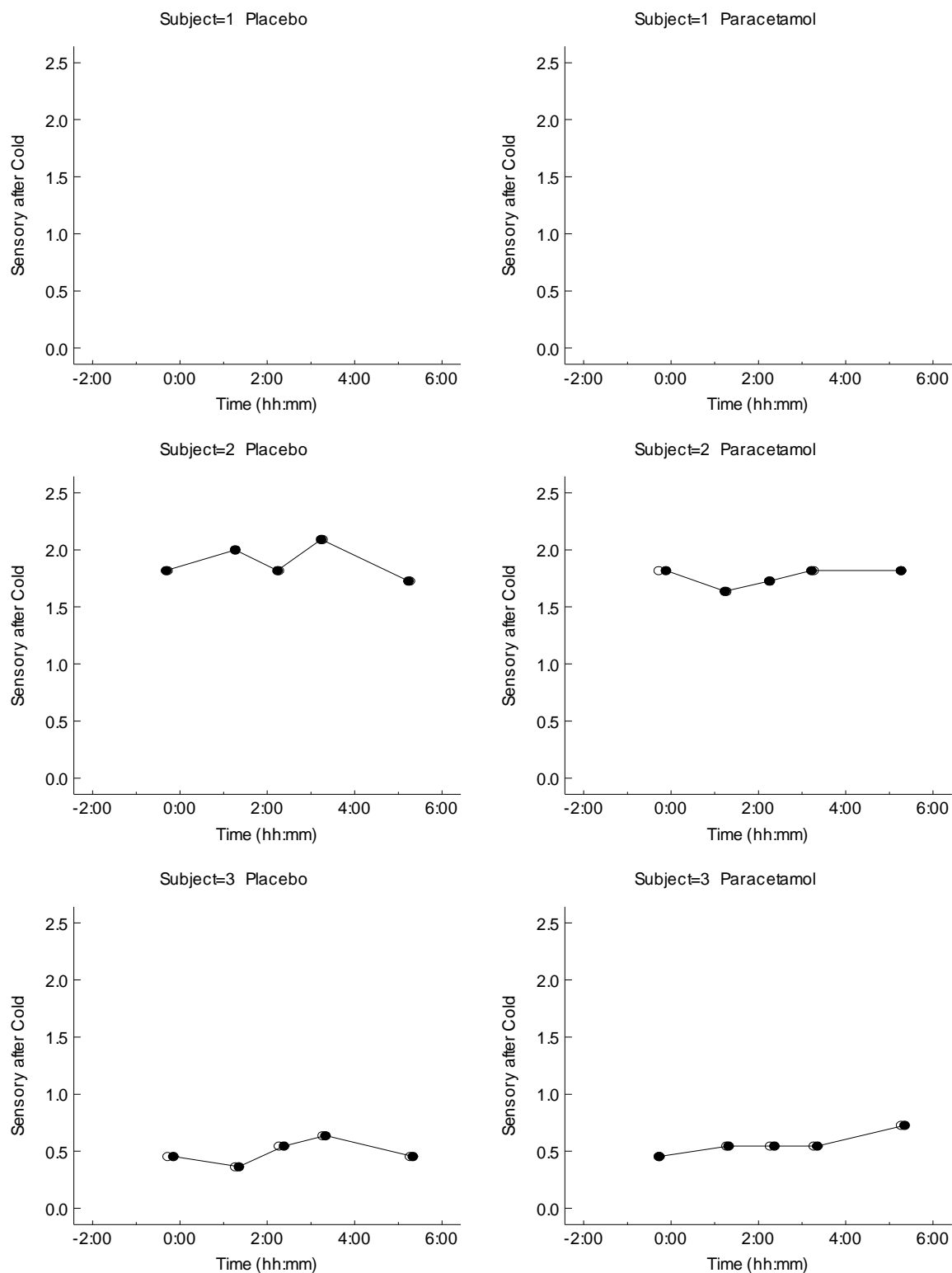
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Individual Plots 15 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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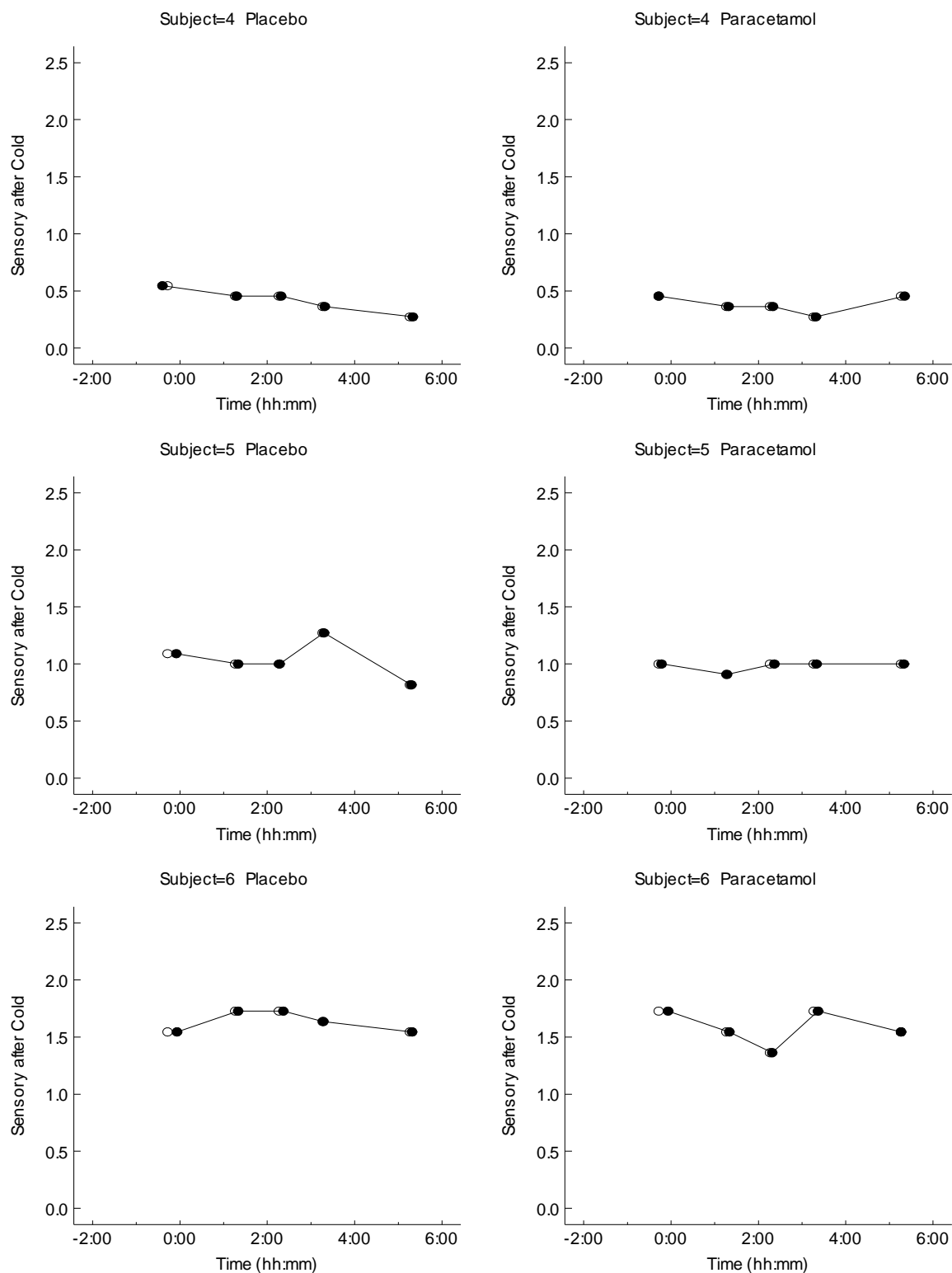
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Individual Plots 15 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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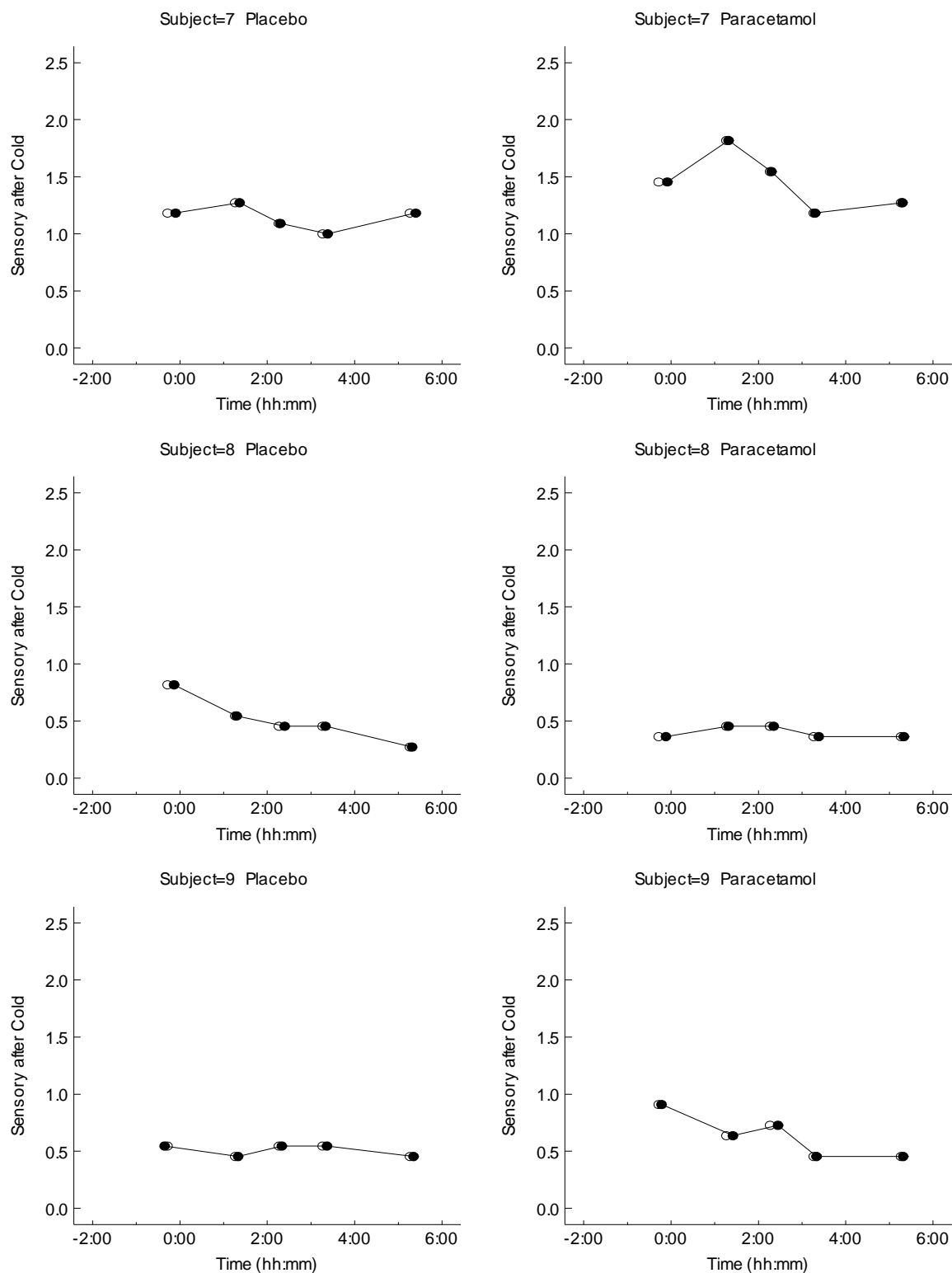
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Individual Plots 15 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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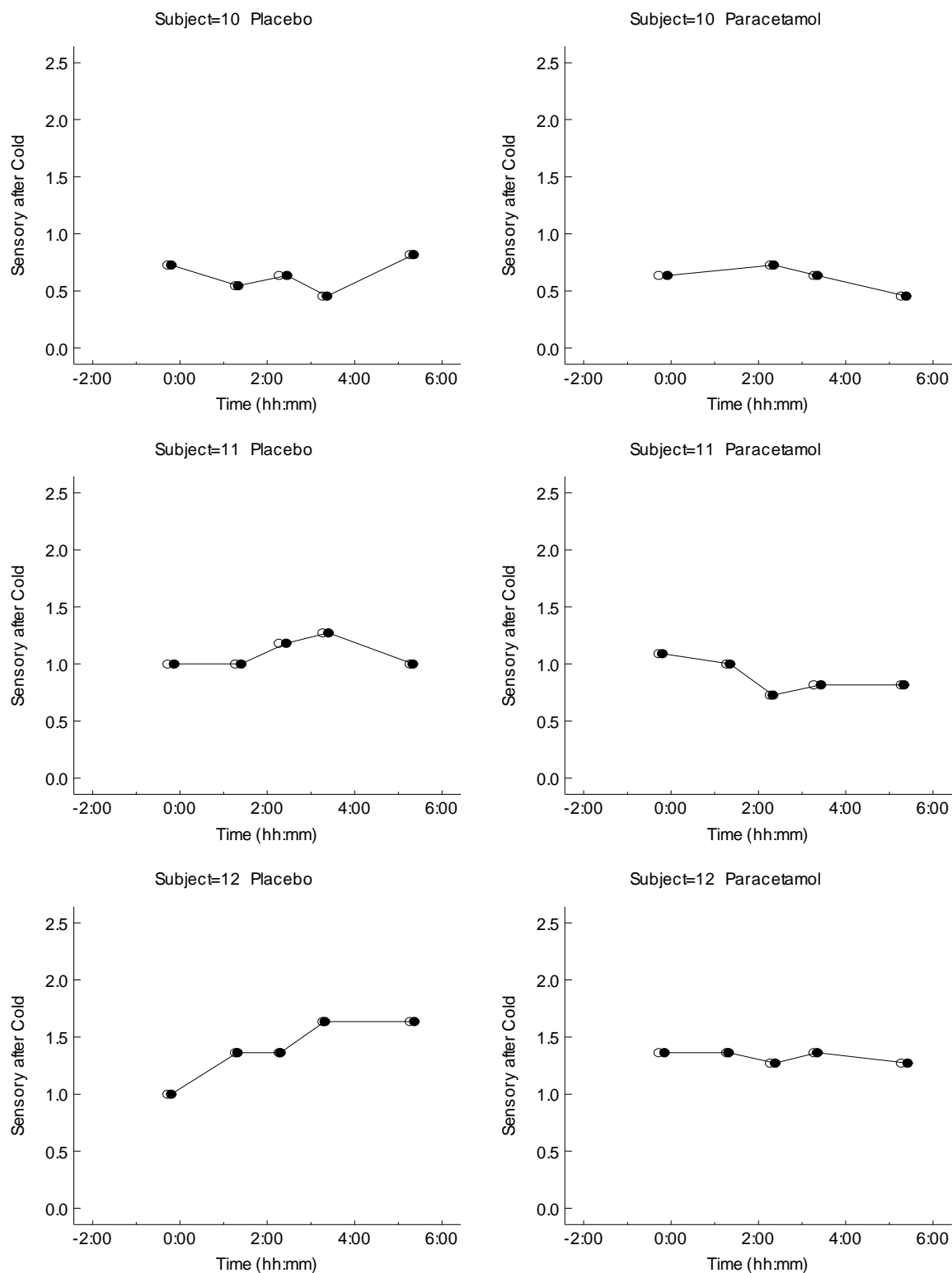
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Individual Plots 15 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 16 Affective after Cold

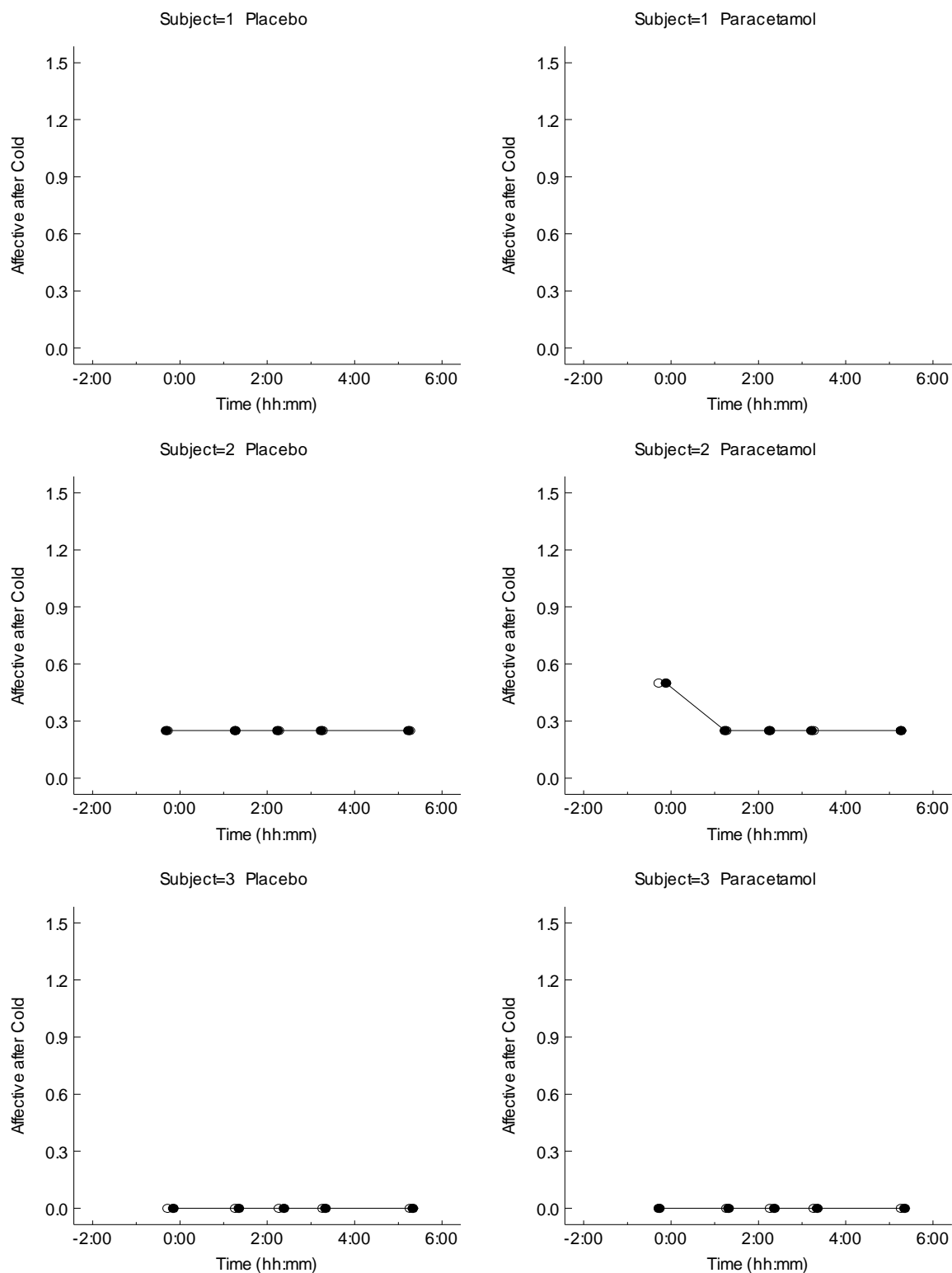
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Individual Plots 16 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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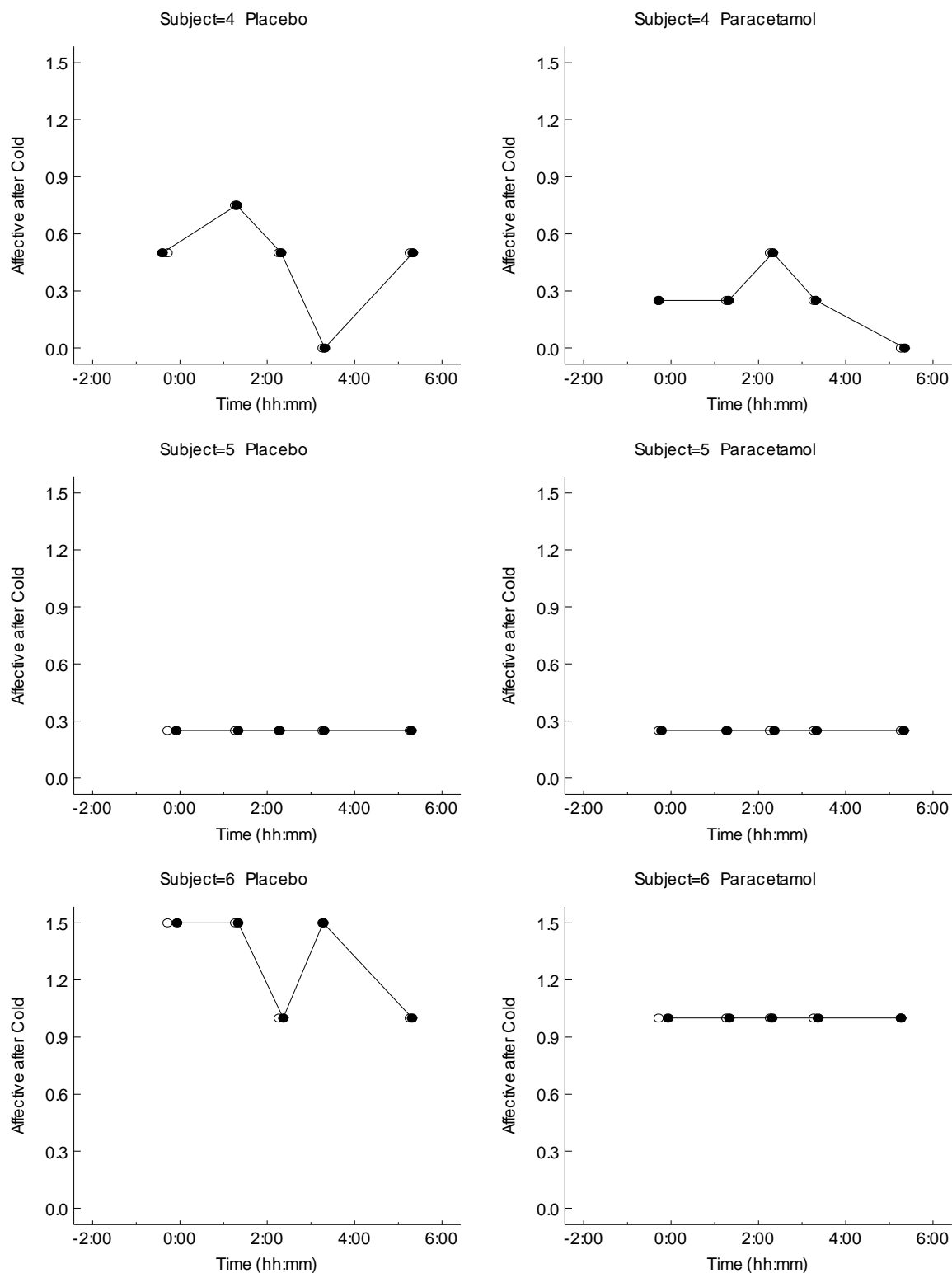
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Individual Plots 16 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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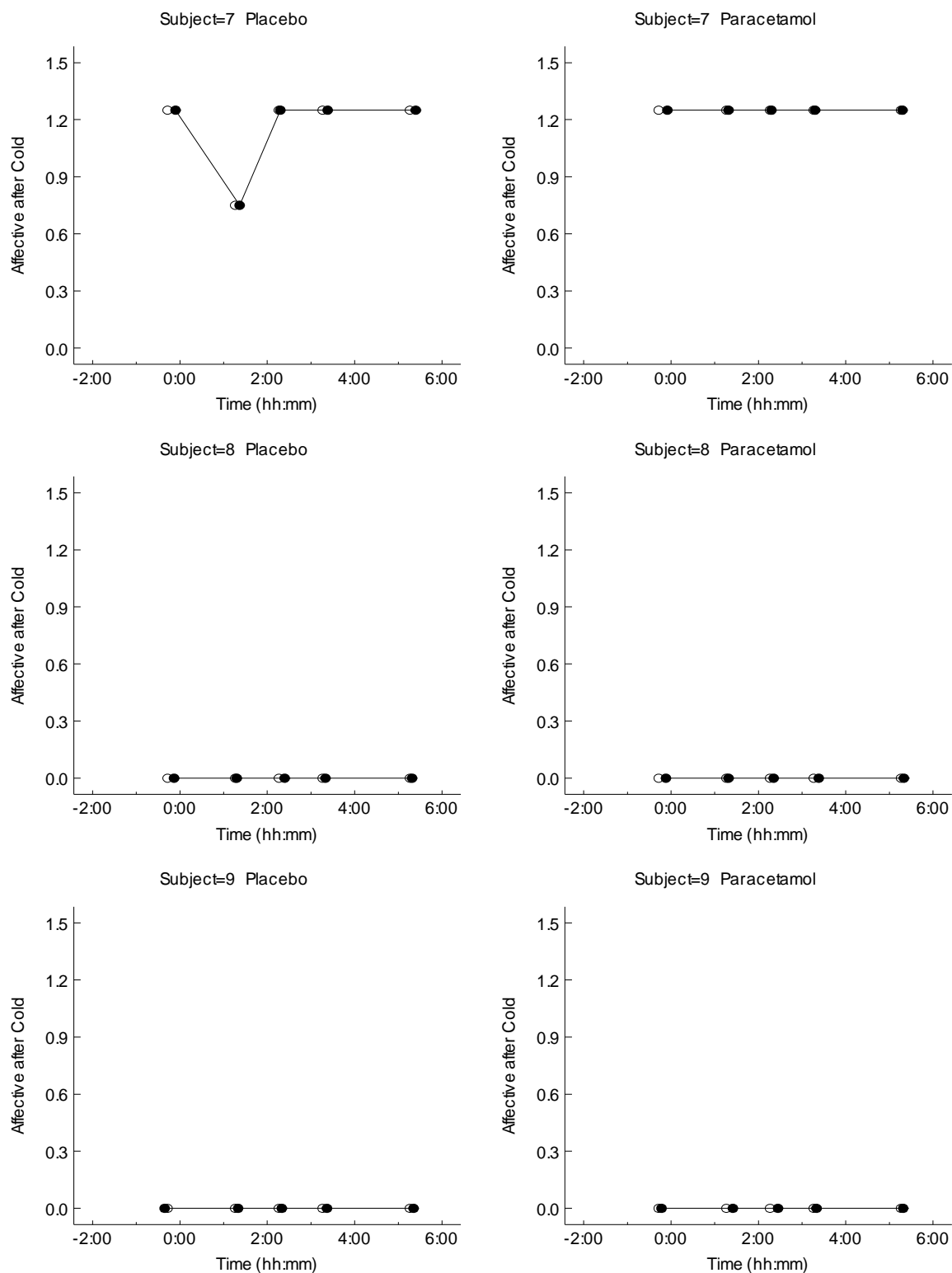
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Individual Plots 16 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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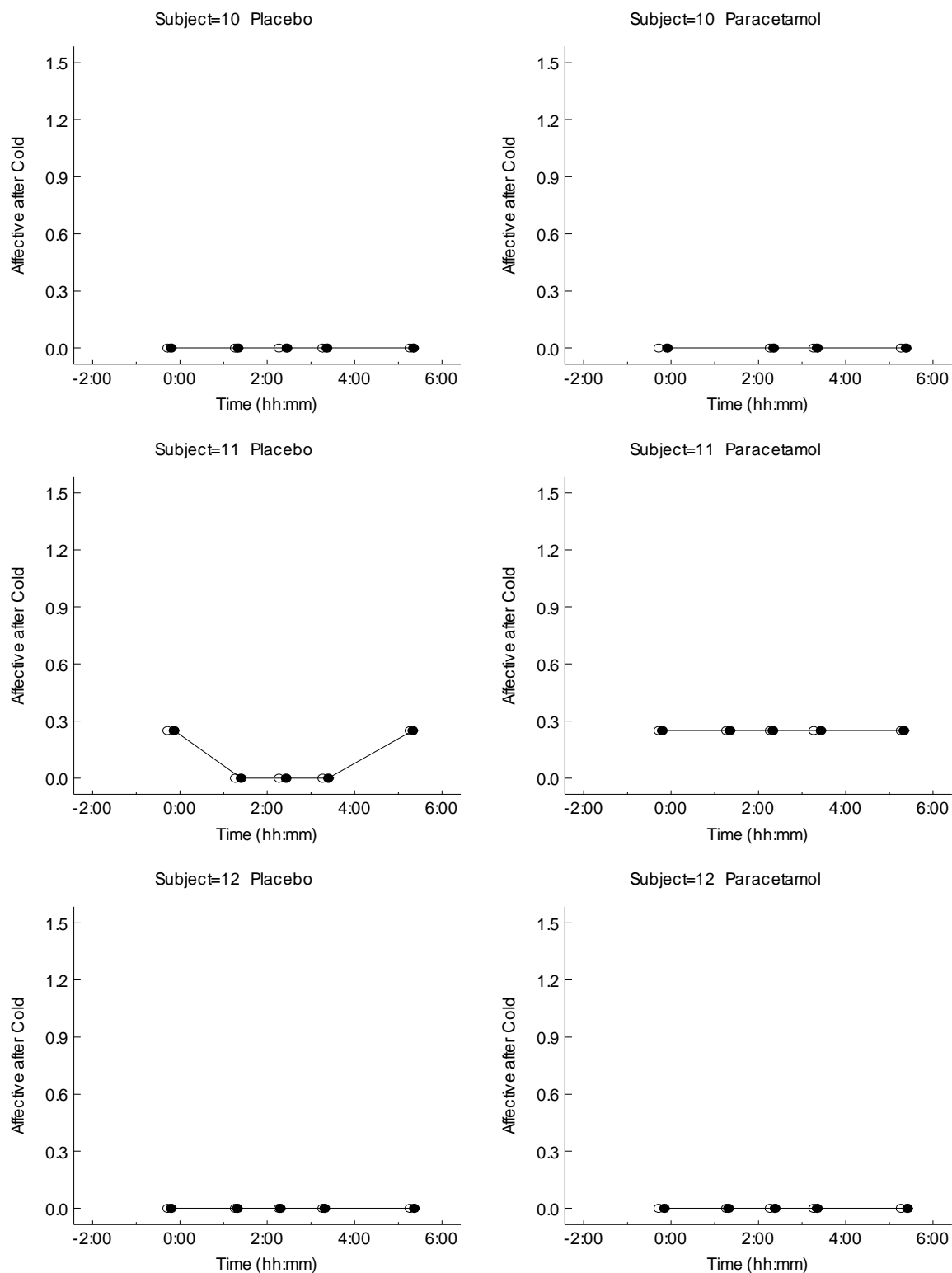
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Individual Plots 16 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 17 MPQ VAS after Cold (mm)

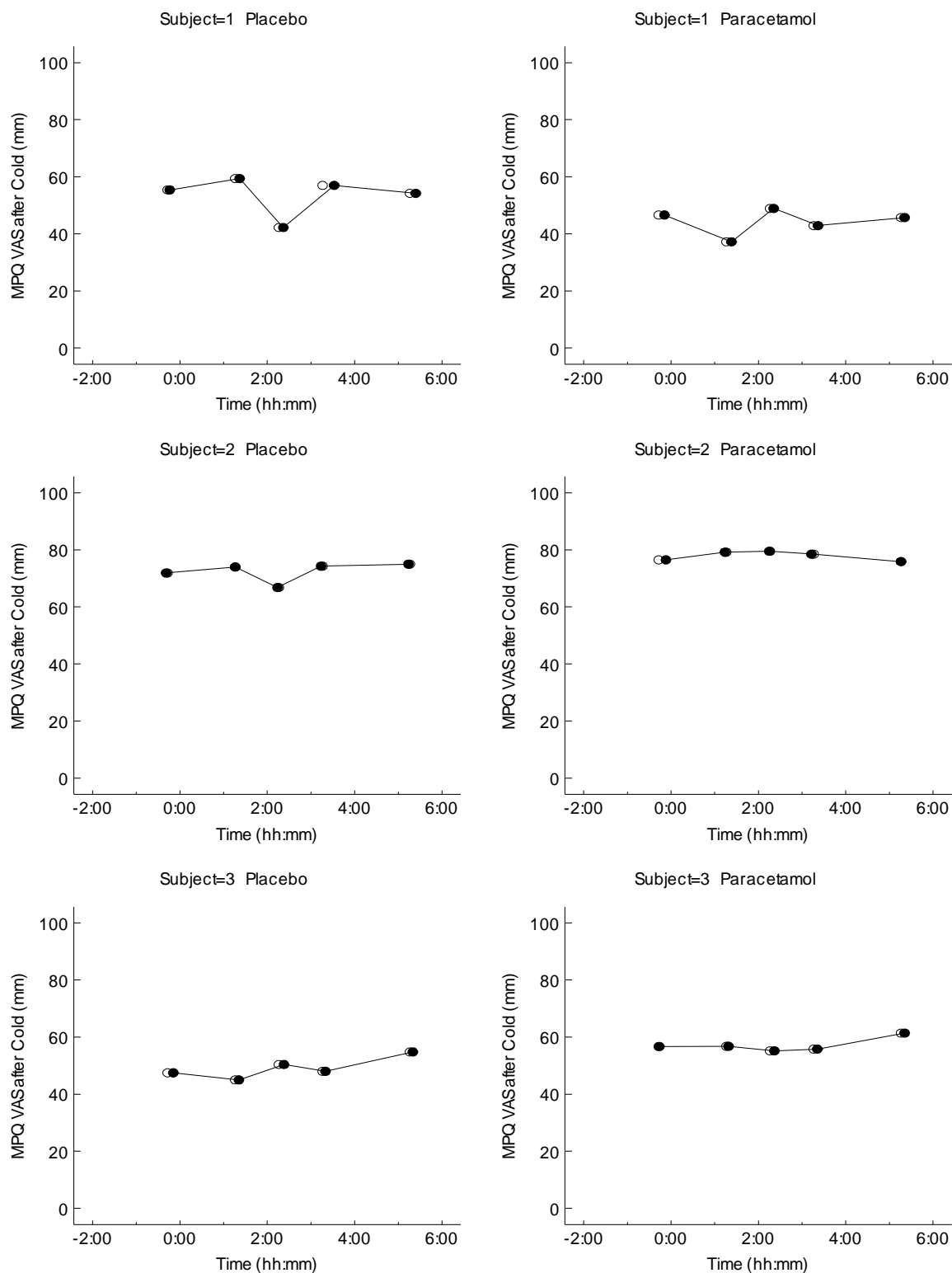
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Individual Plots 17 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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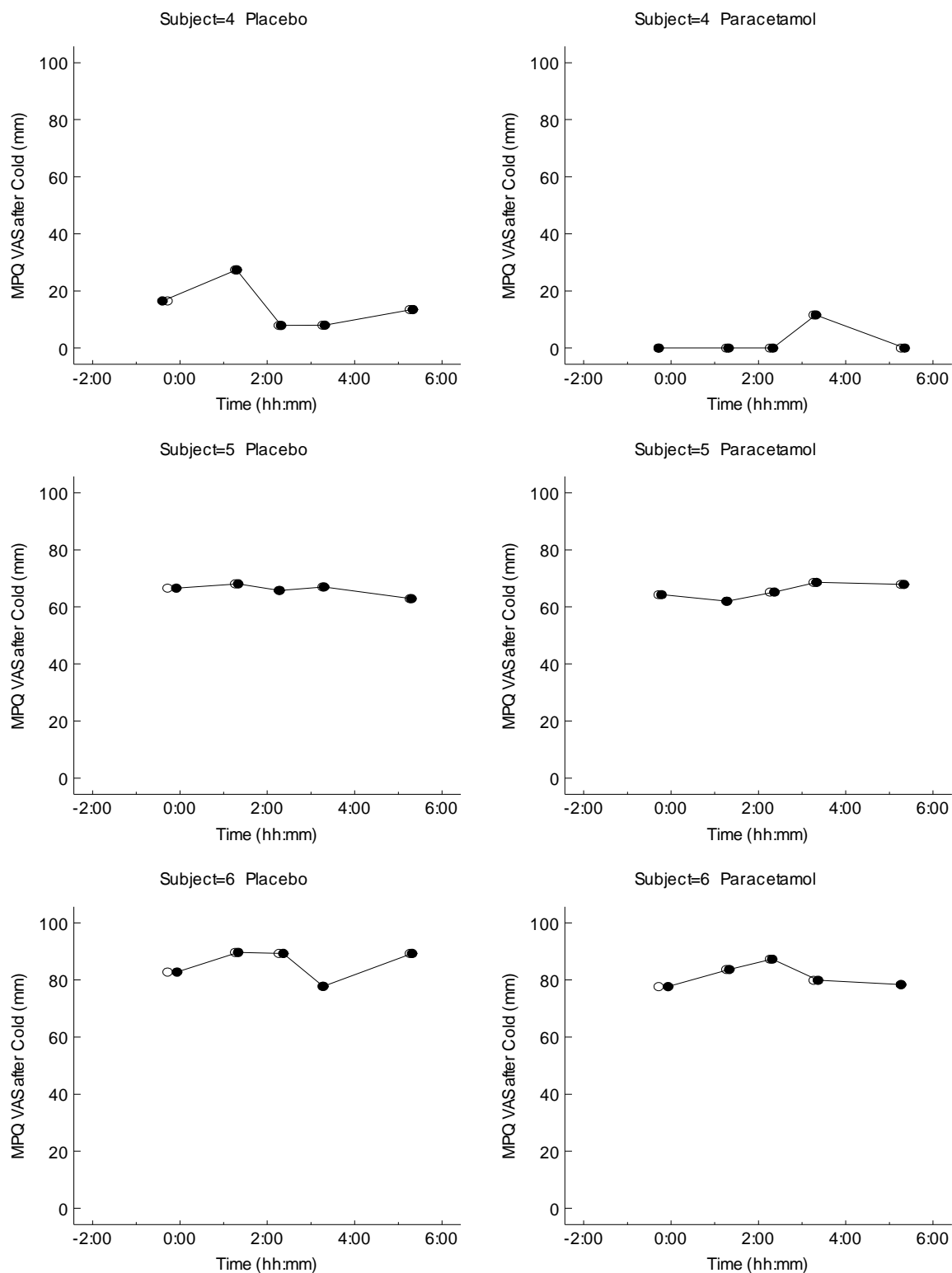
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Individual Plots 17 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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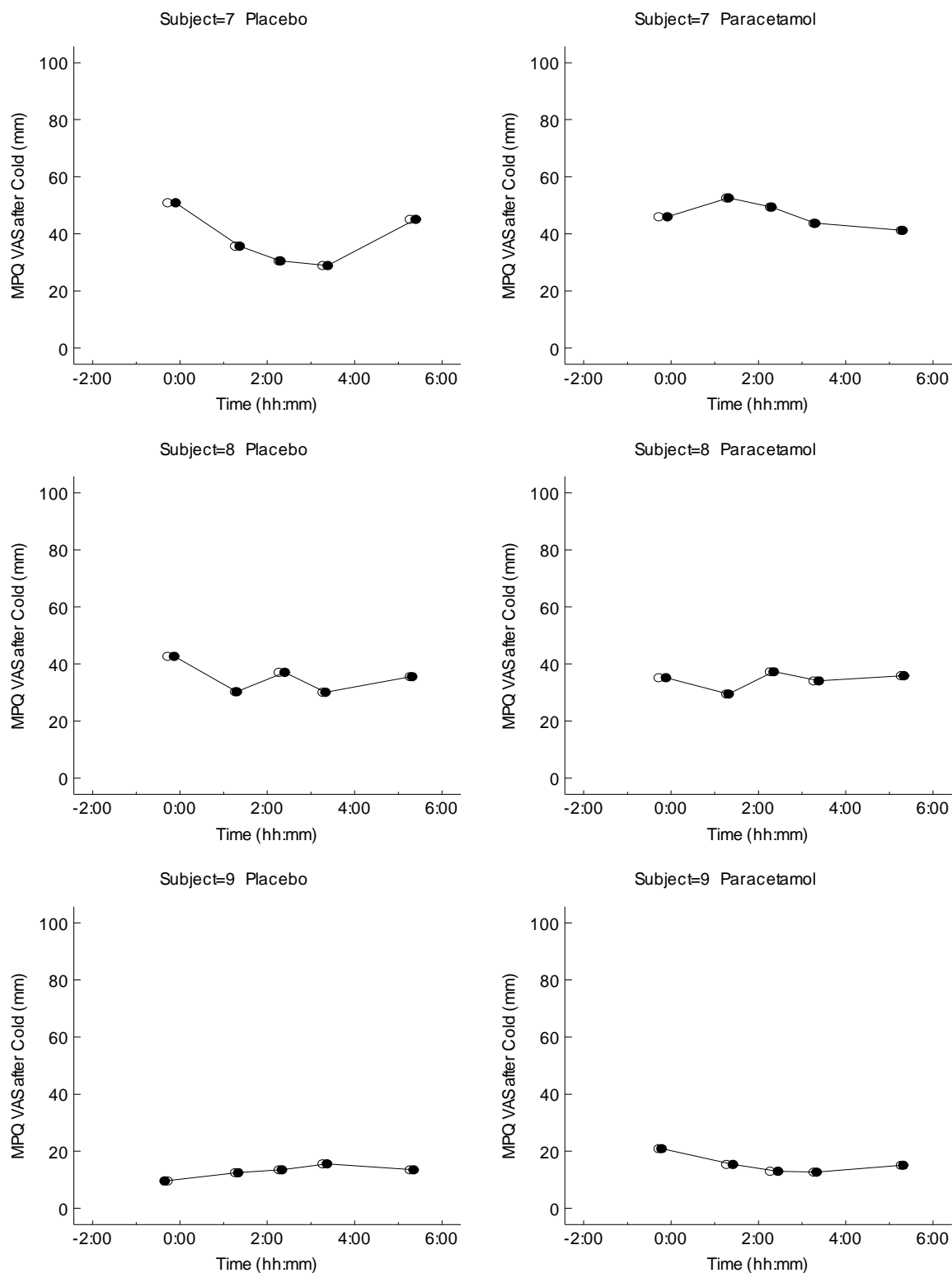
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Individual Plots 17 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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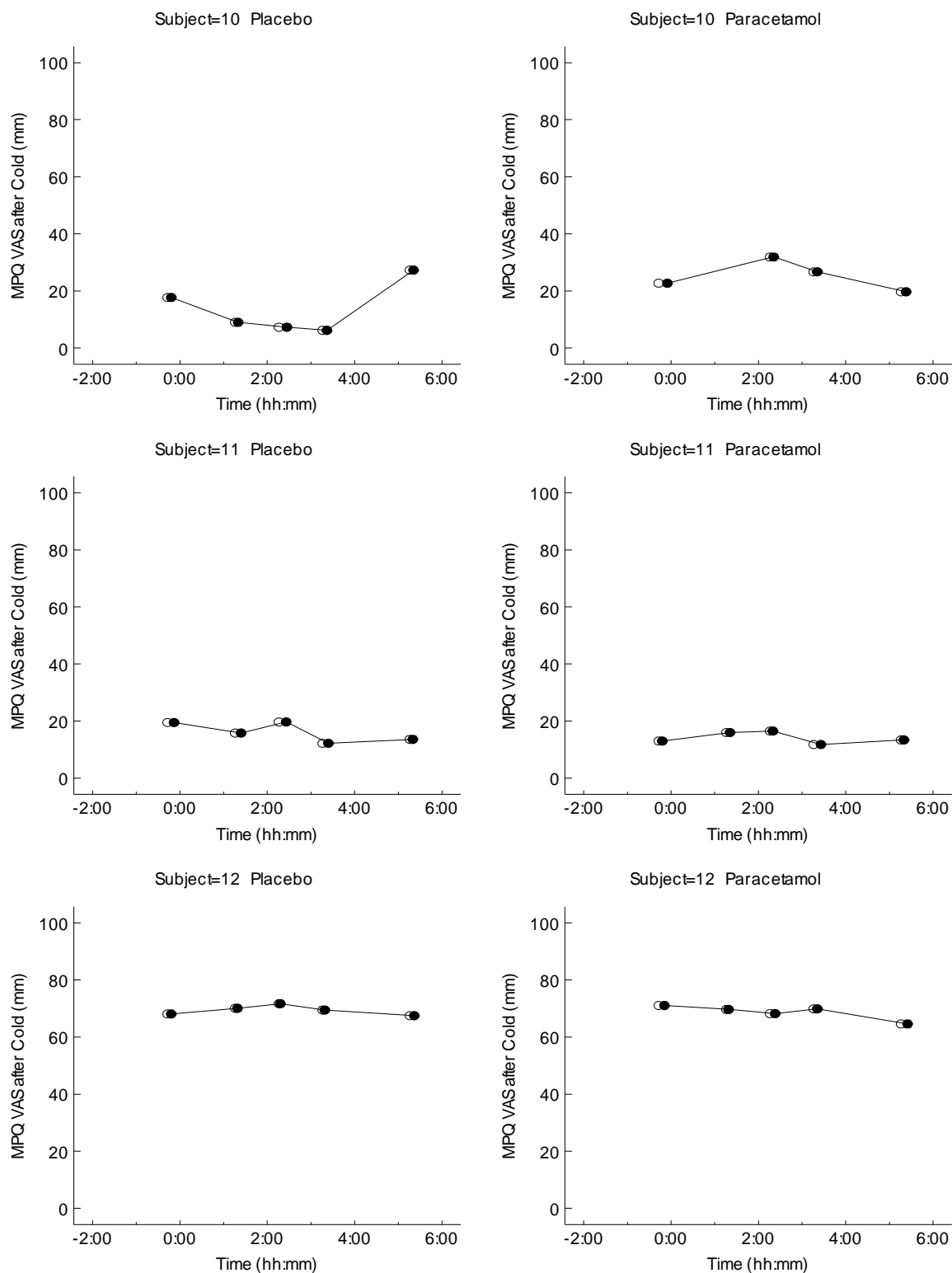
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Individual Plots 17 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 18 Sensory after ES

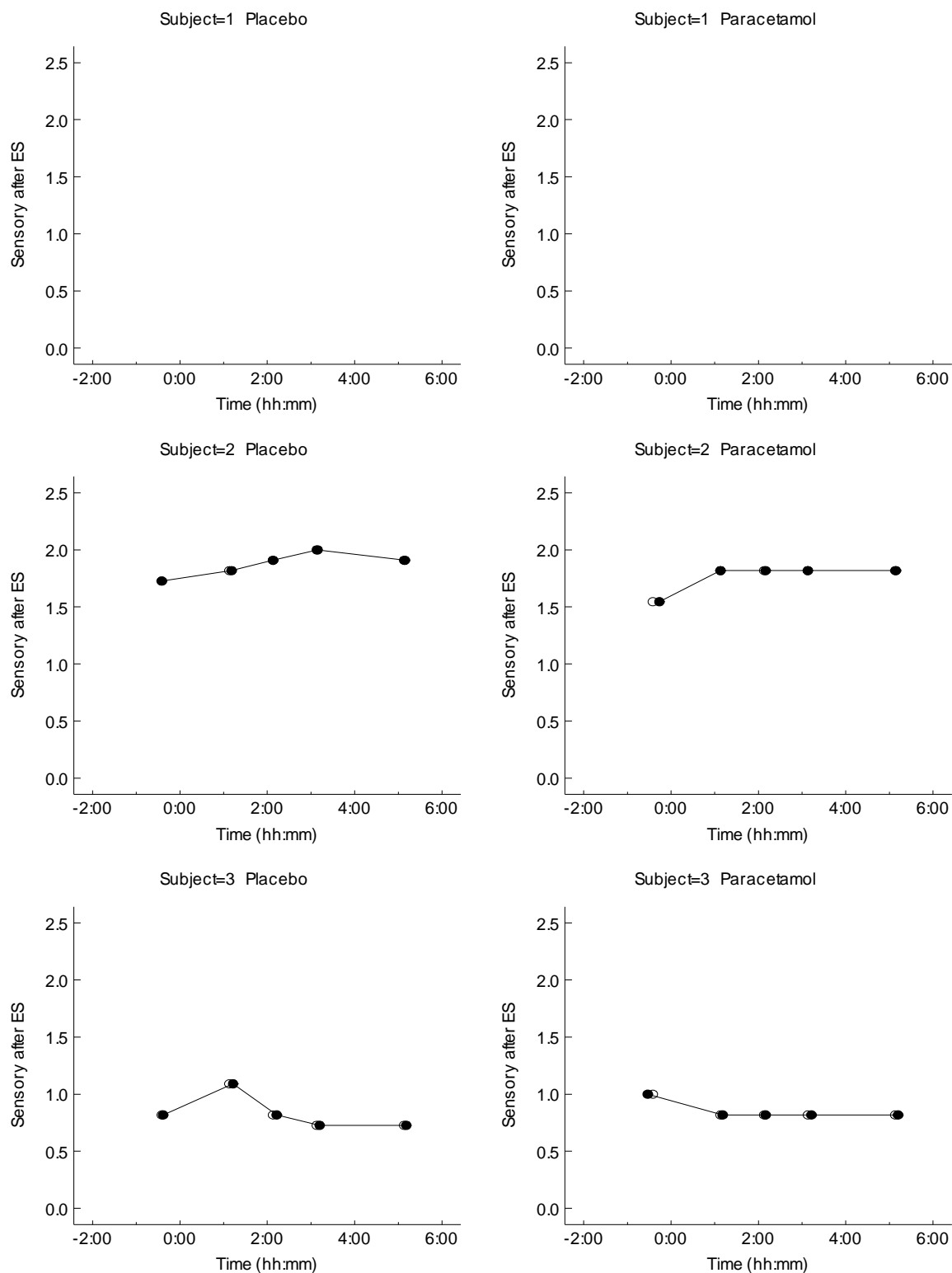
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Individual Plots 18 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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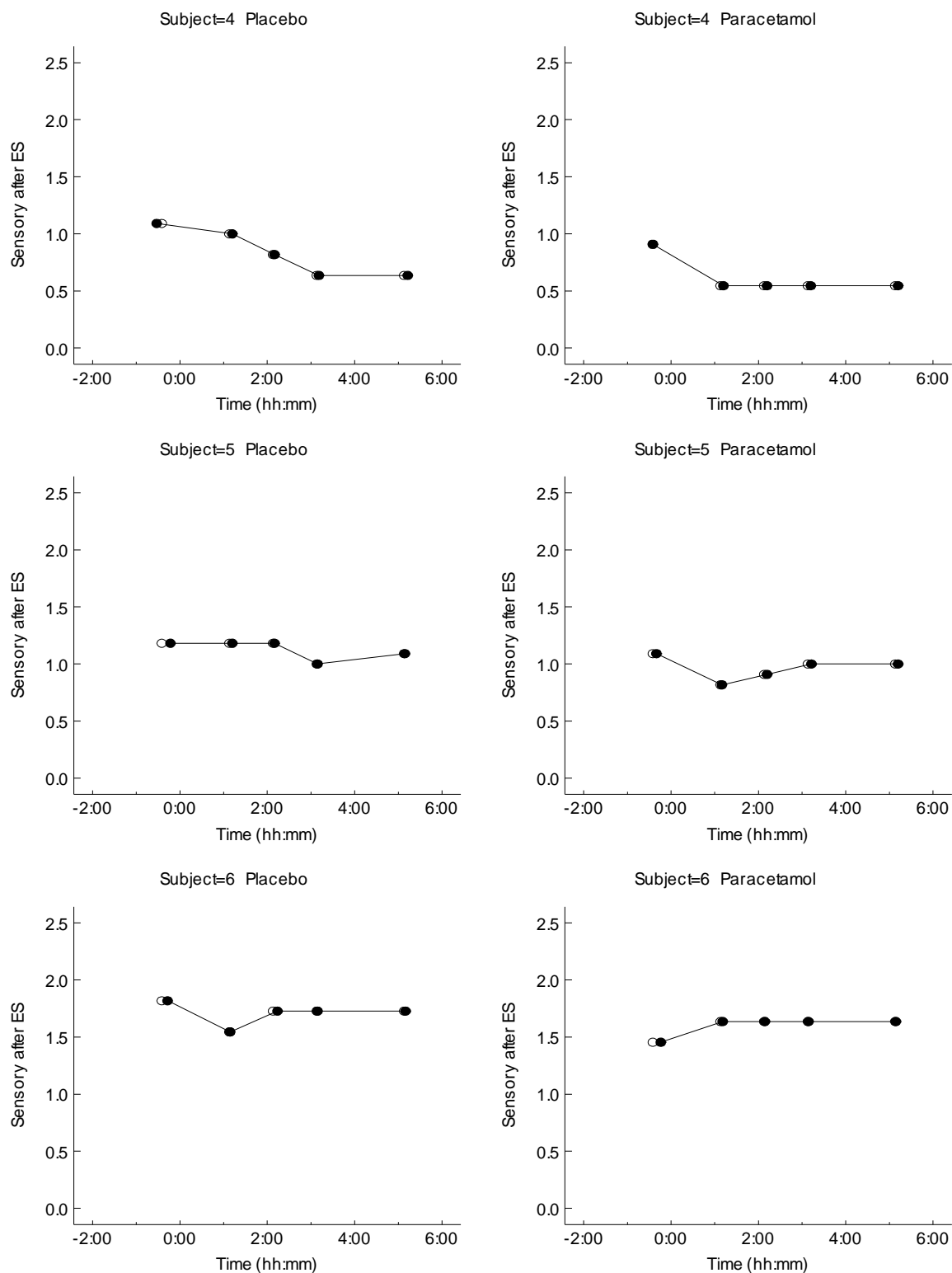
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Individual Plots 18 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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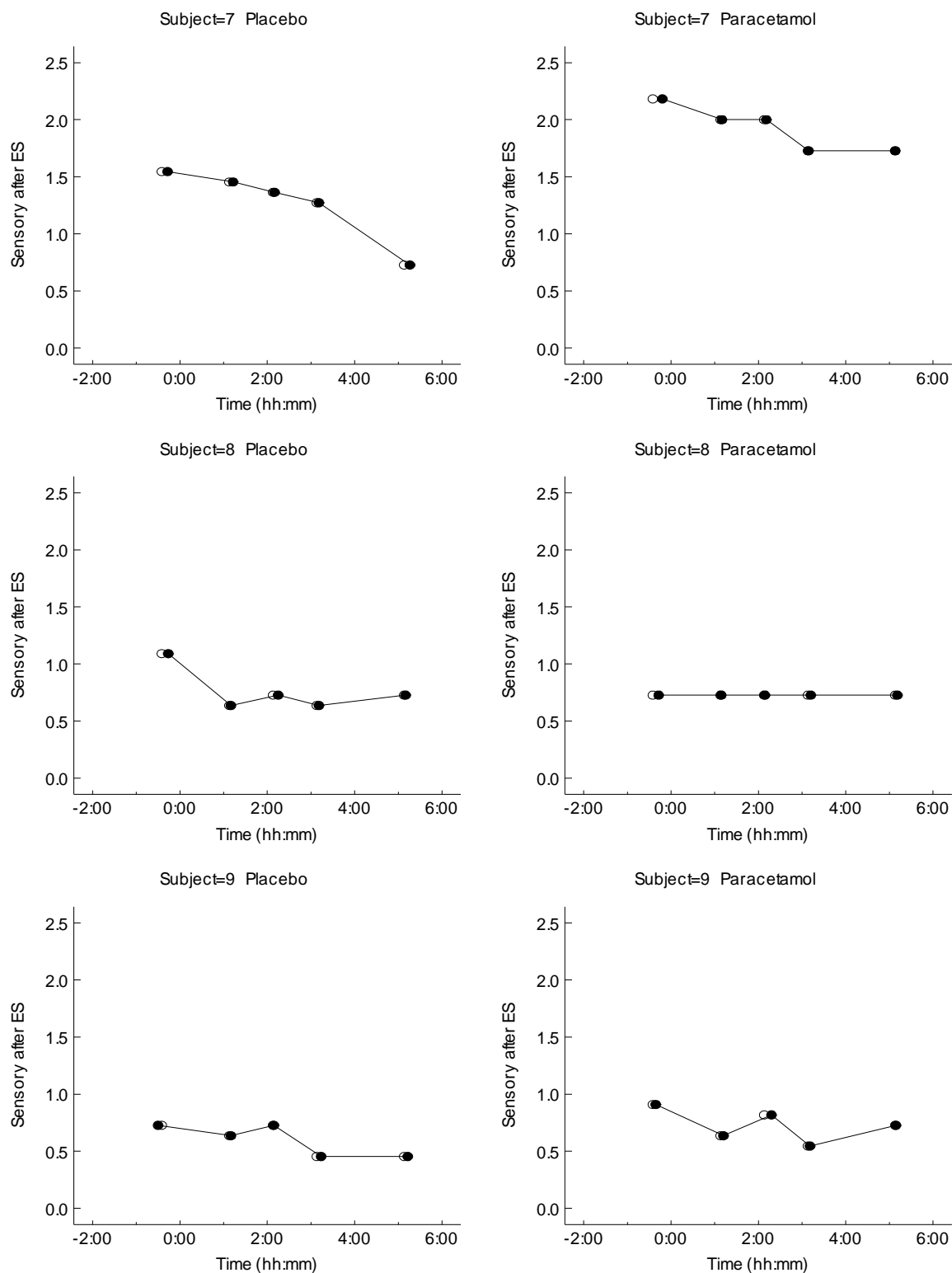
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Individual Plots 18 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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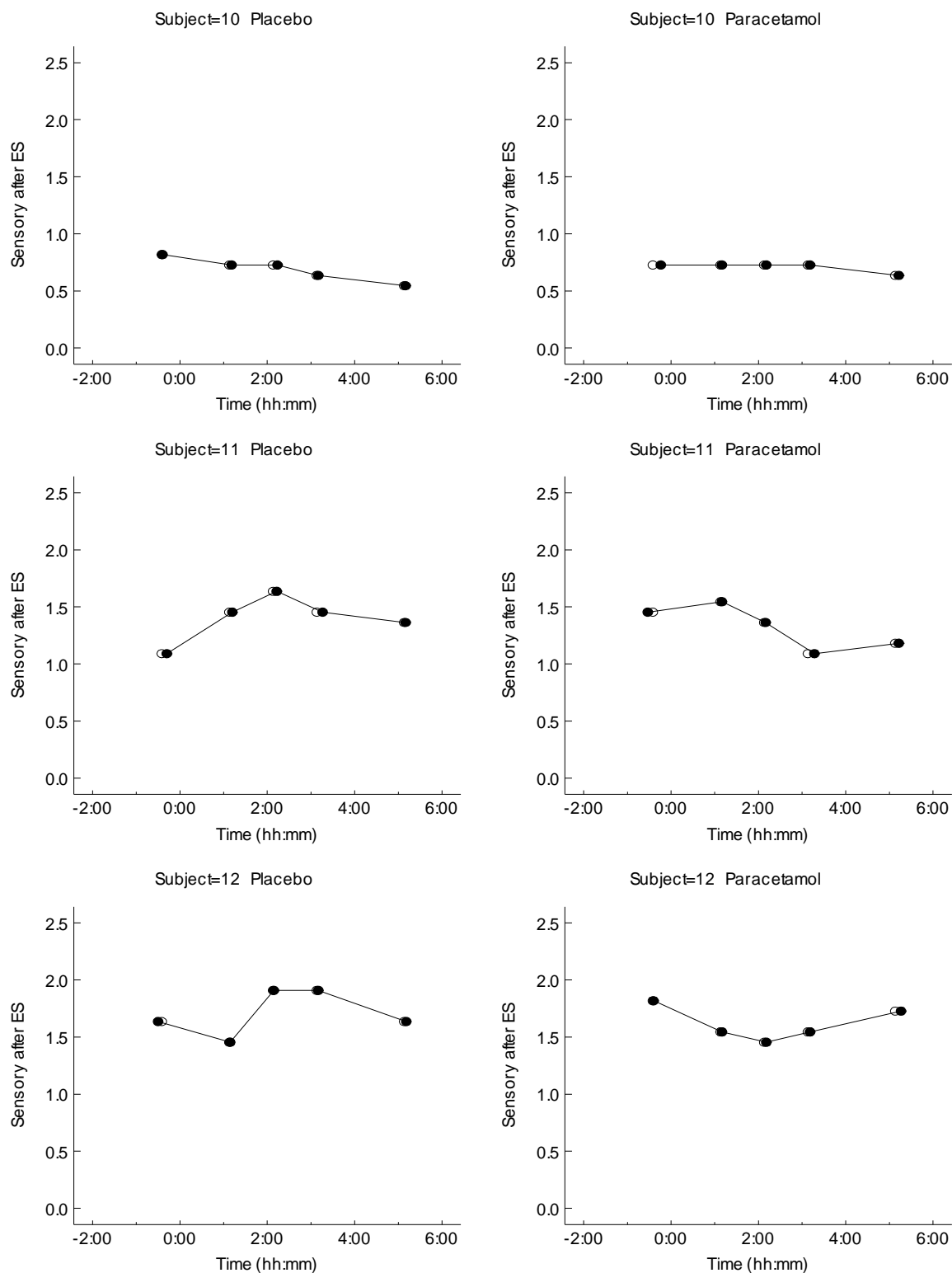
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Individual Plots 18 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 19 Affective after ES

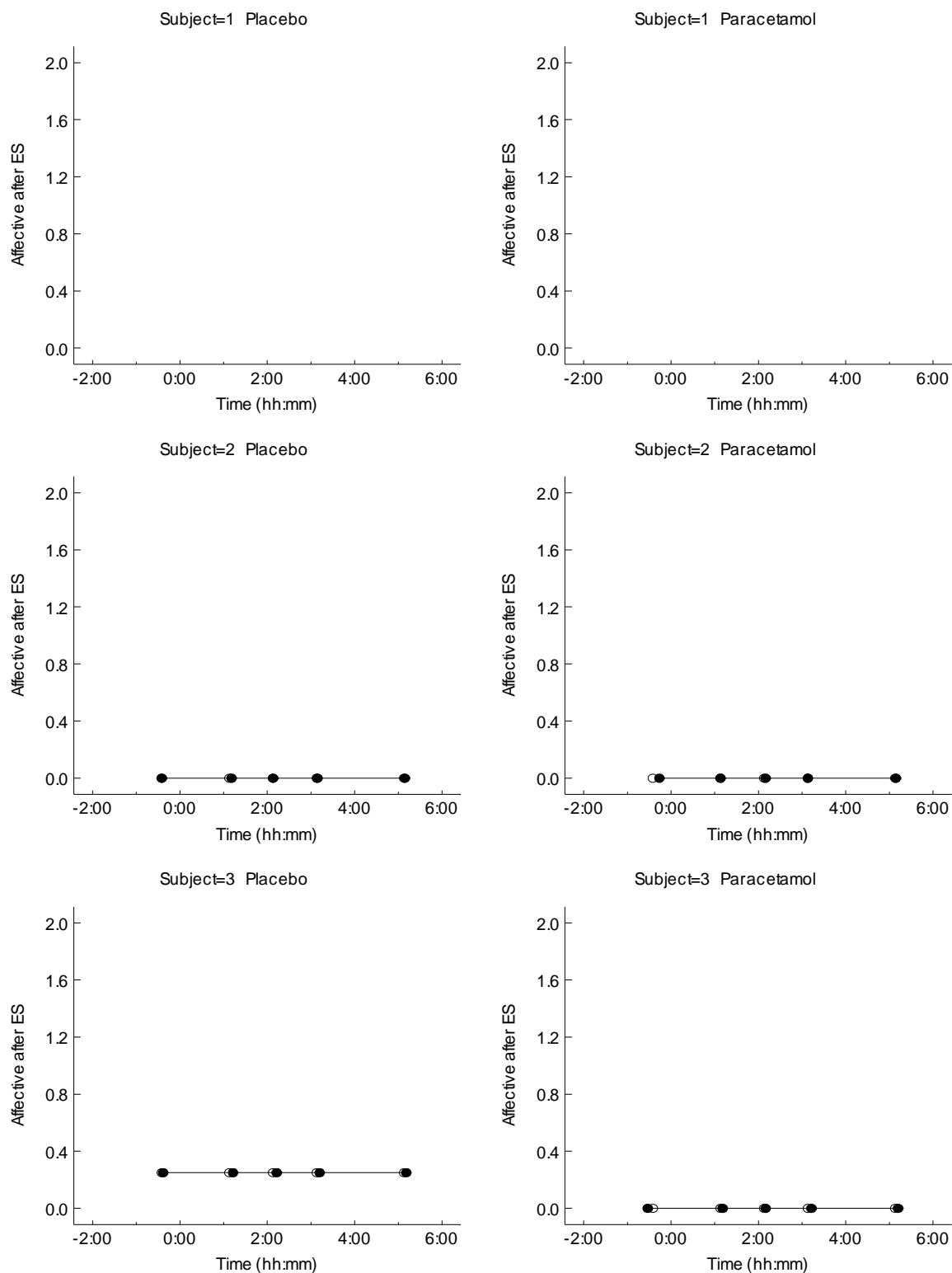
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Individual Plots 19 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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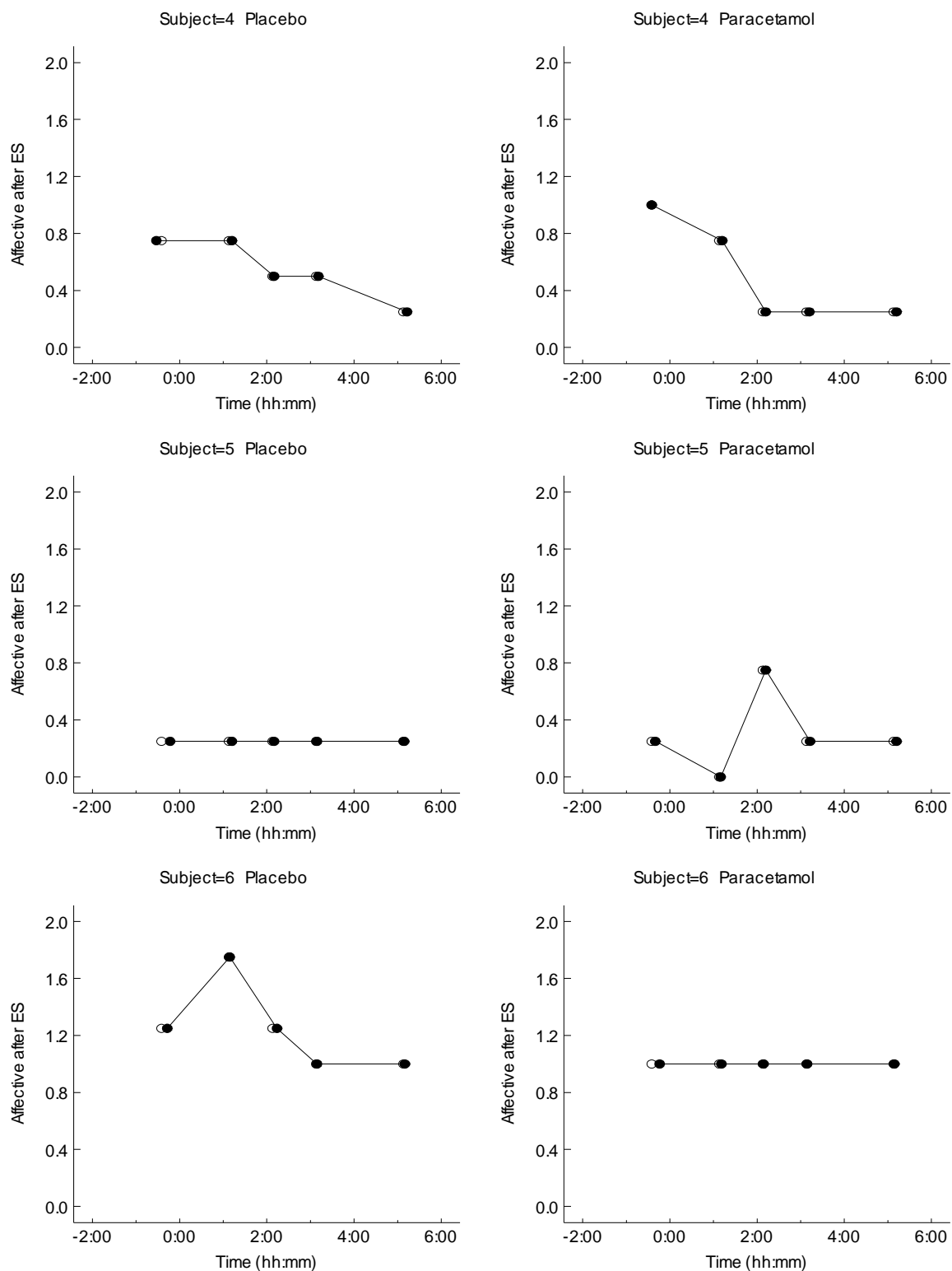
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Individual Plots 19 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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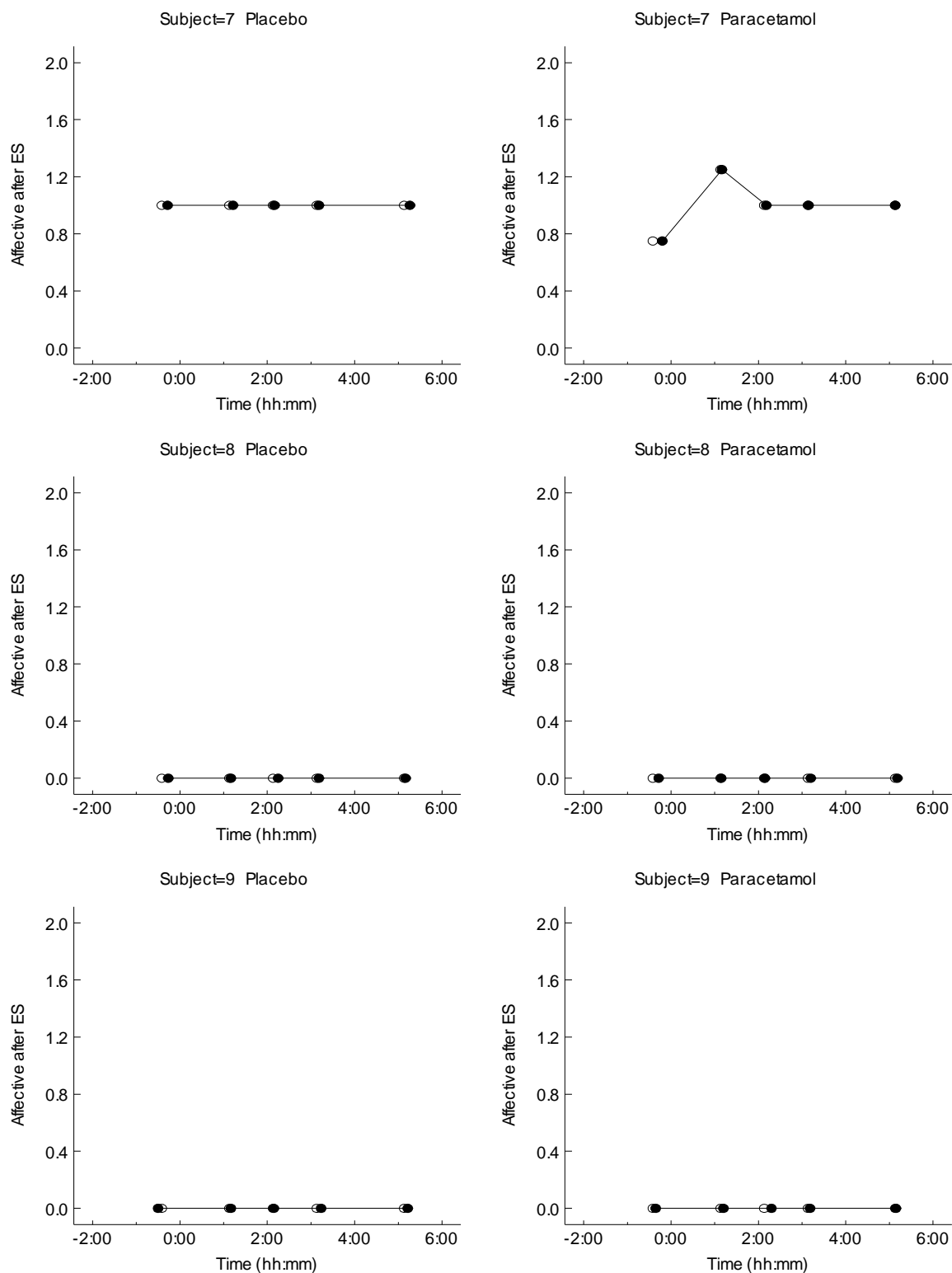
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Individual Plots 19 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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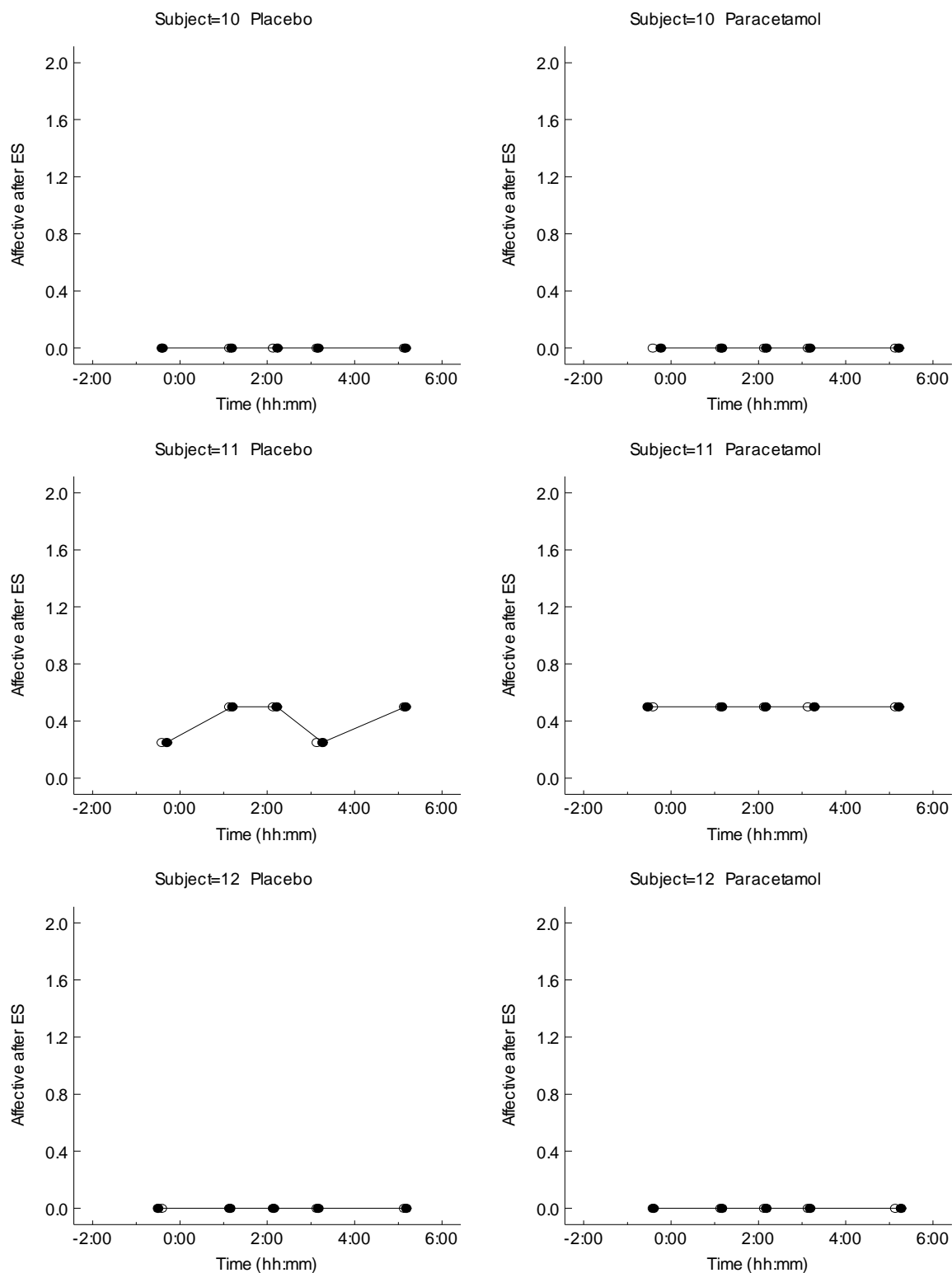
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Individual Plots 19 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 20 MPQ VAS after ES (mm)

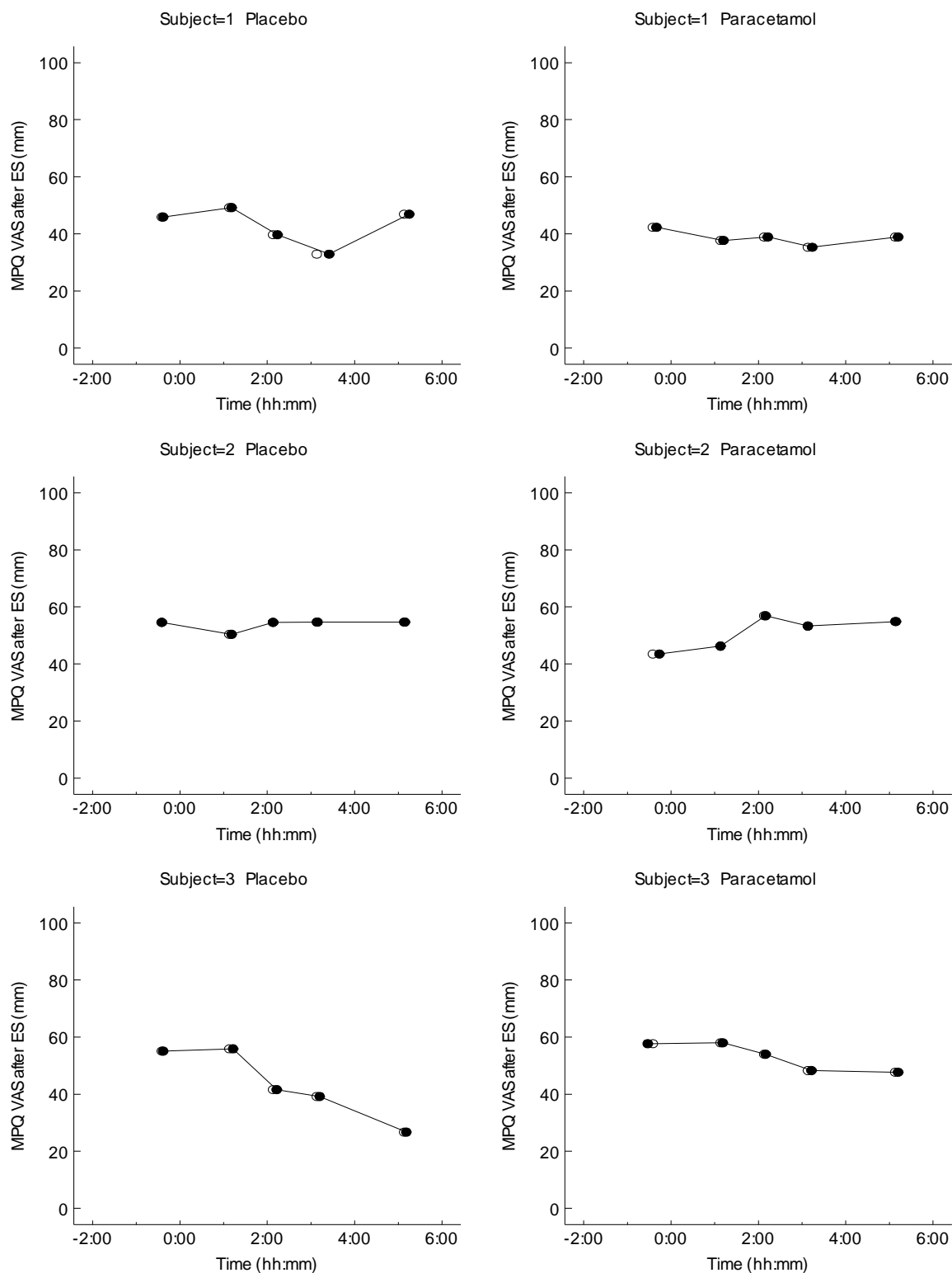
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Individual Plots 20 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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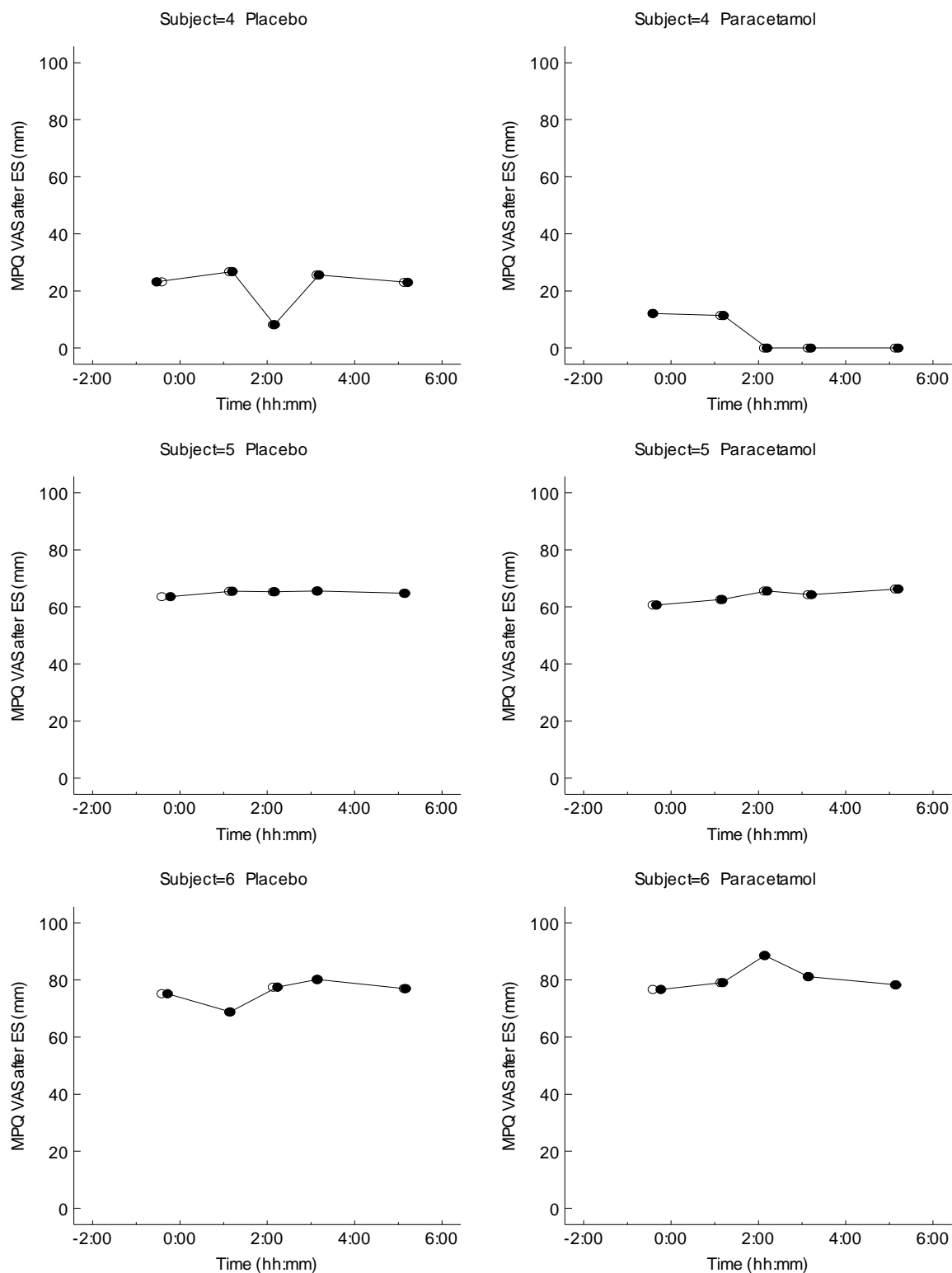
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Individual Plots 20 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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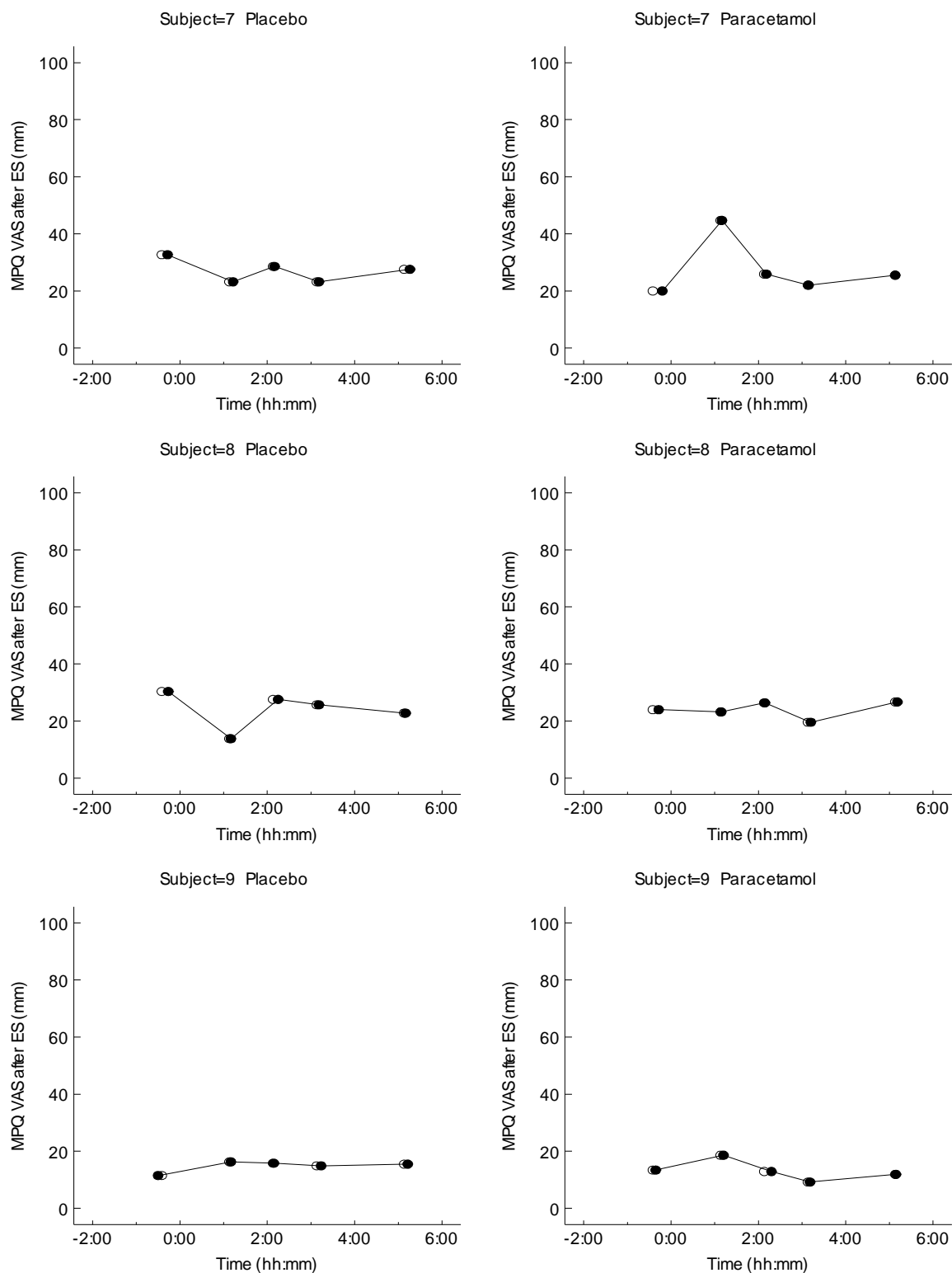
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Individual Plots 20 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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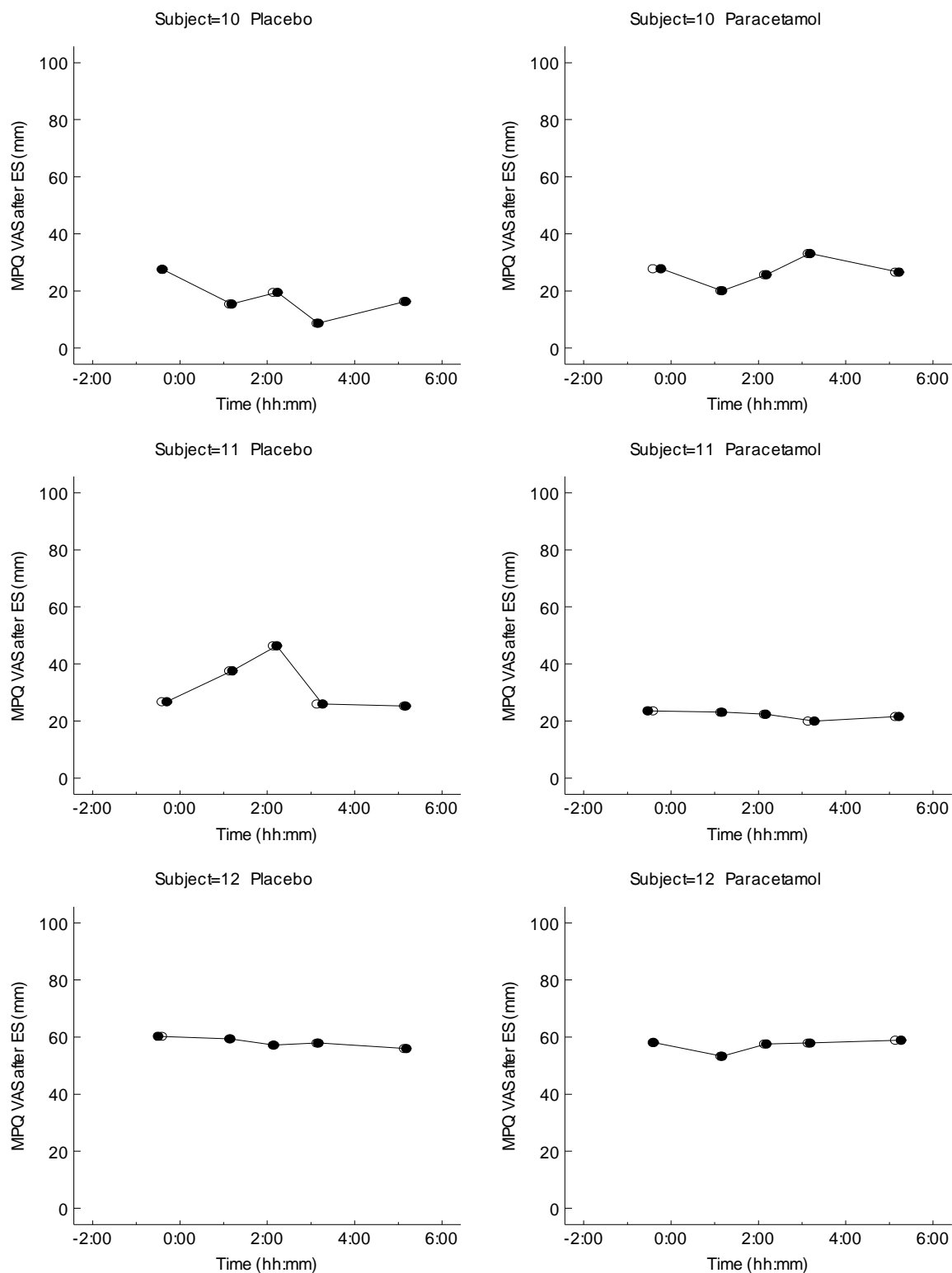
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Individual Plots 20 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 21 Sensory after Pressure

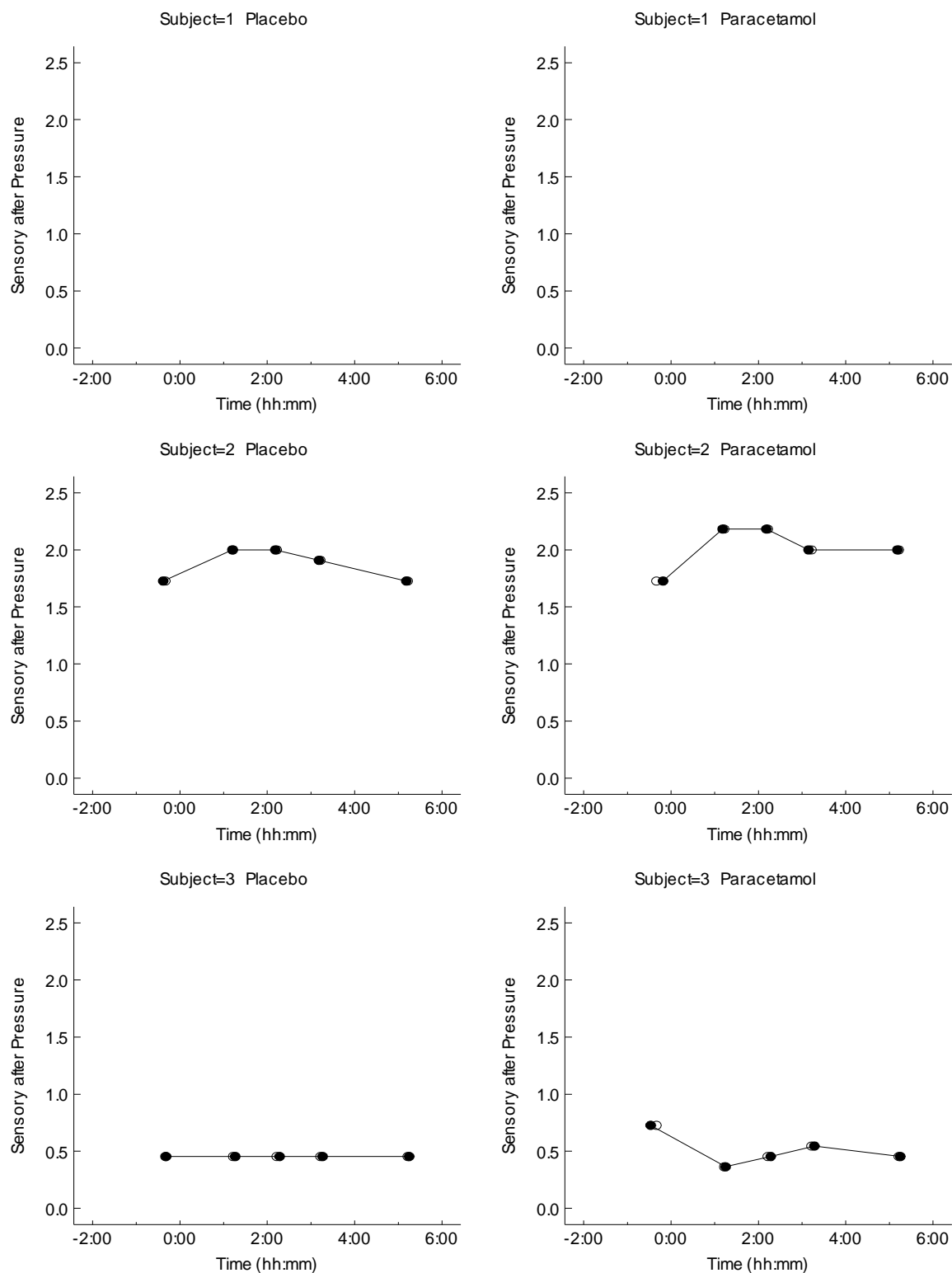
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Individual Plots 21 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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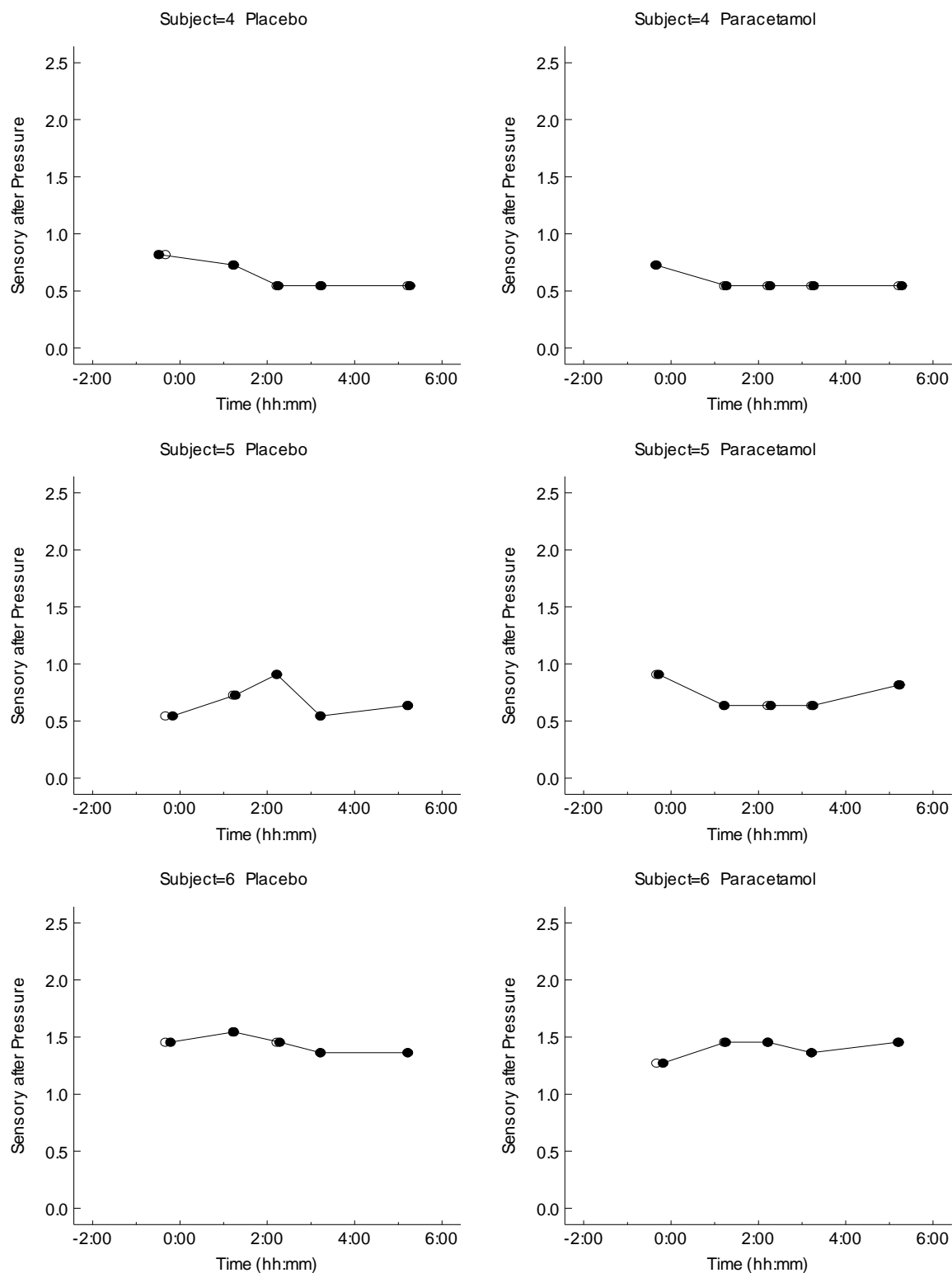
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Individual Plots 21 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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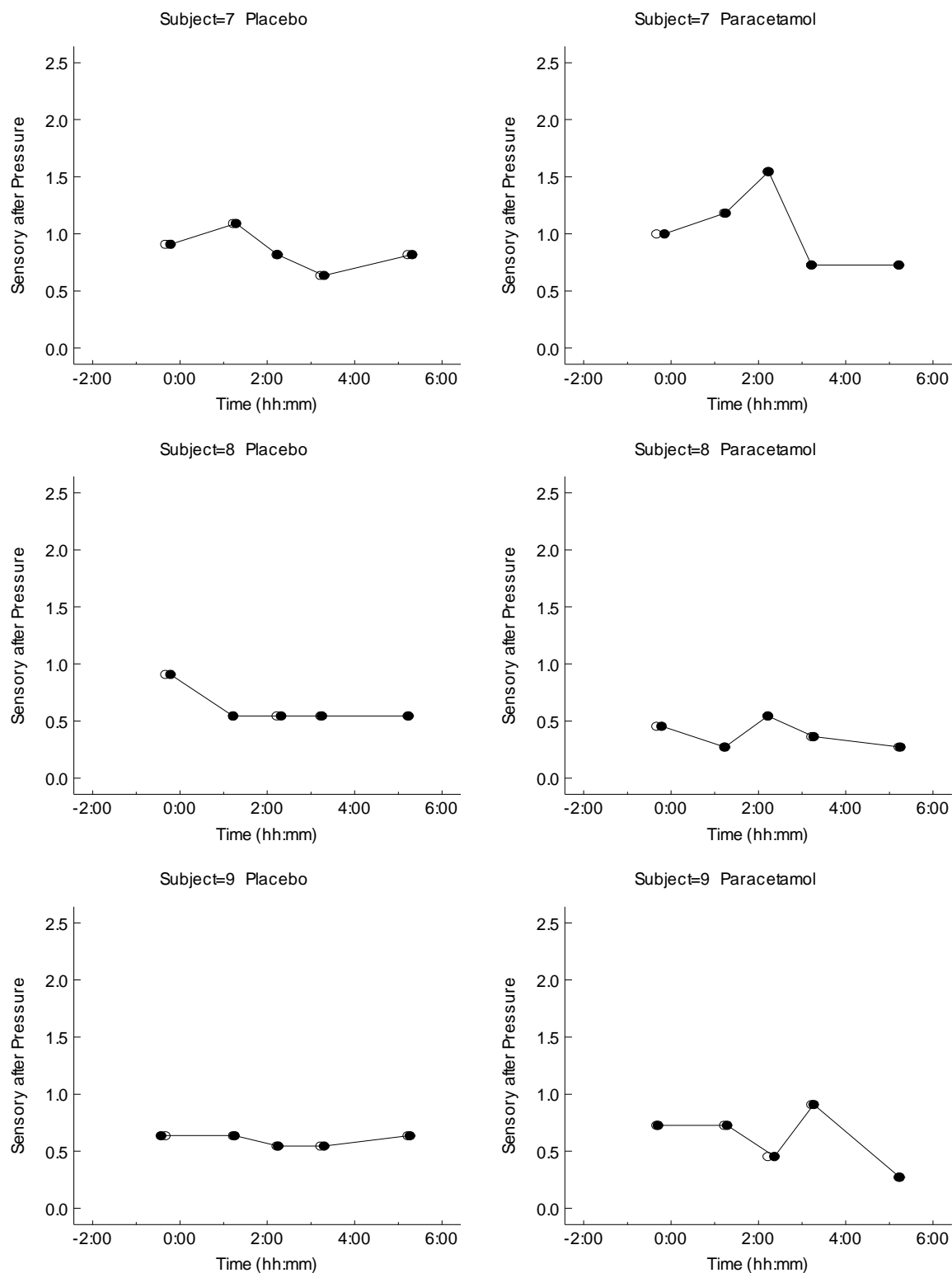
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Individual Plots 21 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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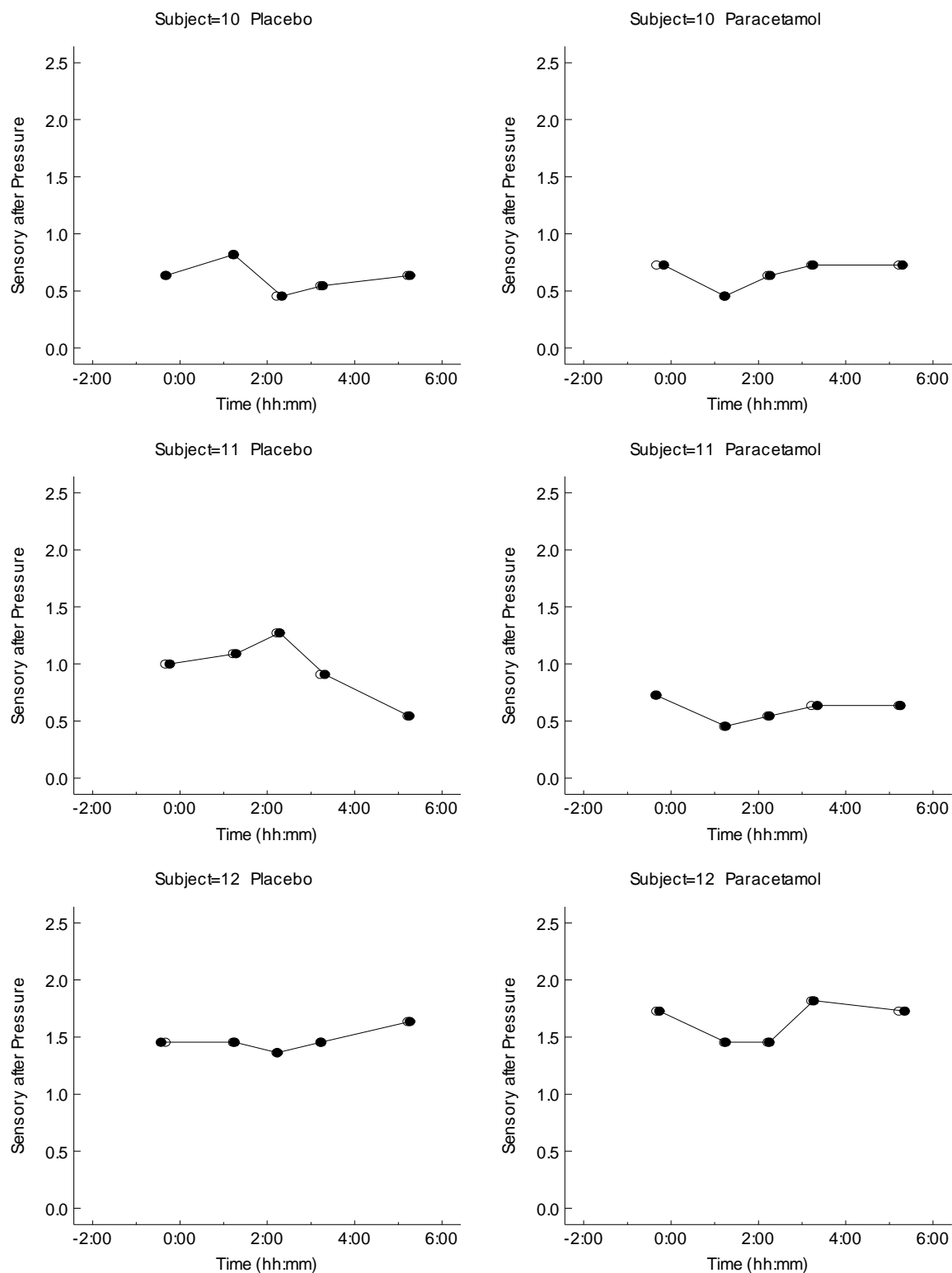
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Individual Plots 21 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 22 Affective after Pressure

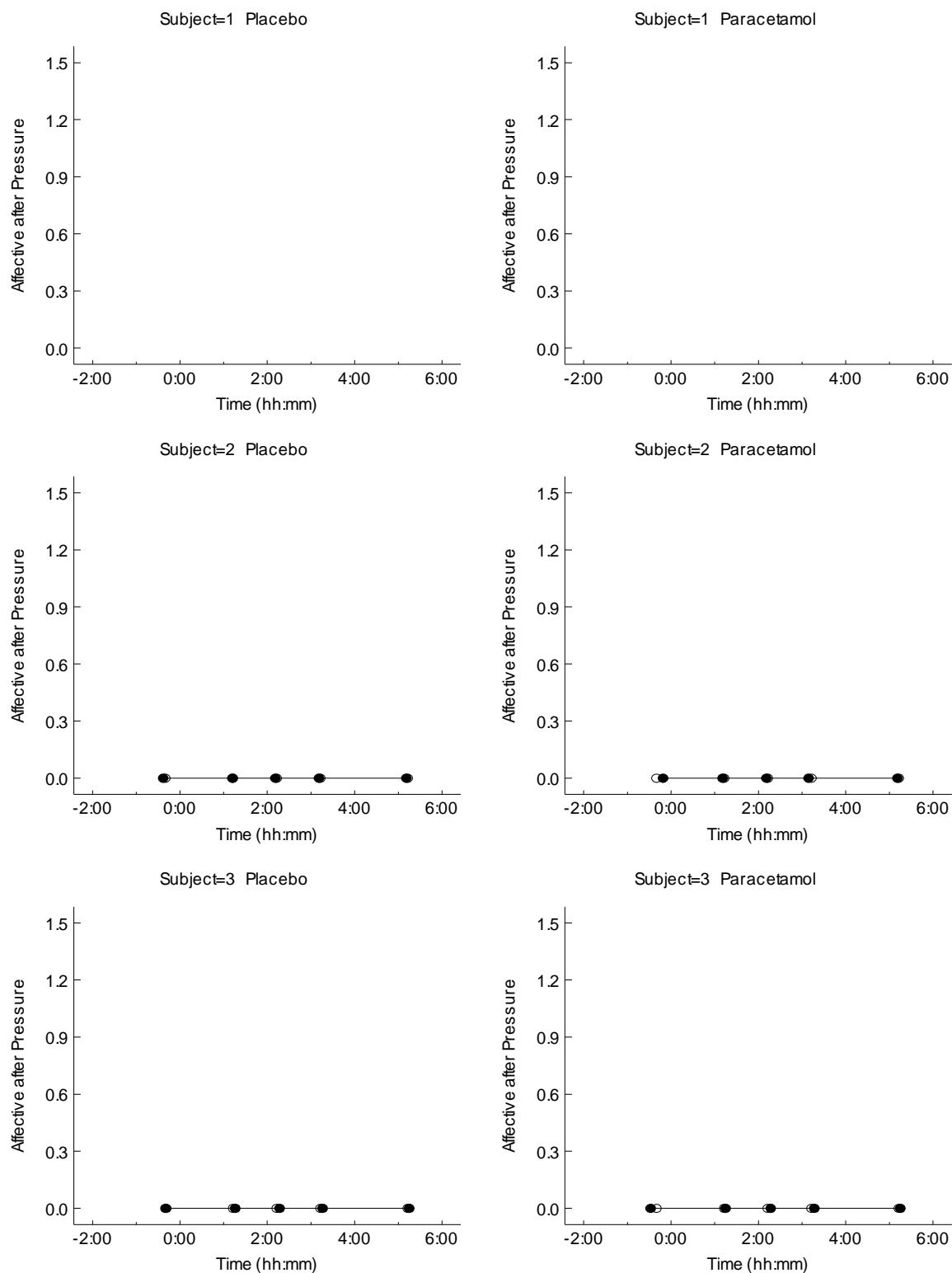
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Individual Plots 22 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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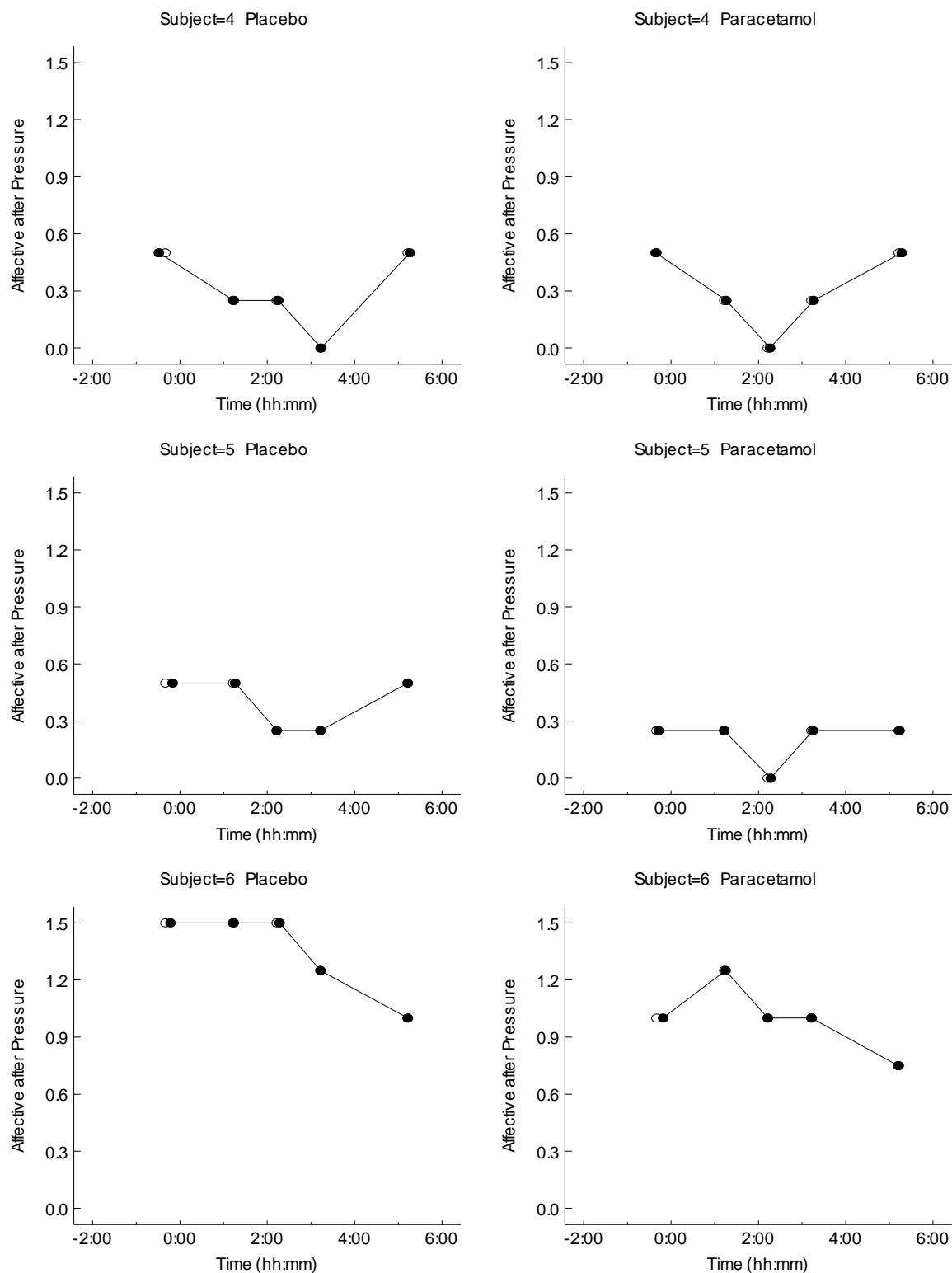
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Individual Plots 22 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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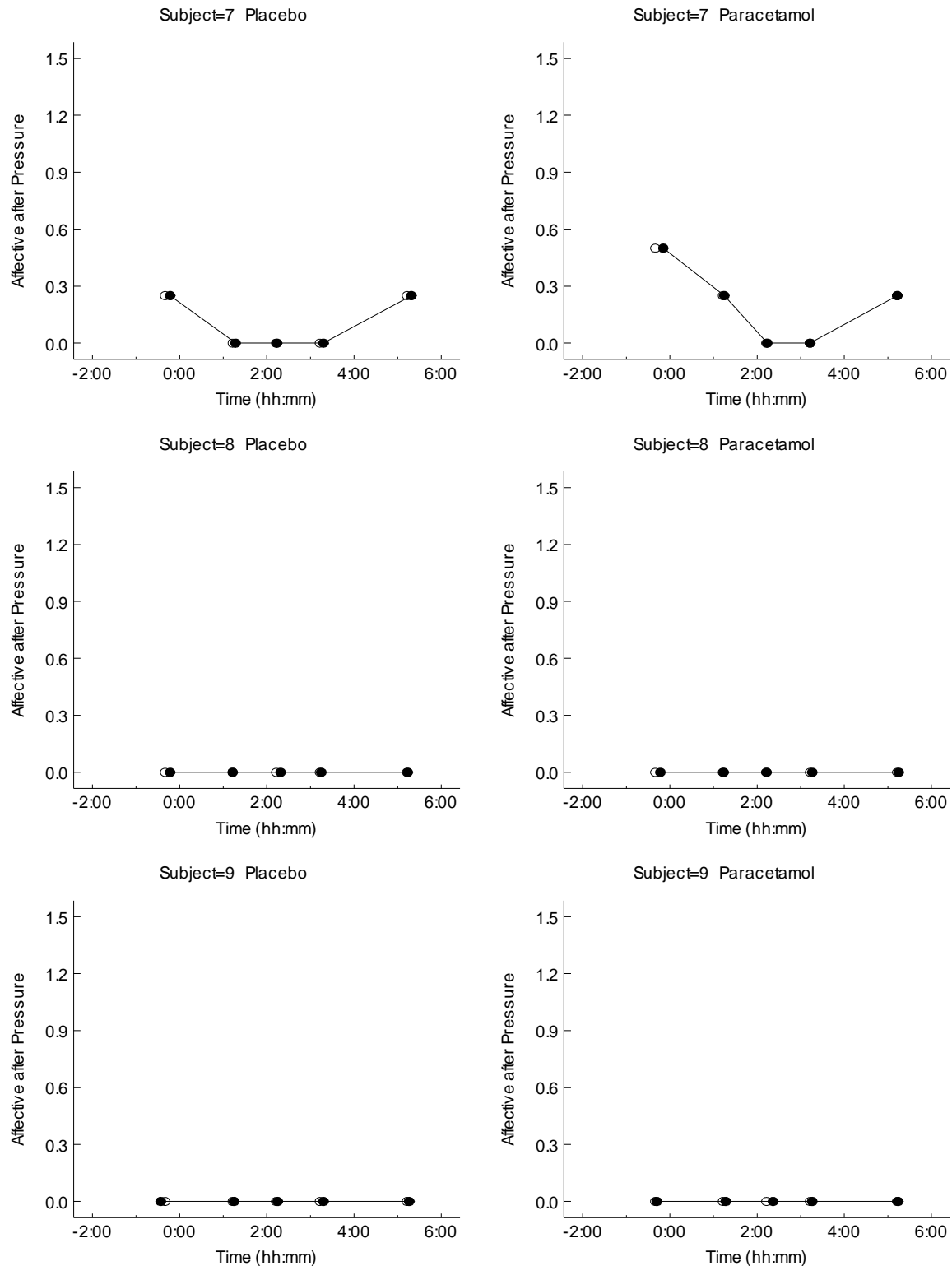
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Individual Plots 22 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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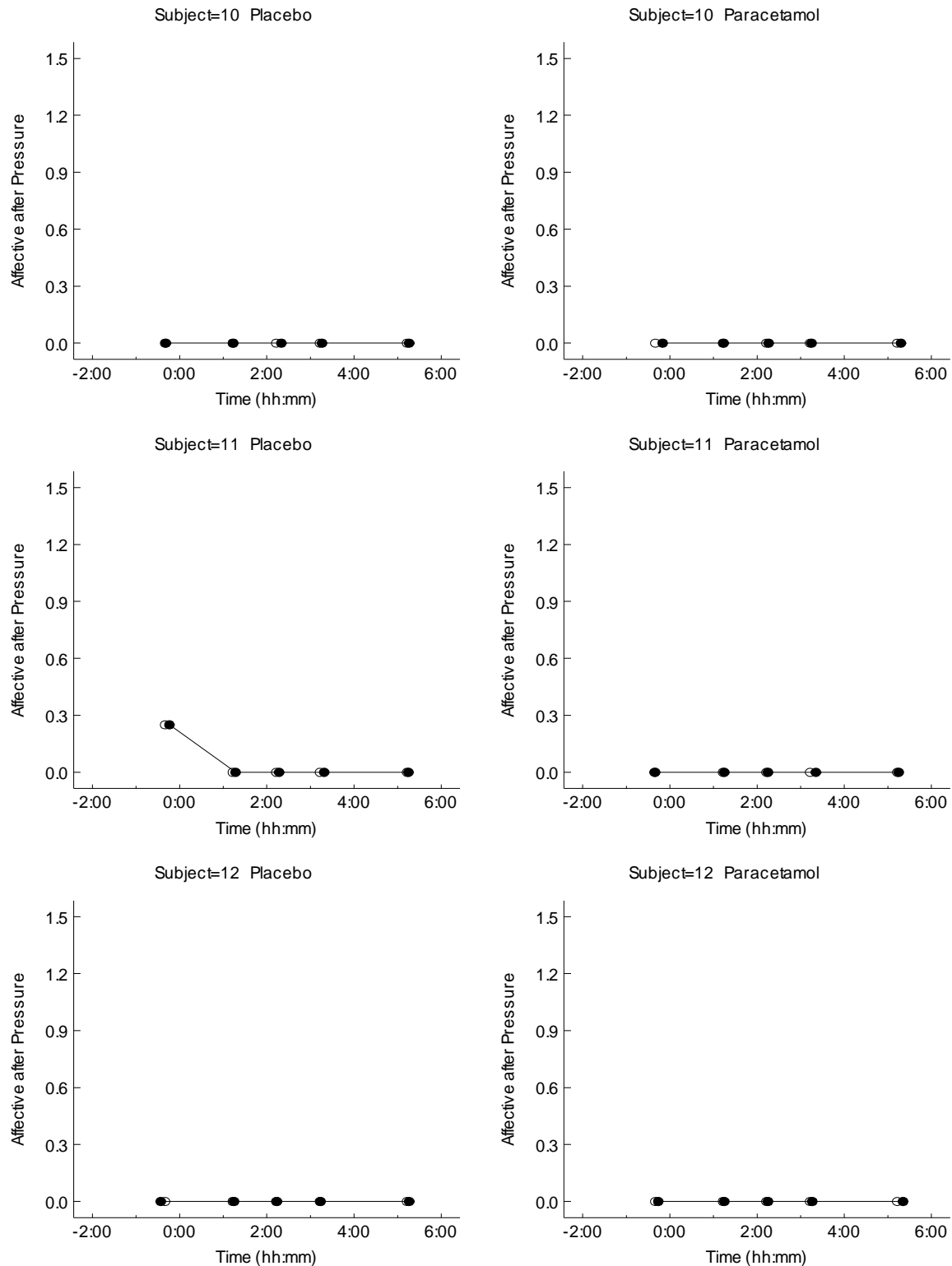
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Individual Plots 22 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Individual plots 23 MPQ VAS after Pressure (mm)

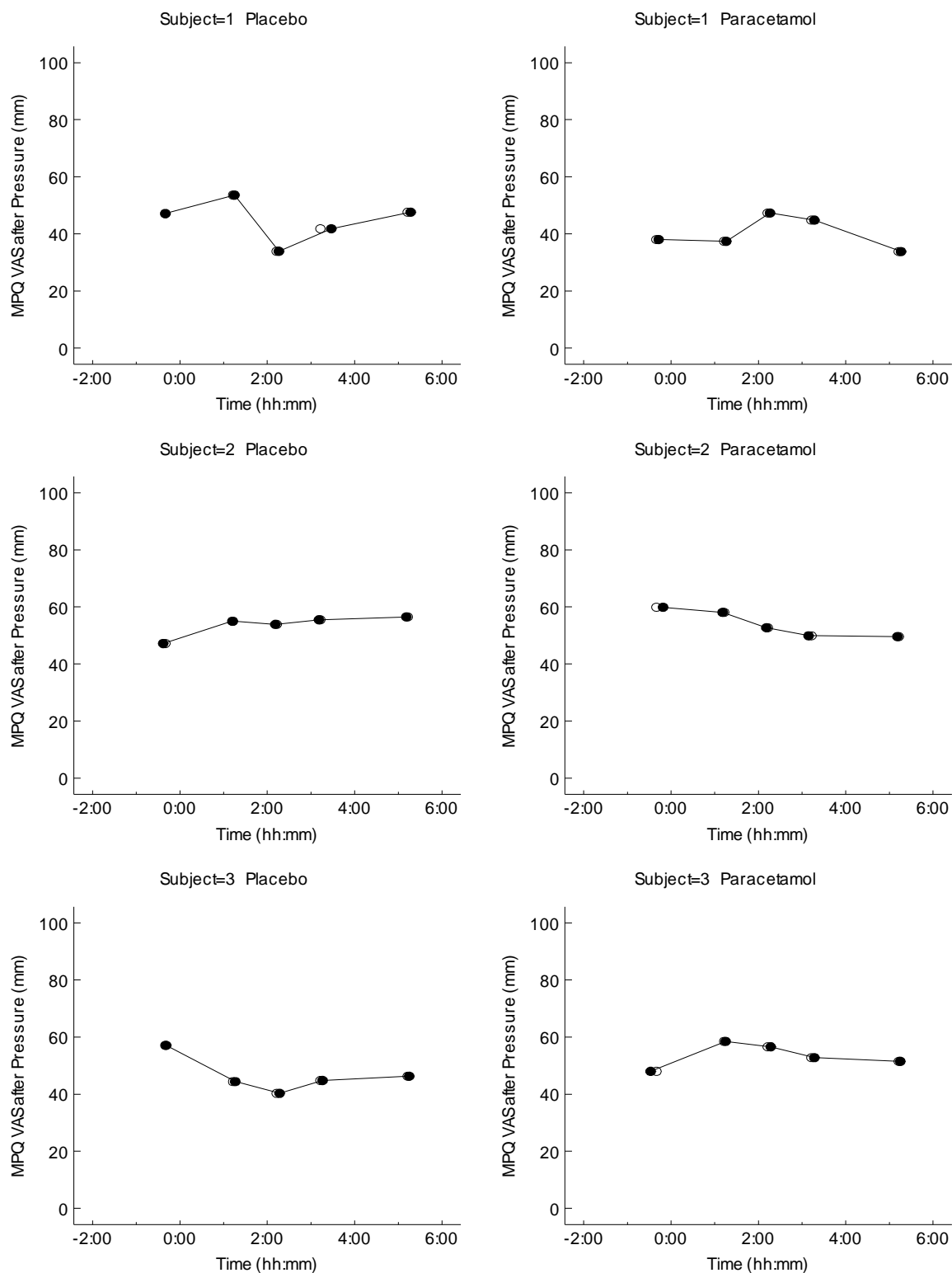
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Individual Plots 23 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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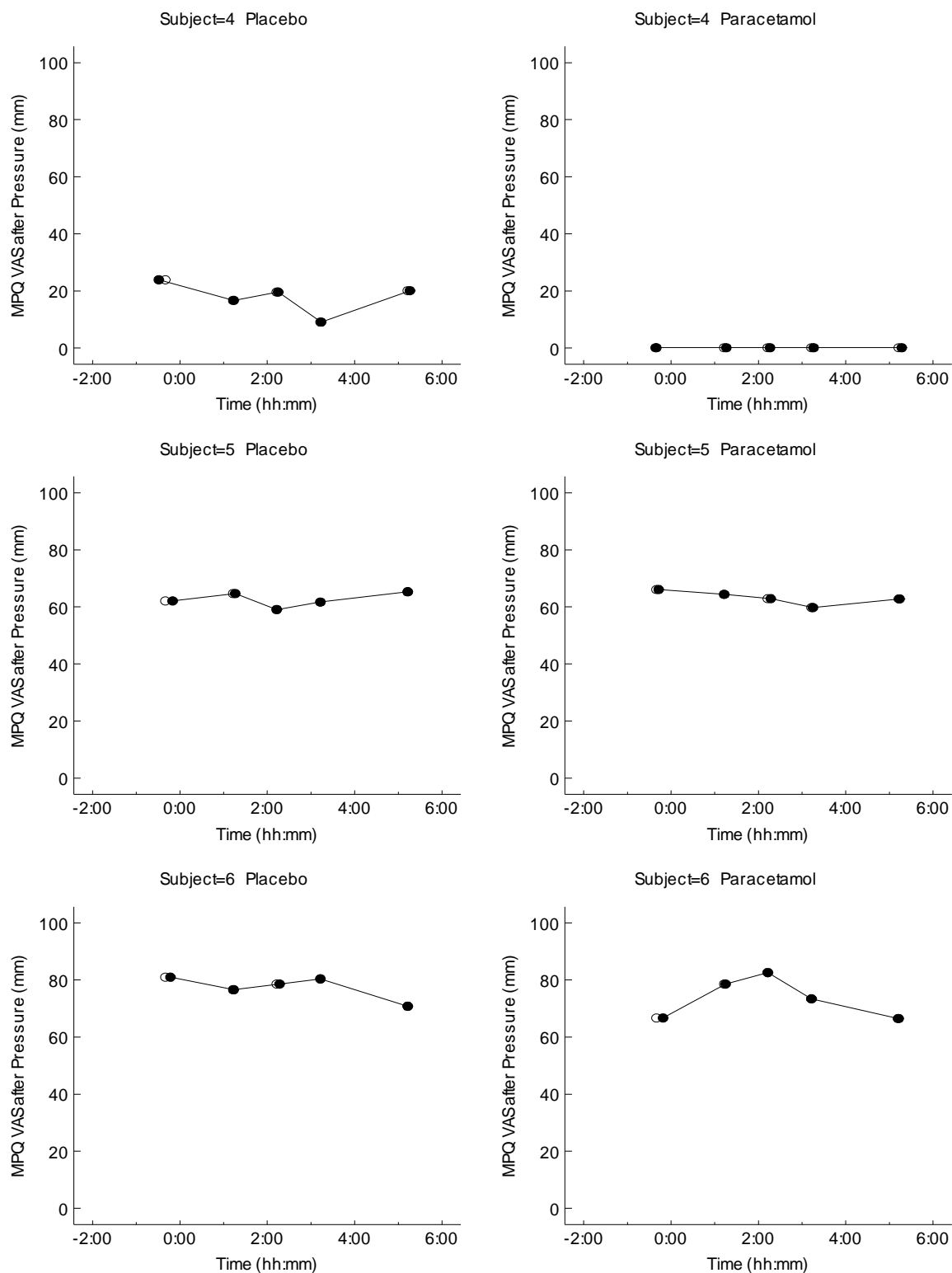
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Individual Plots 23 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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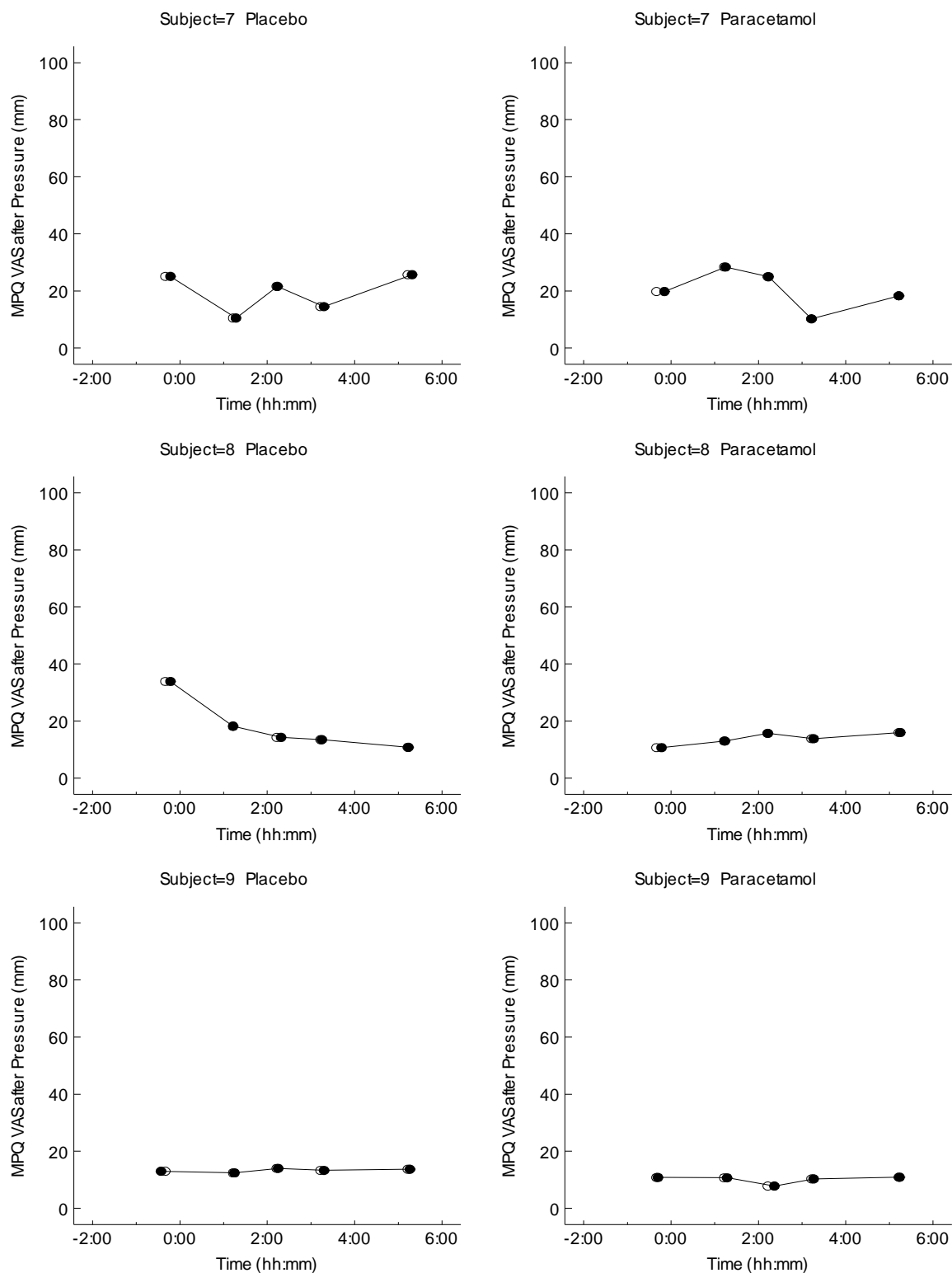
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Individual Plots 23 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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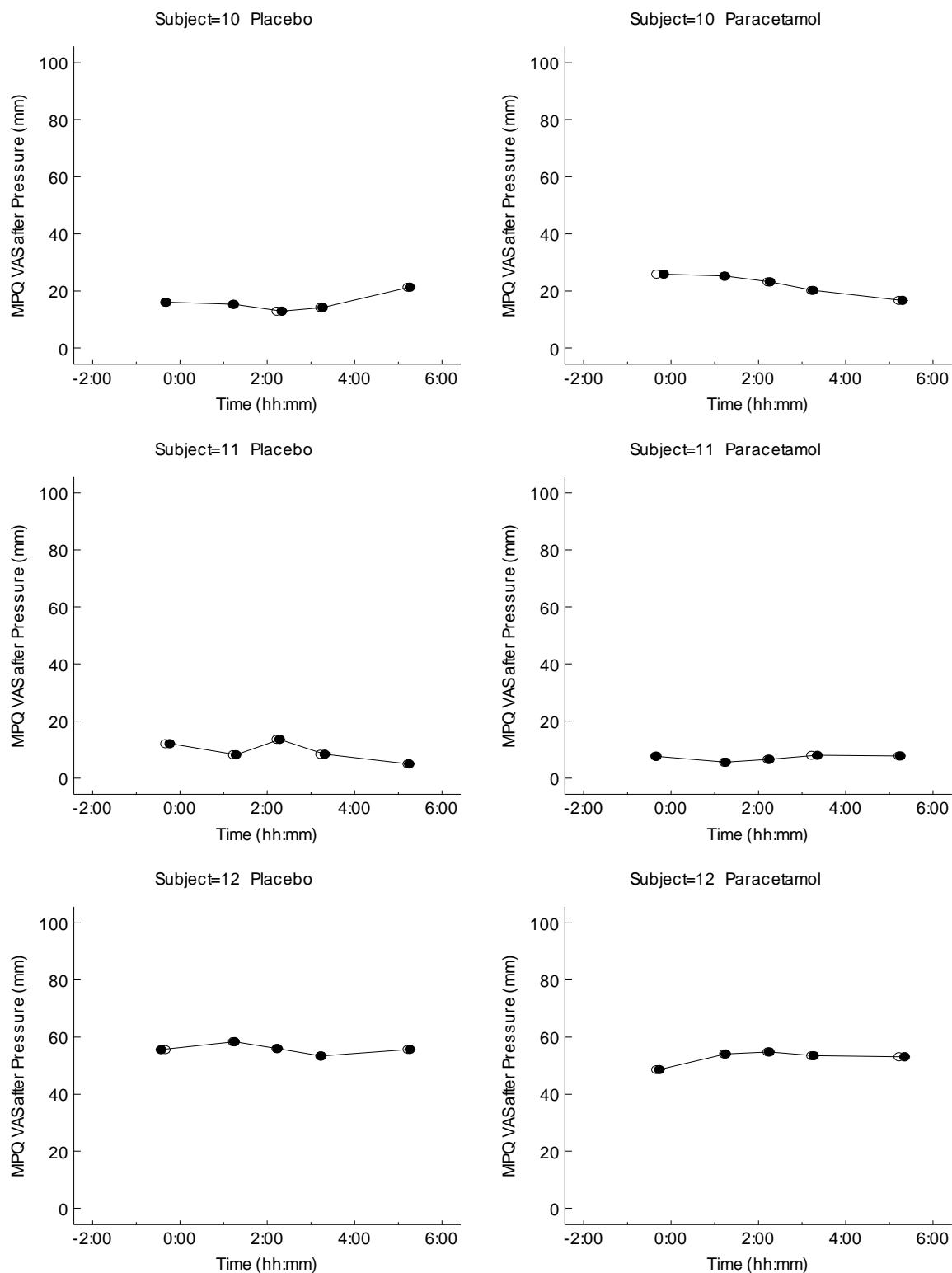
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Individual Plots 23 of dynamic measurements

Safety population

Dot: actual time Circle: protocol time



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Summary pharmacodynamic response table and graph

Cold AAC (s*%)

Summary table 1 Cold AAC (s*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary 1 of dynamic measurements

Analysis population

Summary table: Cold AAC (s*%)

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:17	12	2386.13	1941.728	560.529	81.4	1696.8	690.0	6940.7
	1:16	12	2490.66	2176.152	628.201	87.4	1505.3	599.6	8155.8
	2:16	12	2546.18	2409.595	695.590	94.6	1793.4	626.7	9085.6
	3:16	12	2732.39	2606.490	752.429	95.4	2006.8	754.4	9960.4
	5:16	12	2086.40	1488.885	429.804	71.4	1490.0	167.2	4945.4
Paracetamol	-0:17	12	2237.05	1499.171	432.773	67.0	1657.7	788.8	5081.7
	1:16	11	2187.80	1584.036	477.605	72.4	1290.8	738.9	5419.2
	2:16	12	2214.57	1333.689	385.003	60.2	1787.4	776.1	4713.3
	3:16	12	2415.74	1512.398	436.592	62.6	1935.8	772.7	5117.7
	5:16	12	2313.41	1486.562	429.134	64.3	1846.2	757.3	5085.6

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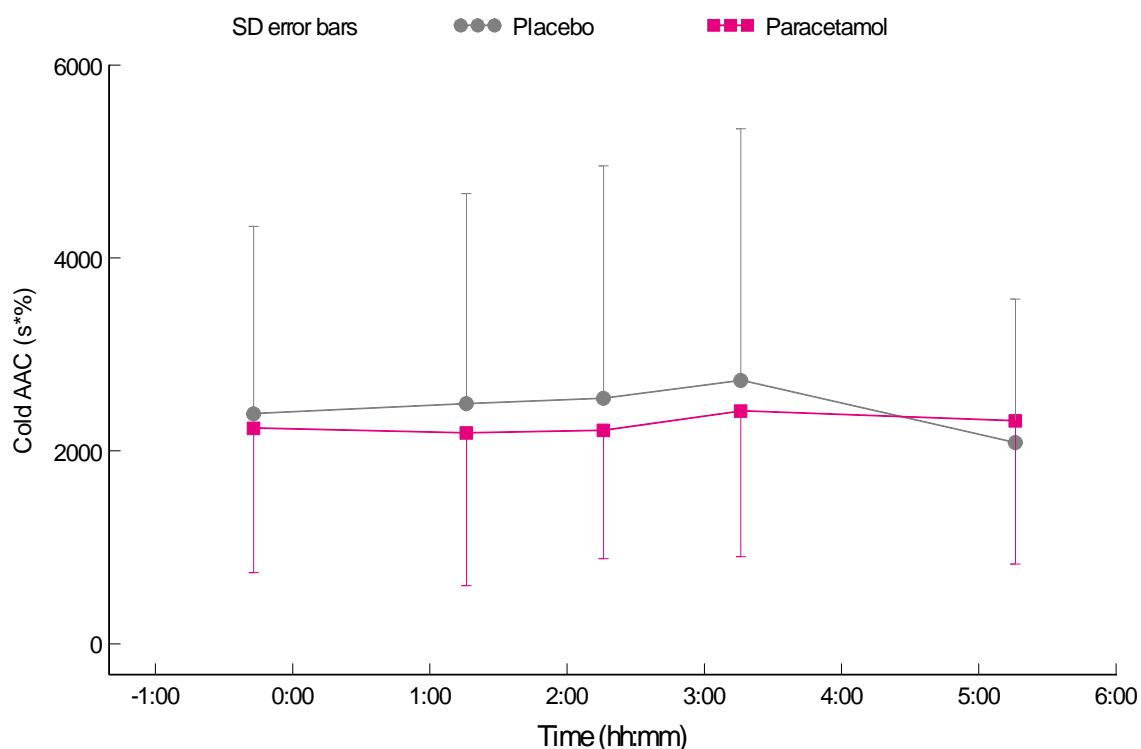
Summary graph 1 Cold AAC (s*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 1 of dynamic measurements

Analysis population



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Cold PDT (s)**Summary table 2 Cold PDT (s)**

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Summary 2 of dynamic measurements

Analysis population

Summary table: Cold PDT (s)

Treatment	Time (hh:mm)	N	Mean	Geometric Mean	SD	SEM	CV (%)	Geometric CV (%)	Median	Min	Max
Placebo	-0:17	12	7.25	4.55	9.140	2.639	126.1	155.4	3.5	0.0	31.2
	1:16	12	7.32	4.22	8.412	2.428	115.0	212.1	2.8	0.0	24.8
	2:16	12	6.50	4.29	6.583	1.900	101.3	117.3	3.7	1.3	21.3
	3:16	12	7.20	4.57	8.055	2.325	111.9	121.0	4.0	1.5	26.7
	5:16	12	6.31	3.93	5.429	1.567	86.1	186.2	4.3	0.2	17.6
Paracetamol	-0:17	12	7.74	4.68	8.496	2.453	109.7	147.9	5.2	1.0	31.1
	1:16	11	6.56	4.55	7.181	2.165	109.4	100.2	3.8	1.8	26.5
	2:16	12	7.75	5.62	6.646	1.919	85.8	105.3	7.0	1.4	24.7
	3:16	12	6.66	4.54	6.380	1.842	95.8	118.7	5.0	0.9	23.1
	5:16	12	7.83	6.08	6.363	1.837	81.2	85.6	5.9	1.4	23.4

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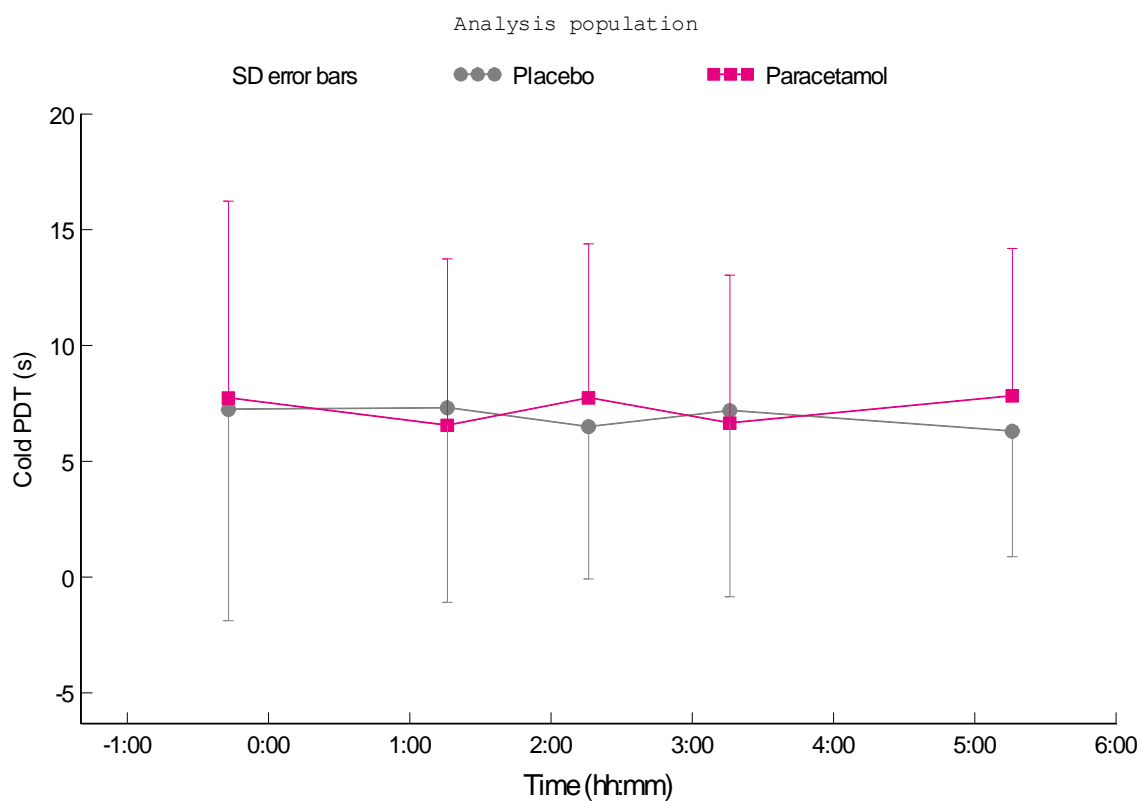
Produced by M.L. de Kam

Summary graph 2 Cold PDT (s)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 2 of dynamic measurements



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Cold PTT (s)**Summary table 3 Cold PTT (s)**

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Summary 3 of dynamic measurements

Analysis population

Summary table: Cold PTT (s)

Treatment	Time (hh:mm)	N	Mean	Geometric Mean	SD	SEM	CV (%)	Geometric CV (%)	Median	Min	Max
Placebo	-0:17	12	42.43	32.89	32.216	9.300	75.9	86.9	29.1	11.3	120.0
	1:16	11	34.09	28.37	20.451	6.166	60.0	73.2	22.0	10.0	62.9
	2:16	12	46.93	33.73	39.667	11.451	84.5	103.9	30.6	10.1	120.0
	3:16	12	42.09	31.82	33.244	9.597	79.0	92.4	29.1	10.3	120.0
	5:16	12	35.18	27.05	22.008	6.353	62.6	105.7	31.2	3.5	67.5
Paracetamol	-0:17	12	40.69	30.20	33.950	9.800	83.4	94.2	27.3	12.4	120.0
	1:16	11	37.62	28.28	32.426	9.777	86.2	90.1	19.0	11.2	120.0
	2:16	12	37.96	30.75	25.346	7.317	66.8	77.0	27.9	13.6	88.8
	3:16	12	39.73	32.23	27.344	7.894	68.8	76.0	31.8	15.2	104.2
	5:16	12	41.13	32.19	31.918	9.214	77.6	82.3	33.0	14.5	120.0

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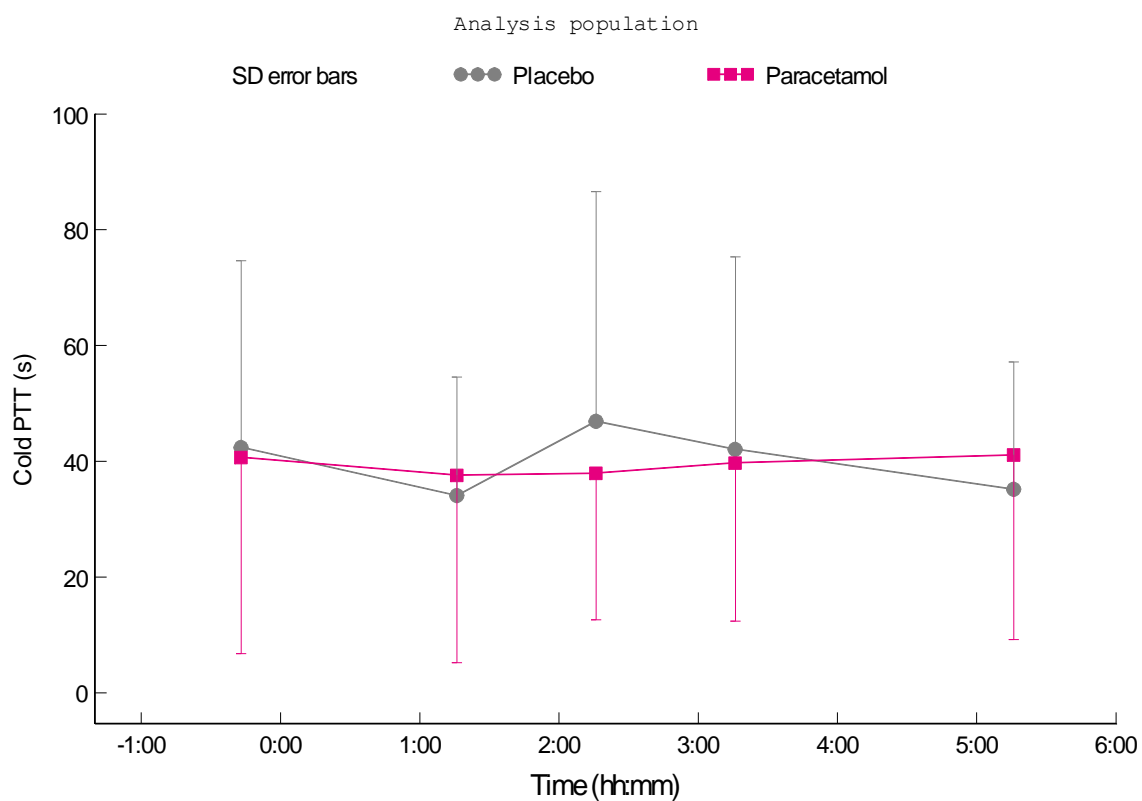
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Summary graph 3 Cold PTT (s)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 3 of dynamic measurements



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Electrical Stair AUC (mA*%)

Summary table 4 Electrical Stair AUC (mA*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary 4 of dynamic measurements

Analysis population

Summary table: Electrical Stair AUC (mA*%)

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:25	12	3331.05	758.454	218.947	22.8	3608.1	1887.5	4161.1
	1:08	12	3074.71	815.219	235.333	26.5	3096.9	1349.2	4186.1
	2:08	12	3047.22	825.323	238.250	27.1	3054.4	1213.0	4185.5
	3:08	12	2980.83	940.797	271.585	31.6	3150.0	918.3	3974.0
	5:08	12	2936.22	975.431	281.583	33.2	3082.4	599.7	4170.6
Paracetamol	-0:25	12	3184.14	989.122	285.535	31.1	3429.2	962.4	4195.3
	1:08	12	3109.51	857.770	247.617	27.6	3318.9	1560.3	4023.6
	2:08	12	2960.53	794.362	229.313	26.8	2903.2	1723.1	3924.0
	3:08	12	2893.79	865.374	249.812	29.9	3027.9	1345.1	3961.7
	5:08	12	2941.50	868.648	250.757	29.5	3098.8	1300.1	4048.6

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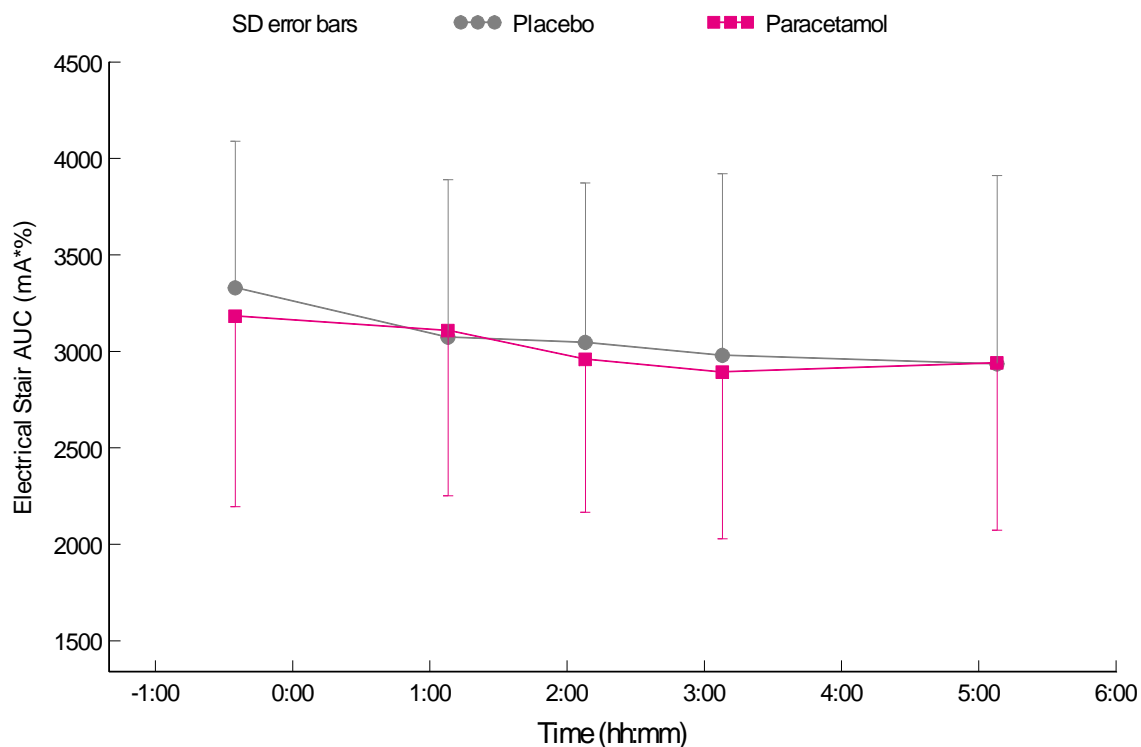
Summary graph 4 Electrical Stair AUC (mA*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 4 of dynamic measurements

Analysis population



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Electrical Stair PDT (mA)

Summary table 5 Electrical Stair PDT (mA)

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Summary 5 of dynamic measurements

Analysis population

Summary table: Electrical Stair PDT (mA)

Treatment	Time (hh:mm)	N	Geometric Mean	Geometric Mean	SD	SEM	CV (%)	Geometric CV (%)	Median	Min	Max
Placebo	-0:25	12	6.13	5.21	3.522	1.017	57.4	67.8	6.2	2.0	12.5
	1:08	12	8.31	7.33	4.043	1.167	48.7	59.4	7.2	2.6	14.6
	2:08	12	8.15	7.14	3.882	1.121	47.6	64.3	7.8	1.8	16.1
	3:08	12	9.23	8.36	4.418	1.275	47.9	49.3	8.0	3.1	19.2
	5:08	12	9.41	8.20	5.940	1.715	63.1	56.3	7.8	3.2	25.9
Paracetamol	-0:25	12	8.71	6.09	7.825	2.259	89.9	112.4	4.9	1.3	26.4
	1:08	12	8.59	6.85	6.090	1.758	70.9	82.1	5.8	1.8	22.4
	2:08	12	8.74	7.22	4.831	1.395	55.3	82.0	8.0	1.4	15.1
	3:08	12	9.49	8.36	4.843	1.398	51.0	57.9	9.0	3.4	19.3
	5:08	12	9.00	7.45	5.171	1.493	57.5	77.6	8.2	1.9	17.7

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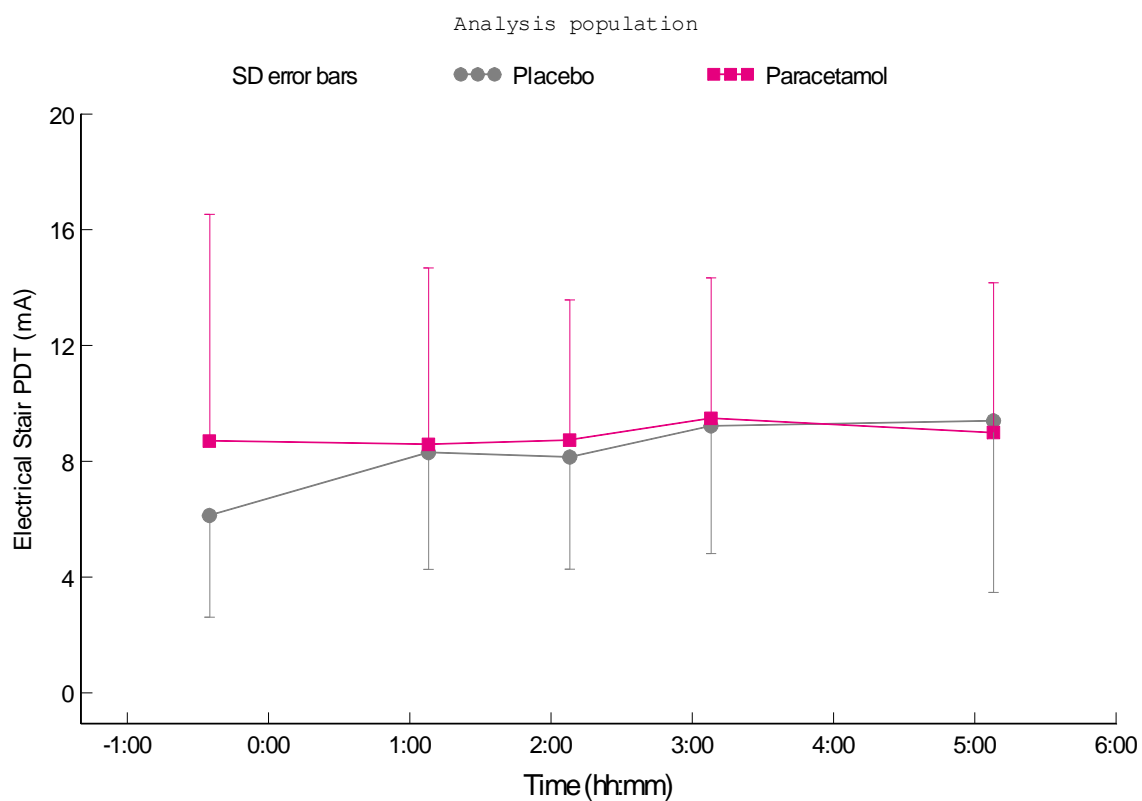
Produced by M.L. de Kam

Summary graph 5 Electrical Stair PDT (mA)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 5 of dynamic measurements



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Electrical Stair PTT (mA)

Summary table 6 Electrical Stair PTT (mA)

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Summary 6 of dynamic measurements

Analysis population

Summary table: Electrical Stair PTT (mA)

Treatment	Time (hh:mm)	N	Geometric Mean	Geometric Mean	SD	SEM	CV (%)	Geometric CV (%)	Median	Min	Max
Placebo	-0:25	11	23.17	21.46	9.508	2.867	41.0	42.9	22.7	11.7	39.2
	1:08	12	26.78	24.28	12.031	3.473	44.9	49.9	27.7	11.7	49.5
	2:08	11	24.99	23.20	10.039	3.027	40.2	42.6	27.4	12.2	45.4
	3:08	11	25.24	23.38	10.870	3.277	43.1	41.9	24.9	14.2	50.2
	5:08	11	25.65	23.79	10.532	3.176	41.1	42.8	26.4	11.3	49.5
Paracetamol	-0:25	10	21.30	20.05	7.956	2.516	37.4	37.6	20.3	13.1	37.3
	1:08	12	26.73	24.32	12.364	3.569	46.3	47.6	25.2	13.7	48.6
	2:08	12	27.29	25.07	11.669	3.369	42.8	45.5	27.2	14.1	48.7
	3:08	12	28.37	25.87	12.734	3.676	44.9	47.4	26.4	13.3	50.3
	5:08	11	25.28	23.57	9.972	3.007	39.4	41.2	25.4	11.7	44.0

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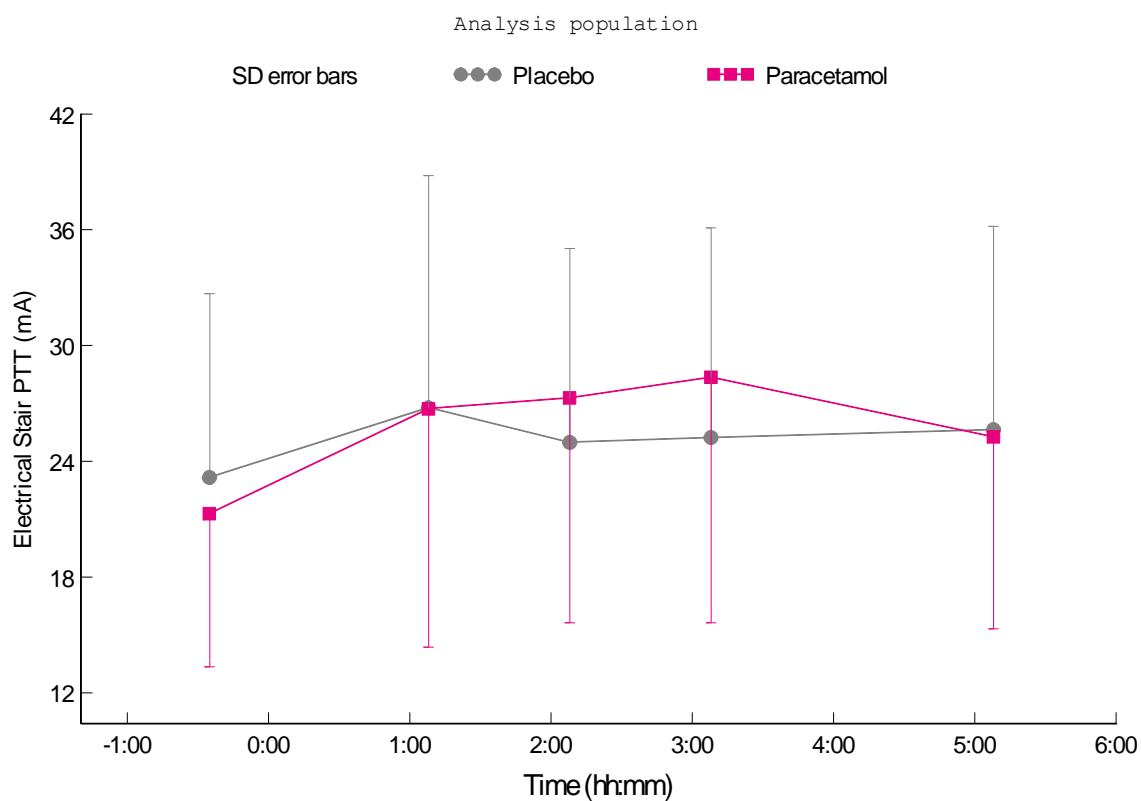
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Summary graph 6 Electrical Stair PTT (mA)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 6 of dynamic measurements



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Delta Electrical Stair AUC (mA*%)

Summary table 7 Delta Electrical Stair AUC (mA*%)

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Summary 7 of dynamic measurements

Analysis population

Summary table: Delta Electrical Stair AUC (mA*%)

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:12	12	-265.52	236.908	68.390	-89.2	-274.5	-653.2	70.6
	1:21	12	-185.25	303.300	87.555	-163.7	-142.8	-669.1	295.5
	2:21	12	-230.50	291.633	84.187	-126.5	-220.8	-786.9	209.9
	3:21	12	-234.28	206.892	59.725	-88.3	-260.3	-583.0	106.6
	5:21	12	-174.89	214.155	61.821	-122.5	-162.8	-673.7	276.7
Paracetamol	-0:12	12	-229.88	275.490	79.527	-119.8	-105.5	-881.0	43.2
	1:21	12	-246.30	277.870	80.214	-112.8	-215.0	-577.5	194.4
	2:21	12	-113.53	241.546	69.728	-212.8	-90.8	-711.2	206.5
	3:21	12	-105.43	299.661	86.505	-284.2	-60.9	-741.0	269.0
	5:21	10	-222.05	333.129	105.345	-150.0	-139.6	-939.0	101.7

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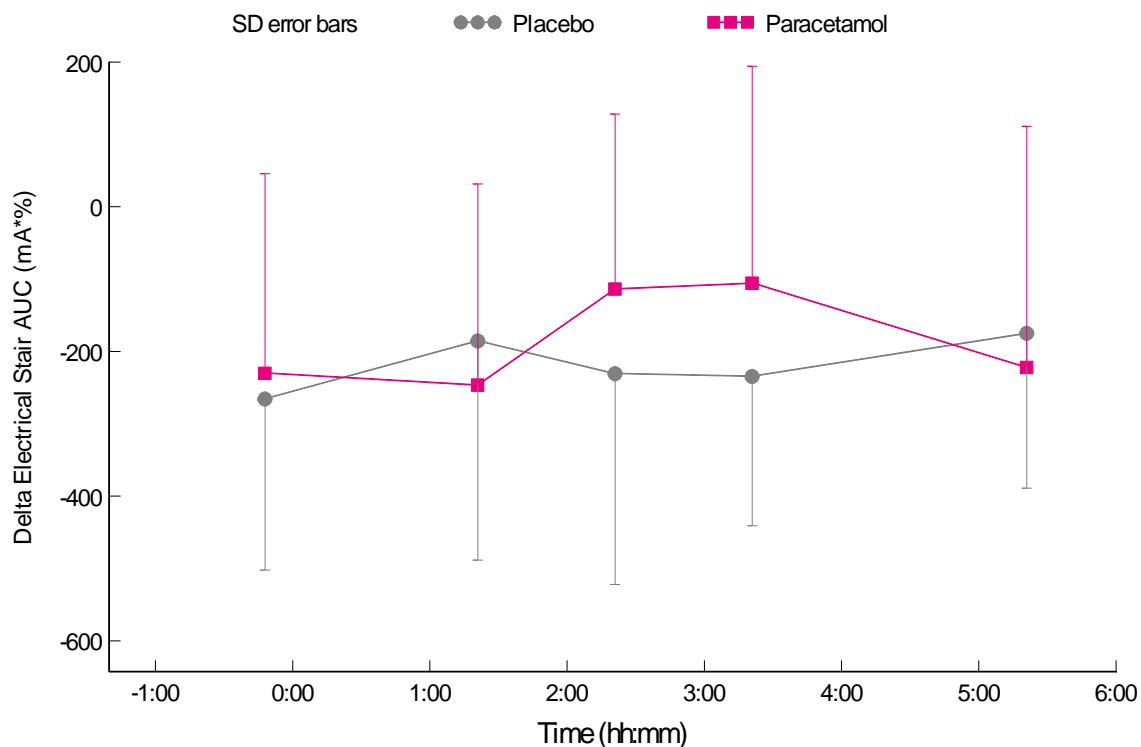
Summary graph 7 Delta Electrical Stair AUC (mA*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 7 of dynamic measurements

Analysis population



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Delta Electrical Stair PDT (mA)

Summary table 8 Delta Electrical Stair PDT (mA)

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Summary 8 of dynamic measurements

Analysis population

Summary table: Delta Electrical Stair PDT (mA)

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:12	12	2.492	3.4440	0.9942	138.2	1.00	0.40	11.80
	1:21	12	1.842	4.0773	1.1770	221.4	0.75	-1.90	13.30
	2:21	12	1.275	3.6891	1.0649	289.3	0.25	-3.00	9.80
	3:21	12	1.542	2.8618	0.8261	185.6	0.75	-2.00	7.20
	5:21	12	2.117	1.9628	0.5666	92.7	2.75	-0.50	4.60
Paracetamol	-0:12	12	1.383	3.0954	0.8936	223.8	0.25	-0.50	10.00
	1:21	12	1.017	2.8055	0.8099	275.9	0.30	-2.50	6.60
	2:21	12	1.558	3.0832	0.8901	197.9	0.75	-2.10	8.60
	3:21	12	1.483	2.2336	0.6448	150.6	1.25	-2.50	4.60
	5:21	10	2.460	5.4569	1.7256	221.8	1.30	-3.50	14.60

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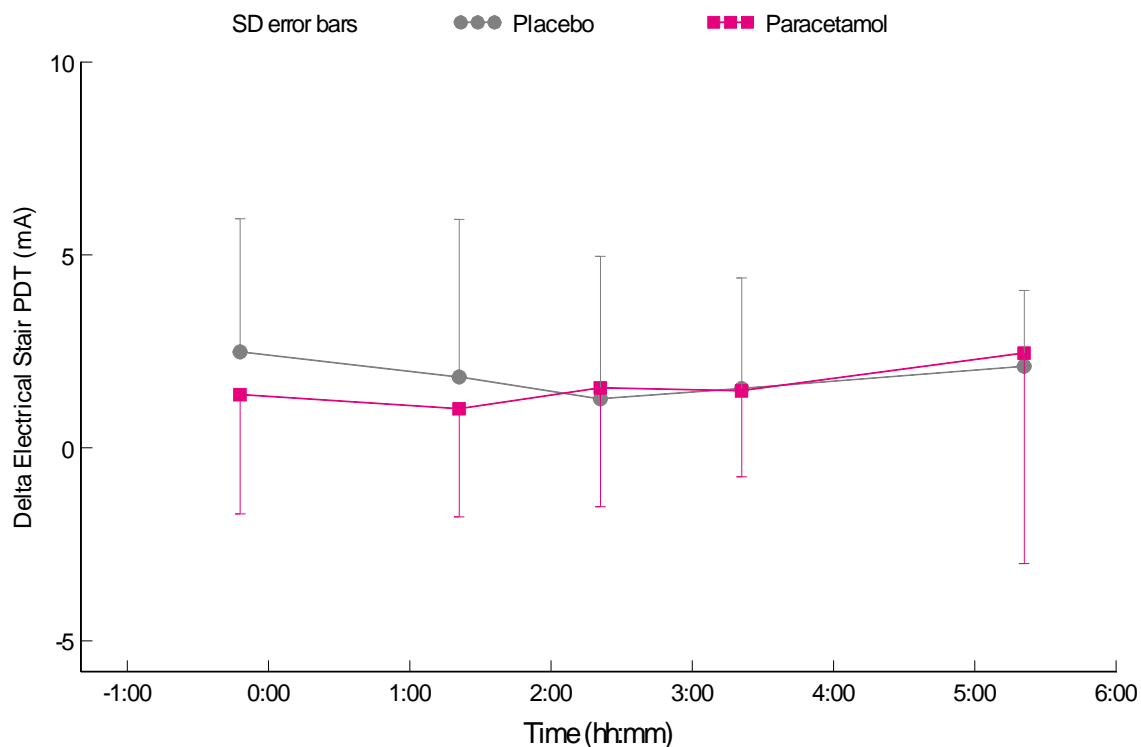
Summary graph 8 Delta Electrical Stair PDT (mA)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 8 of dynamic measurements

Analysis population



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Delta Electrical Stair PTT (mA)

Summary table 9 Delta Electrical Stair PTT (mA)

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Summary 9 of dynamic measurements

Analysis population

Summary table: Delta Electrical Stair PTT (mA)

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:12	11	3.227	3.8228	1.1526	118.5	1.50	-0.50	10.00
	1:21	11	2.291	3.9640	1.1952	173.0	2.50	-3.10	11.10
	2:21	11	2.227	2.4191	0.7294	108.6	2.10	-1.60	7.20
	3:21	11	1.745	2.0201	0.6091	115.7	1.90	-1.10	4.60
	5:21	11	1.736	2.1979	0.6627	126.6	1.40	-1.50	6.70
Paracetamol	-0:12	10	1.500	2.2618	0.7152	150.8	1.75	-1.10	6.50
	1:21	11	1.609	2.6741	0.8063	166.2	1.60	-3.60	6.60
	2:21	11	1.164	1.4179	0.4275	121.9	0.60	-1.00	3.10
	3:21	11	-0.555	4.6101	1.3900	-831.3	-0.50	-11.80	6.80
	5:21	10	2.240	2.3263	0.7356	103.9	2.55	-0.50	5.70

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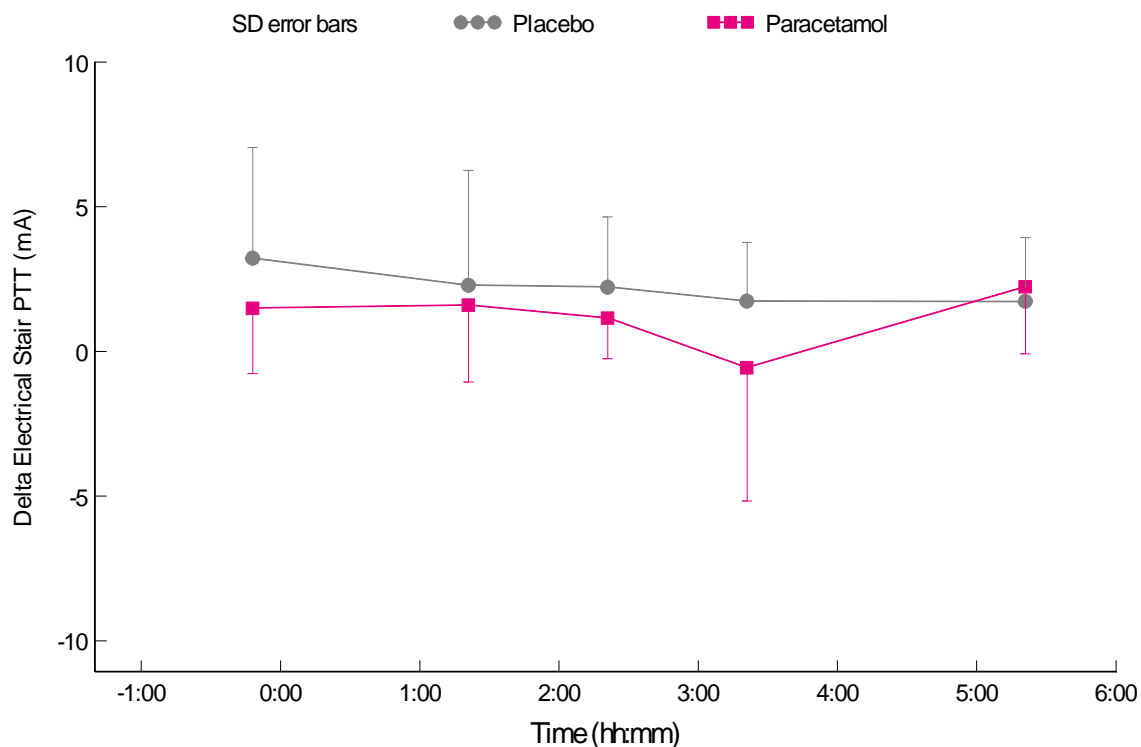
Summary graph 9 Delta Electrical Stair PTT (mA)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 9 of dynamic measurements

Analysis population



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Pressure AUC (kPa*%)

Summary table 10 Pressure AUC (kPa*%)

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Summary 10 of dynamic measurements

Analysis population

Summary table: Pressure AUC (kPa*%)

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:20	12	6660.38	1510.359	436.003	22.7	6740.9	3961.7	8972.3
	1:13	12	6801.78	1365.079	394.064	20.1	7037.0	3092.4	8462.5
	2:13	12	6448.25	1591.575	459.448	24.7	6677.7	3630.5	8705.1
	3:13	12	6439.56	1707.539	492.924	26.5	6810.2	2913.8	8994.6
	5:13	12	6461.80	1452.189	419.211	22.5	6791.6	3371.0	8913.1
Paracetamol	-0:20	12	7056.16	1447.269	417.791	20.5	7228.1	4703.5	8735.8
	1:13	12	6689.62	1466.952	423.472	21.9	6514.8	3990.0	8551.2
	2:13	12	6448.88	1722.617	497.277	26.7	6624.6	3687.5	8601.4
	3:13	12	6386.04	1685.373	486.525	26.4	6025.2	3929.0	8474.8
	5:13	12	6281.36	1907.890	550.760	30.4	6417.4	2858.8	8794.3

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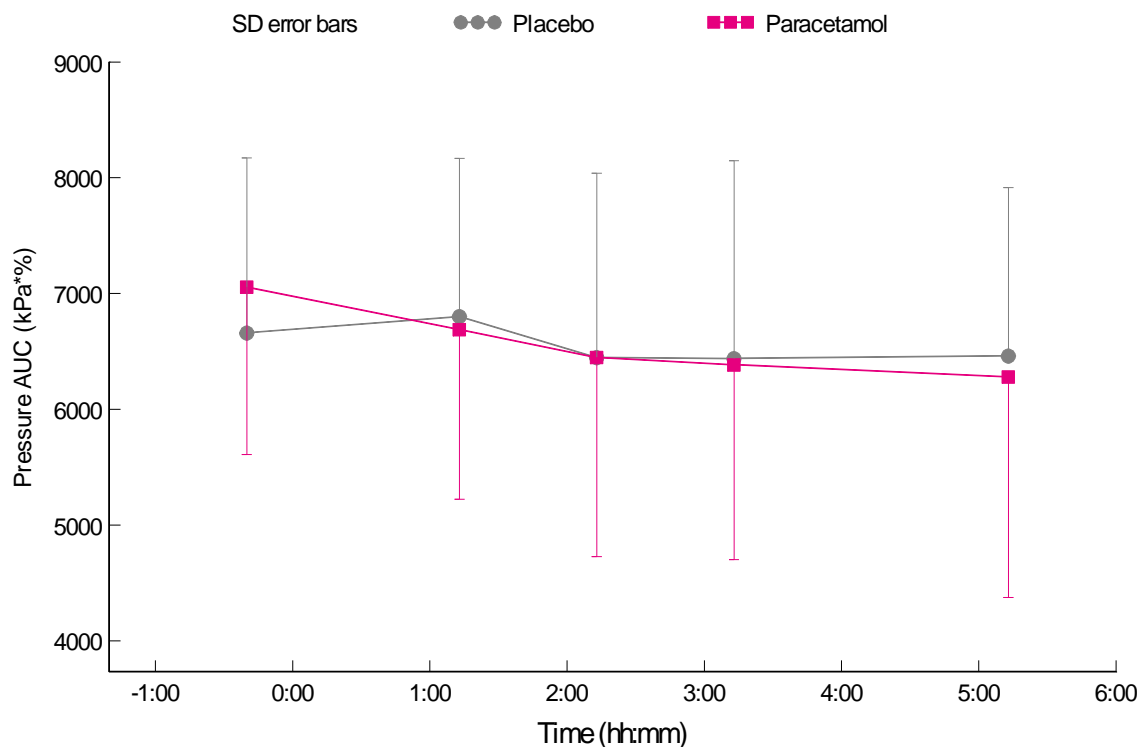
Summary graph 10 Pressure AUC (kPa*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 10 of dynamic measurements

Analysis population



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Pressure PDT (kPa)

Summary table 11 Pressure PDT (kPa)

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Summary 11 of dynamic measurements

Analysis population

Summary table: Pressure PDT (kPa)

Treatment	Time (hh:mm)	N	Mean	Geometric Mean	SD	SEM	CV (%)	Geometric CV (%)	Median	Min	Max
Placebo	-0:20	12	16.67	14.40	9.623	2.778	57.7	62.3	14.4	5.0	40.4
	1:13	12	18.30	16.40	9.493	2.741	51.9	51.7	17.7	7.0	43.3
	2:13	12	17.23	15.06	10.491	3.029	60.9	55.9	15.0	7.0	46.1
	3:13	12	18.04	15.04	13.006	3.755	72.1	66.8	14.5	5.5	54.2
	5:13	12	20.20	16.89	13.619	3.931	67.4	67.9	18.9	6.7	55.5
Paracetamol	-0:20	12	14.62	12.44	8.997	2.597	61.6	66.2	12.7	3.9	37.8
	1:13	12	15.79	13.44	8.796	2.539	55.7	68.8	12.6	3.8	30.2
	2:13	12	19.63	17.08	10.254	2.960	52.2	61.5	18.3	7.7	35.1
	3:13	12	18.43	16.11	9.191	2.653	49.9	63.4	16.2	4.2	35.2
	5:13	12	22.42	20.00	9.976	2.880	44.5	57.4	23.9	6.6	38.7

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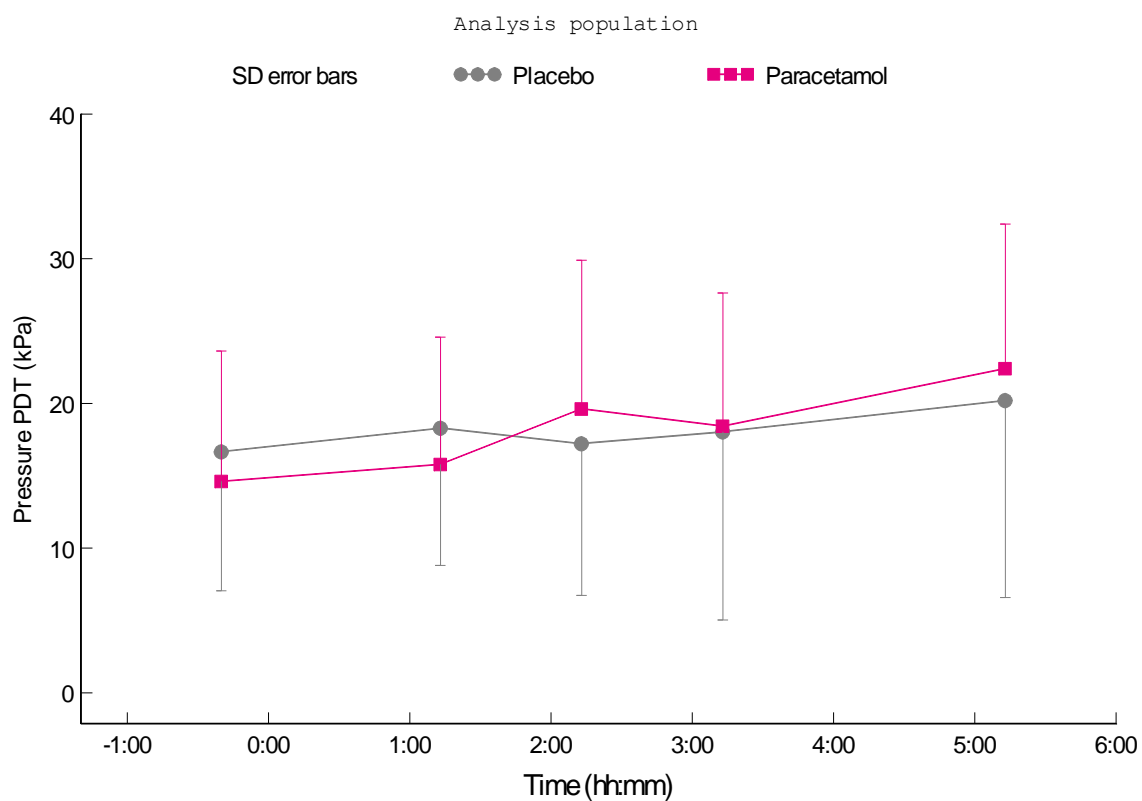
Produced by M.L. de Kam

Summary graph 11 Pressure PDT (kPa)

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Summary graph 11 of dynamic measurements



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Pressure PTT (kPa)

Summary table 12 Pressure PTT (kPa)

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Summary 12 of dynamic measurements

Analysis population

Summary table: Pressure PTT (kPa)

Treatment	Time (hh:mm)	N	Geometric Mean	SD	SEM	CV (%)	Geometric CV (%)	Median	Min	Max
Placebo	-0:20	12	46.61	20.324	5.867	43.6	52.0	44.9	16.1	81.0
	1:13	12	45.37	16.501	4.764	36.4	37.4	43.2	21.4	80.8
	2:13	12	49.25	21.572	6.227	43.8	47.9	42.9	19.6	89.4
	3:13	12	49.76	22.394	6.465	45.0	53.3	48.0	15.5	89.2
	5:13	12	49.09	18.283	5.278	37.2	44.6	47.1	18.2	77.8
Paracetamol	-0:20	12	43.03	23.020	6.645	53.5	54.3	39.4	18.5	96.9
	1:13	12	46.34	22.870	6.602	49.4	53.8	44.9	18.8	97.2
	2:13	12	47.45	23.418	6.760	49.4	59.0	44.8	18.4	84.2
	3:13	12	48.66	24.049	6.942	49.4	61.1	54.1	18.9	88.5
	5:13	12	49.13	26.352	7.607	53.6	62.6	46.9	17.5	94.6

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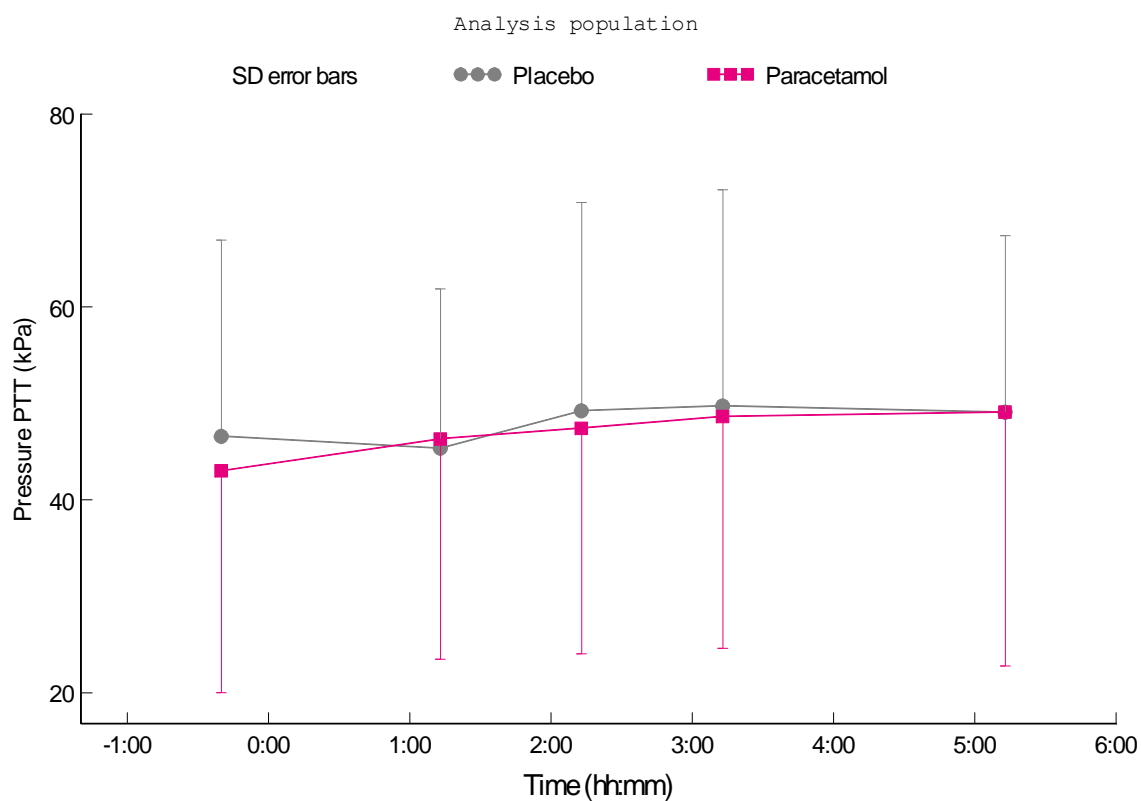
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Summary graph 12 Pressure PTT (kPa)

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Summary graph 12 of dynamic measurements



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Heat PDT (C)

Summary table 13 Heat PDT (C)

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Summary 13 of dynamic measurements

Analysis population

Summary table: Heat PDT (C)

Treatment	Time (hh:mm)	N	Mean	Geometric Mean	SD	SEM	CV (%)	Geometric CV (%)	Median	Min	Max
Placebo	-0:30	12	41.29	41.23	2.261	0.653	5.5	5.5	41.5	38.0	45.0
	1:03	12	40.78	40.73	2.279	0.658	5.6	5.5	40.5	37.4	45.8
	2:03	12	40.87	40.81	2.318	0.669	5.7	5.7	40.9	37.5	45.2
	3:03	12	40.79	40.72	2.460	0.710	6.0	6.0	40.1	37.2	45.3
	5:03	12	40.51	40.44	2.462	0.711	6.1	6.0	40.5	37.2	46.3
Paracetamol	-0:30	12	41.47	41.30	3.909	1.128	9.4	9.4	40.9	36.6	48.5
	1:03	12	42.13	41.98	3.727	1.076	8.8	8.8	41.4	36.9	47.7
	2:03	12	42.05	41.92	3.502	1.011	8.3	8.2	41.3	38.1	49.0
	3:03	12	41.55	41.42	3.526	1.018	8.5	8.4	40.7	37.3	47.5
	5:03	12	41.70	41.56	3.568	1.030	8.6	8.5	41.5	36.5	47.7

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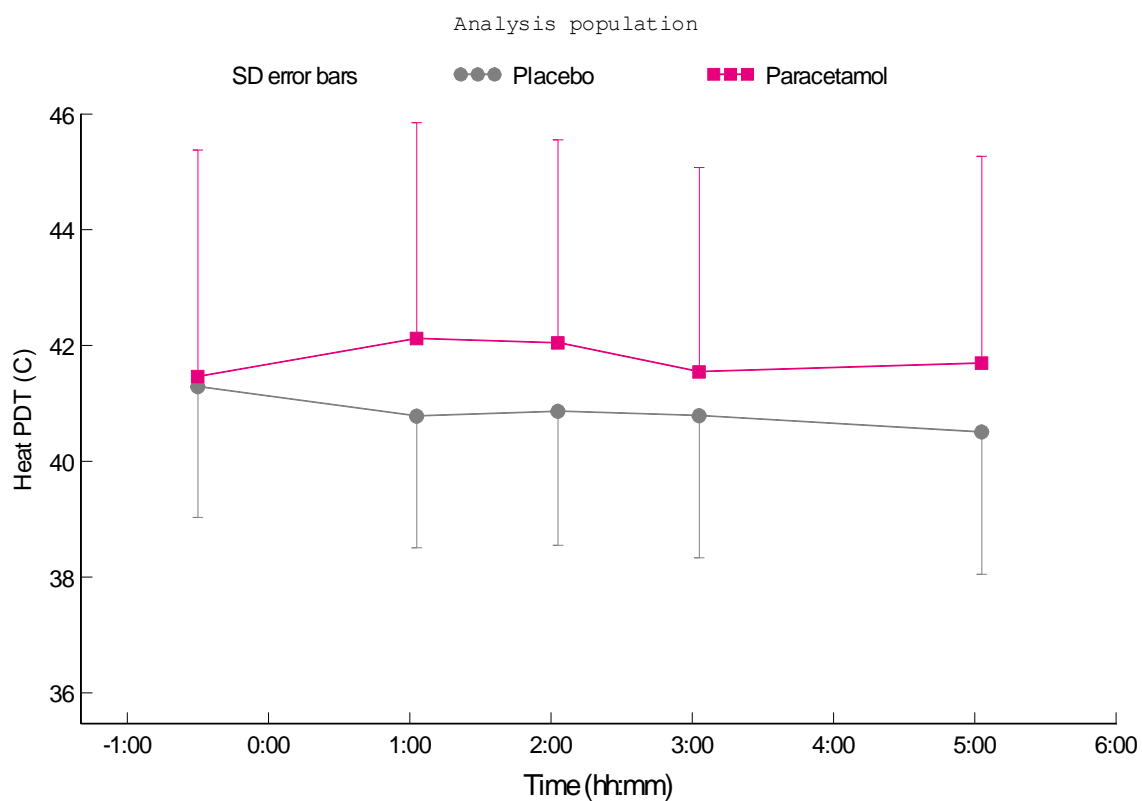
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Summary graph 13 Heat PDT (C)

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Summary graph 13 of dynamic measurements



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Heat PTT (C)

Summary table 14 Heat PTT (C)

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Summary 14 of dynamic measurements

Analysis population

Summary table: Heat PTT (C)

Treatment	Time (hh:mm)	N	Mean	Geometric Mean	SD	SEM	CV (%)	Geometric CV (%)	Median	Min	Max
Placebo	-0:30	12	46.93	46.91	1.353	0.391	2.9	2.9	46.7	44.1	49.4
	1:03	12	47.10	47.08	1.443	0.417	3.1	3.1	47.3	44.2	49.4
	2:03	12	47.49	47.47	1.529	0.441	3.2	3.3	47.6	43.9	49.4
	3:03	12	47.08	47.05	1.545	0.446	3.3	3.3	47.0	44.7	50.1
	5:03	12	46.57	46.53	1.988	0.574	4.3	4.3	46.8	42.7	49.4
Paracetamol	-0:30	12	46.78	46.72	2.519	0.727	5.4	5.4	46.9	42.4	50.5
	1:03	12	46.93	46.88	2.338	0.675	5.0	5.0	47.2	43.2	50.5
	2:03	12	47.05	47.01	2.108	0.608	4.5	4.5	47.0	43.5	50.2
	3:03	12	46.74	46.68	2.479	0.716	5.3	5.4	47.4	41.7	50.5
	5:03	12	46.92	46.87	2.216	0.640	4.7	4.8	47.1	42.3	50.5

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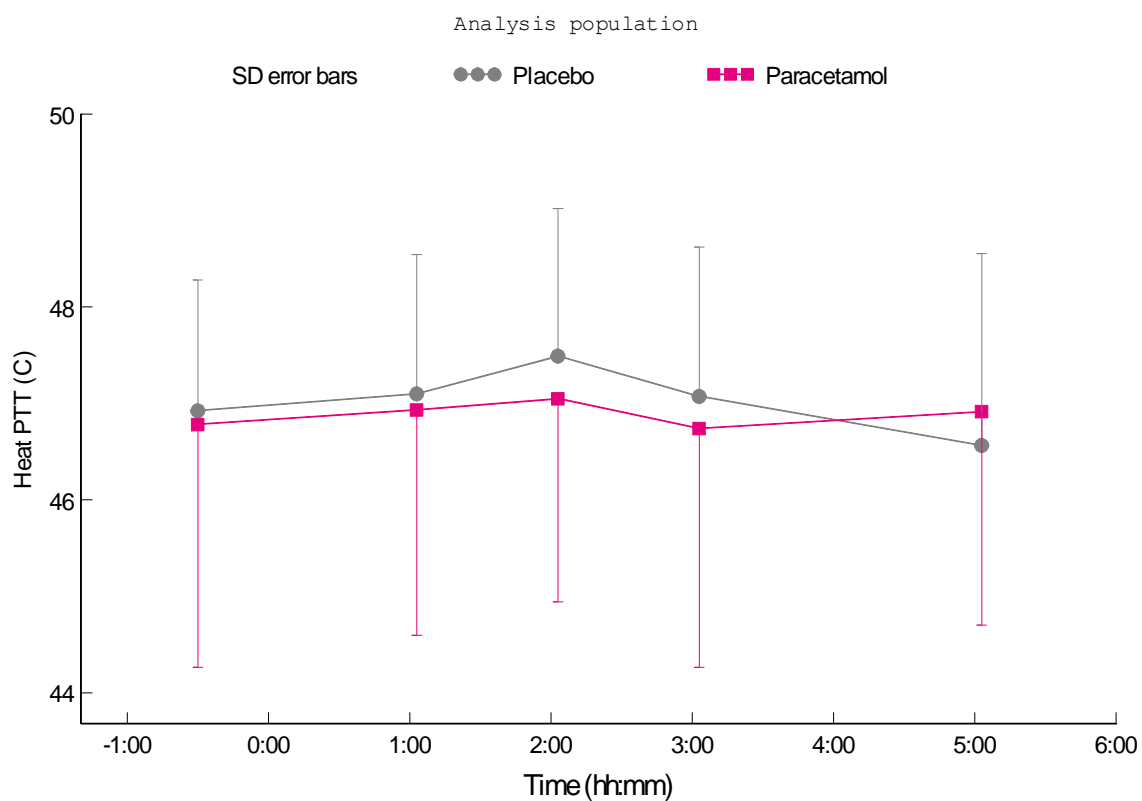
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Summary graph 14 Heat PTT (C)

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Summary graph 14 of dynamic measurements



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Sensory after Cold

Summary table 15 Sensory after Cold

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Summary 15 of dynamic measurements

Analysis population

Summary table: Sensory after Cold

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:17	11	0.975	0.4266	0.1286	43.7	1.00	0.45	1.82
	1:16	11	0.975	0.5605	0.1690	57.5	1.00	0.36	2.00
	2:16	11	0.983	0.5009	0.1510	50.9	1.00	0.45	1.82
	3:16	11	1.033	0.5895	0.1778	57.1	1.00	0.36	2.09
	5:16	11	0.926	0.5406	0.1630	58.4	0.82	0.27	1.73
Paracetamol	-0:17	11	1.025	0.5176	0.1561	50.5	1.00	0.36	1.82
	1:16	10	1.027	0.5319	0.1682	51.8	0.95	0.36	1.82
	2:16	11	0.950	0.4624	0.1394	48.7	0.73	0.36	1.73
	3:16	11	0.926	0.5391	0.1625	58.2	0.82	0.27	1.82
	5:16	11	0.926	0.4960	0.1495	53.6	0.82	0.36	1.82

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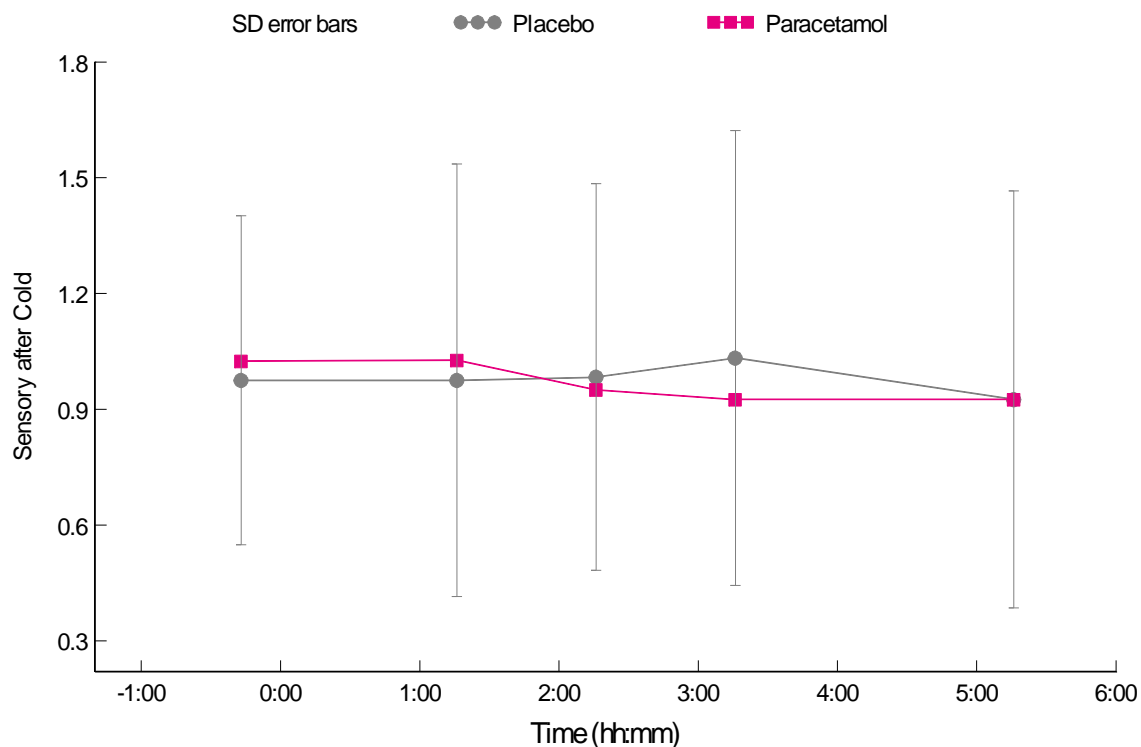
Summary graph 15 Sensory after Cold

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 15 of dynamic measurements

Analysis population



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Affective after Cold

Summary table 16 Affective after Cold

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Summary 16 of dynamic measurements

Analysis population

Summary table: Affective after Cold

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:17	11	0.364	0.5287	0.1594	145.4	0.25	0.00	1.50
	1:16	11	0.318	0.4885	0.1473	153.5	0.00	0.00	1.50
	2:16	11	0.295	0.4447	0.1341	150.5	0.00	0.00	1.25
	3:16	11	0.295	0.5456	0.1645	184.7	0.00	0.00	1.50
	5:16	11	0.318	0.4343	0.1310	136.5	0.25	0.00	1.25
Paracetamol	-0:17	11	0.318	0.4343	0.1310	136.5	0.25	0.00	1.25
	1:16	10	0.325	0.4417	0.1397	135.9	0.25	0.00	1.25
	2:16	11	0.318	0.4343	0.1310	136.5	0.25	0.00	1.25
	3:16	11	0.295	0.4304	0.1298	145.7	0.25	0.00	1.25
	5:16	11	0.273	0.4395	0.1325	161.2	0.00	0.00	1.25

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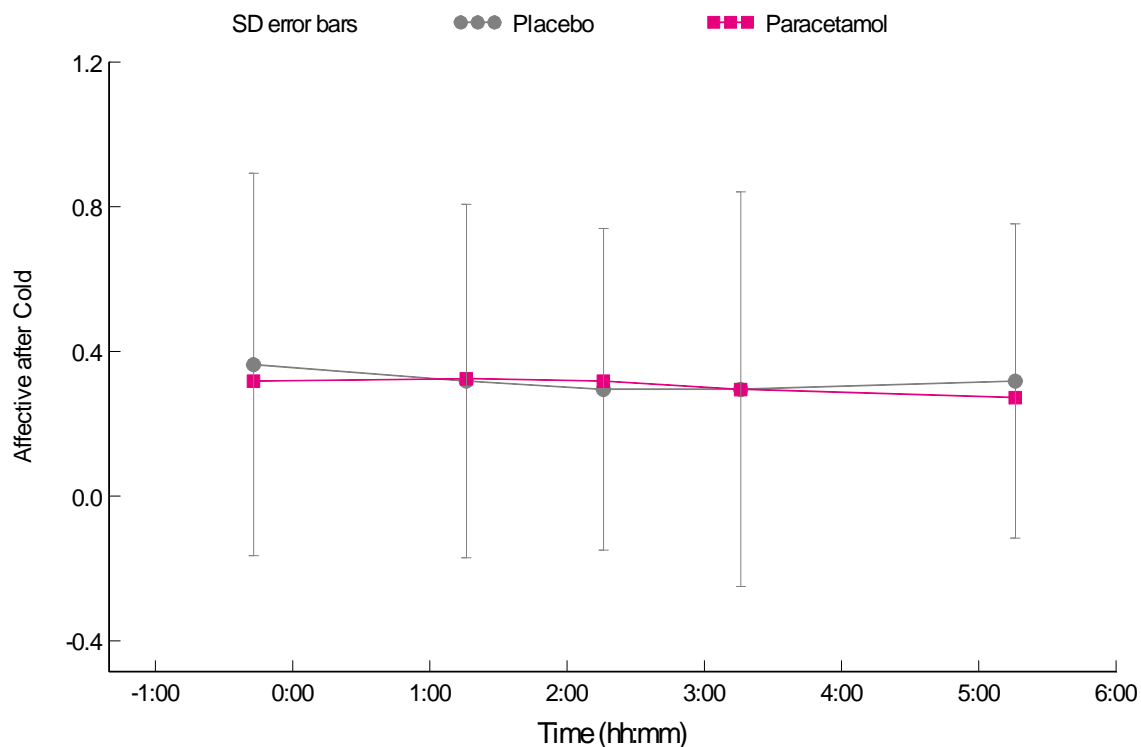
Summary graph 16 Affective after Cold

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Summary graph 16 of dynamic measurements

Analysis population



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MPQ VAS after Cold (mm)

Summary table 17 MPQ VAS after Cold (mm)

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Summary 17 of dynamic measurements

Analysis population

Summary table: MPQ VAS after Cold (mm)

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:17	12	45.77	24.792	7.157	54.2	49.2	9.6	82.8
	1:16	12	44.75	27.013	7.798	60.4	40.4	9.0	89.7
	2:16	12	41.85	27.309	7.884	65.3	39.7	7.3	89.3
	3:16	12	41.22	27.462	7.928	66.6	39.1	6.2	77.8
	5:16	12	46.03	25.636	7.401	55.7	49.7	13.5	89.3
Paracetamol	-0:17	12	44.23	26.062	7.524	58.9	46.3	0.0	77.7
	1:16	11	45.65	27.932	8.422	61.2	52.6	0.0	83.7
	2:16	12	46.03	27.209	7.855	59.1	49.2	0.0	87.3
	3:16	12	44.68	25.855	7.464	57.9	43.3	11.6	79.9
	5:16	12	43.27	26.743	7.720	61.8	43.5	0.0	78.4

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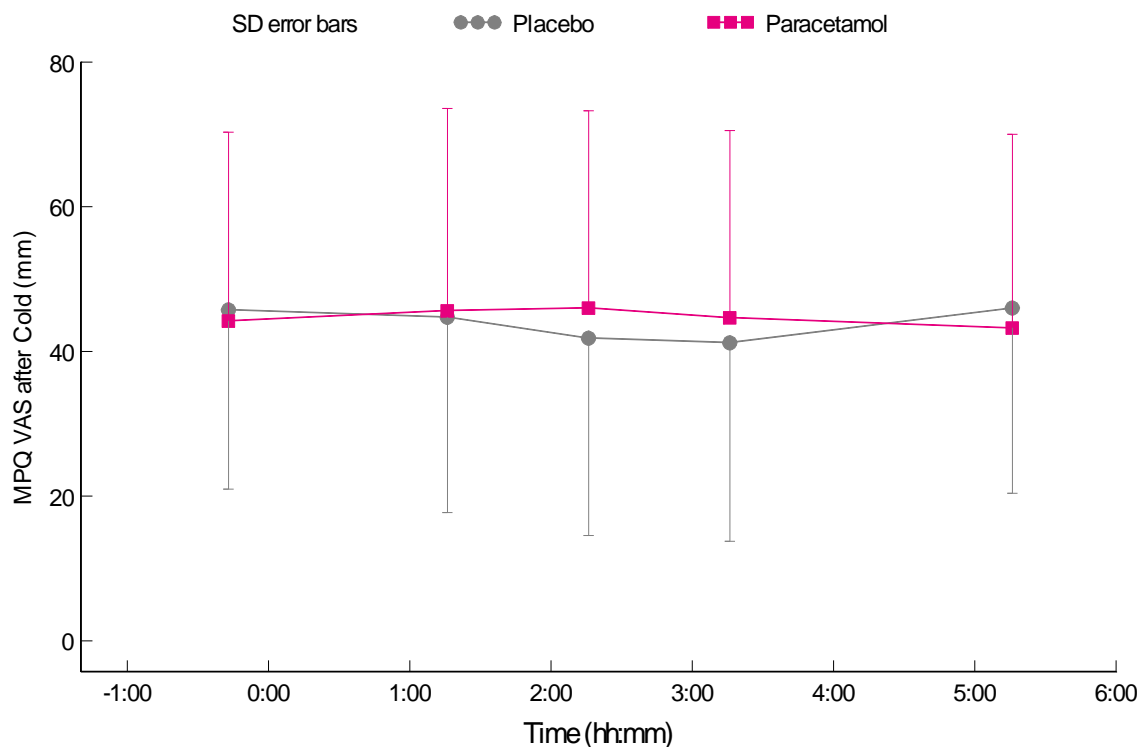
Summary graph 17 MPQ VAS after Cold (mm)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 17 of dynamic measurements

Analysis population



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Sensory after ES

Summary table 18 Sensory after ES

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Summary 18 of dynamic measurements

Analysis population

Summary table: Sensory after ES

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:25	11	1.231	0.3886	0.1172	31.6	1.09	0.73	1.82
	1:08	11	1.182	0.4004	0.1207	33.9	1.18	0.64	1.82
	2:08	11	1.231	0.4952	0.1493	40.2	1.18	0.73	1.91
	3:08	11	1.132	0.5668	0.1709	50.1	1.00	0.45	2.00
	5:08	11	1.050	0.5228	0.1576	49.8	0.73	0.45	1.91
Paracetamol	-0:25	11	1.256	0.4721	0.1423	37.6	1.09	0.73	2.18
	1:08	11	1.165	0.5406	0.1630	46.4	0.82	0.55	2.00
	2:08	11	1.165	0.5042	0.1520	43.3	0.91	0.55	2.00
	3:08	11	1.107	0.4876	0.1470	44.0	1.00	0.55	1.82
	5:08	11	1.140	0.4969	0.1498	43.6	1.00	0.55	1.82

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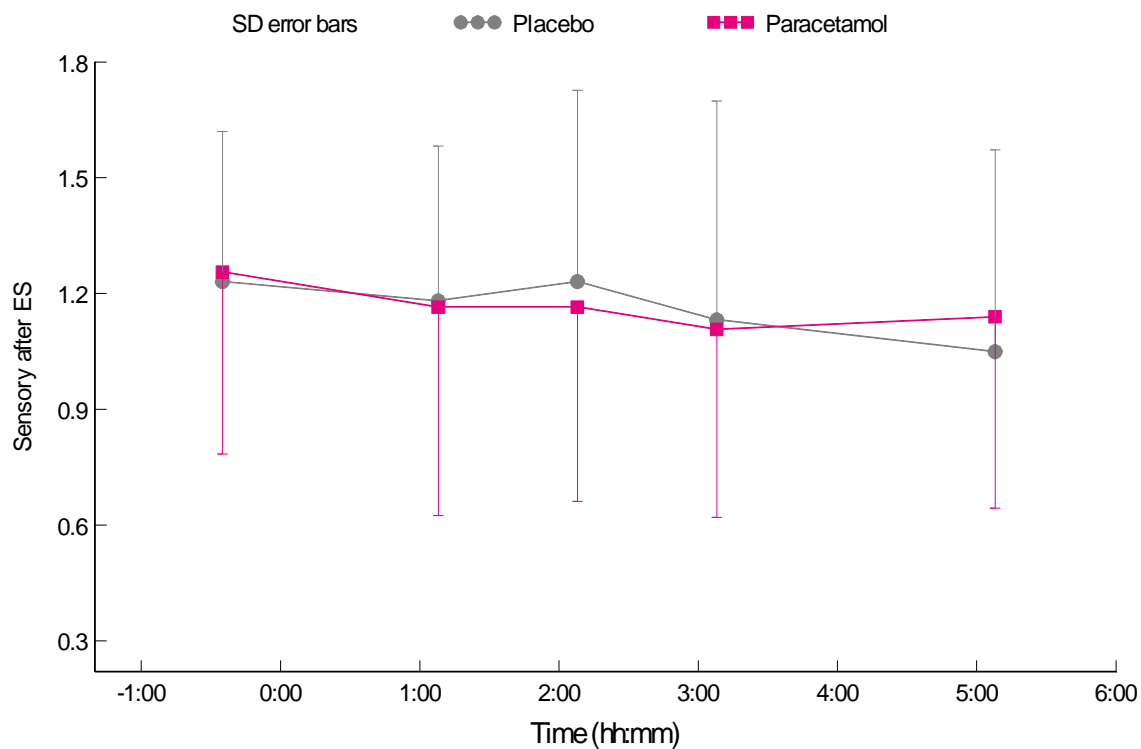
Summary graph 18 Sensory after ES

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 18 of dynamic measurements

Analysis population



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Affective after ES

Summary table 19 Affective after ES

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Summary 19 of dynamic measurements

Analysis population

Summary table: Affective after ES

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:25	11	0.341	0.4510	0.1360	132.3	0.25	0.00	1.25
	1:08	11	0.409	0.5621	0.1695	137.4	0.25	0.00	1.75
	2:08	11	0.341	0.4369	0.1317	128.2	0.25	0.00	1.25
	3:08	11	0.295	0.3844	0.1159	130.1	0.25	0.00	1.00
	5:08	11	0.295	0.3844	0.1159	130.1	0.25	0.00	1.00
Paracetamol	-0:25	11	0.318	0.4197	0.1265	131.9	0.00	0.00	1.00
	1:08	11	0.318	0.4755	0.1434	149.5	0.00	0.00	1.25
	2:08	11	0.318	0.4197	0.1265	131.9	0.00	0.00	1.00
	3:08	11	0.273	0.3946	0.1190	144.7	0.00	0.00	1.00
	5:08	11	0.273	0.3946	0.1190	144.7	0.00	0.00	1.00

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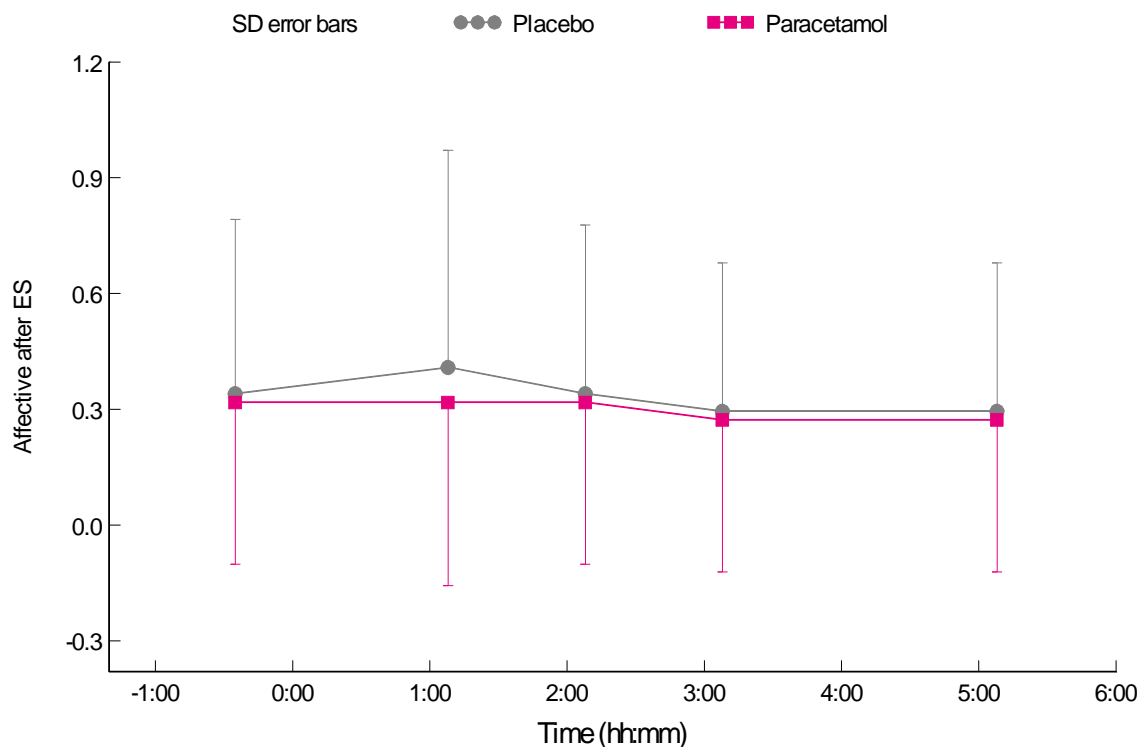
Summary graph 19 Affective after ES

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 19 of dynamic measurements

Analysis population



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MPQ VAS after ES (mm)

Summary table 20 MPQ VAS after ES (mm)

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Summary 20 of dynamic measurements

Analysis population

Summary table: MPQ VAS after ES (mm)

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:25	12	42.24	19.521	5.635	46.2	39.3	11.5	75.2
	1:08	12	40.19	20.487	5.914	51.0	43.4	13.8	68.8
	2:08	12	40.17	21.105	6.092	52.5	40.7	8.2	77.5
	3:08	12	37.88	21.961	6.339	58.0	29.5	8.7	80.2
	5:08	12	38.05	20.784	6.000	54.6	27.2	15.5	77.0
Paracetamol	-0:25	12	38.33	21.234	6.130	55.4	35.1	12.1	76.7
	1:08	12	39.84	20.991	6.060	52.7	41.2	11.4	79.1
	2:08	12	39.58	25.299	7.303	63.9	32.7	0.0	88.6
	3:08	12	37.02	24.319	7.020	65.7	34.2	0.0	81.2
	5:08	12	38.11	23.453	6.770	61.5	32.8	0.0	78.3

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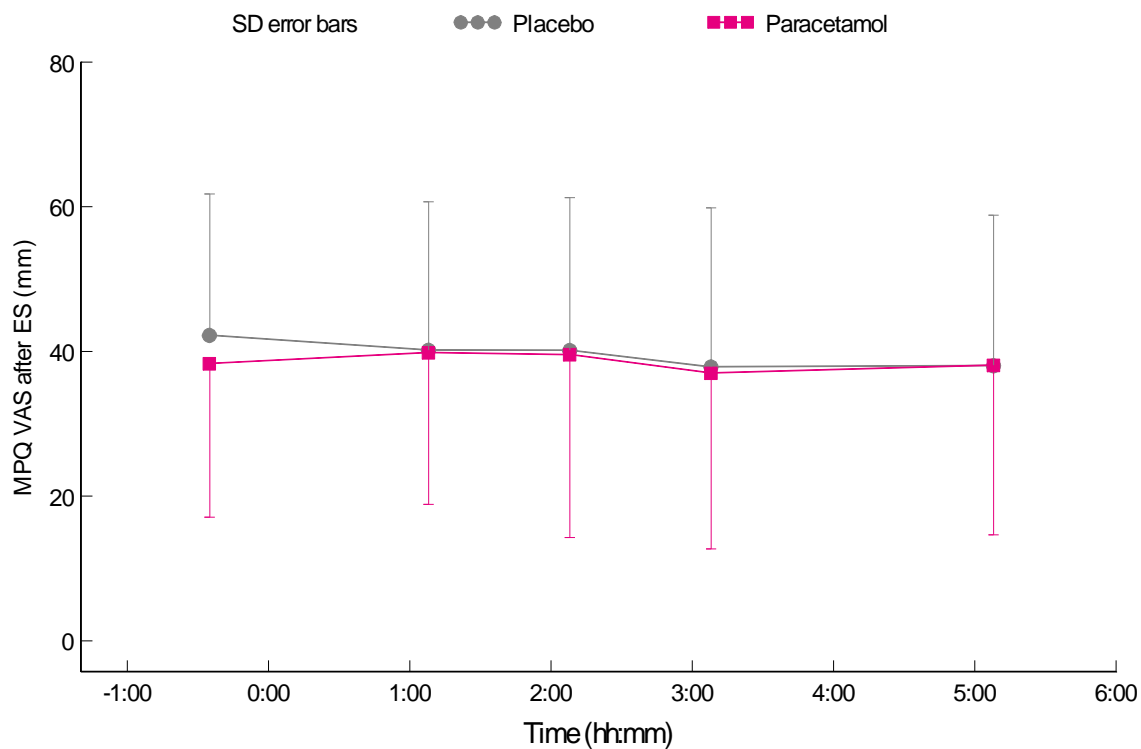
Summary graph 20 MPQ VAS after ES (mm)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 20 of dynamic measurements

Analysis population



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Sensory after Pressure

Summary table 21 Sensory after Pressure

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Summary 21 of dynamic measurements

Analysis population

Summary table: Sensory after Pressure

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:20	11	0.959	0.4173	0.1258	43.5	0.91	0.45	1.73
	1:13	11	1.008	0.4835	0.1458	48.0	0.82	0.45	2.00
	2:13	11	0.942	0.5131	0.1547	54.5	0.82	0.45	2.00
	3:13	11	0.860	0.4919	0.1483	57.2	0.55	0.45	1.91
	5:13	11	0.868	0.4713	0.1421	54.3	0.64	0.45	1.73
Paracetamol	-0:20	11	0.975	0.4246	0.1280	43.5	0.73	0.45	1.73
	1:13	11	0.884	0.6031	0.1819	68.2	0.64	0.27	2.18
	2:13	11	0.950	0.5966	0.1799	62.8	0.64	0.45	2.18
	3:13	11	0.934	0.5471	0.1650	58.6	0.73	0.36	2.00
	5:13	11	0.876	0.5867	0.1769	67.0	0.73	0.27	2.00

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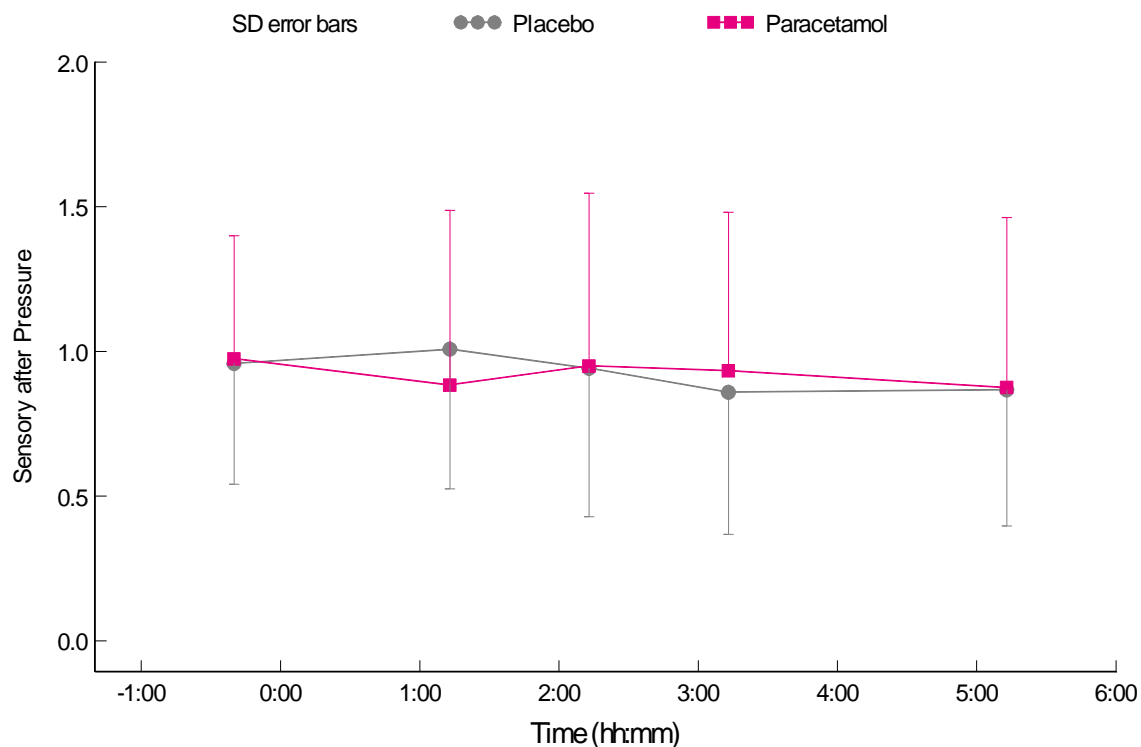
Summary graph 21 Sensory after Pressure

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 21 of dynamic measurements

Analysis population



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Affective after Pressure

Summary table 22 Affective after Pressure

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Summary 22 of dynamic measurements

Analysis population

Summary table: Affective after Pressure

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:20	11	0.273	0.4535	0.1367	166.3	0.00	0.00	1.50
	1:13	11	0.205	0.4585	0.1382	224.2	0.00	0.00	1.50
	2:13	11	0.182	0.4485	0.1352	246.7	0.00	0.00	1.50
	3:13	11	0.136	0.3769	0.1136	276.4	0.00	0.00	1.25
	5:13	11	0.205	0.3320	0.1001	162.3	0.00	0.00	1.00
Paracetamol	-0:20	11	0.205	0.3320	0.1001	162.3	0.00	0.00	1.00
	1:13	11	0.182	0.3723	0.1123	204.8	0.00	0.00	1.25
	2:13	11	0.091	0.3015	0.0909	331.7	0.00	0.00	1.00
	3:13	11	0.136	0.3034	0.0915	222.5	0.00	0.00	1.00
	5:13	11	0.159	0.2567	0.0774	161.4	0.00	0.00	0.75

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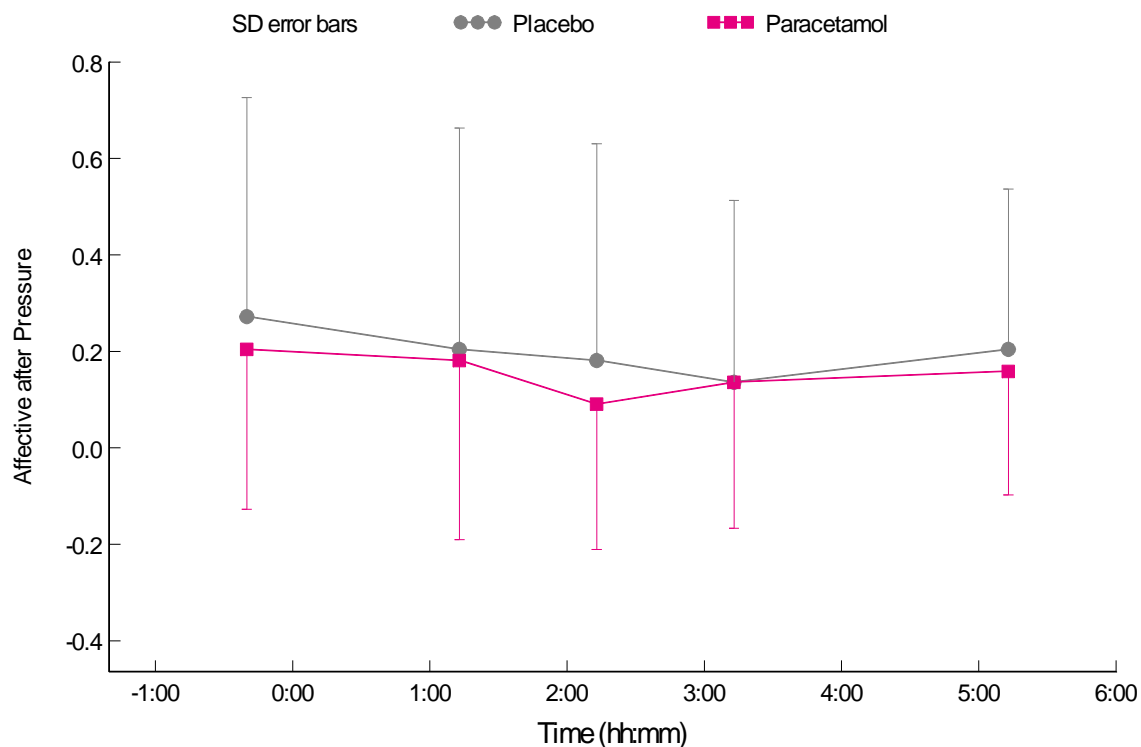
Summary graph 22 Affective after Pressure

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 22 of dynamic measurements

Analysis population



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MPQ VAS after Pressure (mm)

Summary table 23 MPQ VAS after Pressure (mm)

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Summary 23 of dynamic measurements

Analysis population

Summary table: MPQ VAS after Pressure (mm)

Treatment	Time (hh:mm)	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Placebo	-0:20	12	39.51	22.170	6.400	56.1	40.5	12.1	81.0
	1:13	12	36.17	24.886	7.184	68.8	31.3	8.2	76.6
	2:13	12	34.82	22.445	6.479	64.5	27.8	12.9	78.6
	3:13	12	34.22	24.922	7.194	72.8	28.2	8.4	80.4
	5:13	12	36.57	22.929	6.619	62.7	36.0	5.0	70.8
Paracetamol	-0:20	12	33.53	24.087	6.953	71.8	32.0	0.1	66.7
	1:13	12	36.18	26.115	7.539	72.2	32.9	0.1	78.6
	2:13	12	36.28	26.499	7.650	73.0	36.2	0.1	82.6
	3:13	12	33.07	24.977	7.210	75.5	32.5	0.1	73.4
	5:13	12	32.26	23.360	6.744	72.4	26.1	0.1	66.5

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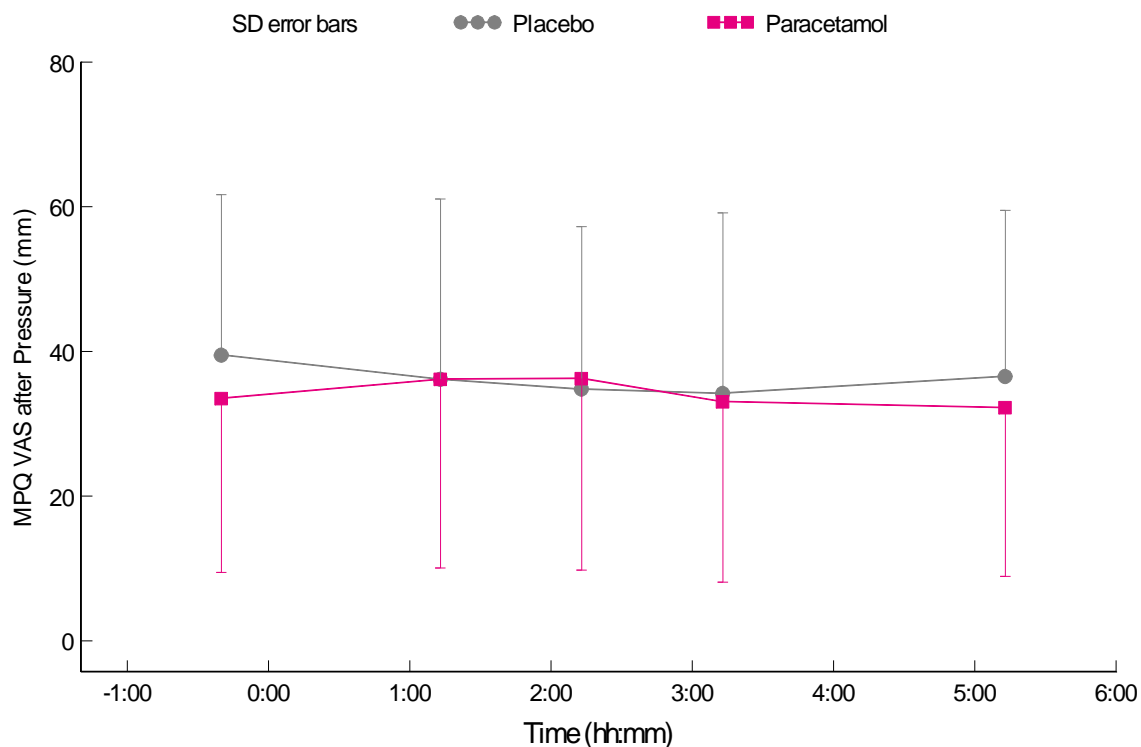
Summary graph 23 MPQ VAS after Pressure (mm)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataSTG.sas

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Summary graph 23 of dynamic measurements

Analysis population



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Analysis results pharmacodynamic response table, LSM table and graphs

Cold AAC (s*%)

Analysis results table 1 Cold AAC (s*%)

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Analysis results 1 of dynamic measurements

Analysis population

Analysis results: Cold AAC (s*%)

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.9986					
Period	0.3551					
Time	0.1493					
Treatment by time	0.3289					
Placebo - Paracetamol	0.9986	2379.1	2379.5	0.40	-510.12	510.92

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LSMs table 1 Cold AAC (s*%)

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LSMs table 1 of dynamic measurements

Analysis population

Least Squares Means

Cold AAC (s*%)

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		2379.1	77.6
	1:16	2405.9	104.4
	2:16	2461.4	159.9
	3:16	2647.6	346.1
	5:16	2001.6	-299.9
Paracetamol		2379.5	78.0
	1:16	2380.6	79.1
	2:16	2279.2	-22.4
	3:16	2480.3	178.8
	5:16	2378.0	76.5

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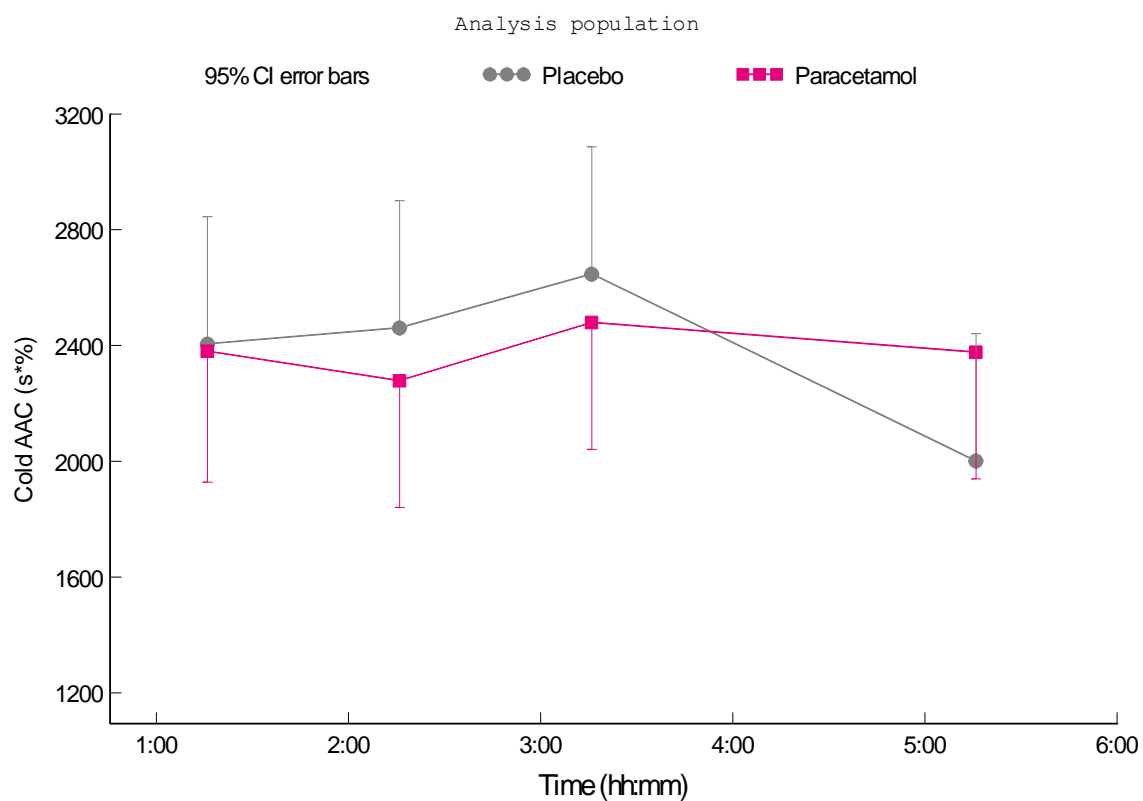
Produced by M.L. de Kam

LSM graph 1 Cold AAC (s*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM graph 1 of dynamic measurements



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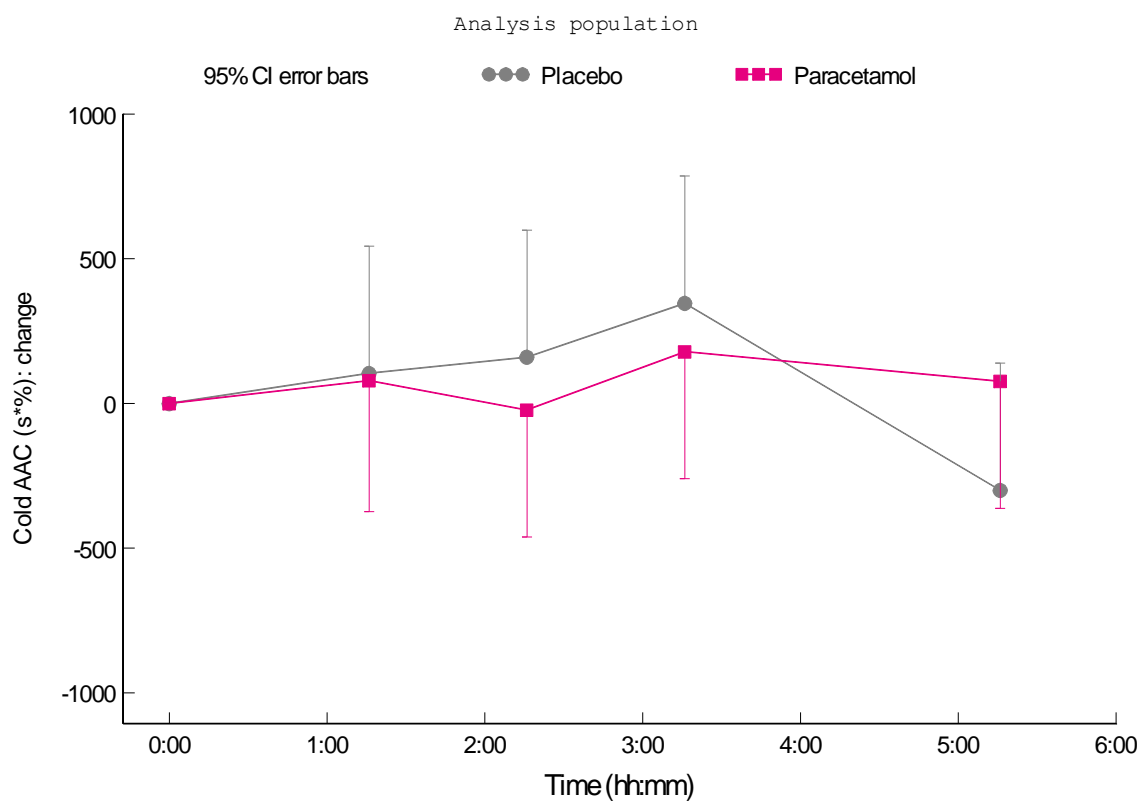
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LSM change from baseline graph 1 Cold AAC (s*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM change from baseline graph 1 of dynamic measurements



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Cold PDT (s)**Analysis results table 2 Cold PDT (s)**

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Analysis results 2 of dynamic measurements

Analysis population

Analysis results: LOG Cold PDT (s)

Back Transformed						

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper

Treatment	0.3505					
Period	0.3231					
Time	0.7615					
Treatment by time	0.4802					
Placebo - Paracetamol	0.3505	4.4	5.2	16.7%	-18.1%	66.4%

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LSMs table 2 Cold PDT (s)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSMs table 2 of dynamic measurements

Analysis population

Back transformed Least Squares Means
Cold PDT (s)

Treatment	Time (hh:mm)	Back Transformed	
		LSM	LSM change from baseline
Placebo		4.4	-4.0%
	1:16	4.2	-9.9%
	2:16	4.7	1.1%
	3:16	4.9	6.3%
	5:16	4.0	-12.4%
Paracetamol		5.2	12.1%
	1:16	4.7	2.9%
	2:16	5.6	20.6%
	3:16	4.5	-2.6%
	5:16	6.0	30.5%

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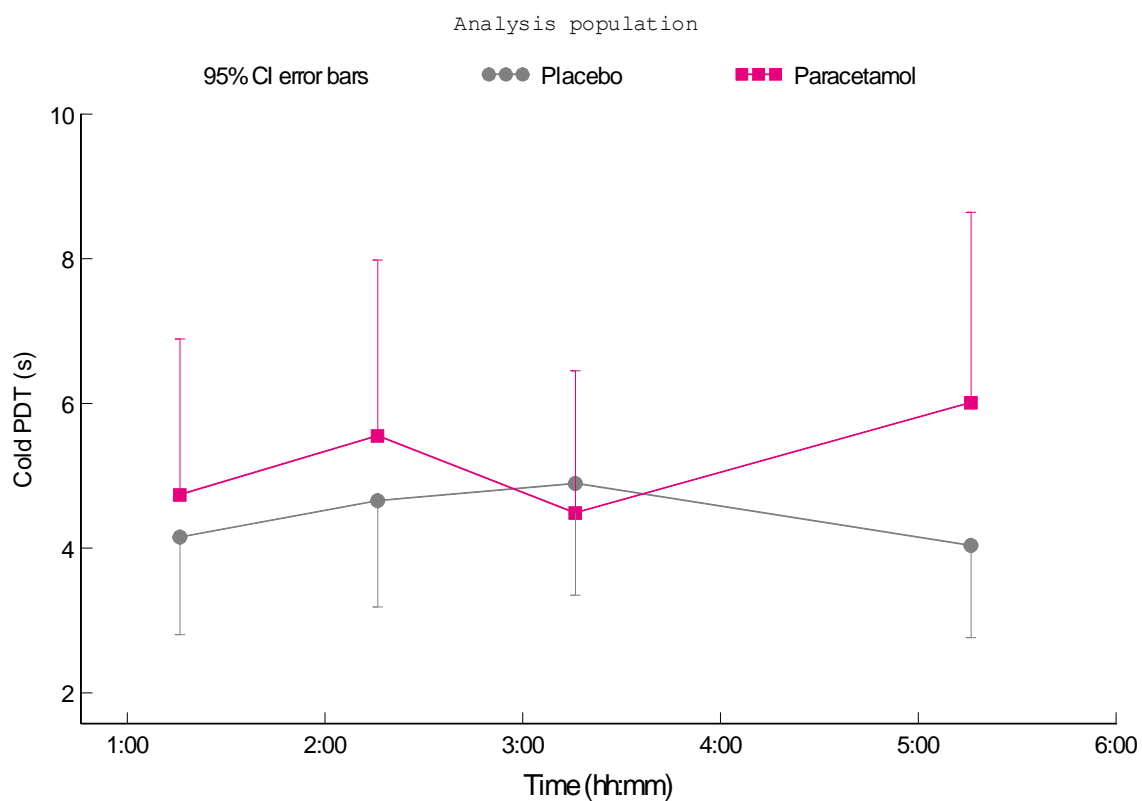
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LSM graph 2 Cold PDT (s)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM graph 2 of dynamic measurements



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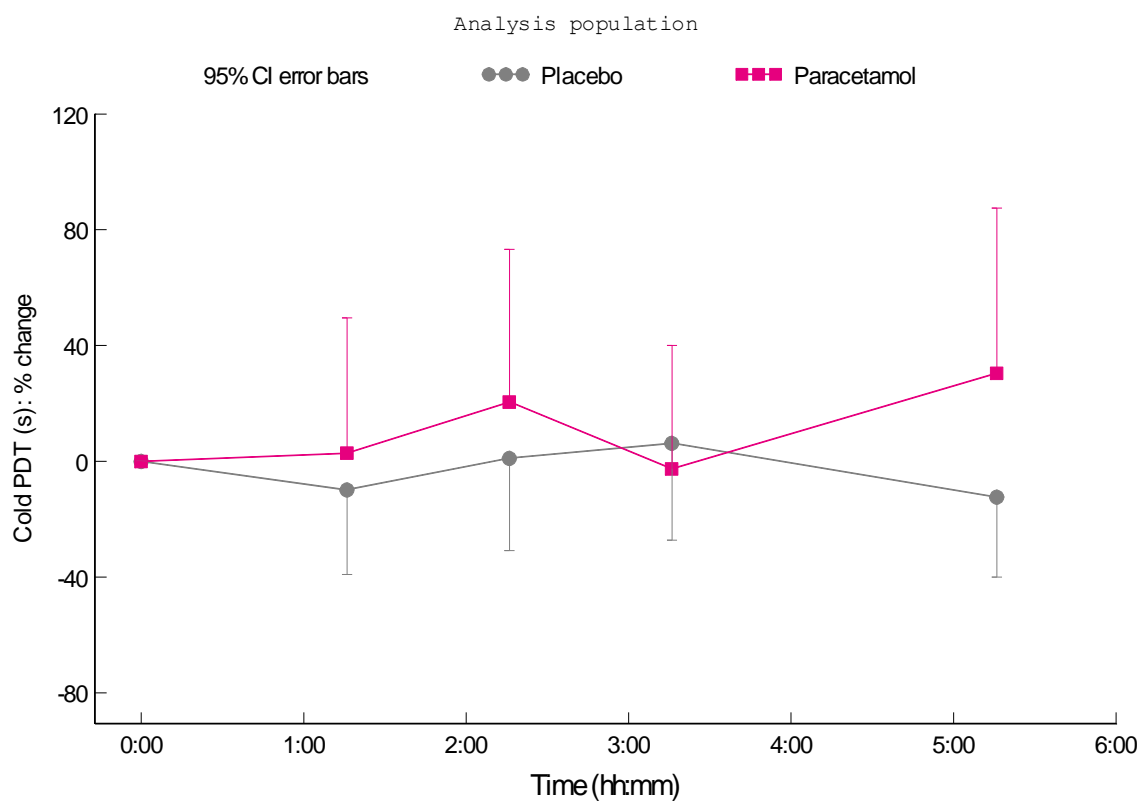
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LSM change from baseline graph 2 Cold PDT (s)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM change from baseline graph 2 of dynamic measurements



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Cold PTT (s)**Analysis results table 3 Cold PTT (s)**

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Analysis results 3 of dynamic measurements

Analysis population

Analysis results: LOG Cold PTT (s)

Back Transformed						

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper

Treatment	0.4088					
Period	0.6440					
Time	0.2195					
Treatment by time	0.0767					
Placebo - Paracetamol	0.4088	29.2	31.9	9.0%	-12.9%	36.3%

Page 1 of 1				Produced by M.L. de Kam		

LSMs table 3 Cold PTT (s)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSMs table 3 of dynamic measurements

Analysis population

Back transformed Least Squares Means
Cold PTT (s)

Treatment	Time (hh:mm)	Back Transformed	
		LSM	LSM change from baseline
Placebo		29.2	-5.7%
	1:16	29.8	-4.1%
	2:16	31.9	2.8%
	3:16	30.1	-3.0%
	5:16	25.6	-17.5%
Paracetamol		31.9	2.7%
	1:16	29.9	-3.5%
	2:16	31.5	1.7%
	3:16	33.1	6.6%
	5:16	33.0	6.5%

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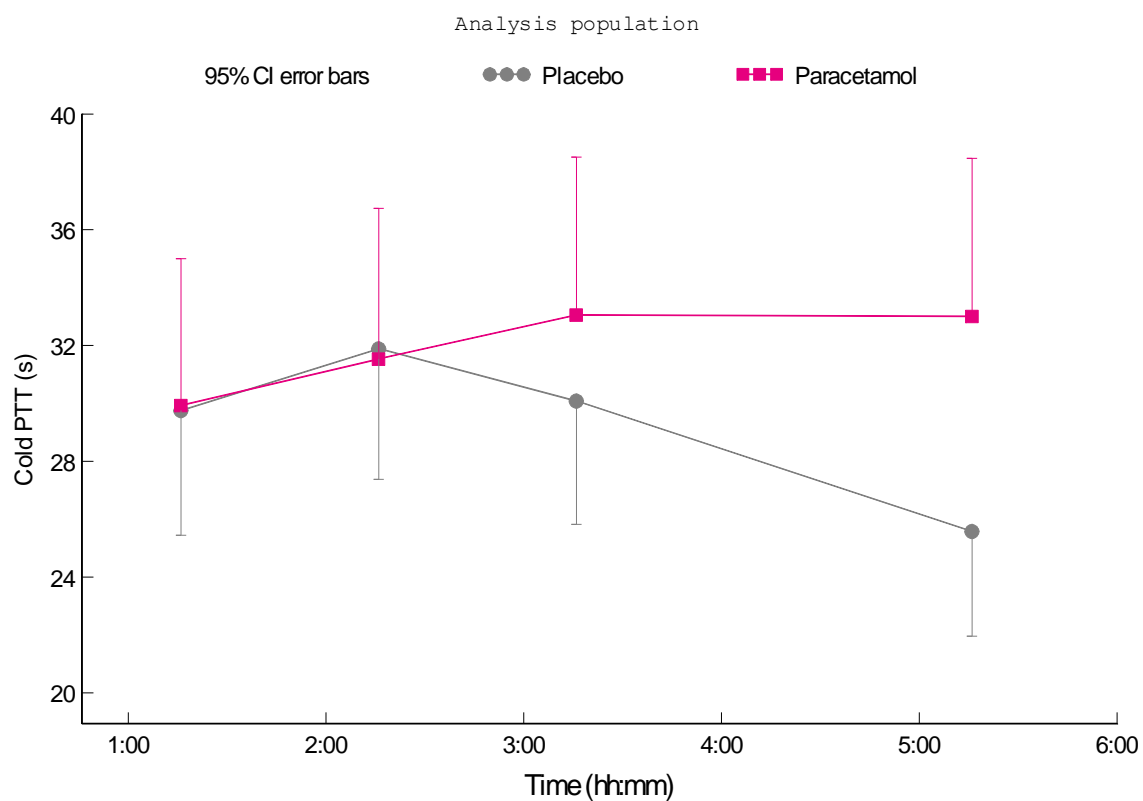
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LSM graph 3 Cold PTT (s)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM graph 3 of dynamic measurements



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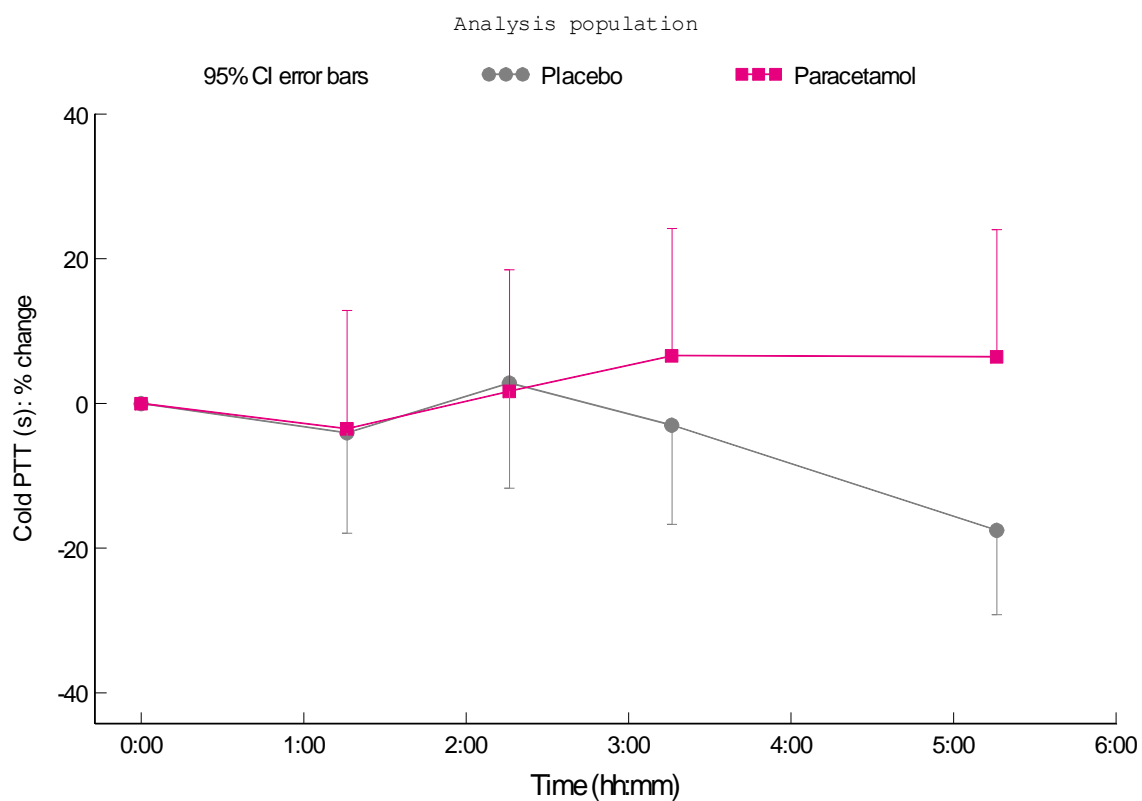
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LSM change from baseline graph 3 Cold PTT (s)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM change from baseline graph 3 of dynamic measurements



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Electrical Stair AUC (mA*%)

Analysis results table 4 Electrical Stair AUC (mA*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Analysis results 4 of dynamic measurements

Analysis population

Analysis results: Electrical Stair AUC (mA*%)

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.4977					
Period	0.0892					
Time	0.0480					
Treatment by time	0.5612					
Placebo - Paracetamol	0.4977	2946.8	3039.3	92.55	-205.57	390.68

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LSMs table 4 Electrical Stair AUC (mA*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSMs table 4 of dynamic measurements

Analysis population

Least Squares Means
Electrical Stair AUC (mA*%)

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		2946.8	-310.8
	1:08	3011.7	-245.9
	2:08	2984.2	-273.4
	3:08	2917.8	-339.8
	5:08	2873.2	-384.4
Paracetamol		3039.3	-218.3
	1:08	3172.5	-85.1
	2:08	3023.5	-234.1
	3:08	2956.8	-300.8
	5:08	3004.5	-253.1

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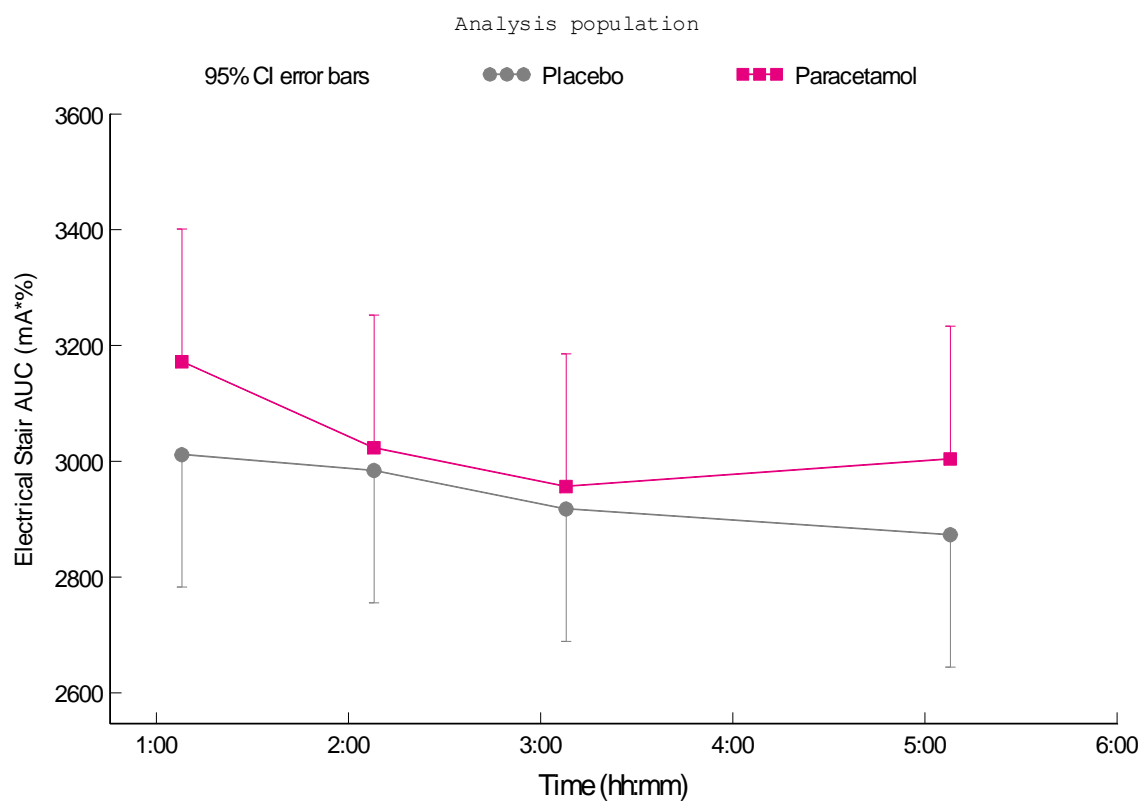
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LSM graph 4 Electrical Stair AUC (mA*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM graph 4 of dynamic measurements



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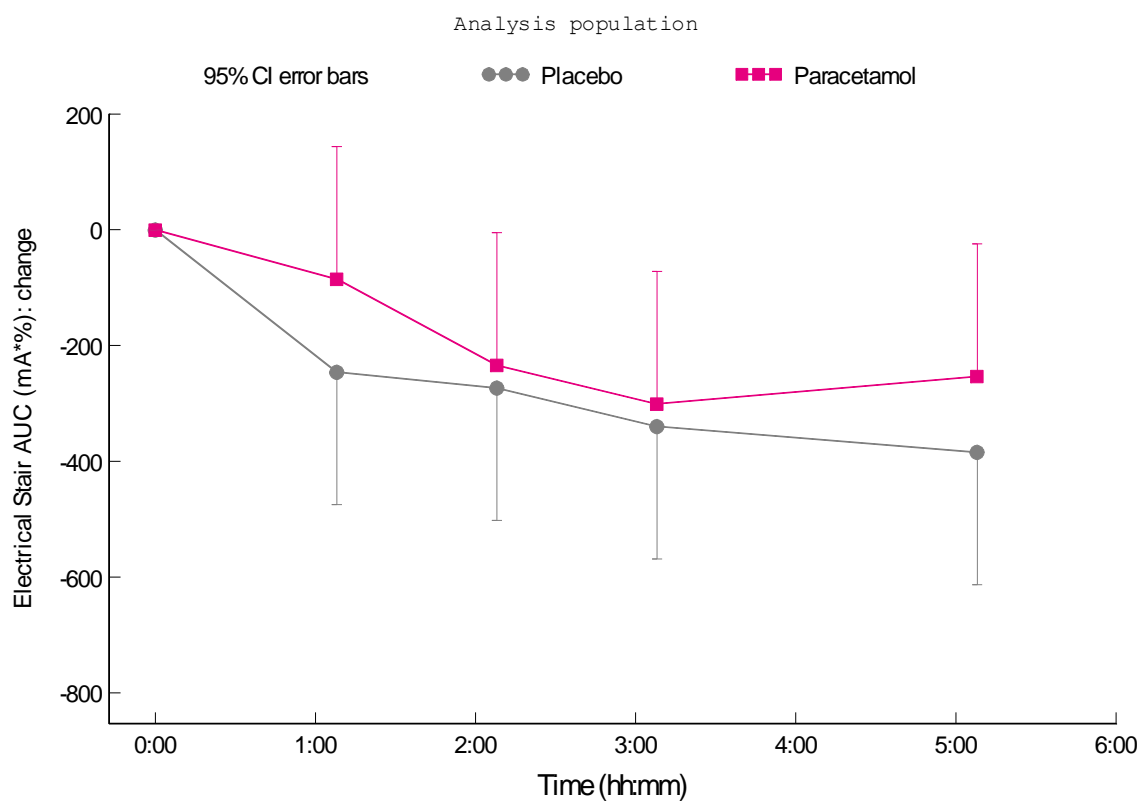
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LSM change from baseline graph 4 Electrical Stair AUC (mA*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM change from baseline graph 4 of dynamic measurements



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Electrical Stair PDT (mA)**Analysis results table 5 Electrical Stair PDT (mA)**

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Analysis results 5 of dynamic measurements

Analysis population

Analysis results: LOG Electrical Stair PDT (mA)

Back Transformed						

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper

Treatment	0.1544					
Period	0.0444					
Time	0.2000					
Treatment by time	0.7799					
Placebo - Paracetamol	0.1544	8.1	7.1	-12.7%	-28.3%	6.3%

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LSMs table 5 Electrical Stair PDT (mA)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSMs table 5 of dynamic measurements

Analysis population

Back transformed Least Squares Means
Electrical Stair PDT (mA)

Treatment	Time (hh:mm)	Back Transformed	
		LSM	LSM change from baseline
Placebo		8.1	44.3%
	1:08	7.7	36.7%
	2:08	7.5	33.2%
	3:08	8.8	56.0%
	5:08	8.6	52.9%
Paracetamol		7.1	26.0%
	1:08	6.5	15.8%
	2:08	6.9	22.1%
	3:08	8.0	41.4%
	5:08	7.1	26.0%

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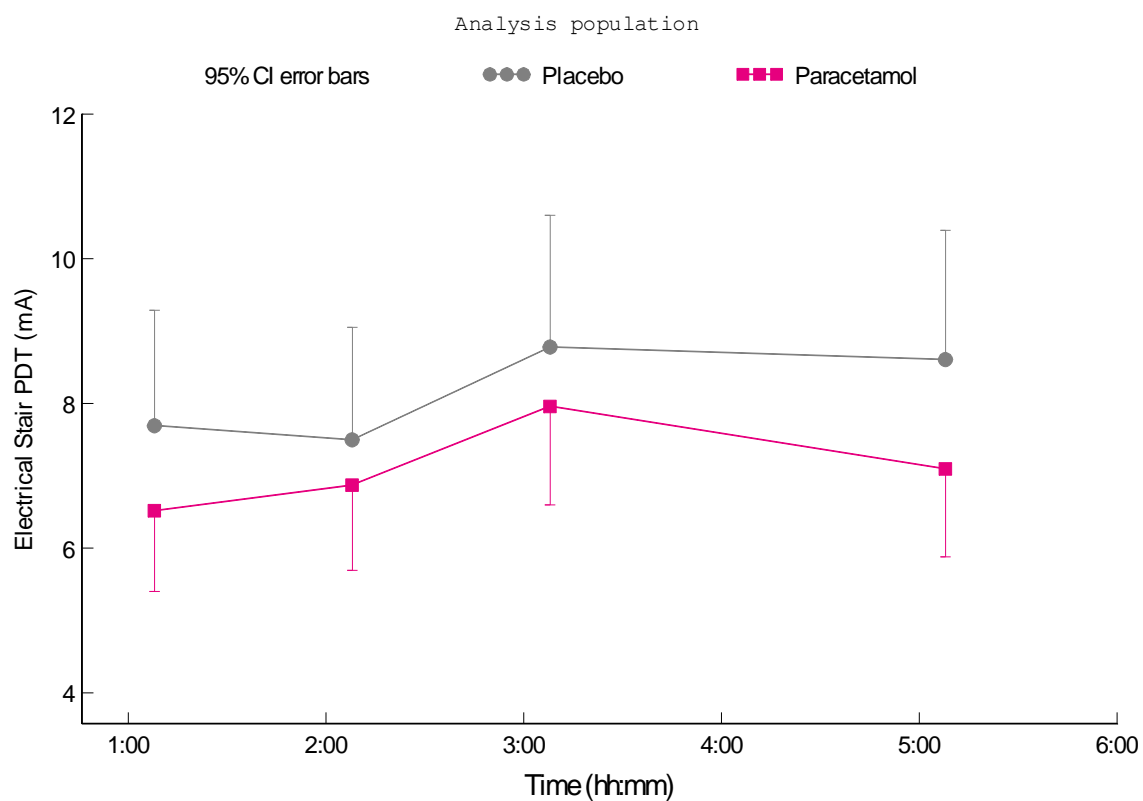
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LSM graph 5 Electrical Stair PDT (mA)

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LSM graph 5 of dynamic measurements



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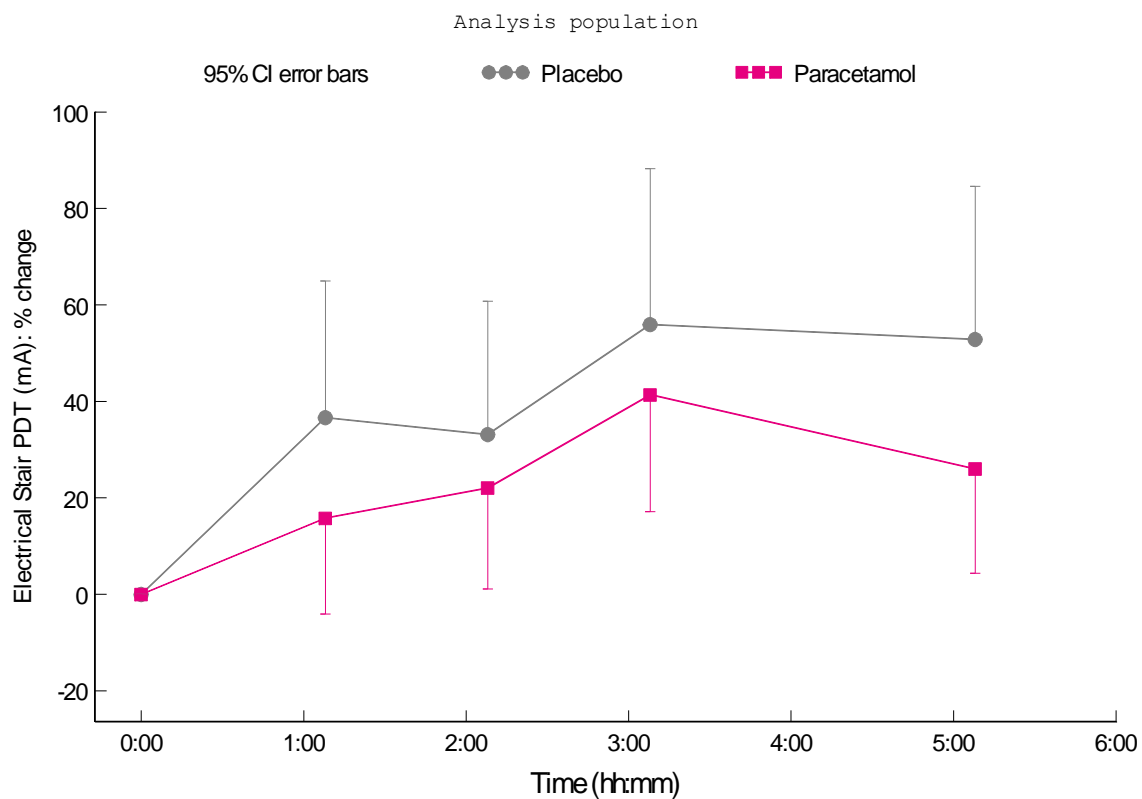
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LSM change from baseline graph 5 Electrical Stair PDT (mA)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM change from baseline graph 5 of dynamic measurements



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Electrical Stair PTT (mA)

Analysis results table 6 Electrical Stair PTT (mA)

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Analysis results 6 of dynamic measurements

Analysis population

Analysis results: LOG Electrical Stair PTT (mA)

Back Transformed						

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper

Treatment	0.8759					
Period	0.5765					
Time	0.6684					
Treatment by time	0.4097					
Placebo - Paracetamol	0.8759	22.2	22.4	0.9%	-10.9% -	14.2%

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LSMs table 6 Electrical Stair PTT (mA)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSMs table 6 of dynamic measurements

Analysis population

Back transformed Least Squares Means
Electrical Stair PTT (mA)

Treatment	Time (hh:mm)	Back Transformed	
		LSM	LSM change from baseline
Placebo		22.2	9.2%
	1:08	22.1	8.7%
	2:08	22.1	8.8%
	3:08	22.1	8.6%
	5:08	22.5	10.9%
Paracetamol		22.4	10.2%
	1:08	21.5	6.1%
	2:08	22.5	10.7%
	3:08	23.0	13.4%
	5:08	22.5	10.7%

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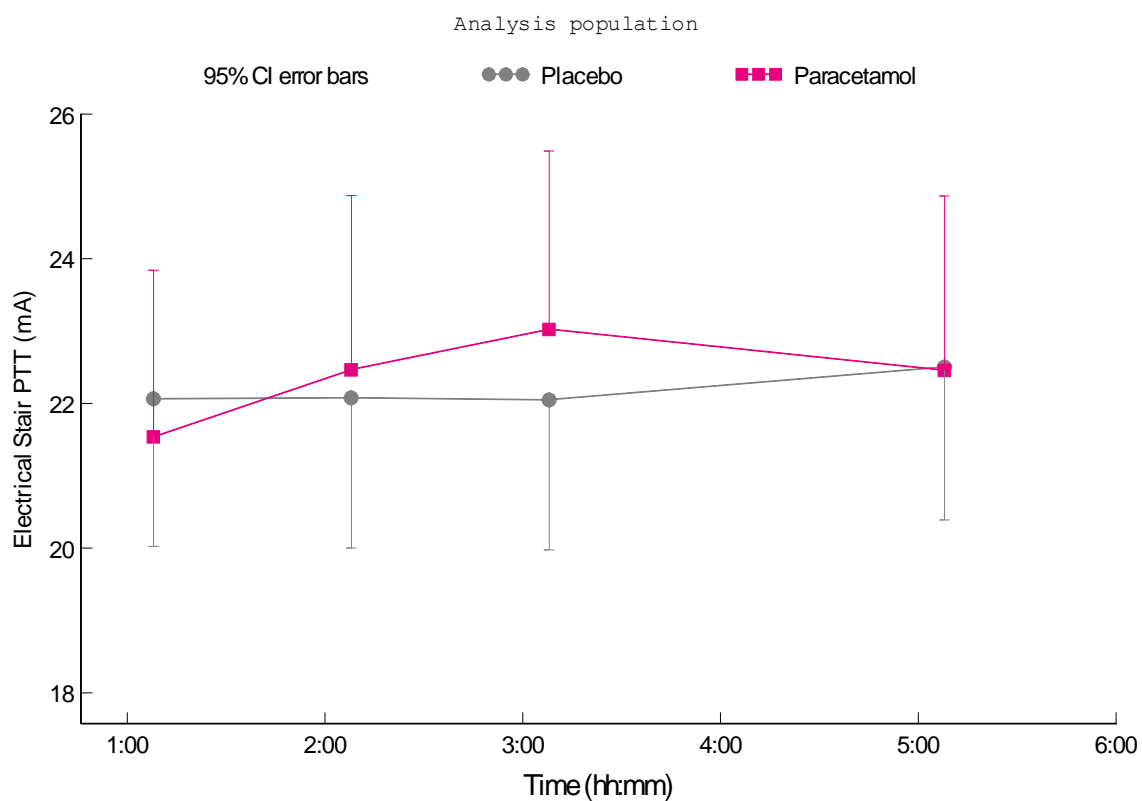
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LSM graph 6 Electrical Stair PTT (mA)

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LSM graph 6 of dynamic measurements



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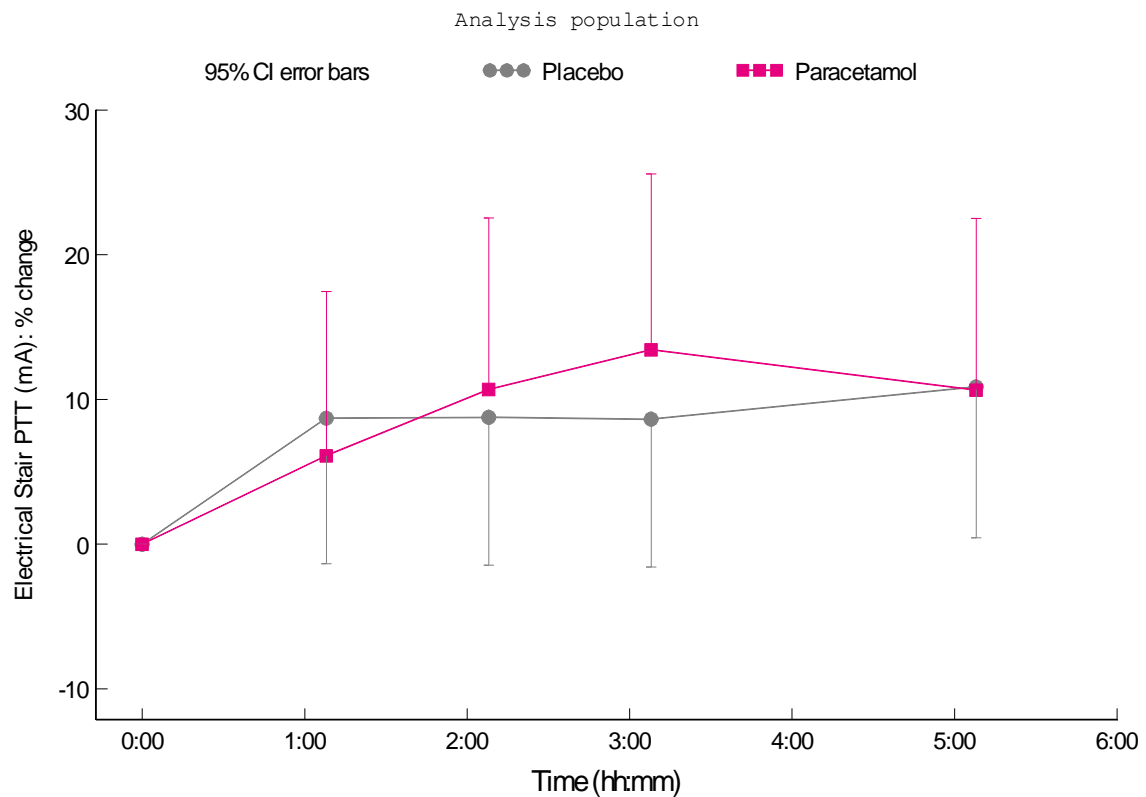
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LSM change from baseline graph 6 Electrical Stair PTT (mA)

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LSM change from baseline graph 6 of dynamic measurements



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Delta Electrical Stair AUC (mA*%)**Analysis results table 7 Delta Electrical Stair AUC (mA*%)**

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Analysis results 7 of dynamic measurements

Analysis population

Analysis results: Delta Electrical Stair AUC (mA*%)

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.8349					
Period	0.2728					
Time	0.8771					
Treatment by time	0.3708					
Placebo - Paracetamol	0.8349	-199.9	-182.0	17.95	-179.51	215.42

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LSMs table 7 Delta Electrical Stair AUC (mA*%)

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LSMs table 7 of dynamic measurements

Analysis population

Least Squares Means
Delta Electrical Stair AUC (mA*%)

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		-199.9	48.3
	1:21	-179.0	69.3
	2:21	-224.2	24.0
	3:21	-228.0	20.2
	5:21	-168.6	79.6
Paracetamol		-182.0	66.2
	1:21	-253.0	-4.8
	2:21	-120.2	128.0
	3:21	-112.1	136.1
	5:21	-242.6	5.6

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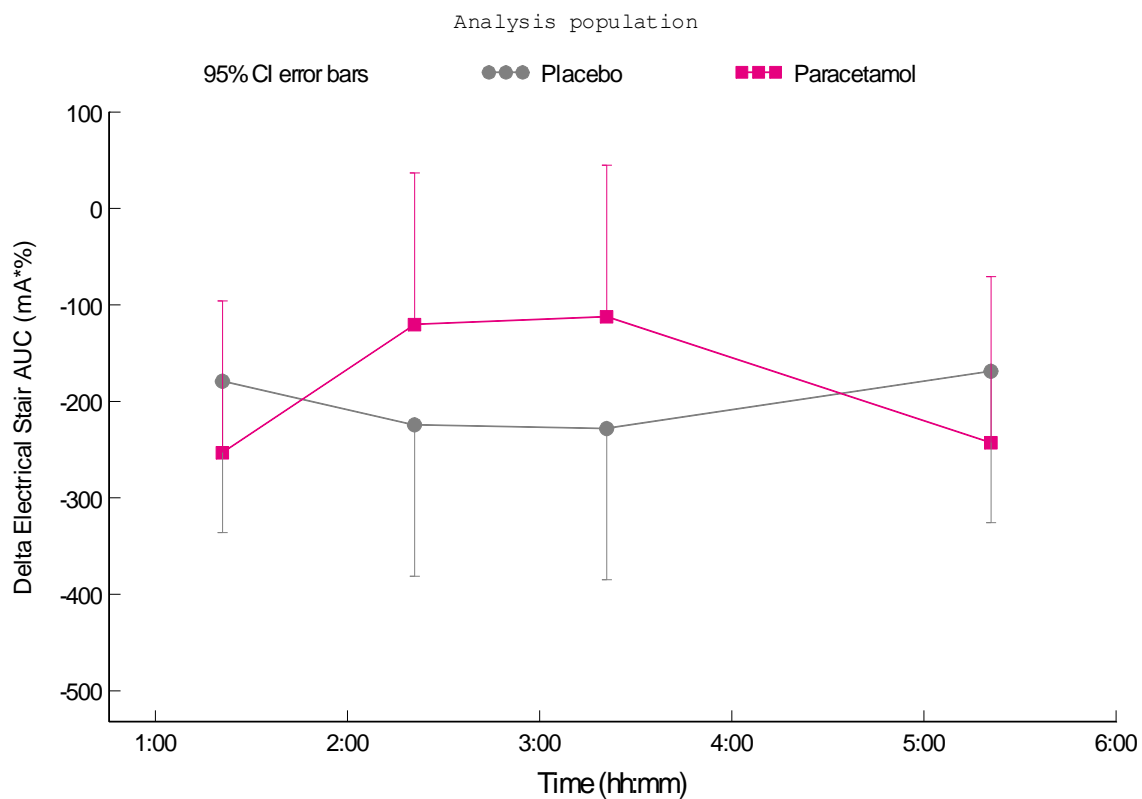
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LSM graph 7 Delta Electrical Stair AUC (mA*%)

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LSM graph 7 of dynamic measurements



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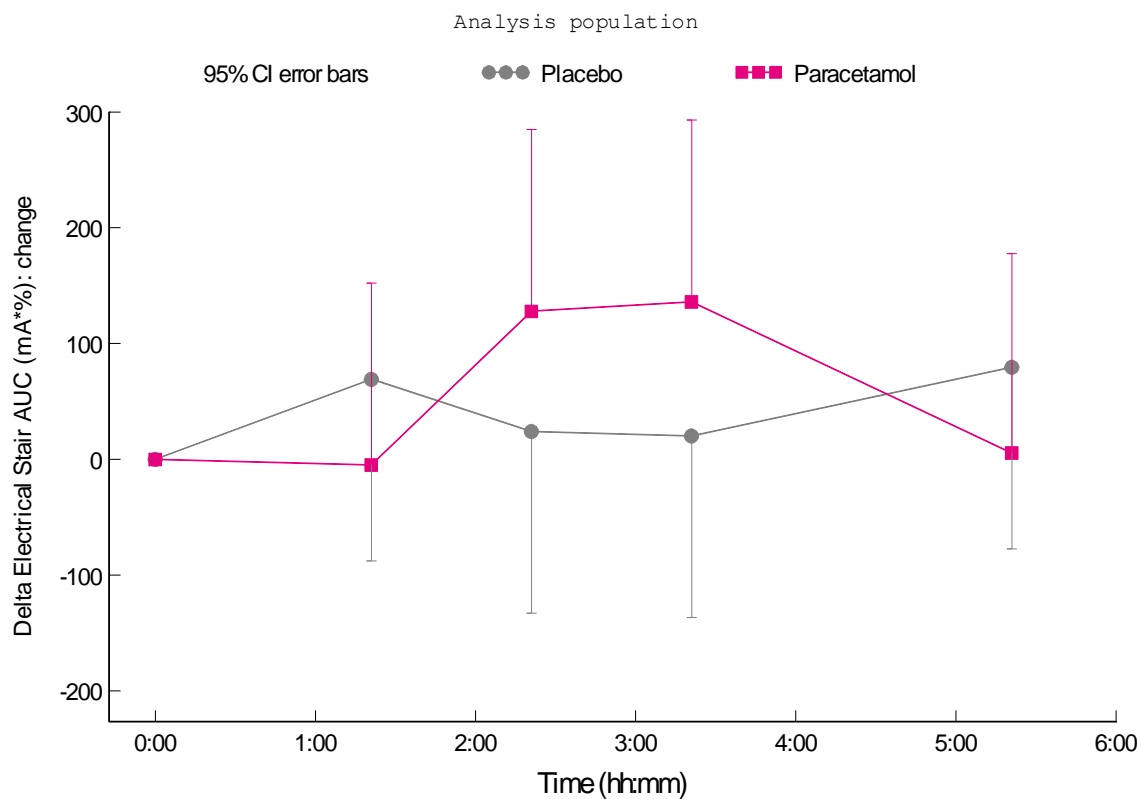
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LSM change from baseline graph 7 Delta Electrical Stair AUC (mA*%)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM change from baseline graph 7 of dynamic measurements



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Delta Electrical Stair PDT (mA)

Analysis results table 8 Delta Electrical Stair PDT (mA)

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Analysis results 8 of dynamic measurements

Analysis population

Analysis results: Delta Electrical Stair PDT (mA)

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.7308					
Period	0.7038					
Time	0.7418					
Treatment by time	0.9170					
Placebo - Paracetamol	0.7308	1.51	1.82	0.303	-1.628	2.234

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LSMs table 8 Delta Electrical Stair PDT (mA)

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LSMs table 8 of dynamic measurements

Analysis population

Least Squares Means
Delta Electrical Stair PDT (mA)

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		1.51	-0.44
	1:21	1.66	-0.29
	2:21	1.09	-0.86
	3:21	1.36	-0.59
	5:21	1.94	-0.02
Paracetamol		1.82	-0.14
	1:21	1.21	-0.74
	2:21	1.75	-0.20
	3:21	1.67	-0.28
	5:21	2.63	0.68

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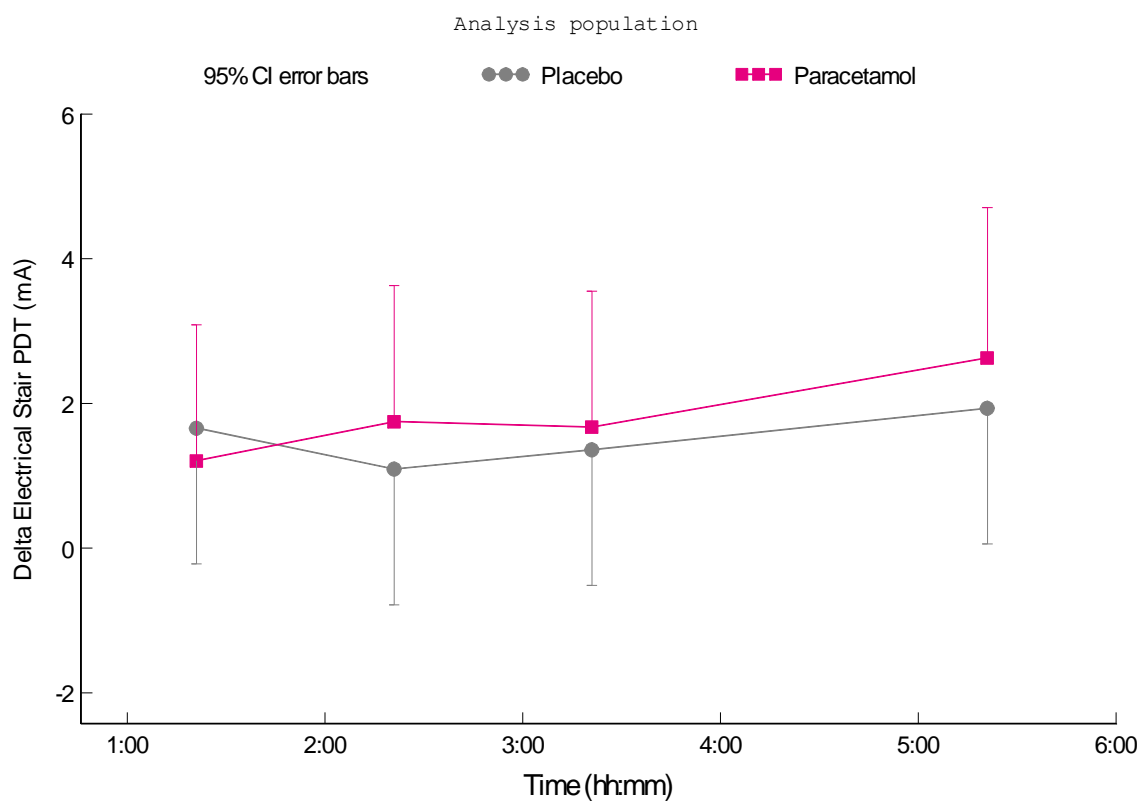
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LSM graph 8 Delta Electrical Stair PDT (mA)

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LSM graph 8 of dynamic measurements



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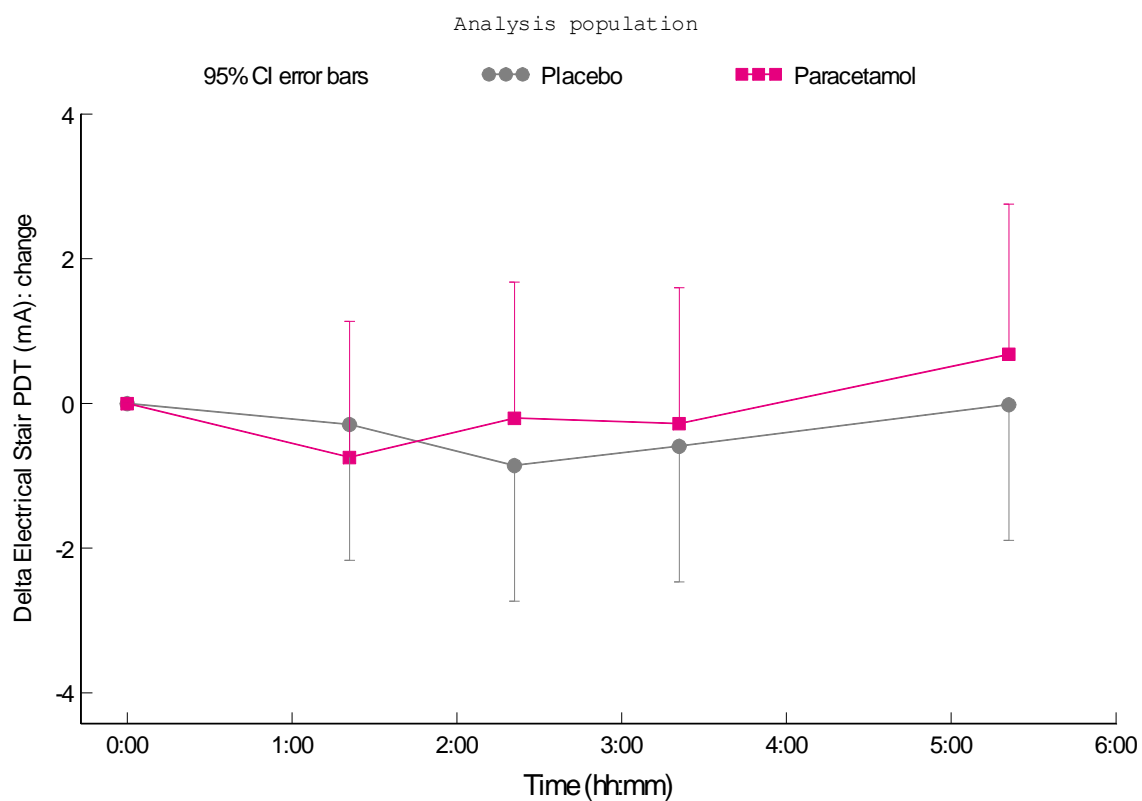
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LSM change from baseline graph 8 Delta Electrical Stair PDT (mA)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM change from baseline graph 8 of dynamic measurements



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Delta Electrical Stair PTT (mA)

Analysis results table 9 Delta Electrical Stair PTT (mA)

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Analysis results 9 of dynamic measurements

Analysis population

Analysis results: Delta Electrical Stair PTT (mA)

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.3993					
Period	0.9347					
Time	0.4577					
Treatment by time	0.2244					
Placebo - Paracetamol	0.3993	1.75	1.25	-0.505	-1.802	0.793

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LSMs table 9 Delta Electrical Stair PTT (mA)

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LSMs table 9 of dynamic measurements

Analysis population

Least Squares Means
Delta Electrical Stair PTT (mA)

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		1.75	-0.27
	1:21	1.36	-0.66
	2:21	1.94	-0.08
	3:21	1.89	-0.13
	5:21	1.81	-0.21
Paracetamol		1.25	-0.78
	1:21	2.18	0.15
	2:21	1.27	-0.76
	3:21	-0.54	-2.57
	5:21	2.10	0.07

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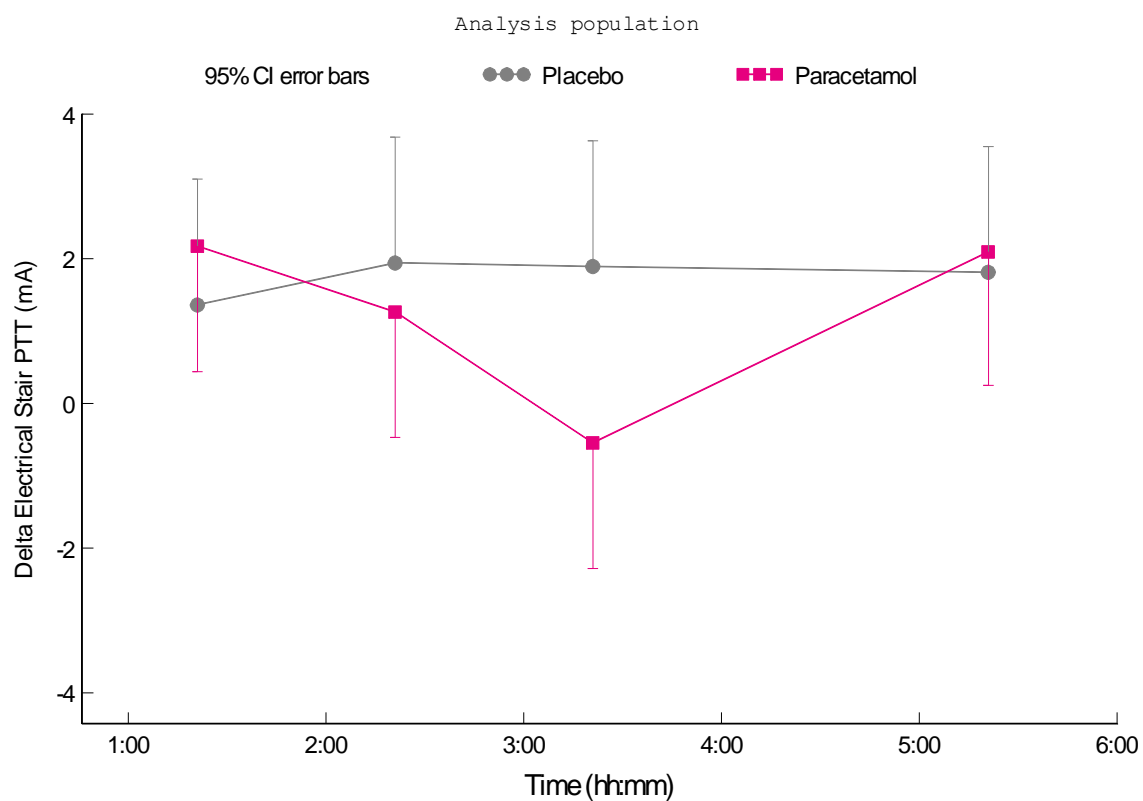
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LSM graph 9 Delta Electrical Stair PTT (mA)

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LSM graph 9 of dynamic measurements



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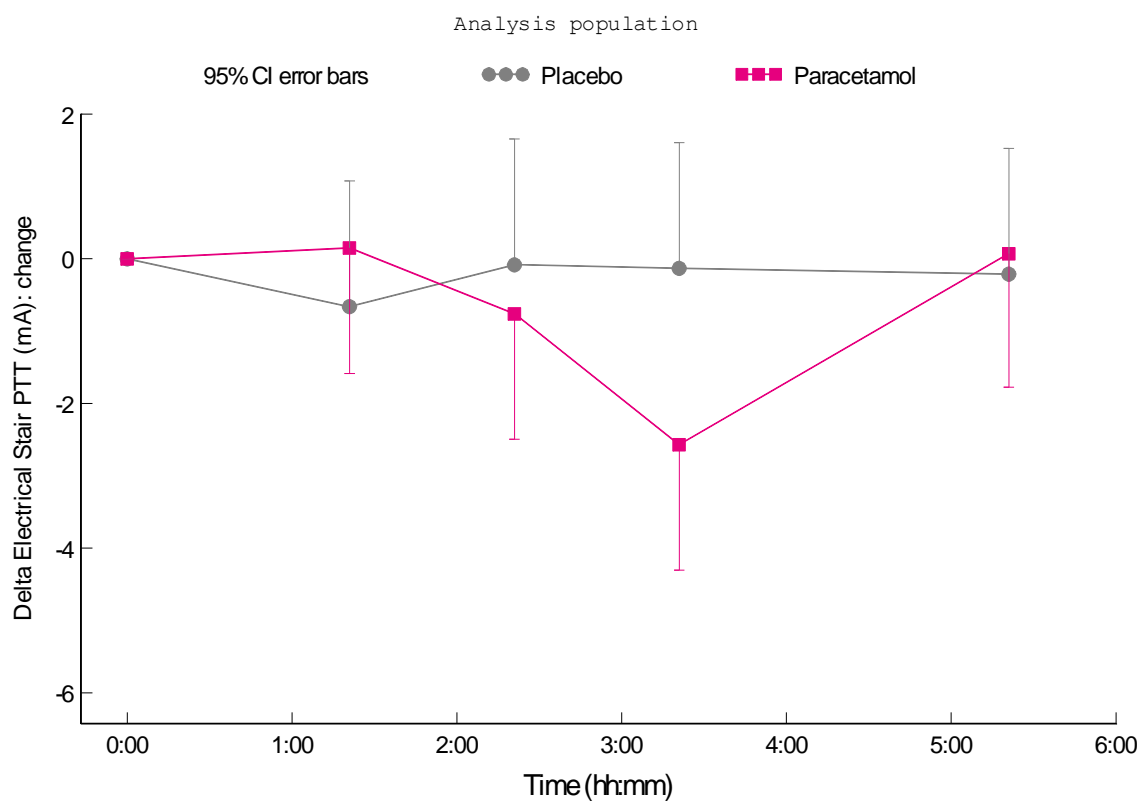
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LSM change from baseline graph 9 Delta Electrical Stair PTT (mA)

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LSM change from baseline graph 9 of dynamic measurements



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Pressure AUC (kPa*%)**Analysis results table 10 Pressure AUC (kPa*%)**

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Analysis results 10 of dynamic measurements

Analysis population

Analysis results: Pressure AUC (kPa*%)

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.0726					
Period	0.2758					
Time	0.0715					
Treatment by time	0.9035					
Placebo - Paracetamol	0.0726	6732.9	6256.4	-476.53	-1005.63	52.57

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LSMs table 10 Pressure AUC (kPa*%)

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LSMs table 10 of dynamic measurements

Analysis population

Least Squares Means
Pressure AUC (kPa*%)

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		6732.9	-125.3
	1:13	6996.9	138.6
	2:13	6643.3	-214.9
	3:13	6634.6	-223.6
	5:13	6656.9	-201.4
Paracetamol		6256.4	-601.9
	1:13	6494.5	-363.7
	2:13	6253.8	-604.5
	3:13	6191.0	-667.3
	5:13	6086.3	-772.0

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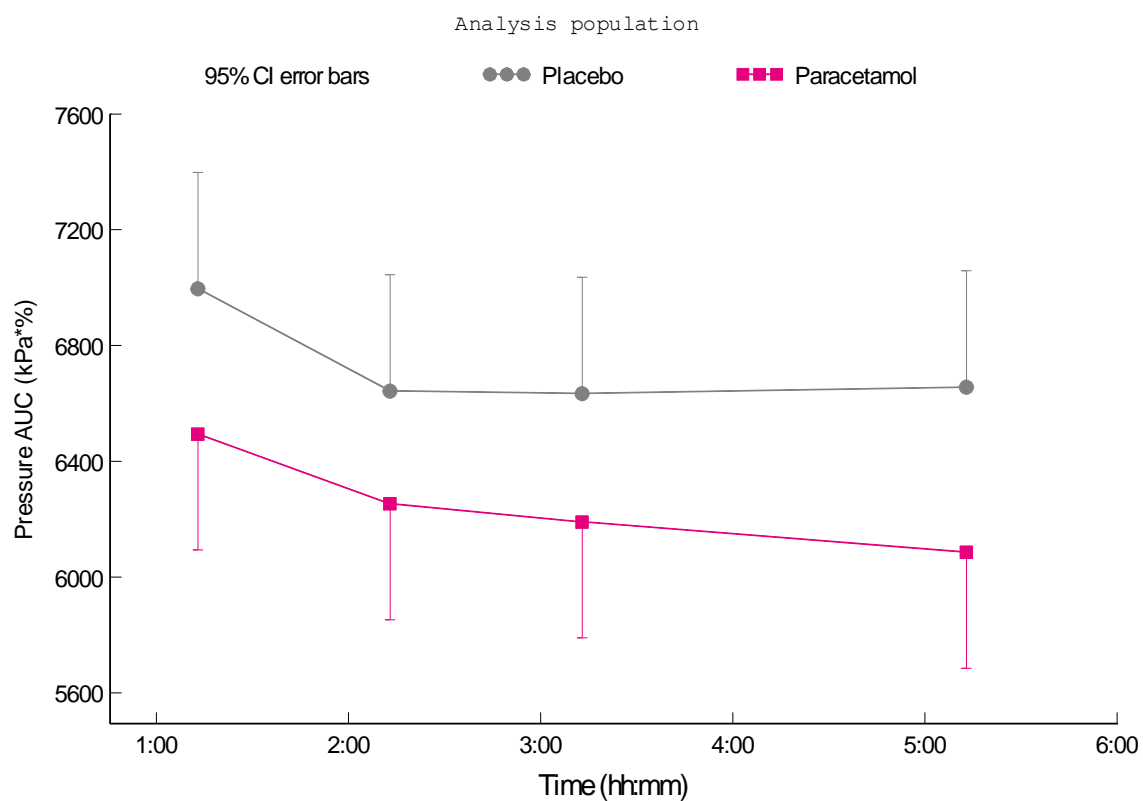
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LSM graph 10 Pressure AUC (kPa*%)

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LSM graph 10 of dynamic measurements



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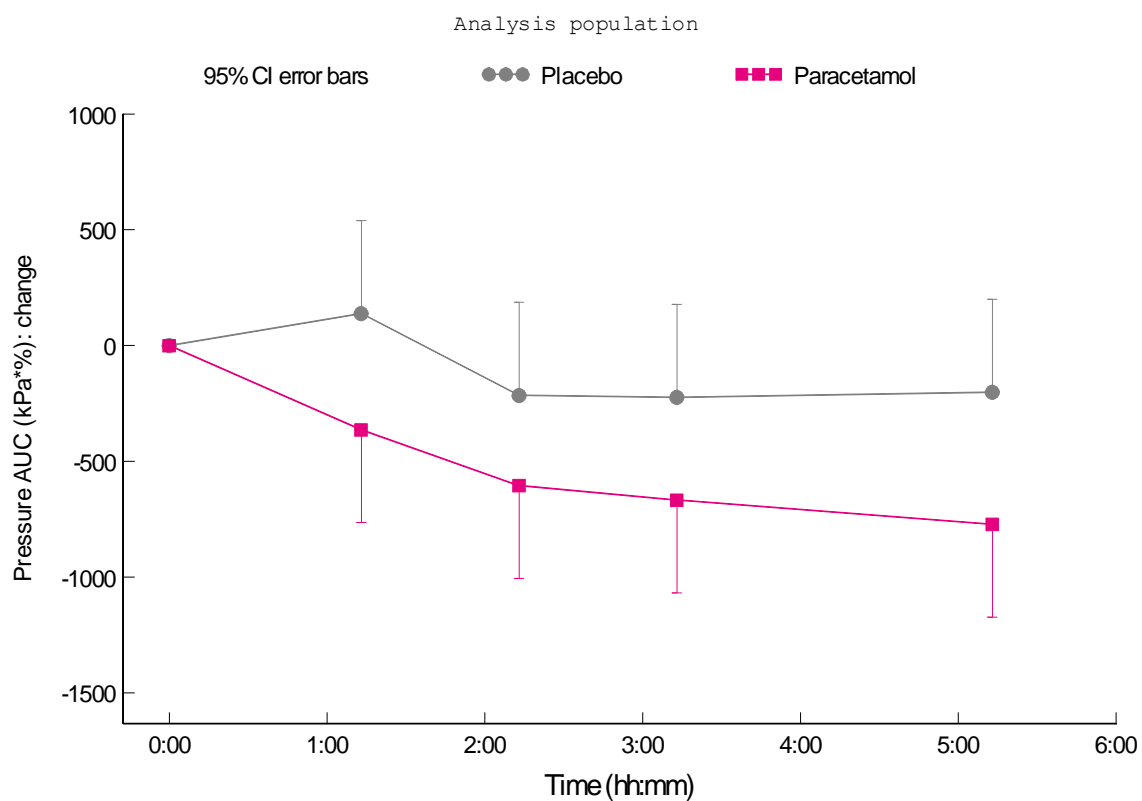
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LSM change from baseline graph 10 Pressure AUC (kPa*%)

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LSM change from baseline graph 10 of dynamic measurements



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Pressure PDT (kPa)**Analysis results table 11 Pressure PDT (kPa)**

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Analysis results 11 of dynamic measurements

Analysis population

Analysis results: LOG Pressure PDT (kPa)

Back Transformed						

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper

Treatment	0.0656					
Period	0.3310					
Time	0.0343					
Treatment by time	0.0352					
Placebo - Paracetamol	0.0656	14.9	17.5	17.5%	-1.2%	39.7%

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LSMs table 11 Pressure PDT (kPa)

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LSMs table 11 of dynamic measurements

Analysis population

Back transformed Least Squares Means

Pressure PDT (kPa)

Treatment	Time (hh:mm)	Back Transformed	
		LSM	LSM change from baseline
Placebo		14.9	11.4%
	1:13	15.4	15.4%
	2:13	14.2	6.0%
	3:13	14.2	5.8%
	5:13	15.9	18.9%
Paracetamol		17.5	30.8%
	1:13	14.3	6.6%
	2:13	18.1	35.5%
	3:13	17.1	27.8%
	5:13	21.2	58.6%

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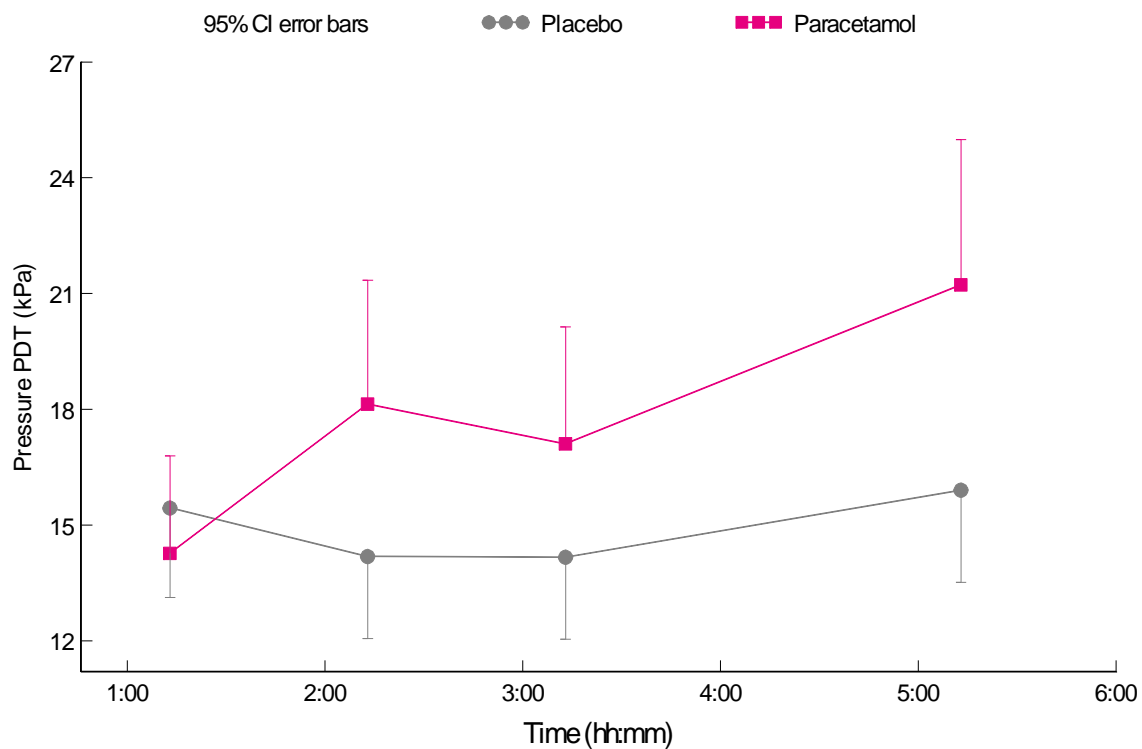
LSM graph 11 Pressure PDT (kPa)

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LSM graph 11 of dynamic measurements

Analysis population



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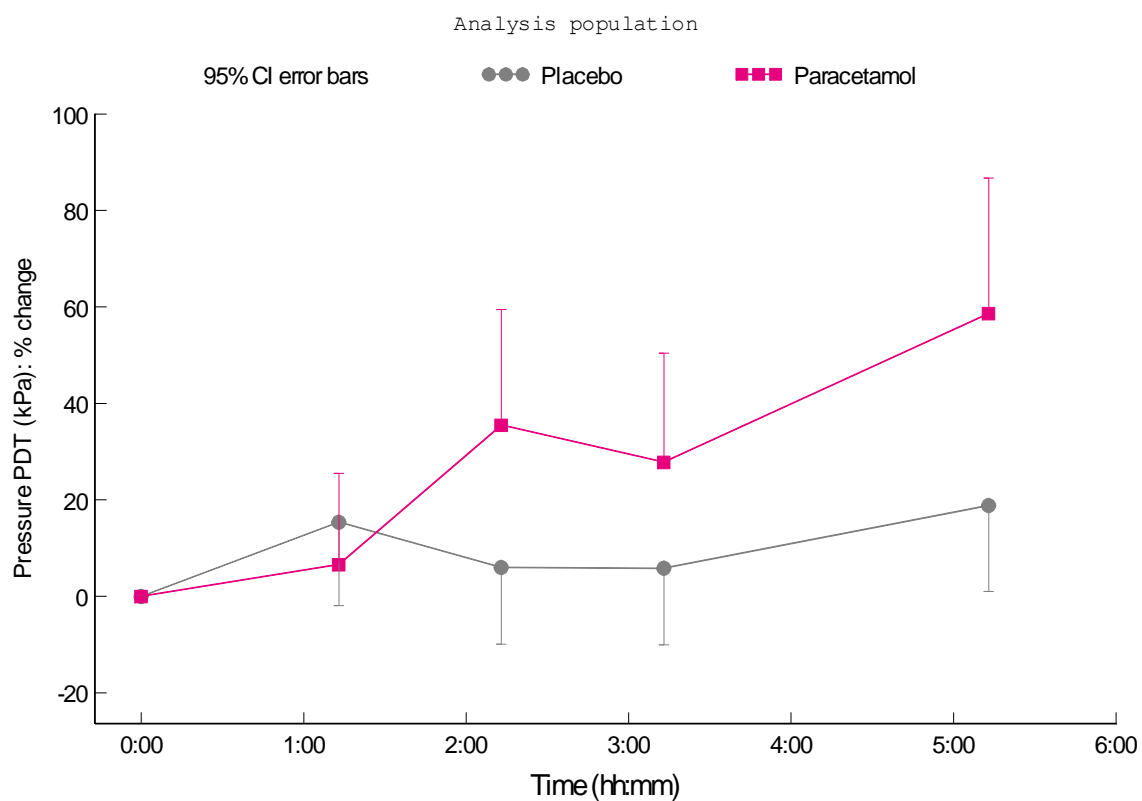
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LSM change from baseline graph 11 Pressure PDT (kPa)

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LSM change from baseline graph 11 of dynamic measurements



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Pressure PTT (kPa)**Analysis results table 12 Pressure PTT (kPa)**

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Analysis results 12 of dynamic measurements

Analysis population

Analysis results: LOG Pressure PTT (kPa)

Back Transformed						

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper

Treatment	0.6460					
Period	0.4684					
Time	0.7315					
Treatment by time	0.8886					
Placebo - Paracetamol	0.6460	42.6	44.0	3.4%	-11.6%	20.9%

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LSMs table 12 Pressure PTT (kPa)

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LSMs table 12 of dynamic measurements

Analysis population

Back transformed Least Squares Means

Pressure PTT (kPa)

Treatment	Time (hh:mm)	Back Transformed	
		LSM	LSM change from baseline
Placebo		42.6	6.2%
	1:13	40.9	2.0%
	2:13	43.0	7.2%
	3:13	42.9	6.9%
	5:13	43.6	8.7%
Paracetamol		44.0	9.7%
	1:13	43.3	7.9%
	2:13	43.7	9.0%
	3:13	44.6	11.1%
	5:13	44.5	11.0%

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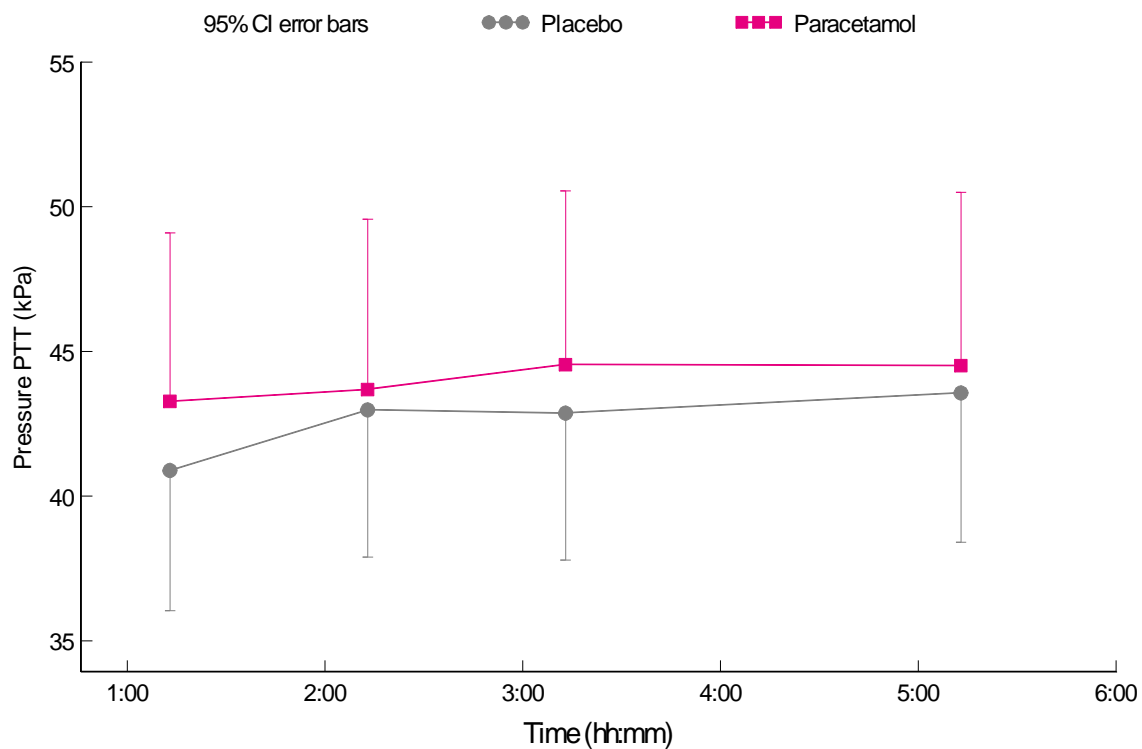
LSM graph 12 Pressure PTT (kPa)

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LSM graph 12 of dynamic measurements

Analysis population



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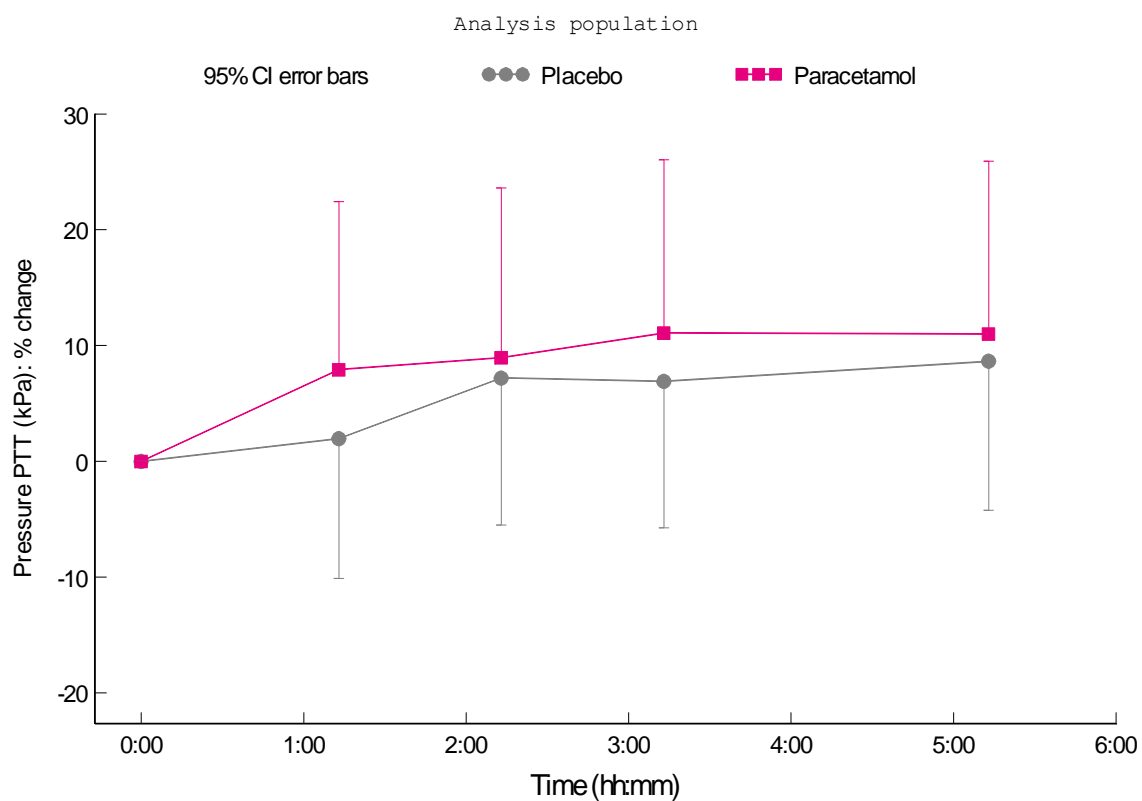
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LSM change from baseline graph 12 Pressure PTT (kPa)

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LSM change from baseline graph 12 of dynamic measurements



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Heat PDT (C)**Analysis results table 13 Heat PDT (C)**

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Analysis results 13 of dynamic measurements

Analysis population

Analysis results: LOG Heat PDT (C)

Back Transformed						

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper

Treatment	0.1096					
Period	0.7535					
Time	0.5734					
Treatment by time	0.8997					
Placebo - Paracetamol	0.1096	40.7	41.7	2.5%	-0.7%	5.7%

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LSMs table 13 Heat PDT (C)

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LSMs table 13 of dynamic measurements

Analysis population

Back transformed Least Squares Means
Heat PDT (C)

Treatment	Time (hh:mm)	Back Transformed	
		LSM	LSM change from baseline
Placebo		40.7	-1.4%
	1:03	40.7	-1.3%
	2:03	40.8	-1.1%
	3:03	40.7	-1.3%
	5:03	40.5	-1.9%
Paracetamol		41.7	1.0%
	1:03	42.0	1.7%
	2:03	41.9	1.5%
	3:03	41.4	0.3%
	5:03	41.5	0.7%

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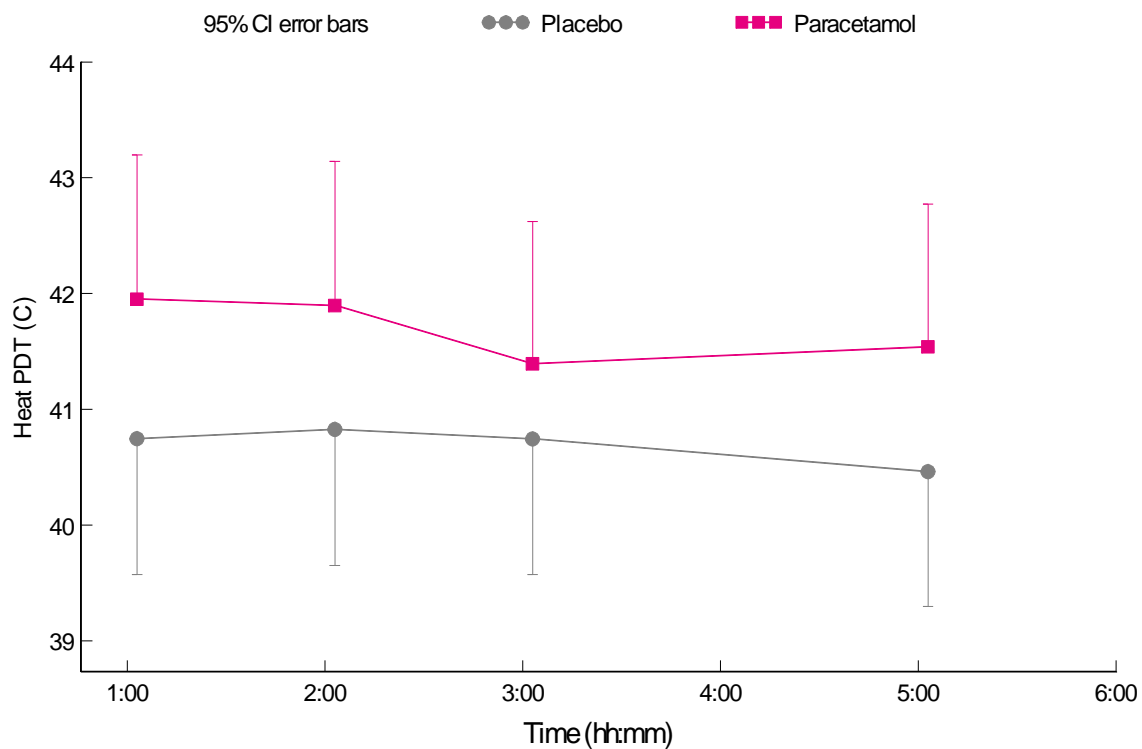
LSM graph 13 Heat PDT (C)

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LSM graph 13 of dynamic measurements

Analysis population



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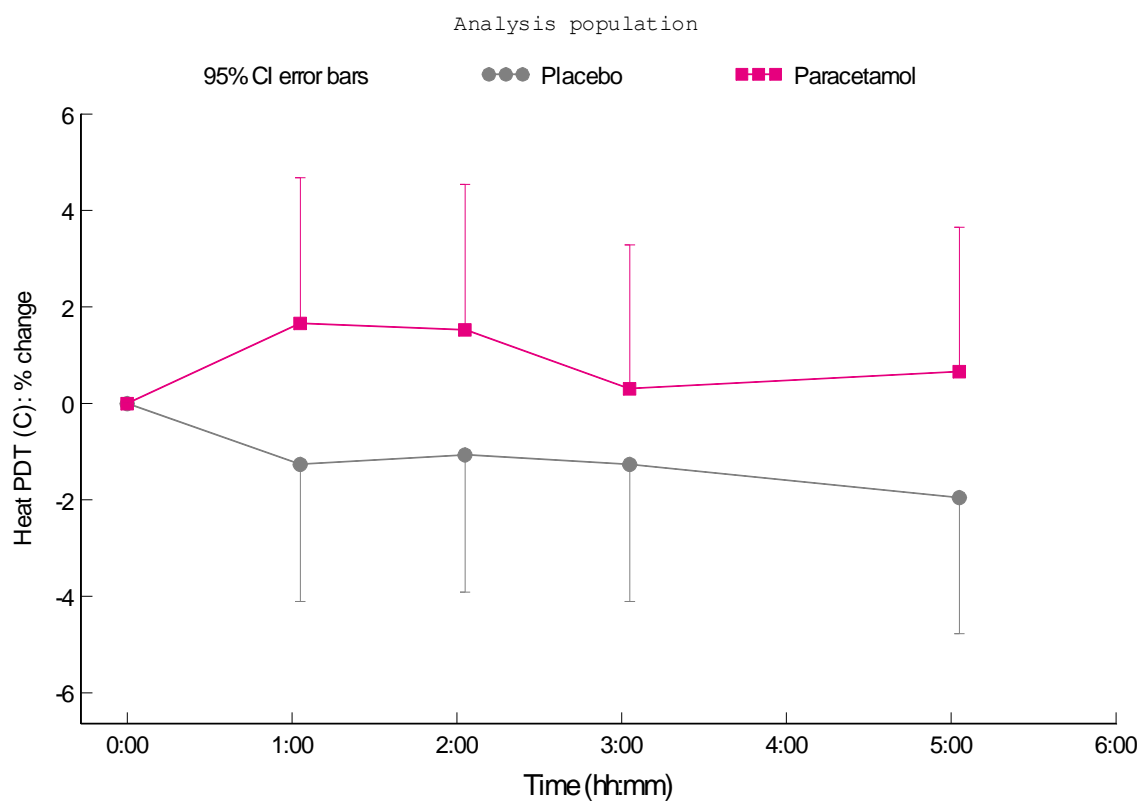
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LSM change from baseline graph 13 Heat PDT (C)

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LSM change from baseline graph 13 of dynamic measurements



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Heat PTT (C)**Analysis results table 14 Heat PTT (C)**

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Analysis results 14 of dynamic measurements

Analysis population

Analysis results: LOG Heat PTT (C)

Back Transformed						

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper

Treatment	0.8946					
Period	0.7389					
Time	0.0703					
Treatment by time	0.2414					
Placebo - Paracetamol	0.8946	47.0	46.9	-0.1%	-2.4% -	2.3%

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LSMs table 14 Heat PTT (C)

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LSMs table 14 of dynamic measurements

Analysis population

Back transformed Least Squares Means
Heat PTT (C)

Treatment	Time (hh:mm)	Back Transformed	
		LSM	LSM change from baseline
Placebo		47.0	0.3%
	1:03	47.0	0.4%
	2:03	47.4	1.3%
	3:03	47.0	0.4%
	5:03	46.5	-0.7%
Paracetamol		46.9	0.2%
	1:03	46.9	0.3%
	2:03	47.1	0.5%
	3:03	46.7	-0.2%
	5:03	46.9	0.2%

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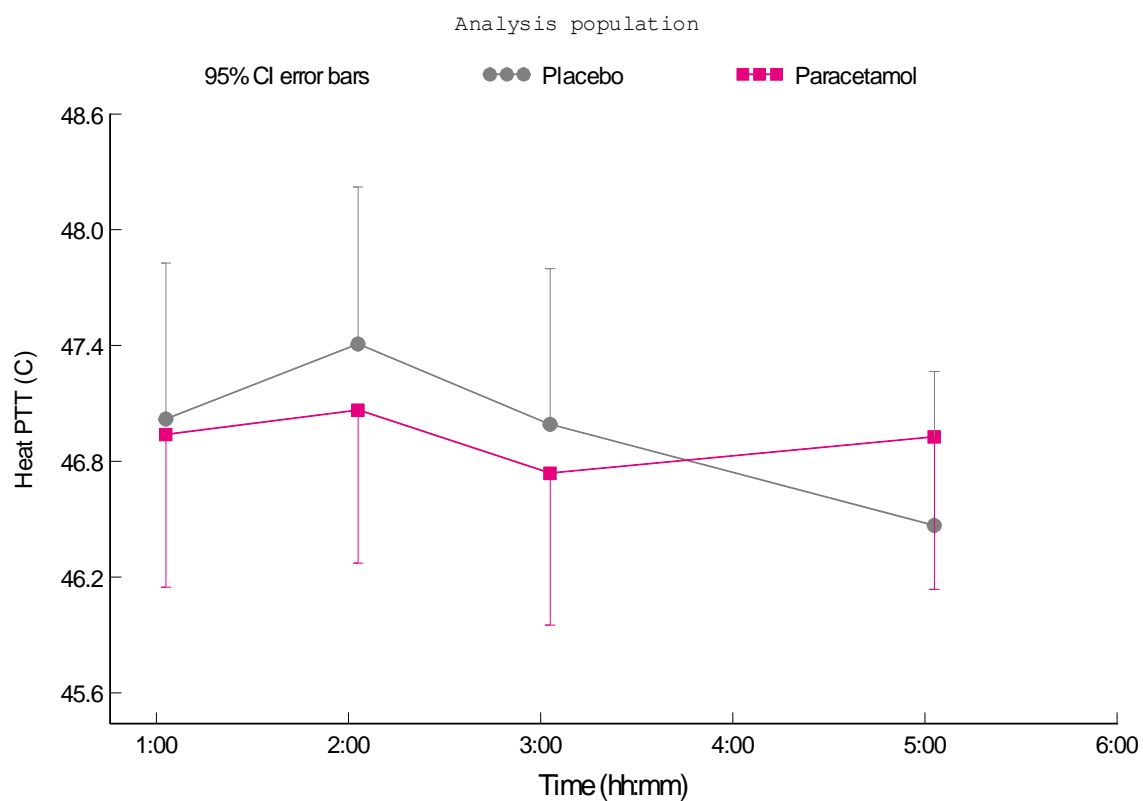
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LSM graph 14 Heat PTT (C)

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LSM graph 14 of dynamic measurements



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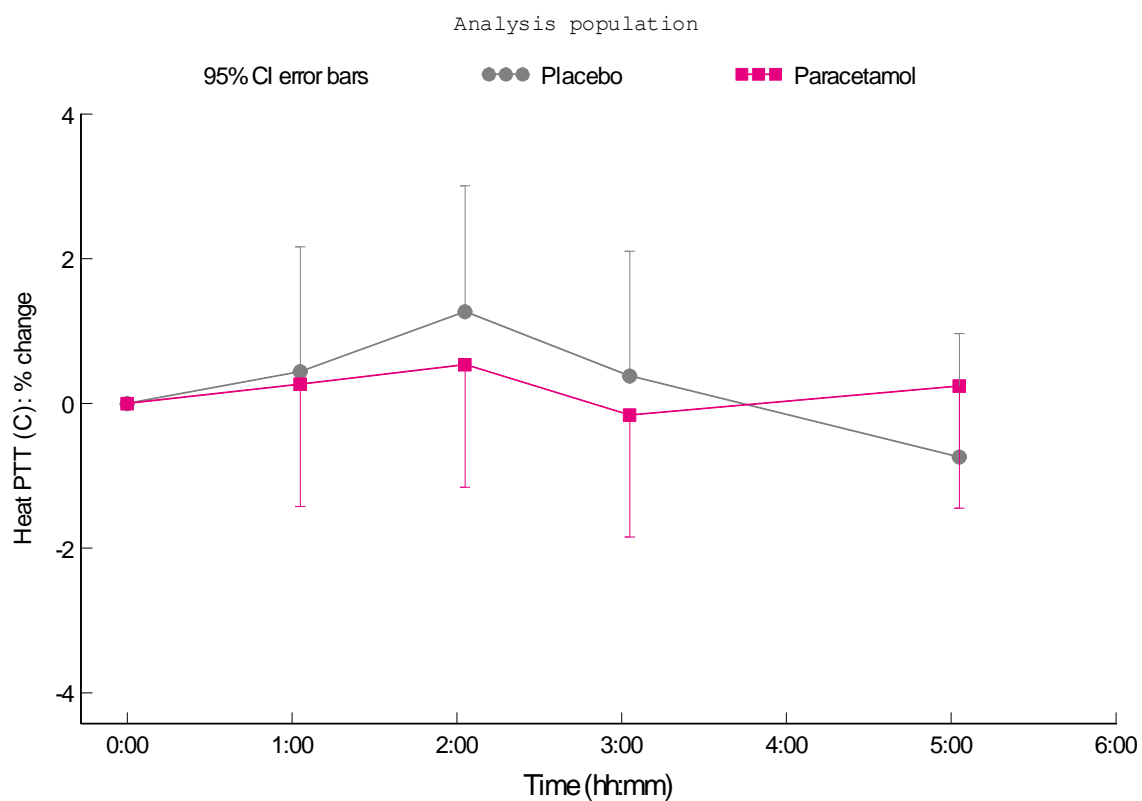
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LSM change from baseline graph 14 Heat PTT (C)

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LSM change from baseline graph 14 of dynamic measurements



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Sensory after Cold

Analysis results table 15 Sensory after Cold

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Analysis results 15 of dynamic measurements

Analysis population

Analysis results: Sensory after Cold

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.4166					
Period	0.4746					
Time	0.4377					
Treatment by time	0.4213					
Placebo - Paracetamol	0.4166	1.01	0.93	-0.076	-0.279	0.127

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LSMs table 15 Sensory after Cold

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LSMs table 15 of dynamic measurements

Analysis population

Least Squares Means

Sensory after Cold

Treatment	Time (hh:mm)	LSM	LSM change from baseline

Placebo		1.01	0.00
	1:16	1.00	-0.00
	2:16	1.01	0.01
	3:16	1.06	0.06
	5:16	0.95	-0.05
Paracetamol		0.93	-0.07
	1:16	0.98	-0.03
	2:16	0.93	-0.07
	3:16	0.91	-0.10
	5:16	0.91	-0.10

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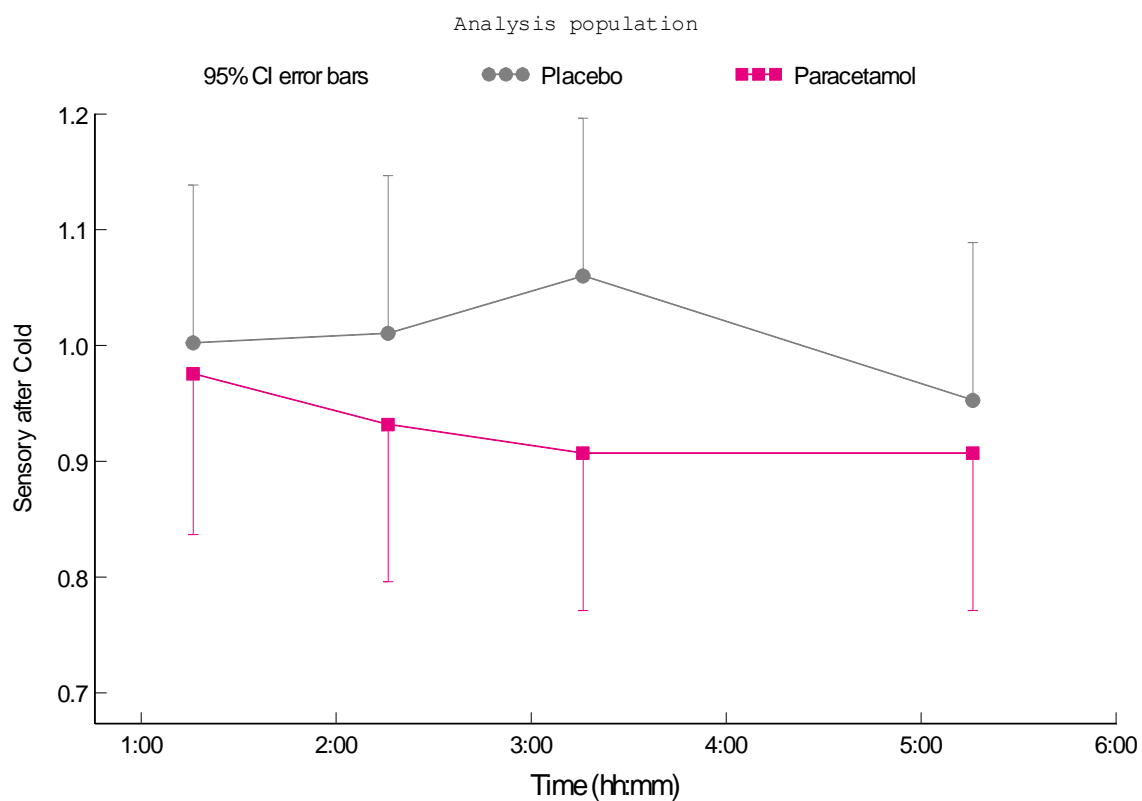
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LSM graph 15 Sensory after Cold

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM graph 15 of dynamic measurements



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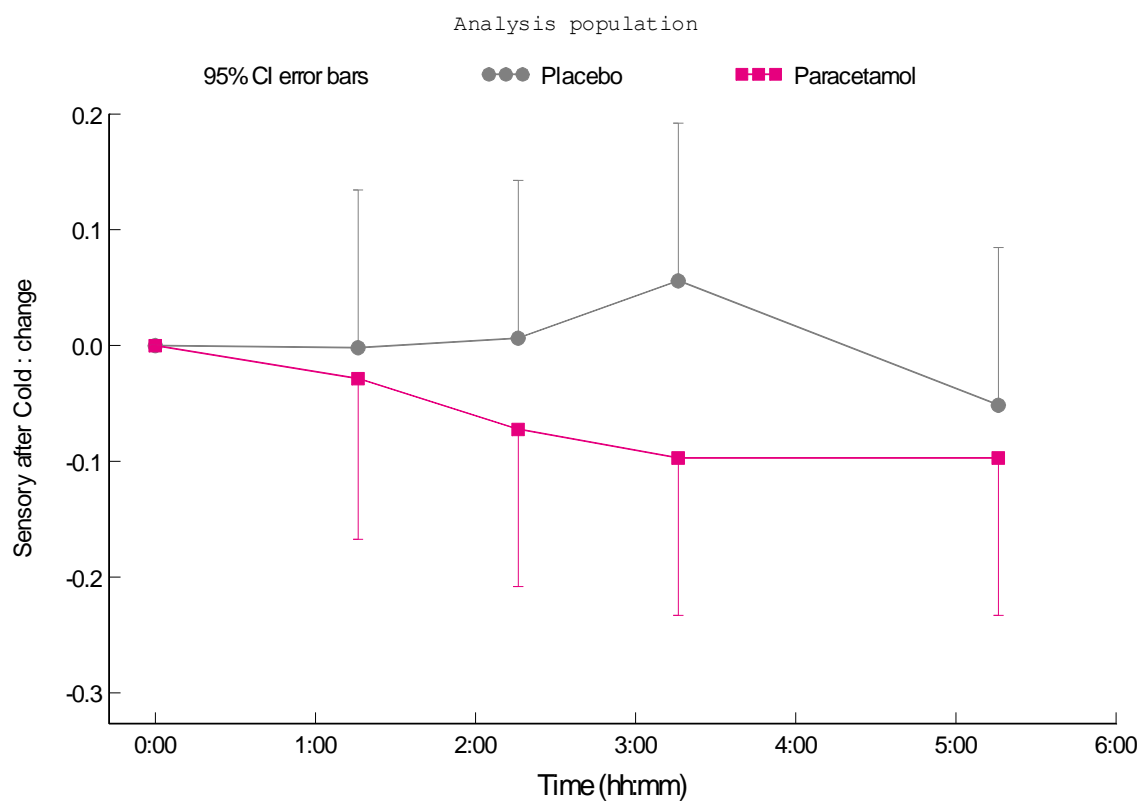
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LSM change from baseline graph 15 Sensory after Cold

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM change from baseline graph 15 of dynamic measurements



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Affective after Cold

Analysis results table 16 Affective after Cold

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Analysis results 16 of dynamic measurements

Analysis population

Analysis results: Affective after Cold

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.3167					
Period	0.1490					
Time	0.9778					
Treatment by time	0.8148					
Placebo - Paracetamol	0.3167	0.29	0.32	0.036	-0.040	0.112

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LSMs table 16 Affective after Cold

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LSMs table 16 of dynamic measurements

Analysis population

Least Squares Means
Affective after Cold

Treatment	Time (hh:mm)	LSM	LSM change from baseline

Placebo		0.29	-0.06
	1:16	0.30	-0.05
	2:16	0.28	-0.07
	3:16	0.28	-0.07
	5:16	0.30	-0.05
Paracetamol		0.32	-0.02
	1:16	0.32	-0.02
	2:16	0.35	0.00
	3:16	0.32	-0.02
	5:16	0.30	-0.05

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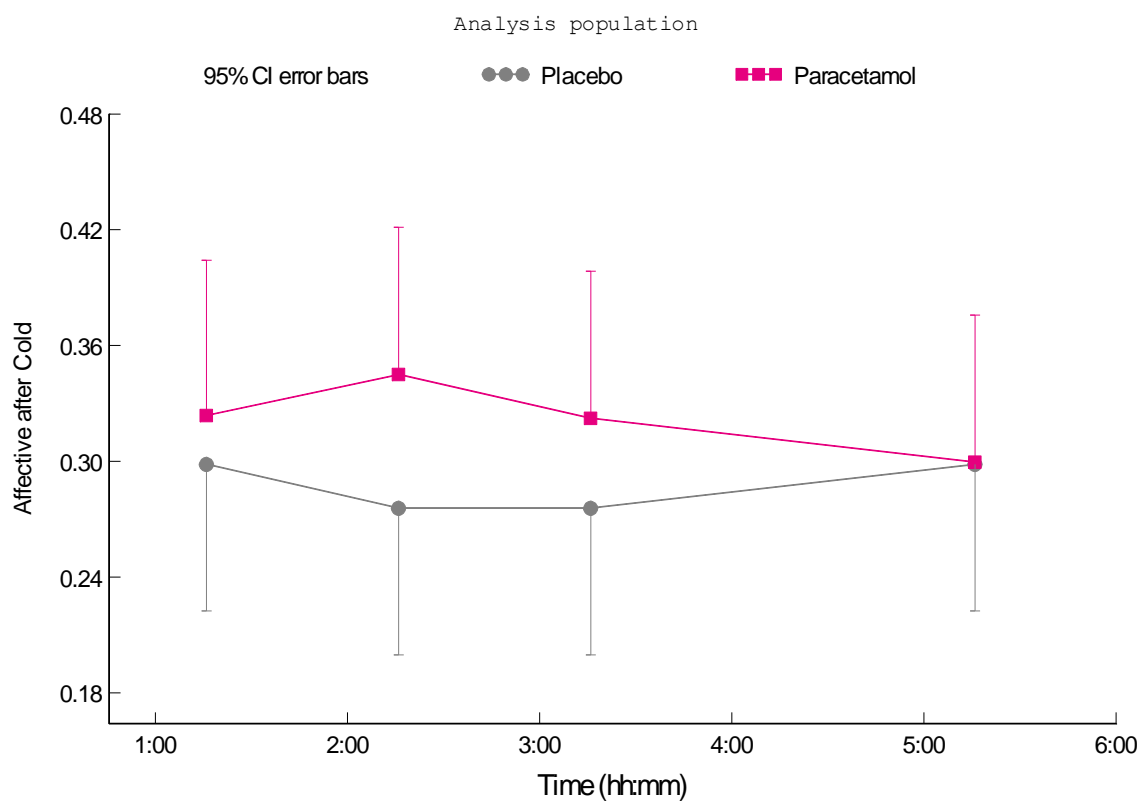
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LSM graph 16 Affective after Cold

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LSM graph 16 of dynamic measurements



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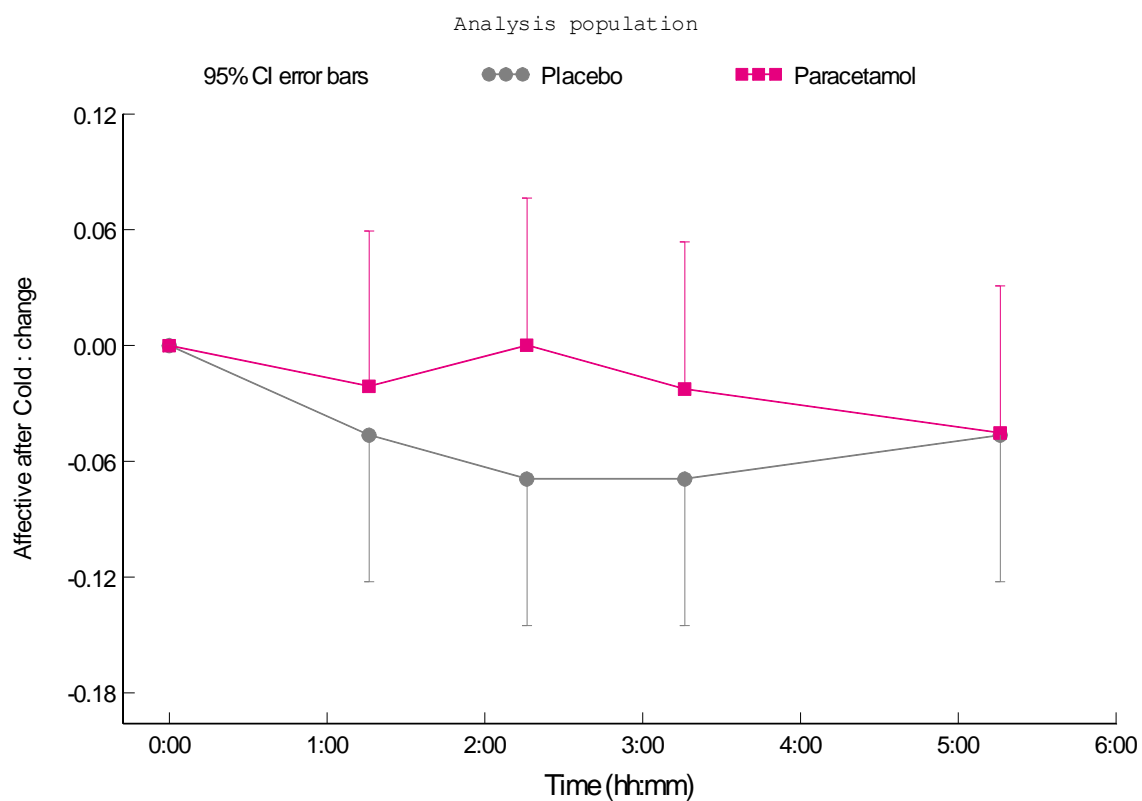
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LSM change from baseline graph 16 Affective after Cold

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LSM change from baseline graph 16 of dynamic measurements



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MPQ VAS after Cold (mm)**Analysis results table 17 MPQ VAS after Cold (mm)**

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Analysis results 17 of dynamic measurements

Analysis population

Analysis results: MPQ VAS after Cold (mm)

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.2331					
Period	0.3030					
Time	0.5096					
Treatment by time	0.0869					
Placebo - Paracetamol	0.2331	42.9	45.5	2.63	-1.99	7.26

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LSMs table 17 MPQ VAS after Cold (mm)

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LSMs table 17 of dynamic measurements

Analysis population

Least Squares Means
MPQ VAS after Cold (mm)

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		42.9	-2.3
	1:16	44.2	-1.0
	2:16	41.3	-3.9
	3:16	40.7	-4.6
	5:16	45.5	0.2
Paracetamol		45.5	0.3
	1:16	45.1	-0.2
	2:16	47.1	1.8
	3:16	45.7	0.5
	5:16	44.3	-0.9

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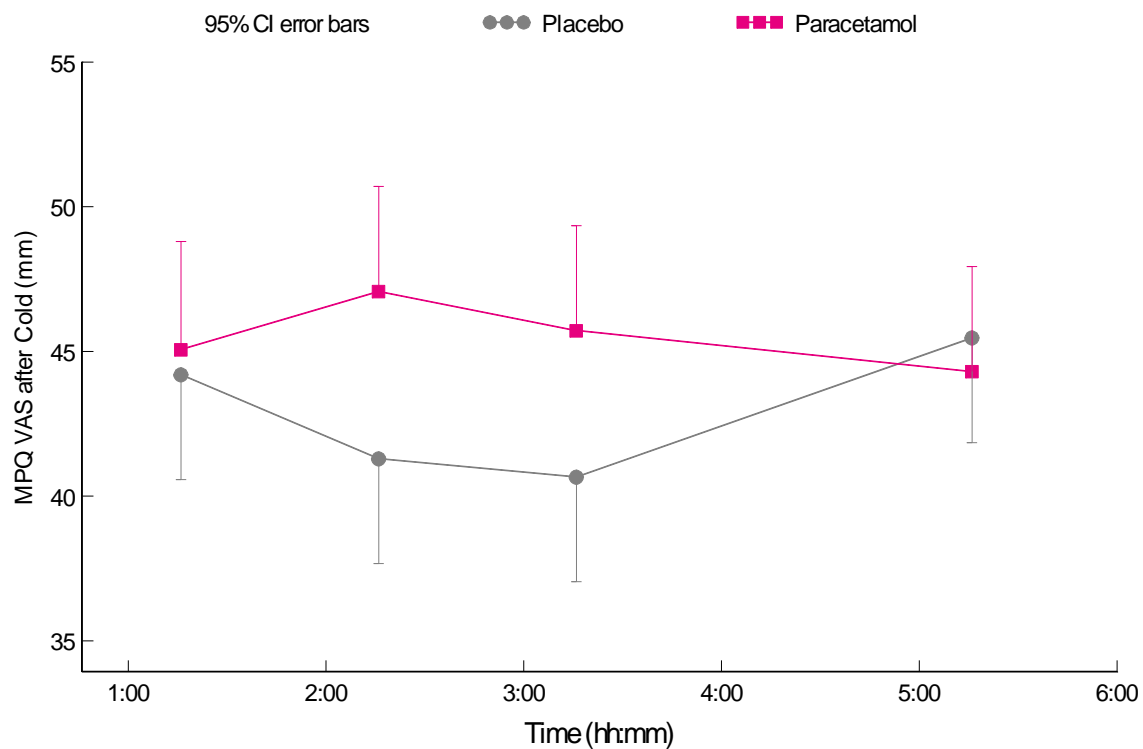
LSM graph 17 MPQ VAS after Cold (mm)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM graph 17 of dynamic measurements

Analysis population



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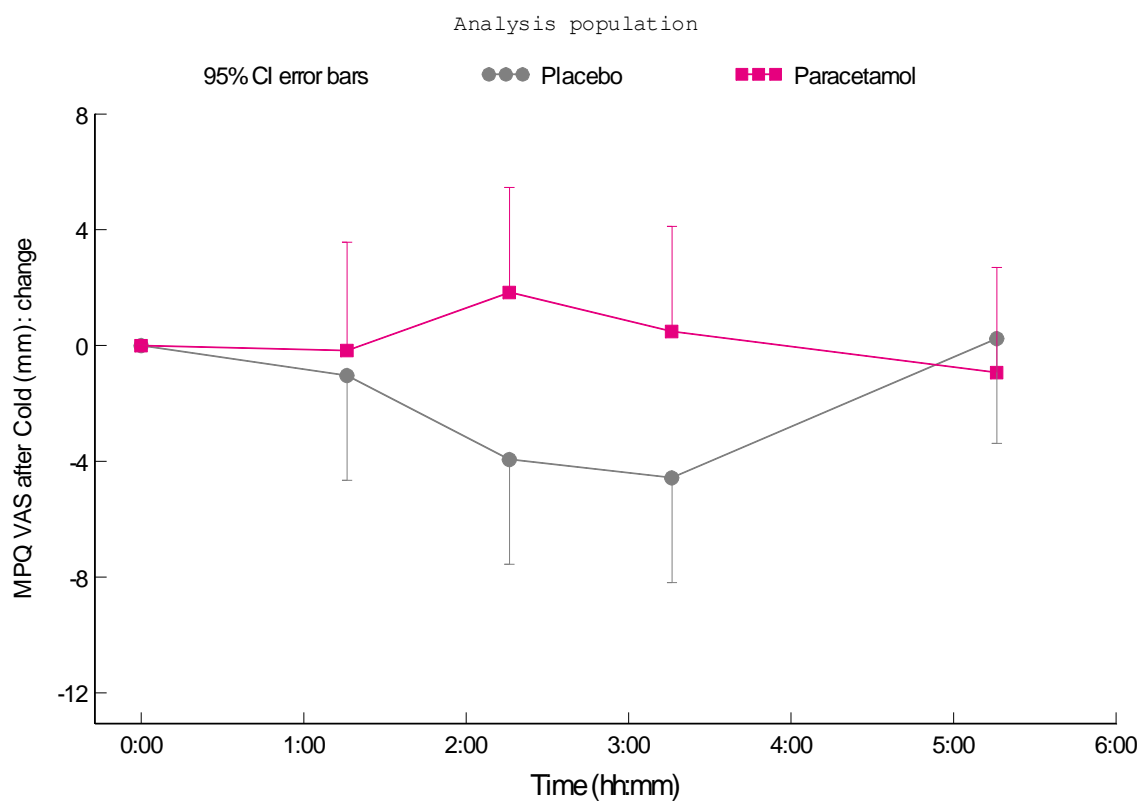
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LSM change from baseline graph 17 MPQ VAS after Cold (mm)

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM change from baseline graph 17 of dynamic measurements



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Sensory after ES

Analysis results table 18 Sensory after ES

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Analysis results 18 of dynamic measurements

Analysis population

Analysis results: Sensory after ES

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.8023					
Period	0.4082					
Time	0.0609					
Treatment by time	0.1403					
Placebo - Paracetamol	0.8023	1.16	1.14	-0.022	-0.217	0.174

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LSMs table 18 Sensory after ES

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LSMs table 18 of dynamic measurements

Analysis population

Least Squares Means

Sensory after ES

Treatment	Time (hh:mm)	LSM	LSM change from baseline

Placebo		1.16	-0.09
	1:08	1.19	-0.05
	2:08	1.24	-0.00
	3:08	1.14	-0.10
	5:08	1.06	-0.19
Paracetamol		1.14	-0.11
	1:08	1.16	-0.09
	2:08	1.16	-0.09
	3:08	1.10	-0.15
	5:08	1.13	-0.11

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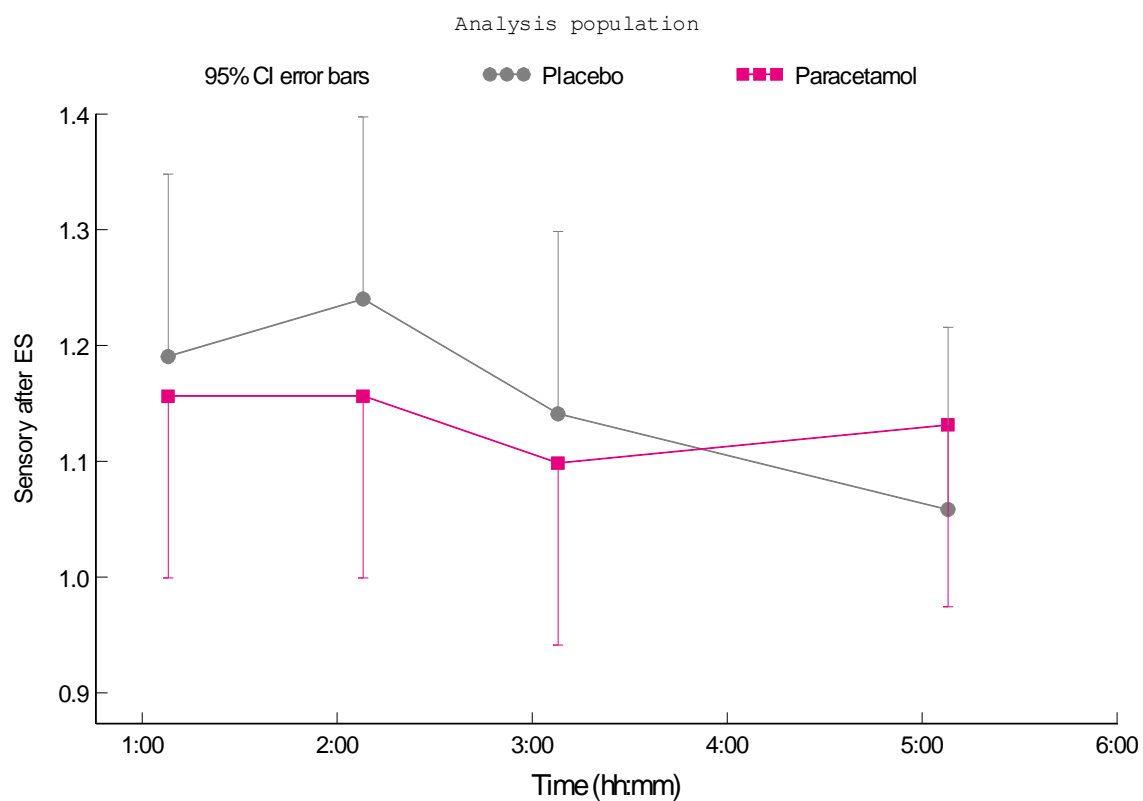
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LSM graph 18 Sensory after ES

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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LSM graph 18 of dynamic measurements



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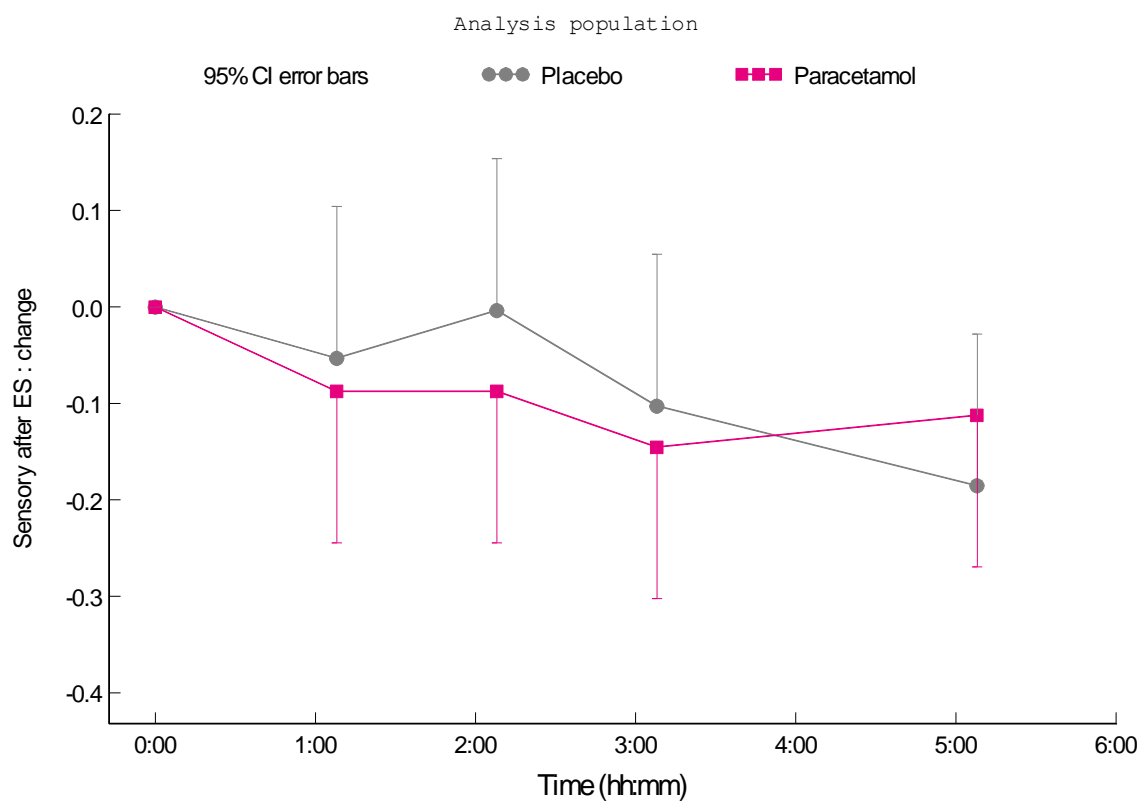
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LSM change from baseline graph 18 Sensory after ES

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LSM change from baseline graph 18 of dynamic measurements



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Affective after ES

Analysis results table 19 Affective after ES

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Analysis results 19 of dynamic measurements

Analysis population

Analysis results: Affective after ES

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.4880					
Period	0.0886					
Time	0.1788					
Treatment by time	0.6948					
Placebo - Paracetamol	0.4880	0.33	0.30	-0.028	-0.117	0.061

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LSMs table 19 Affective after ES

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LSMs table 19 of dynamic measurements

Analysis population

Least Squares Means
Affective after ES

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		0.33	-0.00
	1:08	0.40	0.07
	2:08	0.34	0.01
	3:08	0.29	-0.04
	5:08	0.29	-0.04
Paracetamol		0.30	-0.03
	1:08	0.32	-0.01
	2:08	0.32	-0.01
	3:08	0.28	-0.05
	5:08	0.28	-0.05

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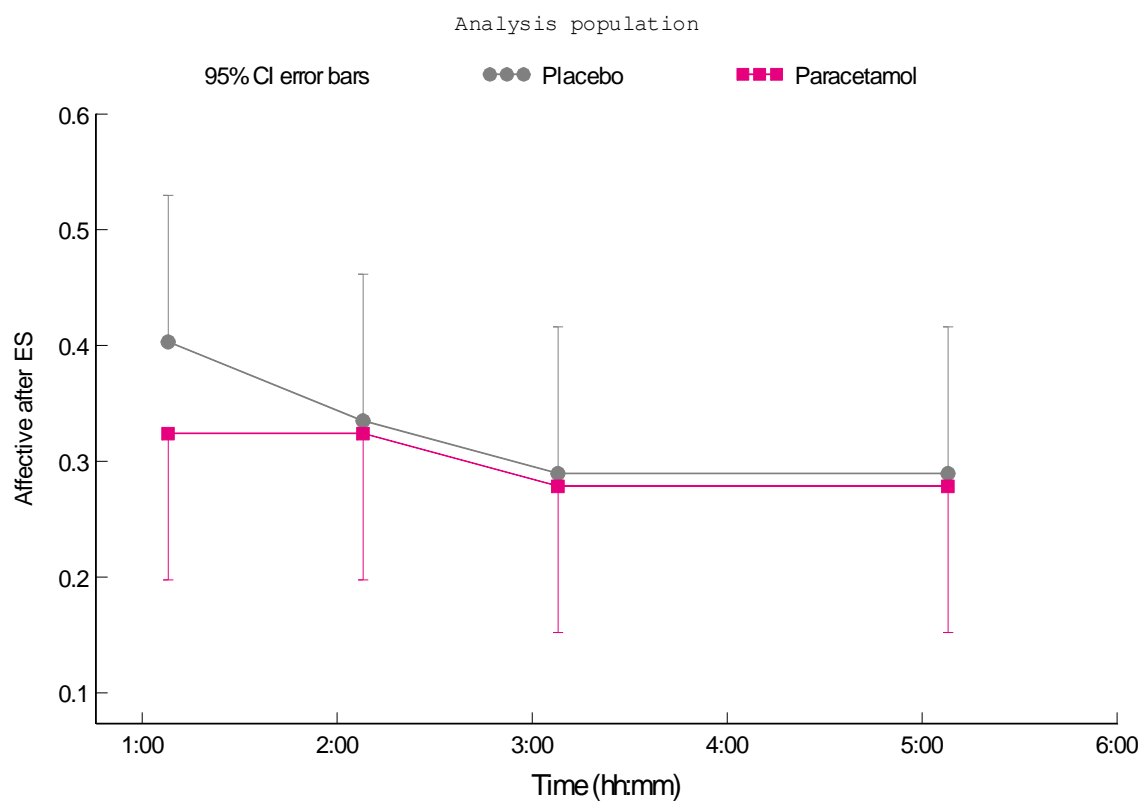
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LSM graph 19 Affective after ES

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LSM graph 19 of dynamic measurements



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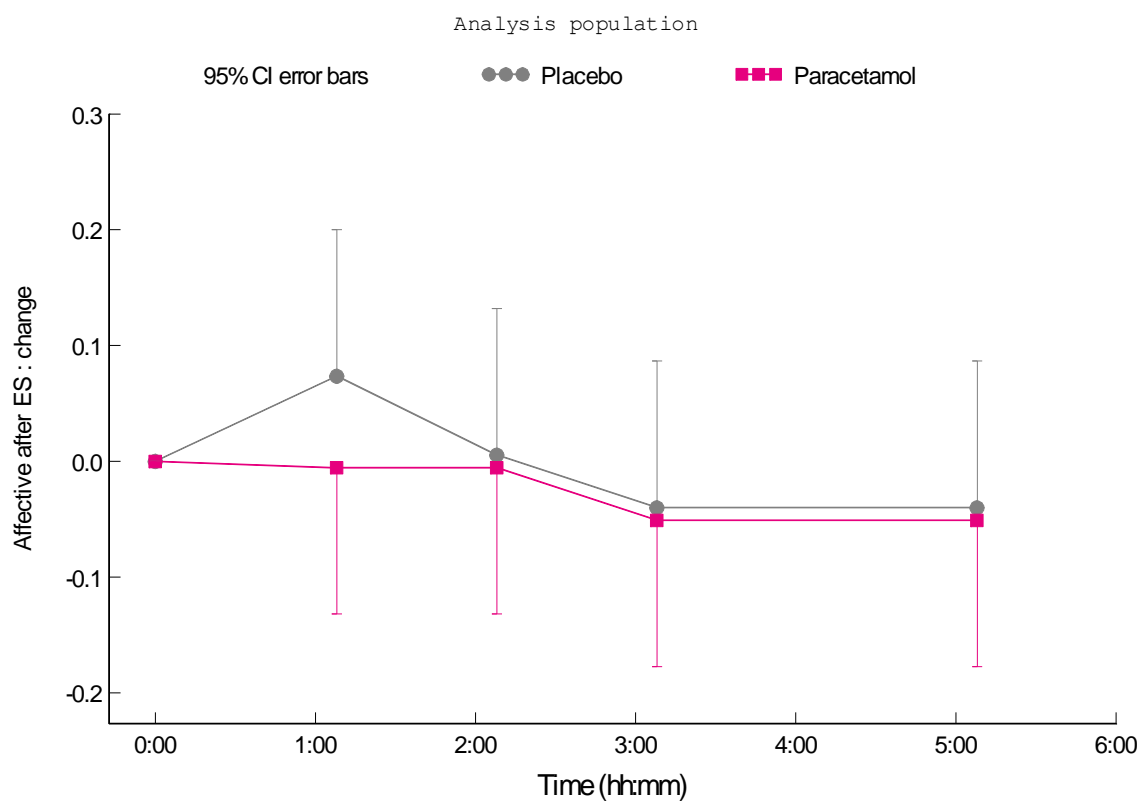
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LSM change from baseline graph 19 Affective after ES

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LSM change from baseline graph 19 of dynamic measurements



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MPQ VAS after ES (mm)**Analysis results table 20 MPQ VAS after ES (mm)**

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Analysis results 20 of dynamic measurements

Analysis population

Analysis results: MPQ VAS after ES (mm)

Effect/Contrast	P-value	First LSM	Second LSM	Estimate	95% CI	
		of contrast	of contrast	of the difference	Lower	Upper

Treatment	0.1462					
Period	0.3243					
Time	0.3834					
Treatment by time	0.9910					
Placebo - Paracetamol	0.1462	37.1	40.6	3.58	-1.47	8.63

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LSMs table 20 MPQ VAS after ES (mm)

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LSMs table 20 of dynamic measurements

Analysis population

Least Squares Means
MPQ VAS after ES (mm)

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		37.1	-3.2
	1:08	38.2	-2.1
	2:08	38.2	-2.1
	3:08	35.9	-4.4
	5:08	36.0	-4.2
Paracetamol		40.6	0.4
	1:08	41.8	1.6
	2:08	41.6	1.3
	3:08	39.0	-1.3
	5:08	40.1	-0.2

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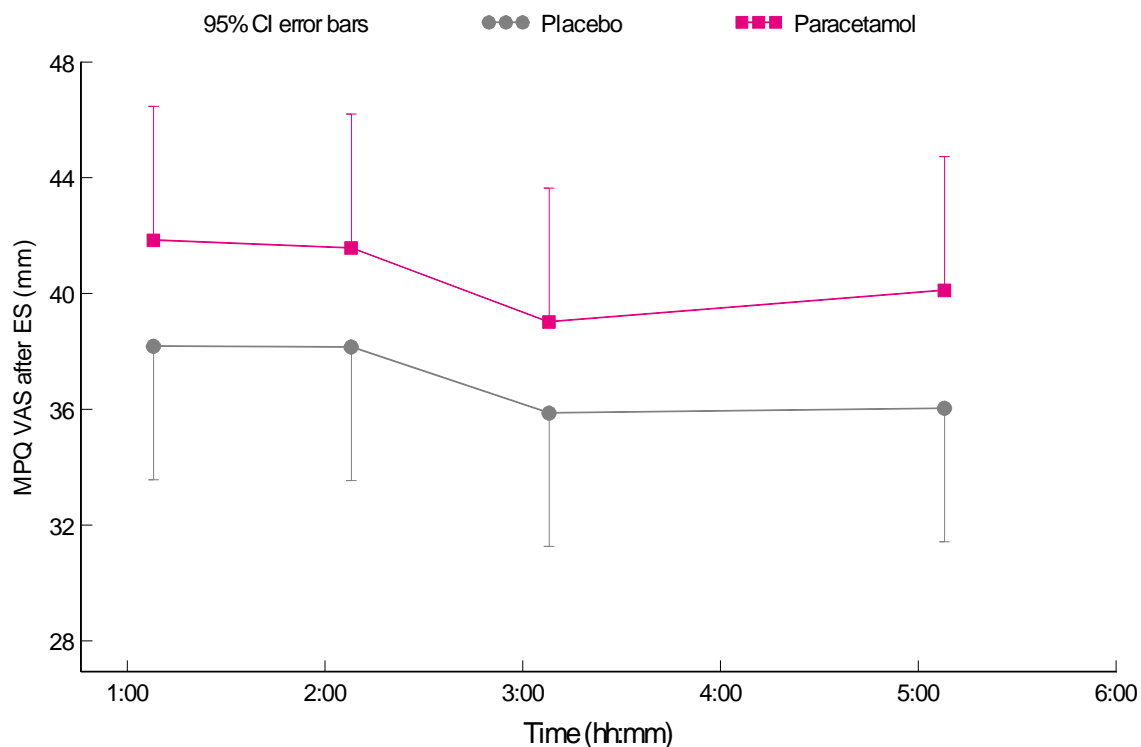
LSM graph 20 MPQ VAS after ES (mm)

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LSM graph 20 of dynamic measurements

Analysis population



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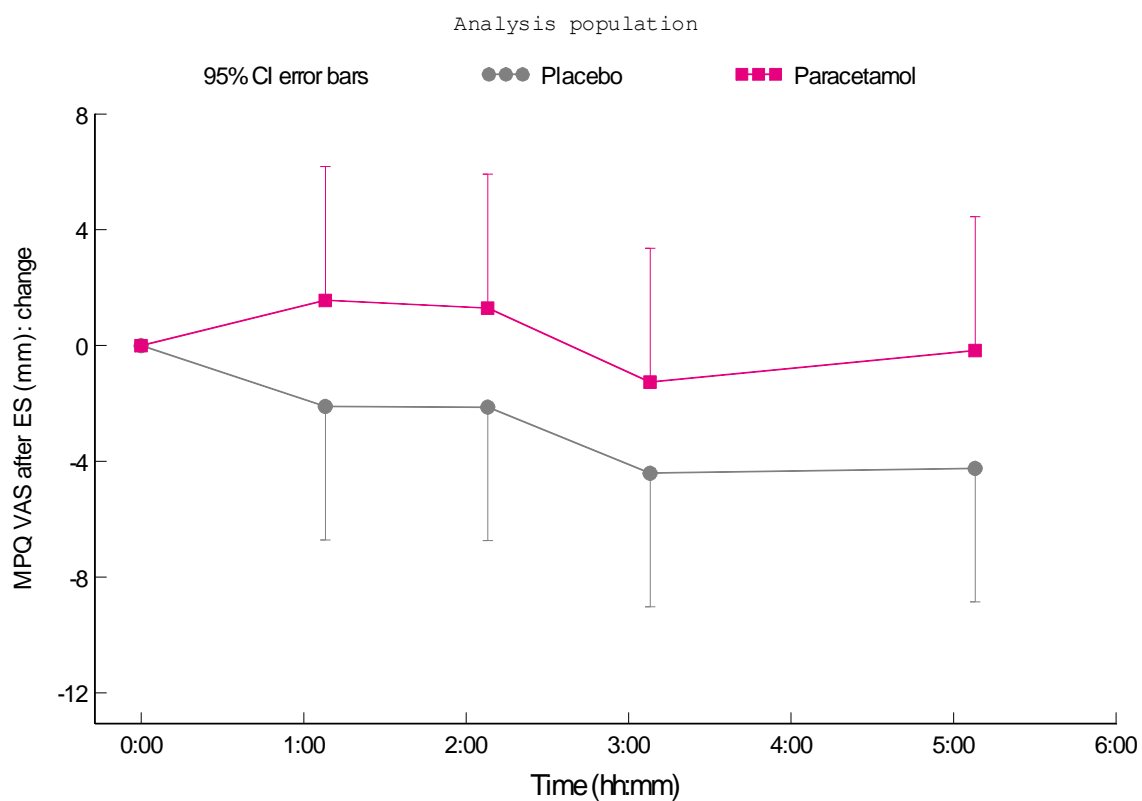
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LSM change from baseline graph 20 MPQ VAS after ES (mm)

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LSM change from baseline graph 20 of dynamic measurements



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Sensory after Pressure

Analysis results table 21 Sensory after Pressure

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Analysis results 21 of dynamic measurements

Analysis population

Analysis results: Sensory after Pressure

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.8057					
Period	0.1108					
Time	0.3514					
Treatment by time	0.1985					
Placebo - Paracetamol	0.8057	0.92	0.91	-0.017	-0.174	0.139

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LSMs table 21 Sensory after Pressure

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LSMs table 21 of dynamic measurements

Analysis population

Least Squares Means
Sensory after Pressure

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		0.92	-0.04
	1:13	1.01	0.05
	2:13	0.95	-0.02
	3:13	0.86	-0.10
	5:13	0.87	-0.09
Paracetamol		0.91	-0.06
	1:13	0.88	-0.09
	2:13	0.95	-0.02
	3:13	0.93	-0.04
	5:13	0.87	-0.10

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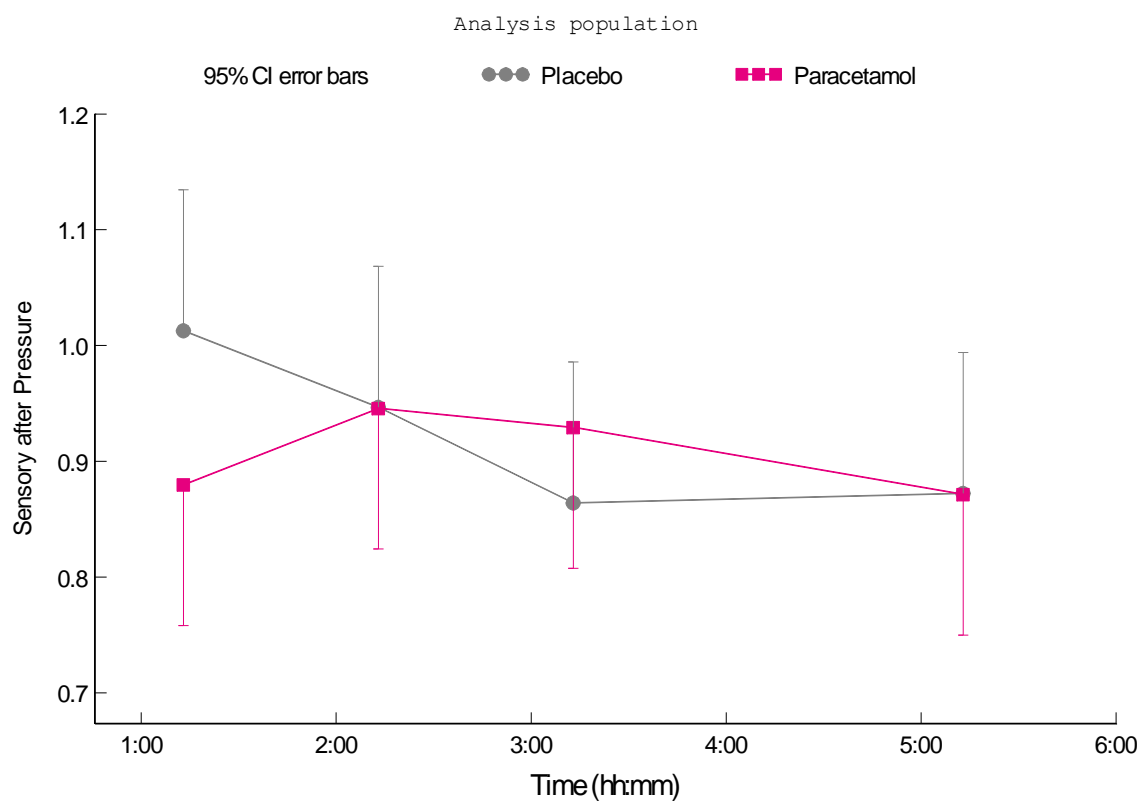
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LSM graph 21 Sensory after Pressure

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LSM graph 21 of dynamic measurements



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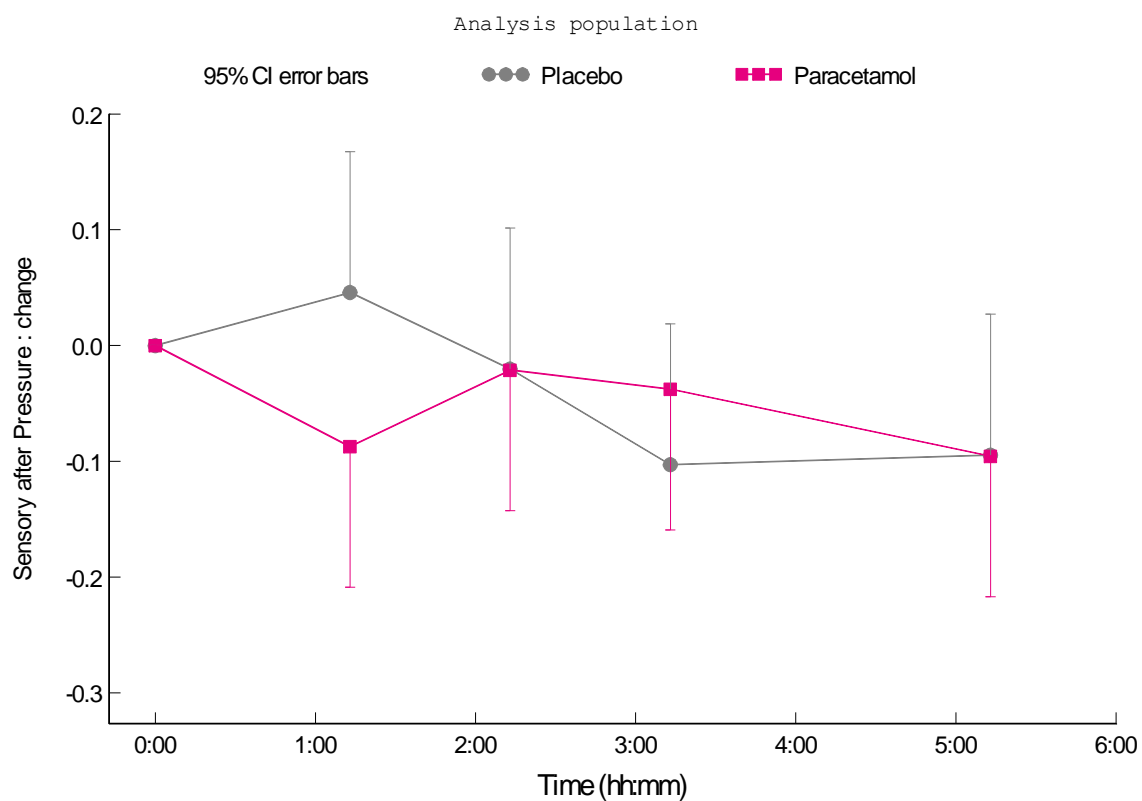
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LSM change from baseline graph 21 Sensory after Pressure

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LSM change from baseline graph 21 of dynamic measurements



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Affective after Pressure

Analysis results table 22 Affective after Pressure

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Analysis results 22 of dynamic measurements

Analysis population

Analysis results: Affective after Pressure

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.5212					
Period	0.1457					
Time	0.3945					
Treatment by time	0.0972					
Placebo - Paracetamol	0.5212	0.15	0.17	0.014	-0.037	0.066

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LSMs table 22 Affective after Pressure

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LSMs table 22 of dynamic measurements

Analysis population

Least Squares Means
Affective after Pressure

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		0.15	-0.08
	1:13	0.18	-0.06
	2:13	0.15	-0.08
	3:13	0.11	-0.13
	5:13	0.18	-0.06
Paracetamol		0.17	-0.07
	1:13	0.21	-0.03
	2:13	0.12	-0.12
	3:13	0.16	-0.08
	5:13	0.19	-0.05

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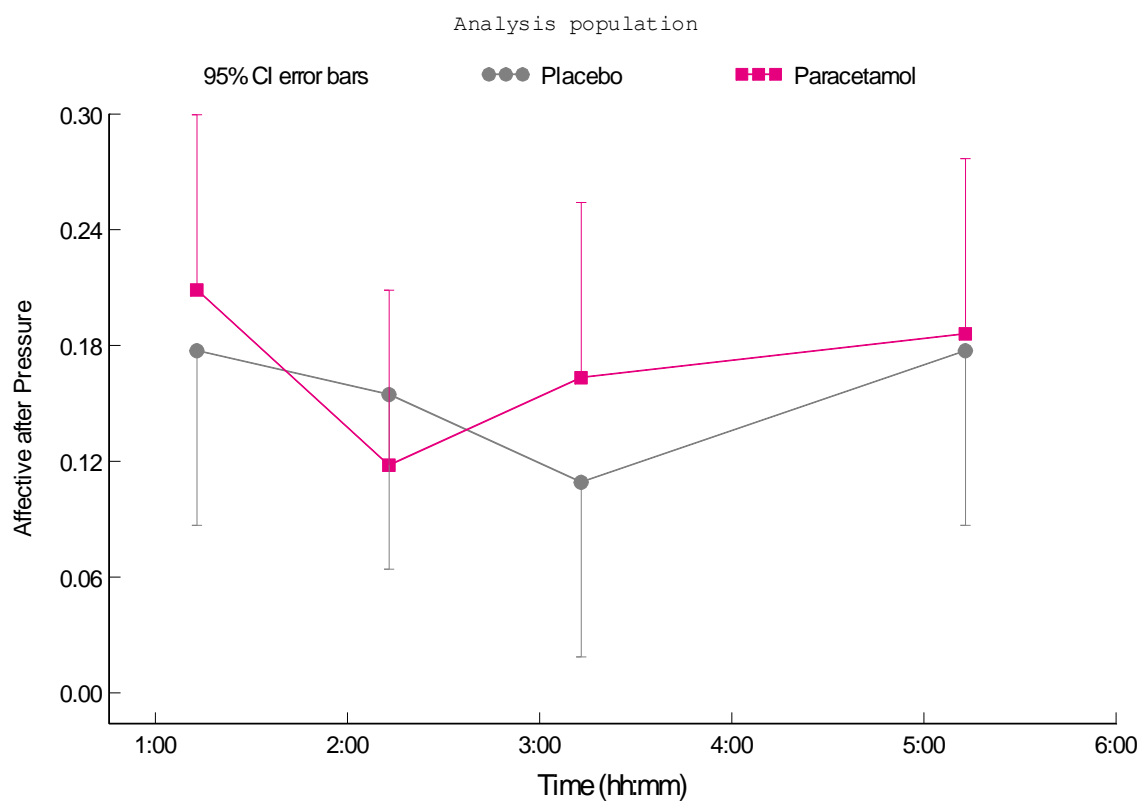
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LSM graph 22 Affective after Pressure

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LSM graph 22 of dynamic measurements



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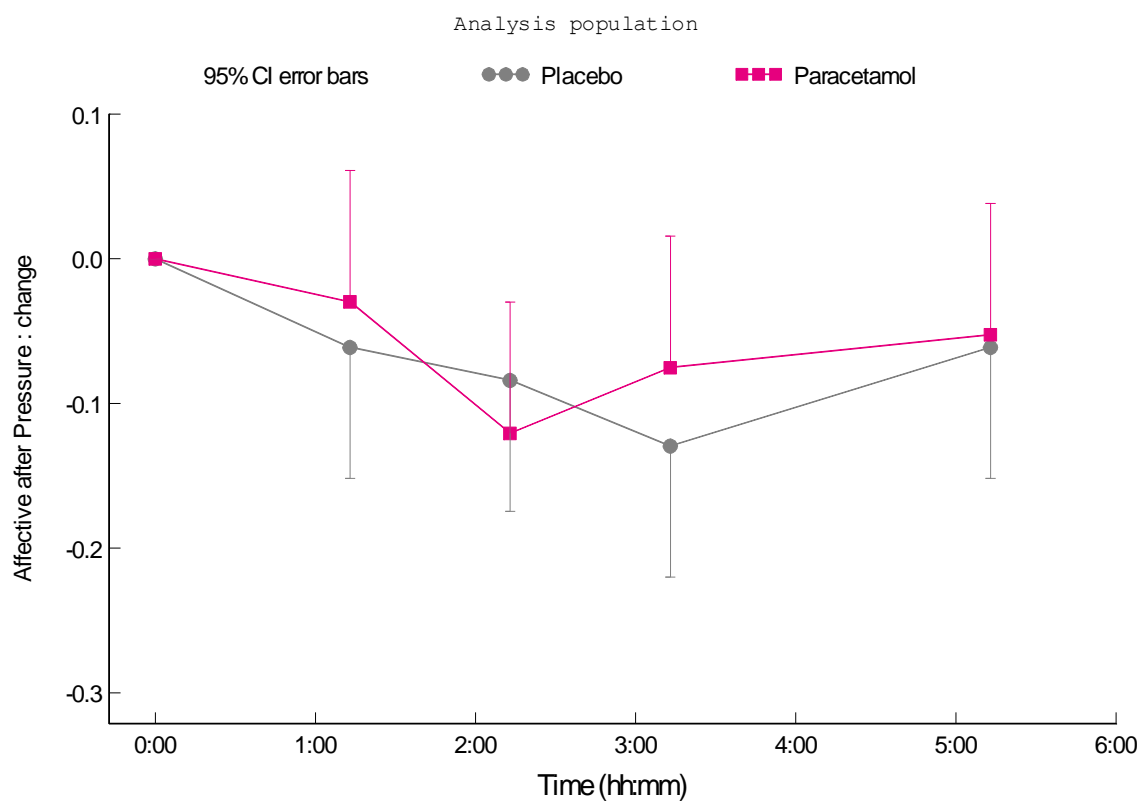
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LSM change from baseline graph 22 Affective after Pressure

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LSM change from baseline graph 22 of dynamic measurements



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MPQ VAS after Pressure (mm)**Analysis results table 23 MPQ VAS after Pressure (mm)**

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Analysis results 23 of dynamic measurements

Analysis population

Analysis results: MPQ VAS after Pressure (mm)

Effect/Contrast	P-value	First LSM of contrast	Second LSM of contrast	Estimate of the difference	95% CI	
					Lower	Upper
Treatment	0.1359					
Period	0.3410					
Time	0.0626					
Treatment by time	0.1755					
Placebo - Paracetamol	0.1359	32.3	37.6	5.34	-2.00	12.68

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LSMs table 23 MPQ VAS after Pressure (mm)

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LSMs table 23 of dynamic measurements

Analysis population

Least Squares Means
MPQ VAS after Pressure (mm)

Treatment	Time (hh:mm)	LSM	LSM change from baseline
Placebo		32.3	-4.2
	1:13	33.0	-3.5
	2:13	31.6	-4.9
	3:13	31.0	-5.5
	5:13	33.4	-3.1
Paracetamol		37.6	1.1
	1:13	39.3	2.8
	2:13	39.4	2.9
	3:13	36.2	-0.3
	5:13	35.4	-1.1

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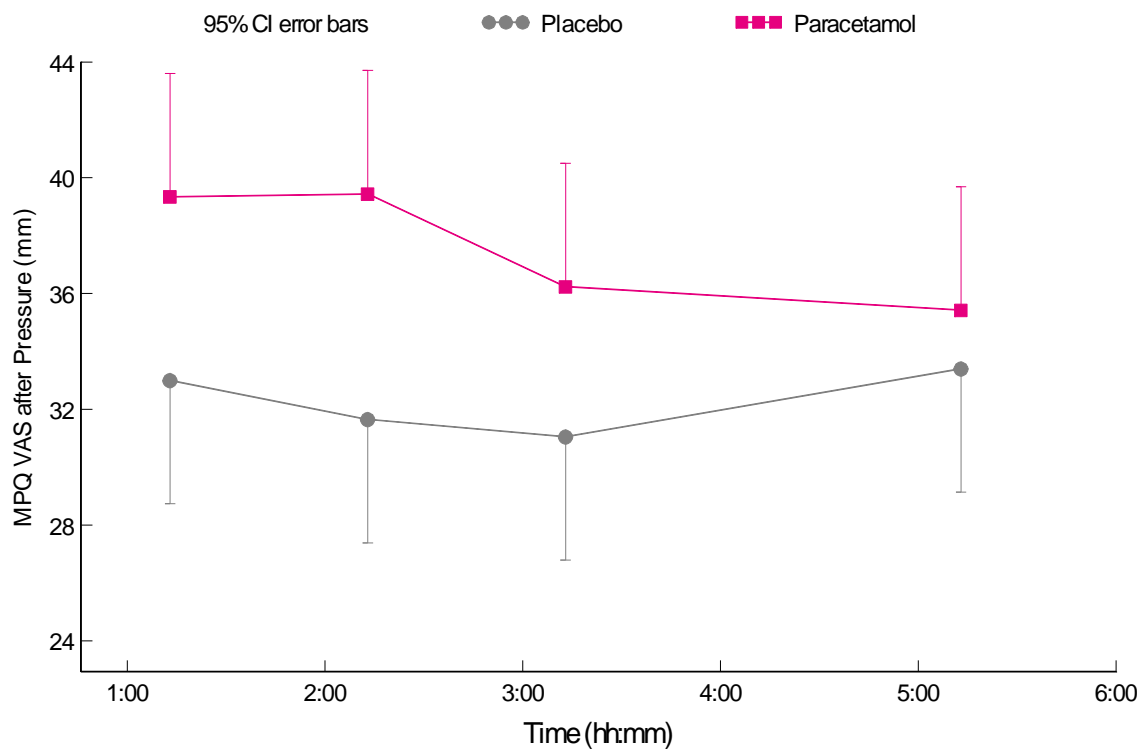
LSM graph 23 MPQ VAS after Pressure (mm)

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LSM graph 23 of dynamic measurements

Analysis population



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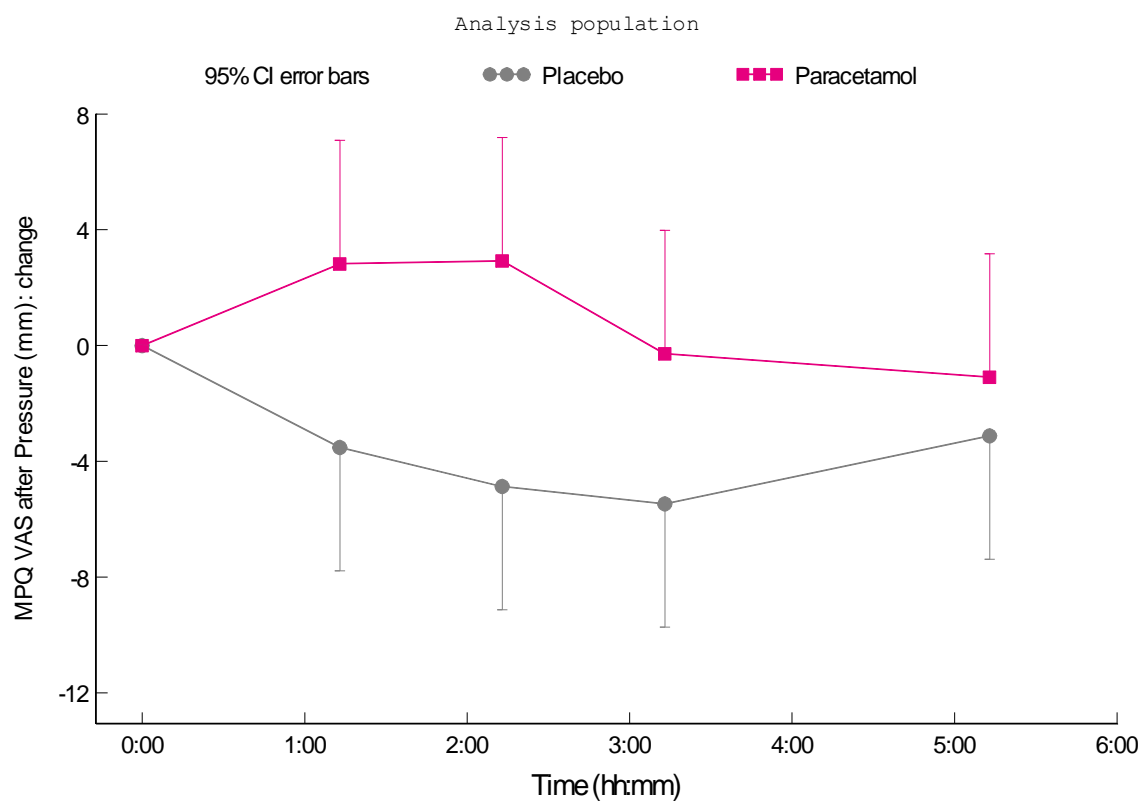
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LSM change from baseline graph 23 MPQ VAS after Pressure (mm)

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LSM change from baseline graph 23 of dynamic measurements



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Summary of analysis results

	LS Means			Contrasts	LS Means change from baseline	
Parameter	Placebo	Paracetamol	Treatment P-value	Paracetamol Placebo	Placebo	Paracetamol
Cold AAC (s*)	2379.1	2379.5	0.9986	0.40 (-510, 510.9) p=0.9986	77.61	78.01
Cold PDT (s)	4.4	5.2	0.3505	16.7% (-18.1%, 66.4%) p=0.3	-4.0%	12.1%
Cold PTT (s)	29.2	31.9	0.4088	9.0% (-12.9%, 36.3%) p=0.4	-5.7%	2.7%
Electrical Stair AUC (mA*%)	2946.8	3039.3	0.4977	92.55 (-206, 390.7) p=0.4977	-310.83	-218.28
Electrical Stair PDT (mA)	8.1	7.1	0.1544	-12.7% (-28.3%, 6.3%) p=0.1	44.3%	26.0%
Electrical Stair PTT (mA)	22.2	22.4	0.8759	0.9% (-10.9%, 14.2%) p=0.8	9.2%	10.2%
Delta Electrical Stair AUC (mA*%)	-199.9	-182.0	0.8349	17.95 (-180, 215.4) p=0.8349	48.28	66.23
Delta Electrical Stair PDT (mA)	1.51	1.82	0.7308	0.303 (-1.63, 2.234) p=0.7308	-0.439	-0.136
Delta Electrical Stair PTT (mA)	1.75	1.25	0.3993	- .505 (-1.80, 0.793) p=0.3993	-0.271	-0.776
Pressure AUC (kPa*%)	6732.9	6256.4	0.0726	-477 (-1006, 52.57) p=0.0726	-125.34	-601.87
Pressure PDT (kPa)	14.9	17.5	0.0656	17.5% (-1.2%, 39.7%) p=0.0	11.4%	30.8%
	LS Means			Contrasts	LS Means change from baseline	

Parameter	Placebo	Paracetamol	Treatment P-value	Paracetamol Placebo	Placebo	Paracetamol
Pressure PTT (kPa)	42.6	44.0	0.6460	3.4% (-11.6%, 20.9%) p=0.6	6.2%	9.7%
Heat PDT (C)	40.7	41.7	0.1096	2.5% (-0.7%, 5.7%) p=0.1	-1.4%	1.0%
Heat PTT (C)	47.0	46.9	0.8946	-0.1% (-2.4%, 2.3%) p=0.8	0.3%	0.2%
Sensory after Cold	1.01	0.93	0.4166	-0.076 (-0.279, 0.127) p=0.4166	0.002	-0.074
Affective after Cold	0.29	0.32	0.3167	0.036 (-0.040, 0.112) p=0.3167	-0.058	-0.022
MPQ VAS after Cold (mm)	42.9	45.5	0.2331	2.63 (-1.99, 7.26) p=0.2331	-2.32	0.31
Sensory after ES	1.16	1.14	0.8023	-0.022 (-0.217, 0.174) p=0.8023	-0.086	-0.108
Affective after ES	0.33	0.30	0.4880	-0.028 (-0.117, 0.061) p=0.4880	-0.000	-0.028
MPQ VAS after ES (mm)	37.1	40.6	0.1462	3.58 (-1.47, 8.63) p=0.1462	-3.22	0.36
Sensory after Pressure	0.92	0.91	0.8057	-0.017 (-0.174, 0.139) p=0.8057	-0.043	-0.060
Affective after Pressure	0.15	0.17	0.5212	0.014 (-0.037, 0.066) p=0.5212	-0.084	-0.069
MPQ VAS after Pressure (mm)	32.3	37.6	0.1359	5.34 (-2.00, 12.68) p=0.1359	-4.24	1.10

Unedited SAS output

Cold AAC (s*%)

SAS output 1.1 Cold AAC (s*%)

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Proc MIXED analysis of Cold AAC

Model Information

Data Set	WORK.MIX
Dependent Variable	ColdAAC
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	95

Number of Observations

Number of Observations Read	95
Number of Observations Used	95
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1408.16302843	
1	2	1389.07078206	0.00000009
2	1	1389.07072796	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	30201
Treatment*SubjectNr	223985
etime*SubjectNr	-22898
Residual	342245

Fit Statistics

-2 Res Log Likelihood	1389.1
AIC (smaller is better)	1397.1

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Proc MIXED analysis of Cold AAC

Fit Statistics

AICC (smaller is better)	1397.6
BIC (smaller is better)	1399.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	19.09	0.0003

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.62	0.00	0.9986
etime	3	33.2	1.90	0.1493
Occasion	1	9.98	0.94	0.3551
Treatment*etime	3	33.2	1.19	0.3289
preColdAAC	1	14.4	164.69	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	0.4006	227.92	9.62	0.00	0.9986	0.05	-510.12	510.92

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		2379.14	166.97	19.9	14.25	<.0001	0.05
Treatment	Paracetamol		2379.54	167.54	20.1	14.20	<.0001	0.05
Treatment*etime	Placebo	1:16:00	2405.89	218.72	50.6	11.00	<.0001	0.05
Treatment*etime	Placebo	2:16:00	2461.41	218.72	50.6	11.25	<.0001	0.05
Treatment*etime	Placebo	3:16:00	2647.62	218.72	50.6	12.11	<.0001	0.05
Treatment*etime	Placebo	5:16:00	2001.63	218.72	50.6	9.15	<.0001	0.05
Treatment*etime	Paracetamol	1:16:00	2380.63	226.02	54.3	10.53	<.0001	0.05
Treatment*etime	Paracetamol	2:16:00	2279.17	218.68	50.6	10.42	<.0001	0.05
Treatment*etime	Paracetamol	3:16:00	2480.35	218.68	50.6	11.34	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		2030.72	2727.56
Treatment	Paracetamol		2030.21	2728.87
Treatment*etime	Placebo	1:16:00	1966.70	2845.08
Treatment*etime	Placebo	2:16:00	2022.23	2900.60
Treatment*etime	Placebo	3:16:00	2208.44	3086.81
Treatment*etime	Placebo	5:16:00	1562.44	2440.82
Treatment*etime	Paracetamol	1:16:00	1927.53	2833.73
Treatment*etime	Paracetamol	2:16:00	1840.07	2718.27
Treatment*etime	Paracetamol	3:16:00	2041.25	2919.44

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Proc MIXED analysis of Cold AAC

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	5:16:00	2378.01	218.68	50.6	10.87	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	5:16:00	1938.91	2817.11

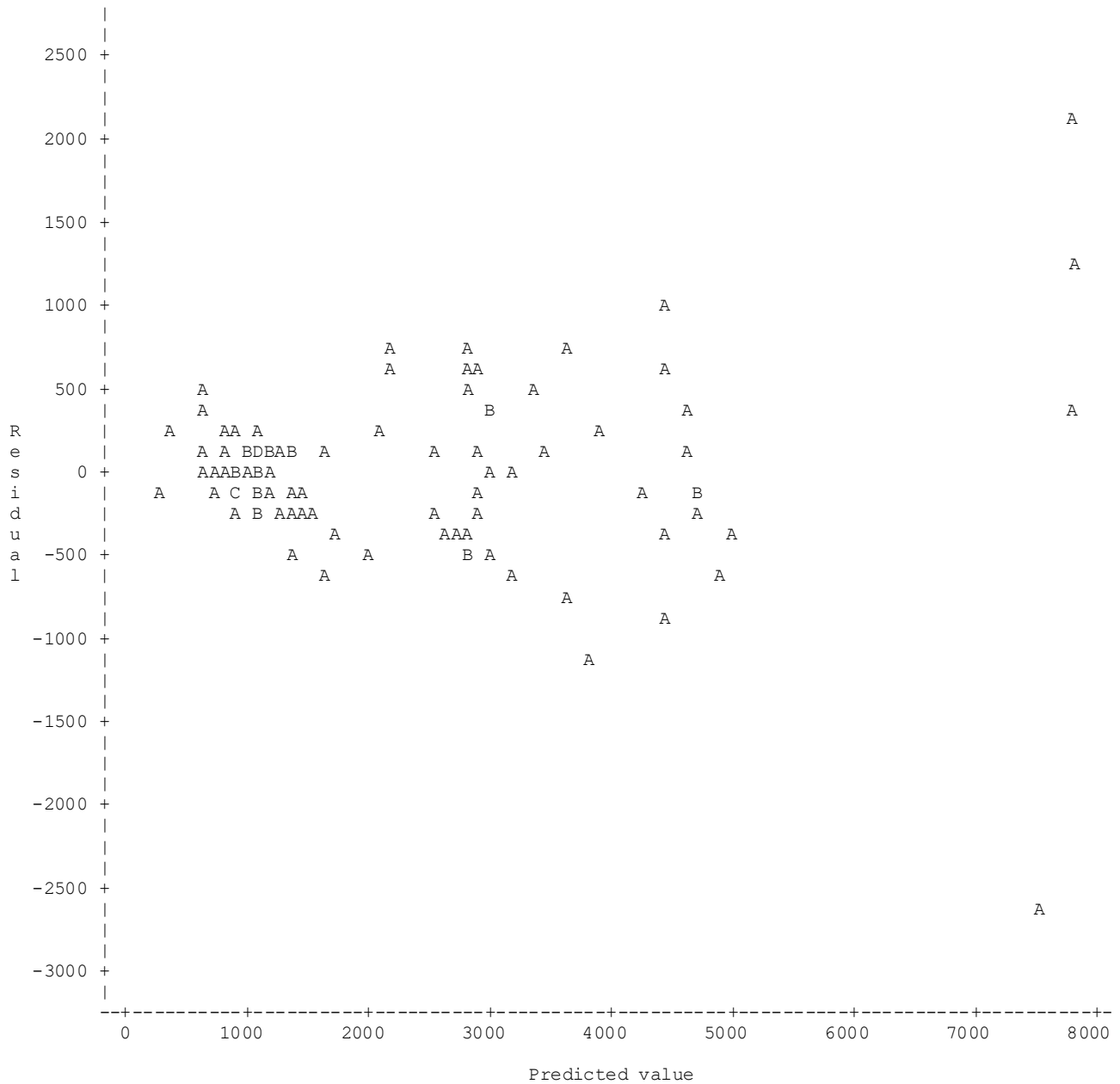
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Proc MIXED analysis of Cold AAC

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



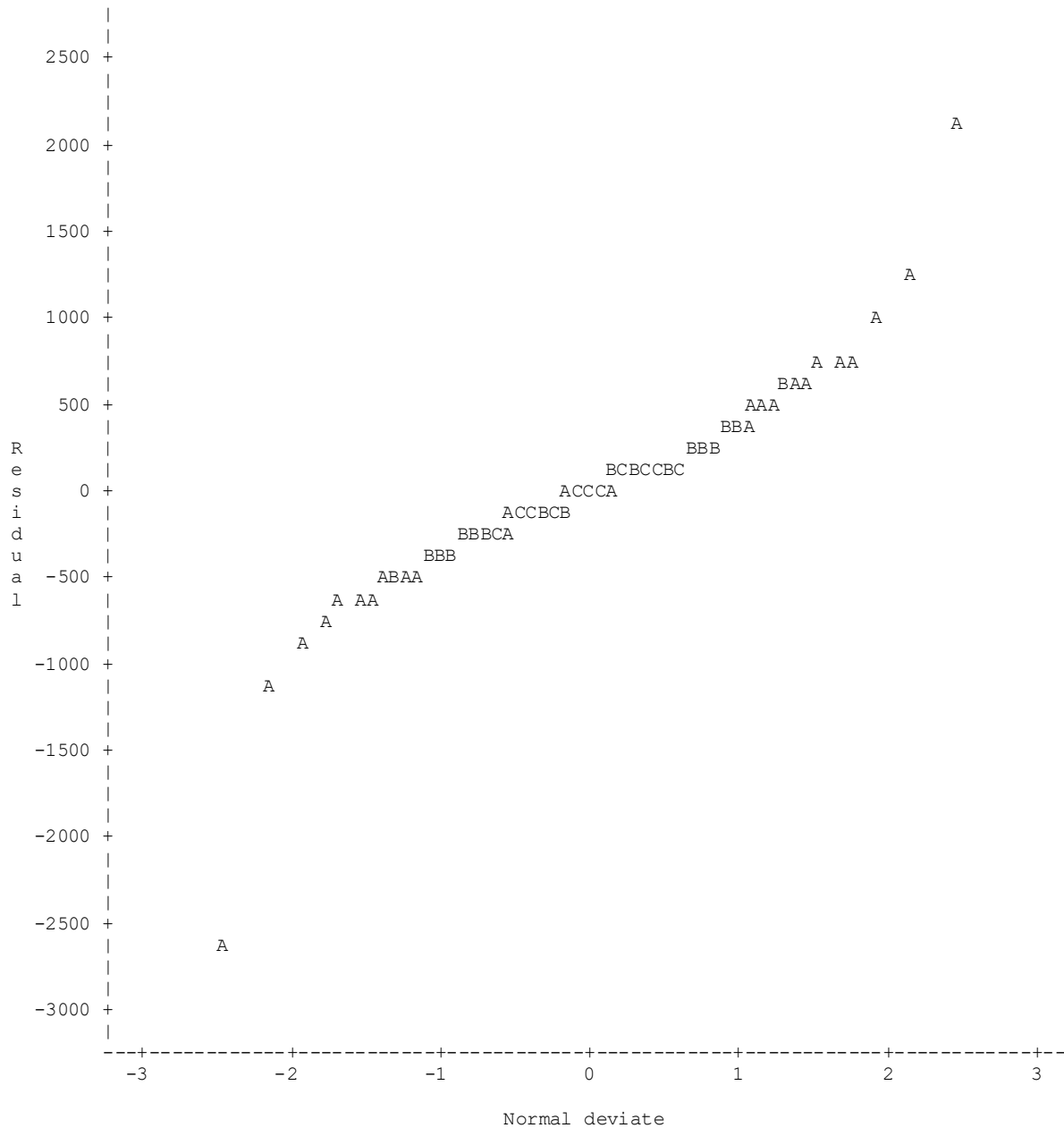
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Proc MIXED analysis of Cold AAC

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.877 : P-value=<0.001)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 1.2 Cold AAC (s*%) change from baseline

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Proc MIXED analysis of Cold AAC
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaColdAAC
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	95

Number of Observations

Number of Observations Read	95
Number of Observations Used	95
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1408.16302843	
1	2	1389.07078206	0.00000009
2	1	1389.07072796	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	30201
Treatment*SubjectNr	223985
etime*SubjectNr	-22898
Residual	342245

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Proc MIXED analysis of Cold AAC
Change from baseline

Fit Statistics

-2 Res Log Likelihood	1389.1
AIC (smaller is better)	1397.1
AICC (smaller is better)	1397.6
BIC (smaller is better)	1399.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	19.09	0.0003

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.62	0.00	0.9986
etime	3	33.2	1.90	0.1493
Occasion	1	9.98	0.94	0.3551
Treatment*etime	3	33.2	1.19	0.3289
preColdAAC	1	14.4	0.00	0.9804

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		77.6101	166.97	19.9	0.46	0.6471	0.05
Treatment	Paracetamol		78.0107	167.54	20.1	0.47	0.6465	0.05
Treatment*etime	Placebo	1:16:00	104.36	218.72	50.6	0.48	0.6353	0.05
Treatment*etime	Placebo	2:16:00	159.89	218.72	50.6	0.73	0.4681	0.05
Treatment*etime	Placebo	3:16:00	346.09	218.72	50.6	1.58	0.1198	0.05
Treatment*etime	Placebo	5:16:00	-299.90	218.72	50.6	-1.37	0.1764	0.05
Treatment*etime	Paracetamol	1:16:00	79.0992	226.02	54.3	0.35	0.7277	0.05
Treatment*etime	Paracetamol	2:16:00	-22.3577	218.68	50.6	-0.10	0.9190	0.05
Treatment*etime	Paracetamol	3:16:00	178.82	218.68	50.6	0.82	0.4174	0.05
Treatment*etime	Paracetamol	5:16:00	76.4840	218.68	50.6	0.35	0.7280	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-270.81	426.03
Treatment	Paracetamol		-271.32	427.34
Treatment*etime	Placebo	1:16:00	-334.83	543.55
Treatment*etime	Placebo	2:16:00	-279.30	599.07
Treatment*etime	Placebo	3:16:00	-93.0932	785.28
Treatment*etime	Placebo	5:16:00	-739.08	139.29
Treatment*etime	Paracetamol	1:16:00	-374.00	532.20
Treatment*etime	Paracetamol	2:16:00	-461.46	416.74
Treatment*etime	Paracetamol	3:16:00	-260.28	617.92
Treatment*etime	Paracetamol	5:16:00	-362.61	515.58

Cold PDT (s)**SAS output 2.1 Cold PDT (s)**

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Proc MIXED analysis of LOG Cold PDT

Model Information

Data Set	WORK.MIX
Dependent Variable	ColdPDT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kacker-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	83
Subjects	1
Max Obs Per Subject	95

Number of Observations

Number of Observations Read	95
Number of Observations Used	90
Number of Observations Not Used	5

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	176.06593620	
1	2	159.72472575	0.00136584
2	1	159.71566663	0.00000761
3	1	159.71561812	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.08885
Treatment*SubjectNr	0.06866
etime*SubjectNr	-0.03836
Residual	0.2703

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Proc MIXED analysis of LOG Cold PDT

Fit Statistics

-2 Res Log Likelihood	159.7
AIC (smaller is better)	167.7
AICC (smaller is better)	168.2
BIC (smaller is better)	169.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	16.35	0.0010

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.32	0.97	0.3505
etime	3	32.5	0.39	0.7615
Occasion	1	9.81	1.08	0.3231
Treatment*etime	3	32.7	0.84	0.4802
preColdPDT	1	13.1	42.96	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	0.1548	0.1575	9.32	0.98	0.3505	0.05	-0.1997	0.5093

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		1.4868	0.1410	17.2	10.54	<.0001	0.05
Treatment	Paracetamol		1.6416	0.1345	16.7	12.20	<.0001	0.05
Treatment*etime	Placebo	1:16:00	1.4240	0.1956	51.3	7.28	<.0001	0.05
Treatment*etime	Placebo	2:16:00	1.5385	0.1887	47.5	8.15	<.0001	0.05
Treatment*etime	Placebo	3:16:00	1.5887	0.1887	47.5	8.42	<.0001	0.05
Treatment*etime	Placebo	5:16:00	1.3959	0.1887	47.5	7.40	<.0001	0.05
Treatment*etime	Paracetamol	1:16:00	1.5559	0.1864	49.8	8.35	<.0001	0.05
Treatment*etime	Paracetamol	2:16:00	1.7147	0.1802	46.3	9.52	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		1.1894	1.7841
Treatment	Paracetamol		1.3574	1.9258
Treatment*etime	Placebo	1:16:00	1.0313	1.8167
Treatment*etime	Placebo	2:16:00	1.1590	1.9180
Treatment*etime	Placebo	3:16:00	1.2092	1.9681
Treatment*etime	Placebo	5:16:00	1.0164	1.7754
Treatment*etime	Paracetamol	1:16:00	1.1815	1.9304
Treatment*etime	Paracetamol	2:16:00	1.3521	2.0772

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Proc MIXED analysis of LOG Cold PDT

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	3:16:00	1.5017	0.1802	46.3	8.34	<.0001	0.05
Treatment*etime	Paracetamol	5:16:00	1.7940	0.1802	46.3	9.96	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	3:16:00	1.1391	1.8643
Treatment*etime	Paracetamol	5:16:00	1.4314	2.1565

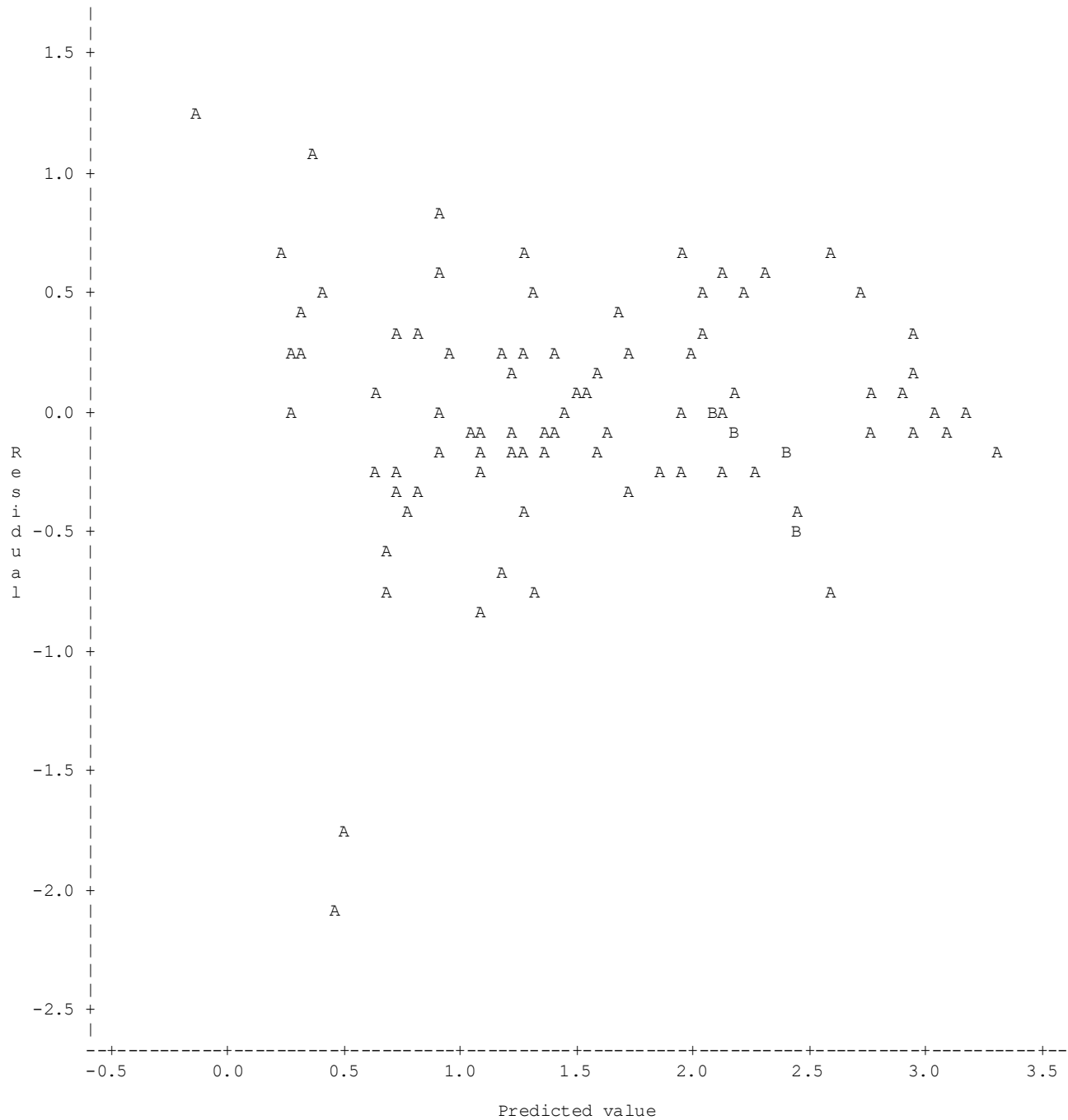
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Proc MIXED analysis of LOG Cold PDT

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



NOTE: 5 obs had missing values.

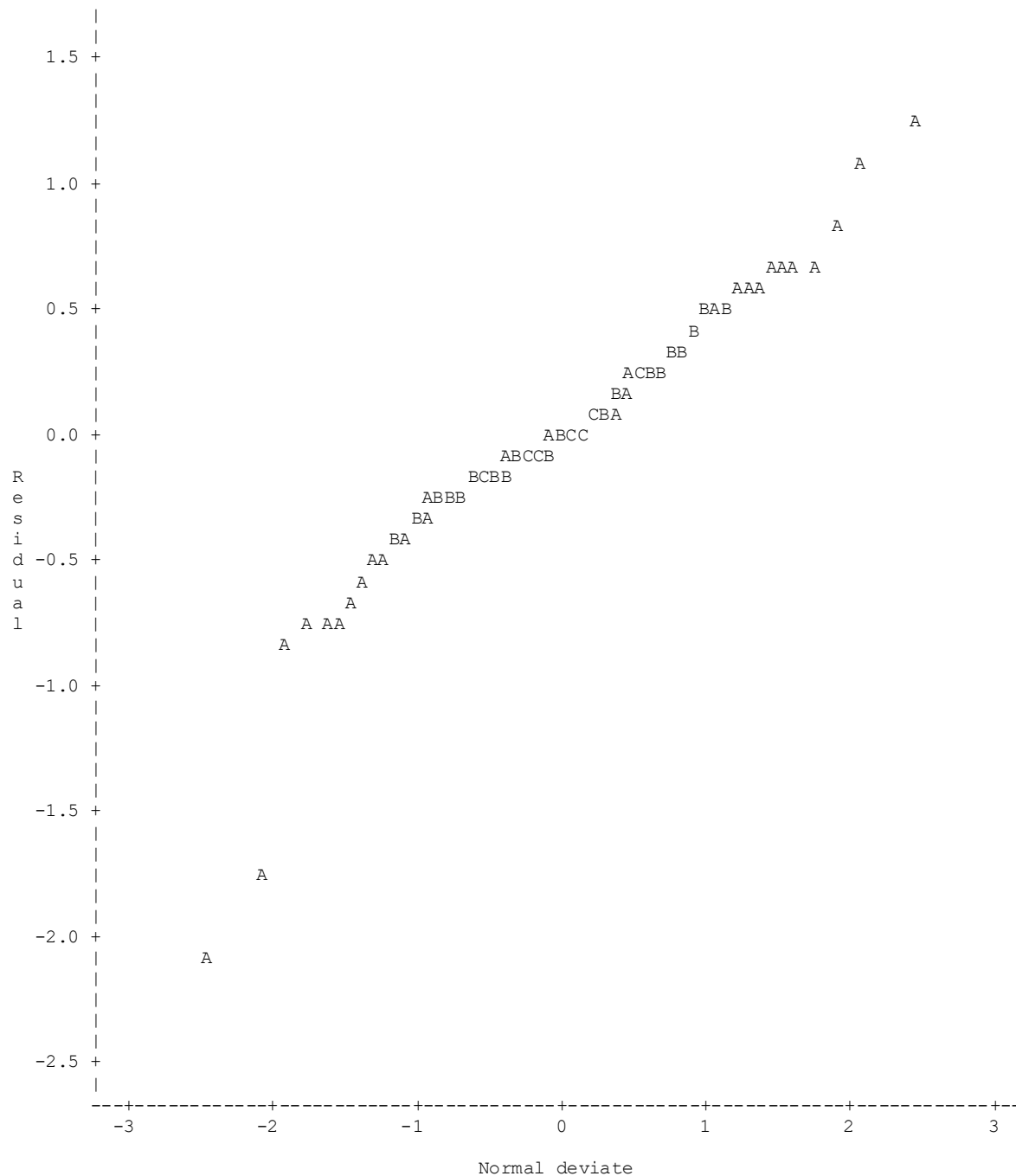
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Proc MIXED analysis of LOG Cold PDT

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.930 : P-value=<0.001)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



NOTE: 5 obs had missing values.

SAS output 2.2 Cold PDT (s) change from baseline

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Proc MIXED analysis of LOG Cold PDT
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaColdPDT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske- Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	83
Subjects	1
Max Obs Per Subject	95

Number of Observations

Number of Observations Read	95
Number of Observations Used	90
Number of Observations Not Used	5

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	176.06593620	
1	2	159.72472575	0.00136584
2	1	159.71566663	0.00000761
3	1	159.71561812	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.08885
Treatment*SubjectNr	0.06866
etime*SubjectNr	-0.03836
Residual	0.2703

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Proc MIXED analysis of LOG Cold PDT
Change from baseline

Fit Statistics

-2 Res Log Likelihood	159.7
AIC (smaller is better)	167.7
AICC (smaller is better)	168.2
BIC (smaller is better)	169.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	16.35	0.0010

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.32	0.97	0.3505
etime	3	32.5	0.39	0.7615
Occasion	1	9.81	1.08	0.3231
Treatment*etime	3	32.7	0.84	0.4802
preColdPDT	1	13.1	6.12	0.0278

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-0.04097	0.1410	17.2	-0.29	0.7749	0.05
Treatment	Paracetamol		0.1138	0.1345	16.7	0.85	0.4095	0.05
Treatment*etime	Placebo	1:16:00	-0.1037	0.1956	51.3	-0.53	0.5982	0.05
Treatment*etime	Placebo	2:16:00	0.01077	0.1887	47.5	0.06	0.9547	0.05
Treatment*etime	Placebo	3:16:00	0.06092	0.1887	47.5	0.32	0.7482	0.05
Treatment*etime	Placebo	5:16:00	-0.1318	0.1887	47.5	-0.70	0.4881	0.05
Treatment*etime	Paracetamol	1:16:00	0.02821	0.1864	49.8	0.15	0.8803	0.05
Treatment*etime	Paracetamol	2:16:00	0.1869	0.1802	46.3	1.04	0.3049	0.05
Treatment*etime	Paracetamol	3:16:00	-0.02602	0.1802	46.3	-0.14	0.8858	0.05
Treatment*etime	Paracetamol	5:16:00	0.2662	0.1802	46.3	1.48	0.1462	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.3383	0.2564
Treatment	Paracetamol		-0.1704	0.3980
Treatment*etime	Placebo	1:16:00	-0.4964	0.2889
Treatment*etime	Placebo	2:16:00	-0.3687	0.3903
Treatment*etime	Placebo	3:16:00	-0.3186	0.4404
Treatment*etime	Placebo	5:16:00	-0.5113	0.2476
Treatment*etime	Paracetamol	1:16:00	-0.3462	0.4026
Treatment*etime	Paracetamol	2:16:00	-0.1757	0.5495
Treatment*etime	Paracetamol	3:16:00	-0.3886	0.3365
Treatment*etime	Paracetamol	5:16:00	-0.09634	0.6288

Cold PTT (s)**SAS output 3.1 Cold PTT (s)**

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Proc MIXED analysis of LOG Cold PTT

Model Information

Data Set	WORK.MIX
Dependent Variable	ColdPTT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	83
Subjects	1
Max Obs Per Subject	94

Number of Observations

Number of Observations Read	94
Number of Observations Used	94
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	36.39431653	
1	2	7.28034528	0.00006238
2	1	7.27556952	0.00000026
3	1	7.27555025	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-0.01337
Treatment*SubjectNr	0.05029
etime*SubjectNr	-0.00361
Residual	0.03499

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Proc MIXED analysis of LOG Cold PTT

Fit Statistics

-2 Res Log Likelihood	7.3
AIC (smaller is better)	15.3
AICC (smaller is better)	15.8
BIC (smaller is better)	17.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	29.12	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.34	0.75	0.4088
etime	3	32.2	1.55	0.2195
Occasion	1	9.39	0.23	0.6440
Treatment*etime	3	32.1	2.50	0.0767
preColdPTT	1	10.8	348.57	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	0.08604	0.09950	9.34	0.86	0.4088	0.05	-0.1378	0.3099

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		3.3753	0.06130	18	55.07	<.0001	0.05
Treatment	Paracetamol		3.4614	0.06126	18	56.51	<.0001	0.05
Treatment*etime	Placebo	1:16:00	3.3930	0.07748	41.3	43.79	<.0001	0.05
Treatment*etime	Placebo	2:16:00	3.4624	0.07551	38.4	45.86	<.0001	0.05
Treatment*etime	Placebo	3:16:00	3.4040	0.07551	38.4	45.08	<.0001	0.05
Treatment*etime	Placebo	5:16:00	3.2419	0.07551	38.4	42.93	<.0001	0.05
Treatment*etime	Paracetamol	1:16:00	3.3989	0.07749	41.3	43.86	<.0001	0.05
Treatment*etime	Paracetamol	2:16:00	3.4512	0.07546	38.4	45.74	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		3.2465	3.5041
Treatment	Paracetamol		3.3326	3.5901
Treatment*etime	Placebo	1:16:00	3.2365	3.5494
Treatment*etime	Placebo	2:16:00	3.3096	3.6152
Treatment*etime	Placebo	3:16:00	3.2512	3.5568
Treatment*etime	Placebo	5:16:00	3.0891	3.3947
Treatment*etime	Paracetamol	1:16:00	3.2425	3.5554
Treatment*etime	Paracetamol	2:16:00	3.2985	3.6039

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Proc MIXED analysis of LOG Cold PTT

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	3:16:00	3.4983	0.07546	38.4	46.36	<.0001	0.05
Treatment*etime	Paracetamol	5:16:00	3.4970	0.07546	38.4	46.34	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	3:16:00	3.3456	3.6510
Treatment*etime	Paracetamol	5:16:00	3.3443	3.6497

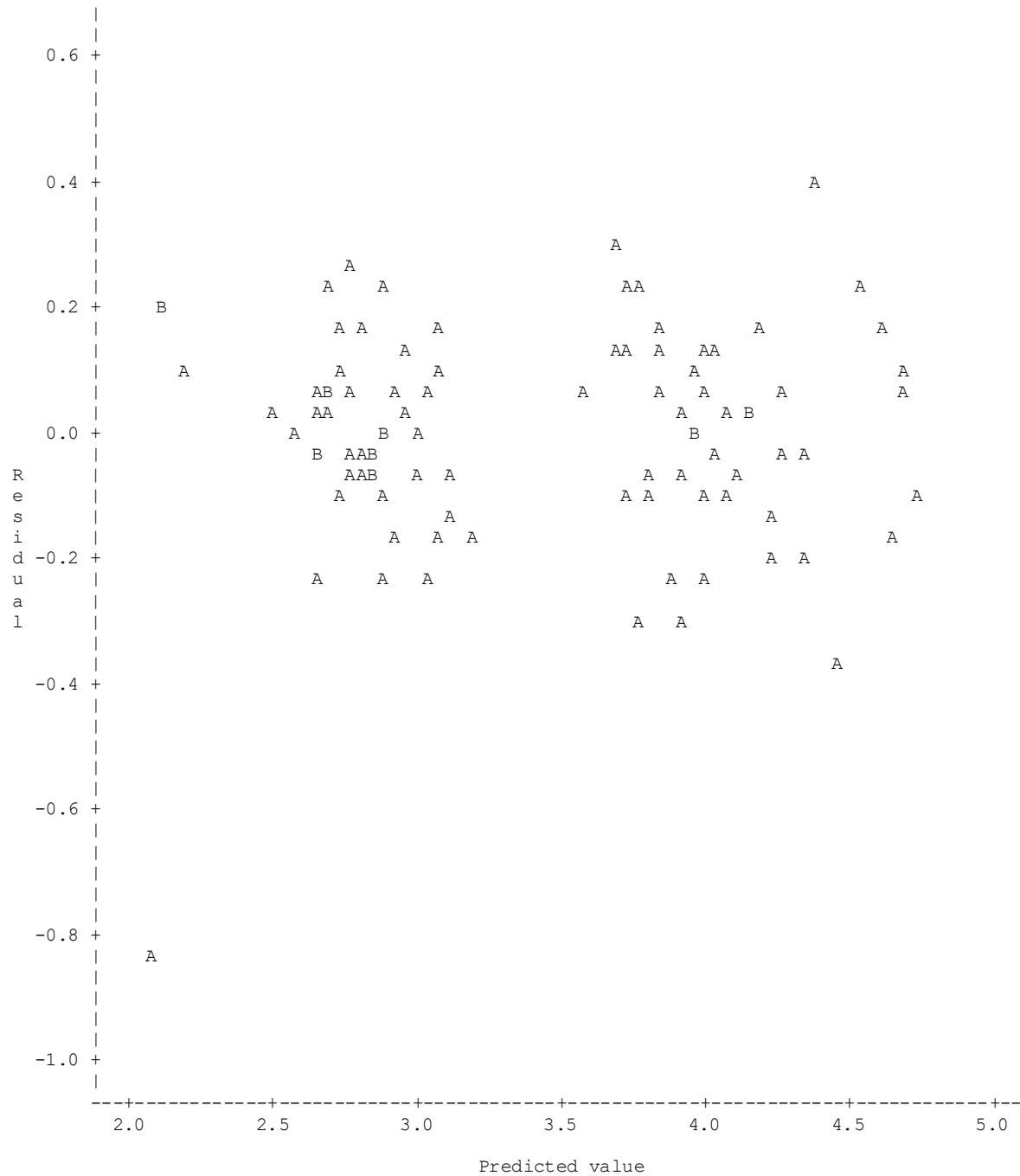
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Cold PTT

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



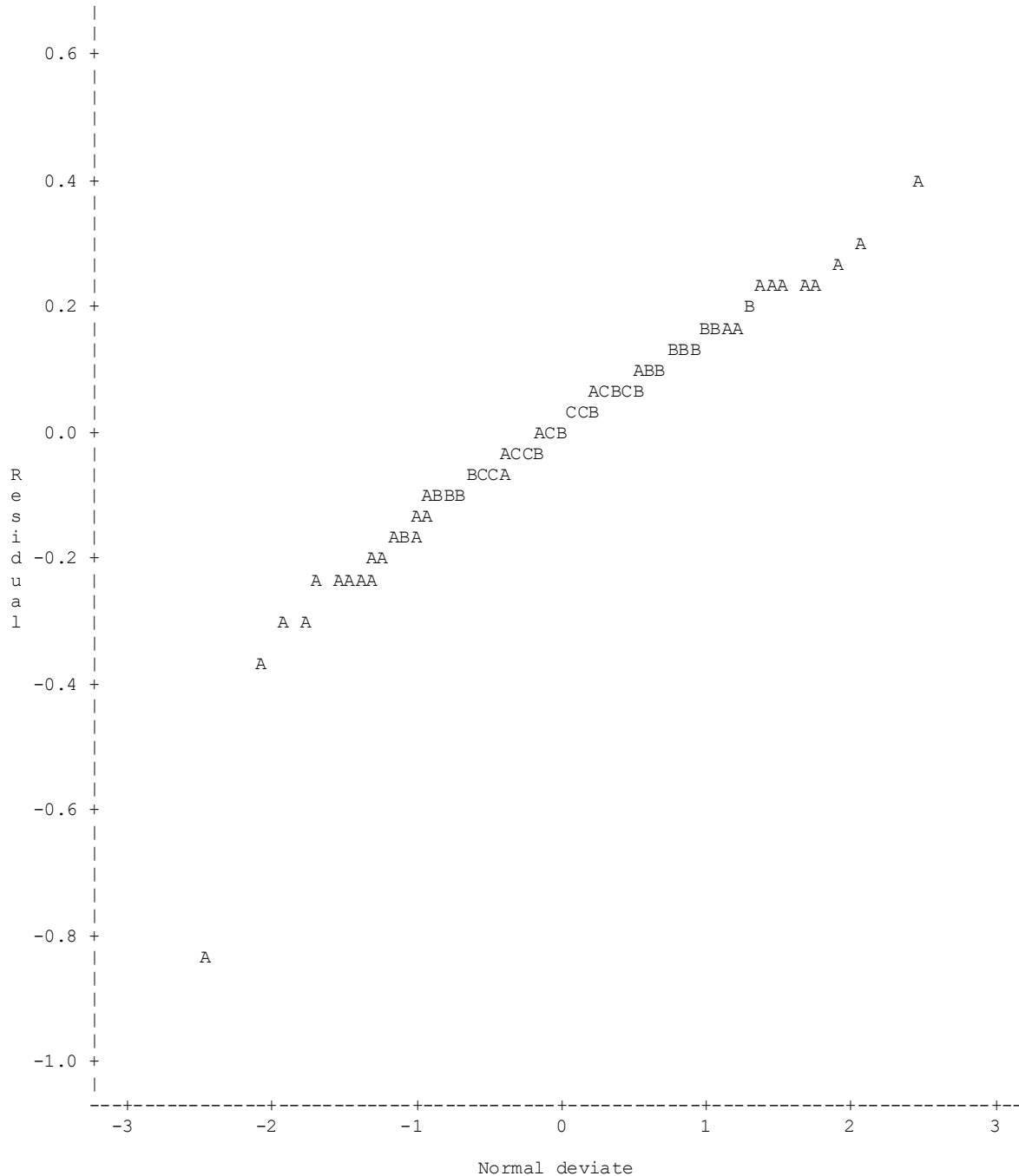
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Cold PTT

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.936 : P-value=<0.001)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 3.2 Cold PTT (s) change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Cold PTT
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaColdPTT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	83
Subjects	1
Max Obs Per Subject	94

Number of Observations

Number of Observations Read	94
Number of Observations Used	94
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	36.39431653	
1	2	7.28034528	0.00006238
2	1	7.27556952	0.00000026
3	1	7.27555025	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-0.01337
Treatment*SubjectNr	0.05029
etime*SubjectNr	-0.00361
Residual	0.03499

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Cold PTT
Change from baseline

Fit Statistics

-2 Res Log Likelihood	7.3
AIC (smaller is better)	15.3
AICC (smaller is better)	15.8
BIC (smaller is better)	17.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	29.12	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.34	0.75	0.4088
etime	3	32.2	1.55	0.2195
Occasion	1	9.39	0.23	0.6440
Treatment*etime	3	32.1	2.50	0.0767
preColdPTT	1	10.8	0.83	0.3822

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-0.05908	0.06130	18	-0.96	0.3479	0.05
Treatment	Paracetamol		0.02696	0.06126	18	0.44	0.6651	0.05
Treatment*etime	Placebo	1:16:00	-0.04145	0.07748	41.3	-0.53	0.5956	0.05
Treatment*etime	Placebo	2:16:00	0.02802	0.07551	38.4	0.37	0.7127	0.05
Treatment*etime	Placebo	3:16:00	-0.03038	0.07551	38.4	-0.40	0.6897	0.05
Treatment*etime	Placebo	5:16:00	-0.1925	0.07551	38.4	-2.55	0.0149	0.05
Treatment*etime	Paracetamol	1:16:00	-0.03546	0.07749	41.3	-0.46	0.6496	0.05
Treatment*etime	Paracetamol	2:16:00	0.01681	0.07546	38.4	0.22	0.8249	0.05
Treatment*etime	Paracetamol	3:16:00	0.06390	0.07546	38.4	0.85	0.4024	0.05
Treatment*etime	Paracetamol	5:16:00	0.06259	0.07546	38.4	0.83	0.4120	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.1879	0.06971
Treatment	Paracetamol		-0.1018	0.1557
Treatment*etime	Placebo	1:16:00	-0.1979	0.1150
Treatment*etime	Placebo	2:16:00	-0.1248	0.1808
Treatment*etime	Placebo	3:16:00	-0.1832	0.1224
Treatment*etime	Placebo	5:16:00	-0.3453	-0.03972
Treatment*etime	Paracetamol	1:16:00	-0.1919	0.1210
Treatment*etime	Paracetamol	2:16:00	-0.1359	0.1695
Treatment*etime	Paracetamol	3:16:00	-0.08881	0.2166
Treatment*etime	Paracetamol	5:16:00	-0.09012	0.2153

Electrical Stair AUC (mA*%)**SAS output 4.1 Electrical Stair AUC (mA*%)**

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Electrical Stair AUC

Model Information

Data Set	WORK.MIX
Dependent Variable	ElecStairAUC
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1305.45680908	
1	2	1243.66617231	0.00000007
2	1	1243.66613596	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	18290
Treatment*SubjectNr	92840
etime*SubjectNr	4769.59
Residual	34094

Fit Statistics

-2 Res Log Likelihood	1243.7
AIC (smaller is better)	1251.7

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Proc MIXED analysis of Electrical Stair AUC

Fit Statistics

AICC (smaller is better)	1252.2
BIC (smaller is better)	1253.6

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	61.79	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.54	0.50	0.4977
etime	3	33	2.93	0.0480
Occasion	1	8.36	3.70	0.0892
Treatment*etime	3	33	0.70	0.5612
preElecStairAUC	1	10.8	83.79	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	92.5529	130.70	8.54	0.71	0.4977	0.05	-205.57	390.68

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		2946.76	100.59	19.4	29.30	<.0001	0.05
Treatment	Paracetamol		3039.31	100.59	19.4	30.22	<.0001	0.05
Treatment*etime	Placebo	1:08:00	3011.73	112.01	29.3	26.89	<.0001	0.05
Treatment*etime	Placebo	2:08:00	2984.24	112.01	29.3	26.64	<.0001	0.05
Treatment*etime	Placebo	3:08:00	2917.84	112.01	29.3	26.05	<.0001	0.05
Treatment*etime	Placebo	5:08:00	2873.24	112.01	29.3	25.65	<.0001	0.05
Treatment*etime	Paracetamol	1:08:00	3172.49	112.01	29.3	28.32	<.0001	0.05
Treatment*etime	Paracetamol	2:08:00	3023.51	112.01	29.3	26.99	<.0001	0.05
Treatment*etime	Paracetamol	3:08:00	2956.77	112.01	29.3	26.40	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		2736.51	3157.02
Treatment	Paracetamol		2829.06	3249.57
Treatment*etime	Placebo	1:08:00	2782.74	3240.72
Treatment*etime	Placebo	2:08:00	2755.25	3213.23
Treatment*etime	Placebo	3:08:00	2688.85	3146.83
Treatment*etime	Placebo	5:08:00	2644.25	3102.23
Treatment*etime	Paracetamol	1:08:00	2943.50	3401.48
Treatment*etime	Paracetamol	2:08:00	2794.52	3252.50
Treatment*etime	Paracetamol	3:08:00	2727.78	3185.76

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Proc MIXED analysis of Electrical Stair AUC

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	5:08:00	3004.48	112.01	29.3	26.82	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	5:08:00	2775.49	3233.47

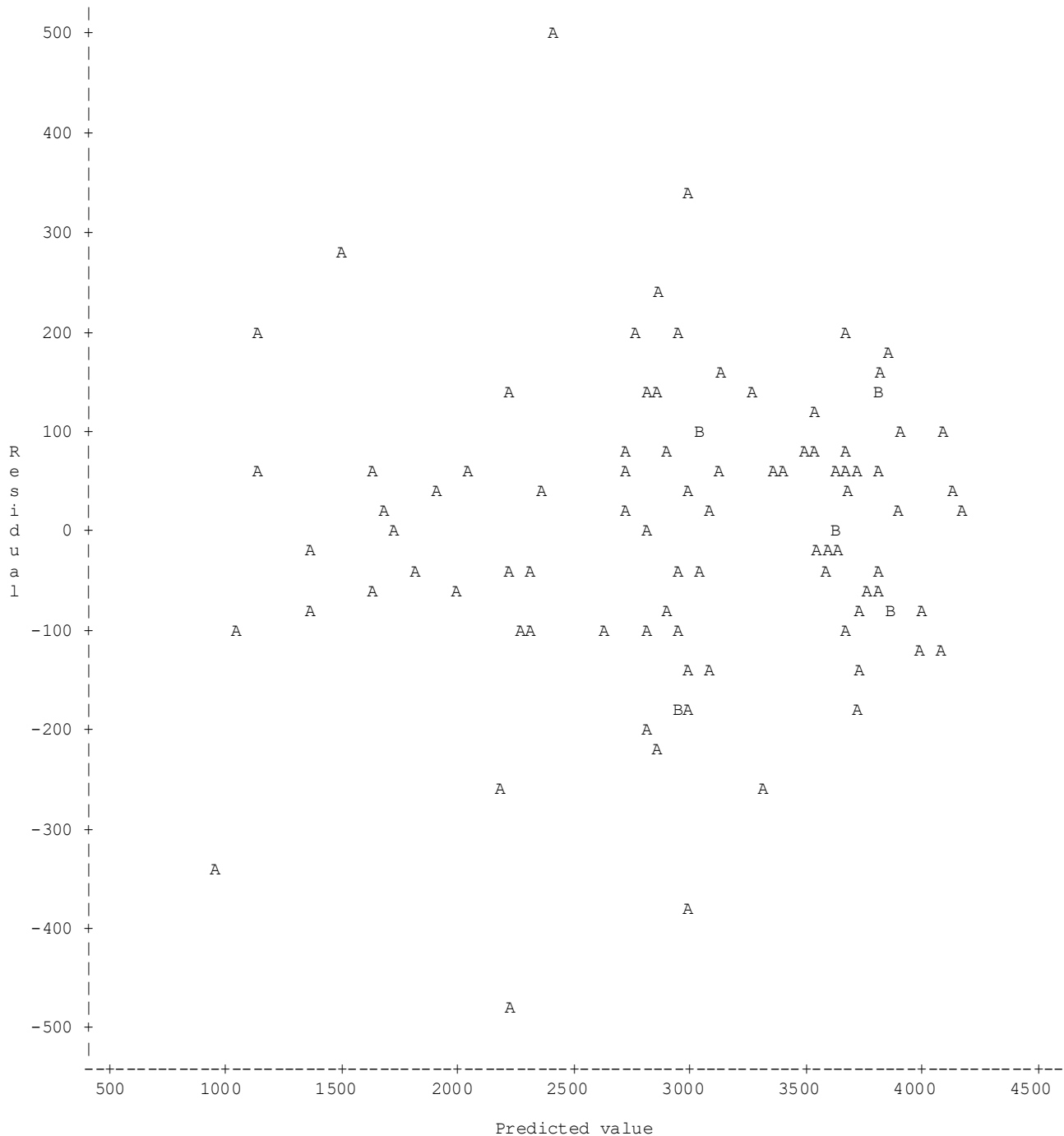
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Electrical Stair AUC

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



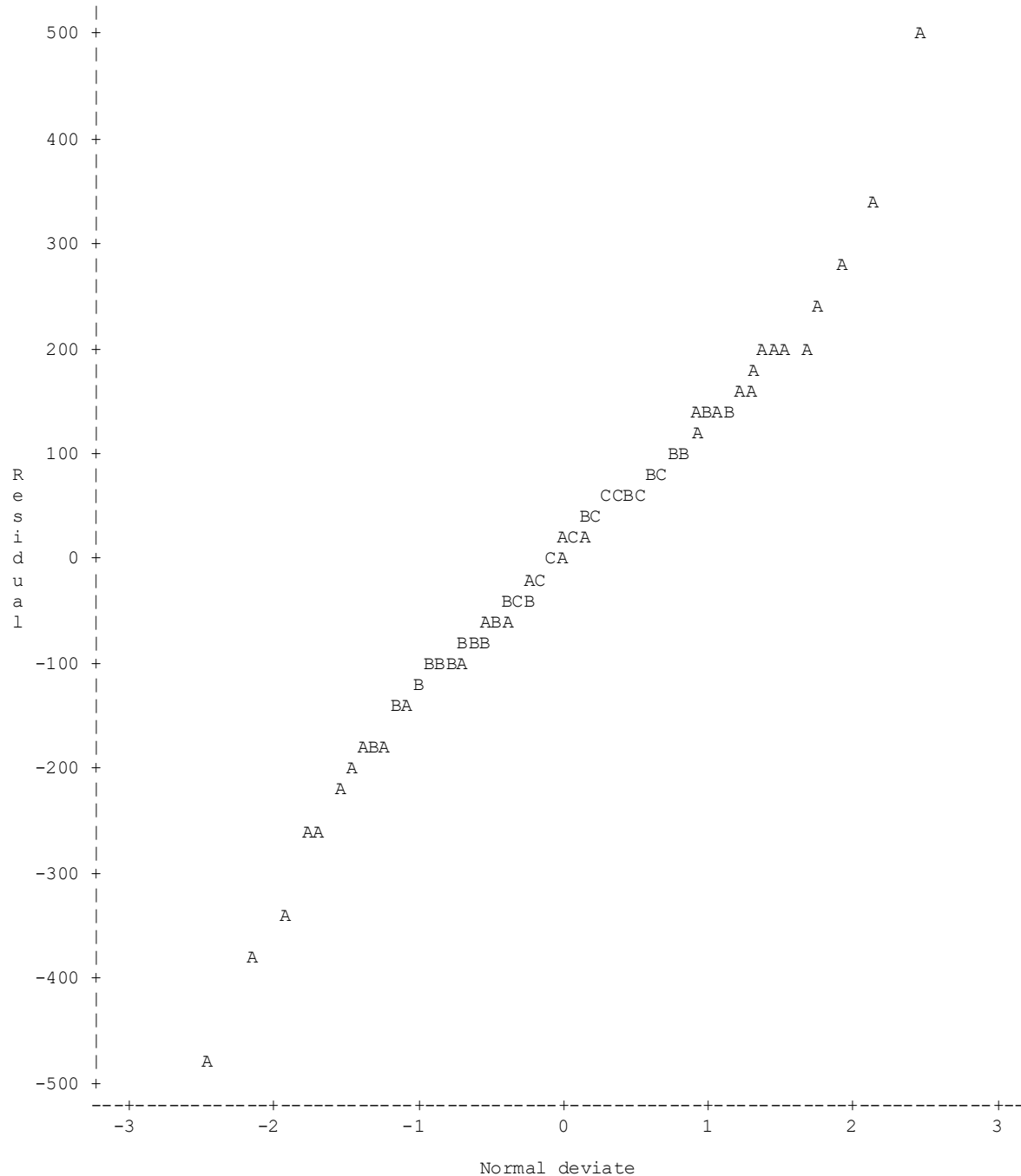
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Proc MIXED analysis of Electrical Stair AUC

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.978 : P-value= 0.104)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 4.2 Electrical Stair AUC (mA*%) change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Electrical Stair AUC
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaElecStairAUC
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1305.45680908	
1	2	1243.66617231	0.00000007
2	1	1243.66613596	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	18290
Treatment*SubjectNr	92840
etime*SubjectNr	4769.59
Residual	34094

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Proc MIXED analysis of Electrical Stair AUC
Change from baseline

Fit Statistics

-2 Res Log Likelihood	1243.7
AIC (smaller is better)	1251.7
AICC (smaller is better)	1252.2
BIC (smaller is better)	1253.6

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	61.79	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.54	0.50	0.4977
etime	3	33	2.93	0.0480
Occasion	1	8.36	3.70	0.0892
Treatment*etime	3	33	0.70	0.5612
preElecStairAUC	1	10.8	2.32	0.1566

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-310.83	100.59	19.4	-3.09	0.0059	0.05
Treatment	Paracetamol		-218.28	100.59	19.4	-2.17	0.0426	0.05
Treatment*etime	Placebo	1:08:00	-245.87	112.01	29.3	-2.20	0.0362	0.05
Treatment*etime	Placebo	2:08:00	-273.36	112.01	29.3	-2.44	0.0209	0.05
Treatment*etime	Placebo	3:08:00	-339.75	112.01	29.3	-3.03	0.0050	0.05
Treatment*etime	Placebo	5:08:00	-384.36	112.01	29.3	-3.43	0.0018	0.05
Treatment*etime	Paracetamol	1:08:00	-85.1069	112.01	29.3	-0.76	0.4534	0.05
Treatment*etime	Paracetamol	2:08:00	-234.08	112.01	29.3	-2.09	0.0454	0.05
Treatment*etime	Paracetamol	3:08:00	-300.82	112.01	29.3	-2.69	0.0118	0.05
Treatment*etime	Paracetamol	5:08:00	-253.12	112.01	29.3	-2.26	0.0314	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-521.09	-100.58
Treatment	Paracetamol		-428.54	-8.0259
Treatment*etime	Placebo	1:08:00	-474.86	-16.8775
Treatment*etime	Placebo	2:08:00	-502.35	-44.3692
Treatment*etime	Placebo	3:08:00	-568.74	-110.76
Treatment*etime	Placebo	5:08:00	-613.35	-155.37
Treatment*etime	Paracetamol	1:08:00	-314.10	143.88
Treatment*etime	Paracetamol	2:08:00	-463.07	-5.0913
Treatment*etime	Paracetamol	3:08:00	-529.81	-71.8330
Treatment*etime	Paracetamol	5:08:00	-482.11	-24.1247

Electrical Stair PDT (mA)**SAS output 5.1 Electrical Stair PDT (mA)**

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Electrical Stair PDT

Model Information

Data Set	WORK.MIX
Dependent Variable	ElecStairPDT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	75.44645827	
1	2	57.77055067	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.004317
Treatment*SubjectNr	0.03486
etime*SubjectNr	0.02226
Residual	0.04407

Fit Statistics

-2 Res Log Likelihood	57.8
AIC (smaller is better)	65.8
AICC (smaller is better)	66.3

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Proc MIXED analysis of LOG Electrical Stair PDT

Fit Statistics

BIC (smaller is better) 67.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	17.68	0.0005

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.88	2.38	0.1544
etime	3	33	1.64	0.2000
Occasion	1	9.86	5.31	0.0444
Treatment*etime	3	33	0.36	0.7799
preElecStairPDT	1	12.4	75.05	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	-0.1360	0.08817	9.88	-1.54	0.1544	0.05	-0.3328	0.06079

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		2.0952	0.06840	19.4	30.63	<.0001	0.05
Treatment	Paracetamol		1.9592	0.06840	19.4	28.64	<.0001	0.05
Treatment*etime	Placebo	1:08:00	2.0406	0.09394	55	21.72	<.0001	0.05
Treatment*etime	Placebo	2:08:00	2.0147	0.09394	55	21.45	<.0001	0.05
Treatment*etime	Placebo	3:08:00	2.1727	0.09394	55	23.13	<.0001	0.05
Treatment*etime	Placebo	5:08:00	2.1528	0.09394	55	22.92	<.0001	0.05
Treatment*etime	Paracetamol	1:08:00	1.8749	0.09394	55	19.96	<.0001	0.05
Treatment*etime	Paracetamol	2:08:00	1.9277	0.09394	55	20.52	<.0001	0.05
Treatment*etime	Paracetamol	3:08:00	2.0747	0.09394	55	22.09	<.0001	0.05
Treatment*etime	Paracetamol	5:08:00	1.9596	0.09394	55	20.86	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		1.9522	2.2382
Treatment	Paracetamol		1.8162	2.1022
Treatment*etime	Placebo	1:08:00	1.8523	2.2289
Treatment*etime	Placebo	2:08:00	1.8264	2.2030
Treatment*etime	Placebo	3:08:00	1.9844	2.3609
Treatment*etime	Placebo	5:08:00	1.9646	2.3411
Treatment*etime	Paracetamol	1:08:00	1.6866	2.0631
Treatment*etime	Paracetamol	2:08:00	1.7394	2.1159
Treatment*etime	Paracetamol	3:08:00	1.8864	2.2629
Treatment*etime	Paracetamol	5:08:00	1.7713	2.1478

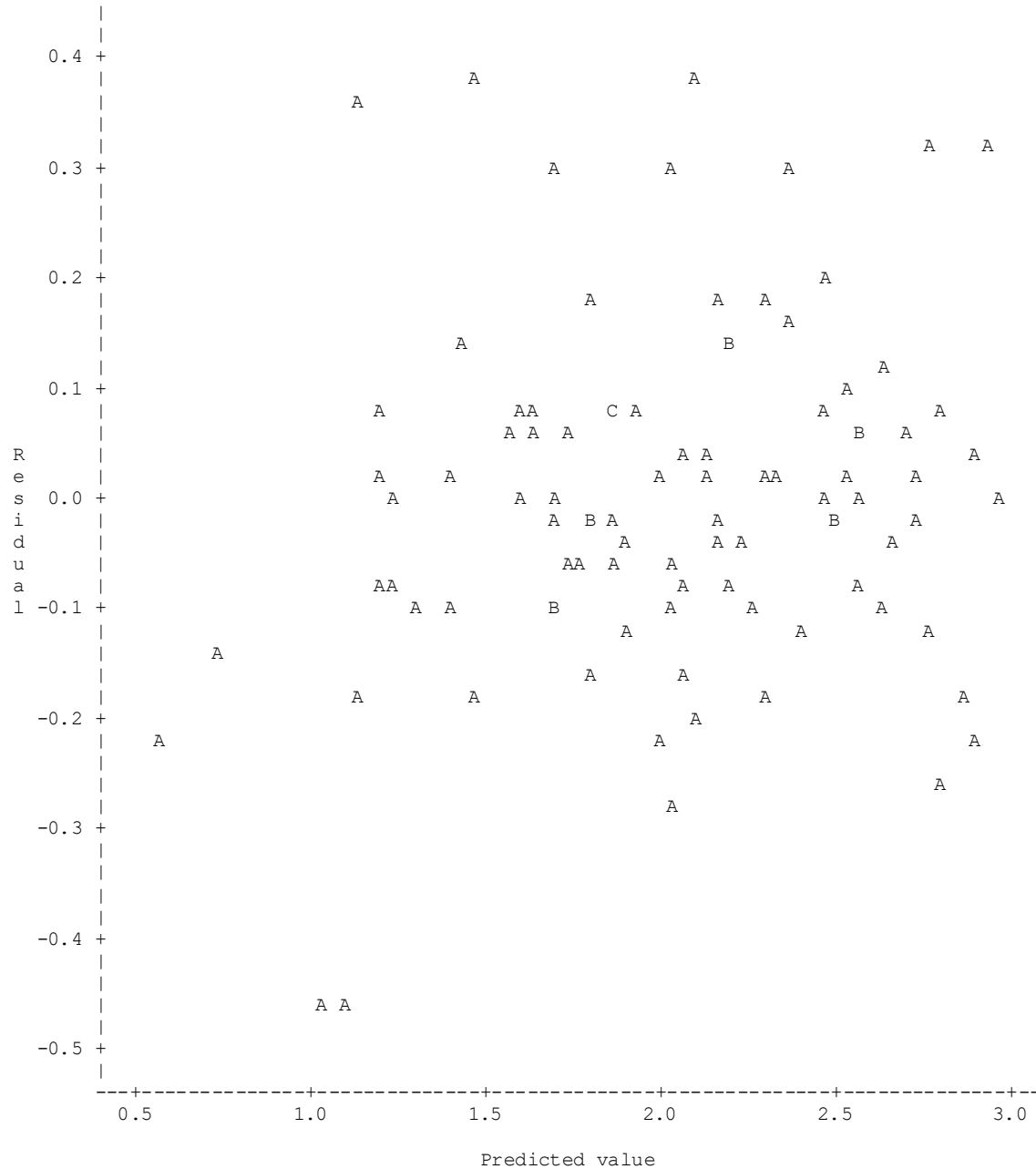
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Electrical Stair PDT

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



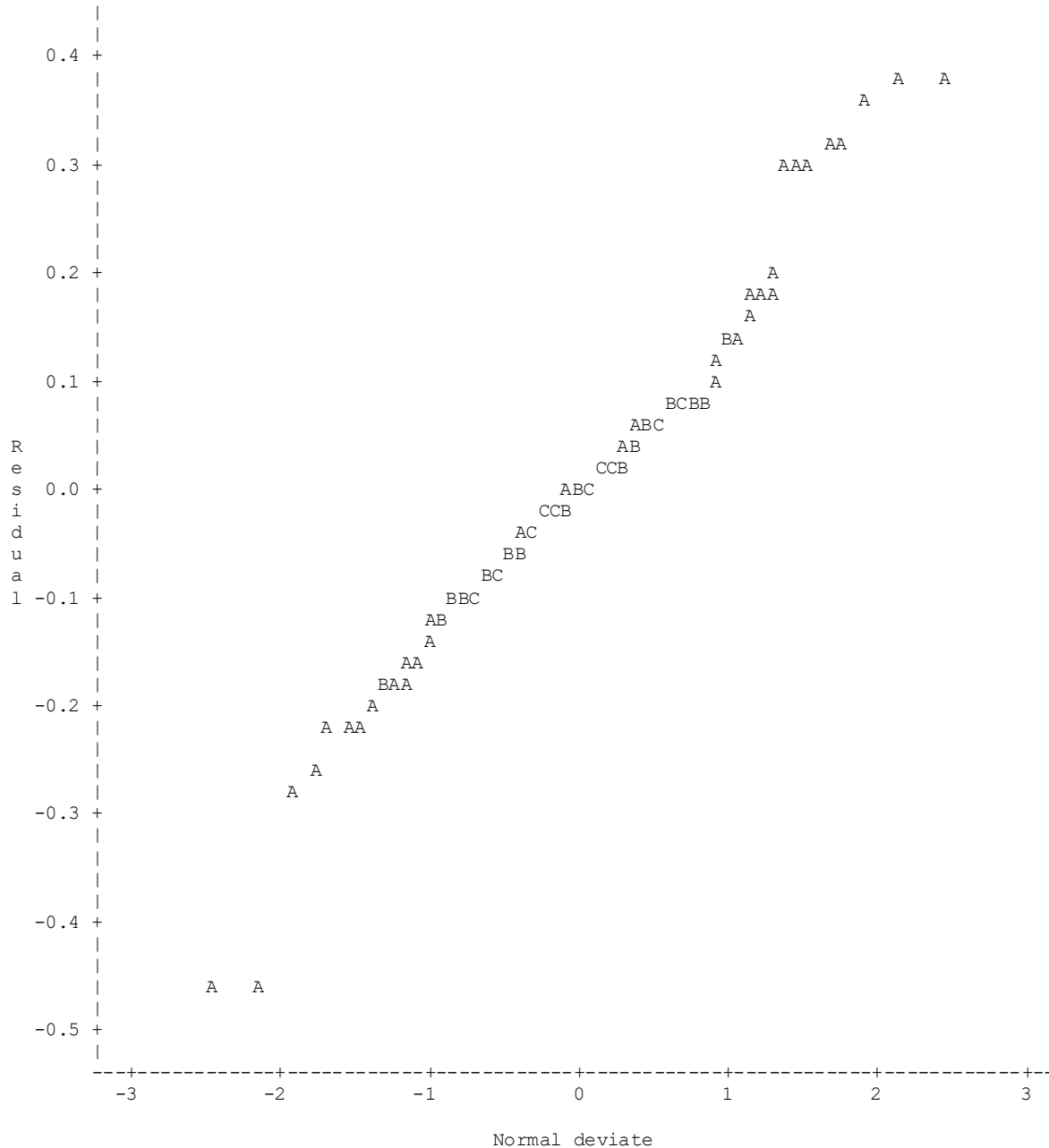
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Electrical Stair PDT

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.970 : P-value= 0.025)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 5.2 Electrical Stair PDT (mA) change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Electrical Stair PDT
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaElecStairPDT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	75.44645827	
1	2	57.77055067	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.004317
Treatment*SubjectNr	0.03486
etime*SubjectNr	0.02226
Residual	0.04407

Fit Statistics

-2 Res Log Likelihood	57.8
AIC (smaller is better)	65.8

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Electrical Stair PDT
Change from baseline

Fit Statistics

AICC (smaller is better)	66.3
BIC (smaller is better)	67.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	17.68	0.0005

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.88	2.38	0.1544
etime	3	33	1.64	0.2000
Occasion	1	9.86	5.31	0.0444
Treatment*etime	3	33	0.36	0.7799
preElecStairPDT	1	12.4	25.88	0.0002

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		0.3669	0.06840	19.4	5.36	<.0001	0.05
Treatment	Paracetamol		0.2309	0.06840	19.4	3.38	0.0031	0.05
Treatment*etime	Placebo	1:08:00	0.3123	0.09394	55	3.32	0.0016	0.05
Treatment*etime	Placebo	2:08:00	0.2864	0.09394	55	3.05	0.0035	0.05
Treatment*etime	Placebo	3:08:00	0.4444	0.09394	55	4.73	<.0001	0.05
Treatment*etime	Placebo	5:08:00	0.4246	0.09394	55	4.52	<.0001	0.05
Treatment*etime	Paracetamol	1:08:00	0.1466	0.09394	55	1.56	0.1244	0.05
Treatment*etime	Paracetamol	2:08:00	0.1994	0.09394	55	2.12	0.0383	0.05
Treatment*etime	Paracetamol	3:08:00	0.3464	0.09394	55	3.69	0.0005	0.05
Treatment*etime	Paracetamol	5:08:00	0.2313	0.09394	55	2.46	0.0170	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		0.2240	0.5099
Treatment	Paracetamol		0.08798	0.3739
Treatment*etime	Placebo	1:08:00	0.1241	0.5006
Treatment*etime	Placebo	2:08:00	0.09818	0.4747
Treatment*etime	Placebo	3:08:00	0.2561	0.6327
Treatment*etime	Placebo	5:08:00	0.2363	0.6128
Treatment*etime	Paracetamol	1:08:00	-0.04166	0.3349
Treatment*etime	Paracetamol	2:08:00	0.01115	0.3877
Treatment*etime	Paracetamol	3:08:00	0.1581	0.5347
Treatment*etime	Paracetamol	5:08:00	0.04306	0.4196

Electrical Stair PTT (mA)**SAS output 6.1 Electrical Stair PTT (mA)**

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Electrical Stair PTT

Model Information

Data Set	WORK.MIX
Dependent Variable	ElecStairPTT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kacker-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	73
Subjects	1
Max Obs Per Subject	92

Number of Observations

Number of Observations Read	92
Number of Observations Used	81
Number of Observations Not Used	11

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-44.84812379	
1	2	-96.07309002	0.00001049
2	1	-96.07430104	0.00000001

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.004190
Treatment*SubjectNr	0.01348
etime*SubjectNr	0.002290
Residual	0.004128

Fit Statistics

-2 Res Log Likelihood	-96.1
AIC (smaller is better)	-88.1

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Proc MIXED analysis of LOG Electrical Stair PTT

Fit Statistics

AICC (smaller is better)	-87.5
BIC (smaller is better)	-86.5

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	51.23	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	7.92	0.03	0.8759
etime	3	27	0.53	0.6684
Occasion	1	8.35	0.34	0.5765
Treatment*etime	3	27	1.00	0.4097
preElecStairPTT	1	11.2	91.41	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	0.008638	0.05356	7.92	0.16	0.8759	0.05	-0.1151	0.1324

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		3.0990	0.04249	16	72.93	<.0001	0.05
Treatment	Paracetamol		3.1076	0.04414	15.9	70.40	<.0001	0.05
Treatment*etime	Placebo	1:08:00	3.0940	0.04710	23.9	65.70	<.0001	0.05
Treatment*etime	Placebo	2:08:00	3.0946	0.04804	25.4	64.42	<.0001	0.05
Treatment*etime	Placebo	3:08:00	3.0934	0.04804	25.4	64.40	<.0001	0.05
Treatment*etime	Placebo	5:08:00	3.1138	0.04804	25.4	64.82	<.0001	0.05
Treatment*etime	Paracetamol	1:08:00	3.0699	0.04921	24.4	62.38	<.0001	0.05
Treatment*etime	Paracetamol	2:08:00	3.1121	0.04932	24.4	63.11	<.0001	0.05
Treatment*etime	Paracetamol	3:08:00	3.1366	0.04932	24.4	63.60	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		3.0089	3.1891
Treatment	Paracetamol		3.0140	3.2012
Treatment*etime	Placebo	1:08:00	2.9968	3.1913
Treatment*etime	Placebo	2:08:00	2.9958	3.1935
Treatment*etime	Placebo	3:08:00	2.9945	3.1923
Treatment*etime	Placebo	5:08:00	3.0149	3.2127
Treatment*etime	Paracetamol	1:08:00	2.9684	3.1714
Treatment*etime	Paracetamol	2:08:00	3.0104	3.2138
Treatment*etime	Paracetamol	3:08:00	3.0349	3.2383

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Proc MIXED analysis of LOG Electrical Stair PTT

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	5:08:00	3.1118	0.04932	24.4	63.10	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	5:08:00	3.0101	3.2135

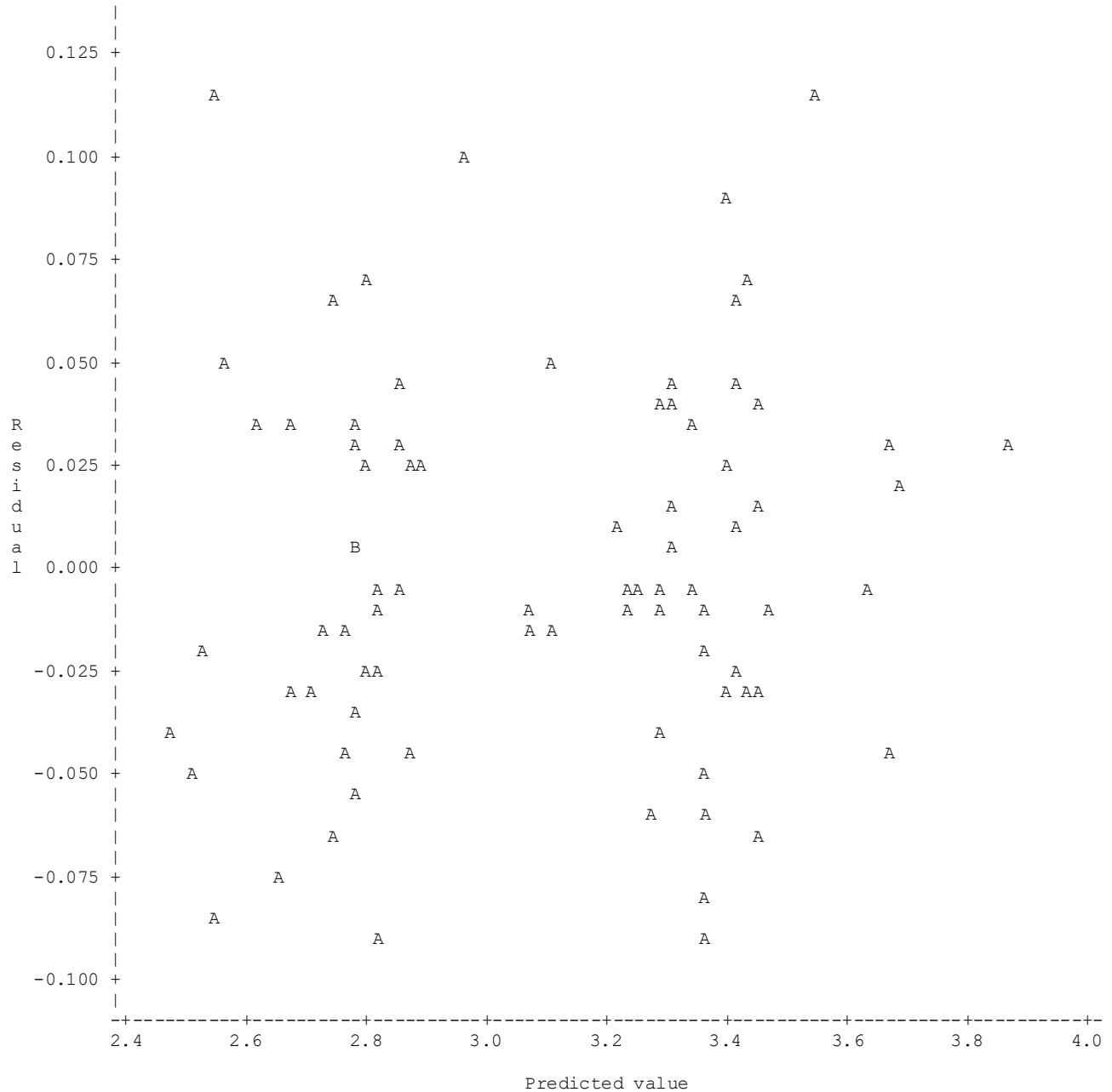
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Electrical Stair PTT

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



NOTE: 11 obs had missing values.

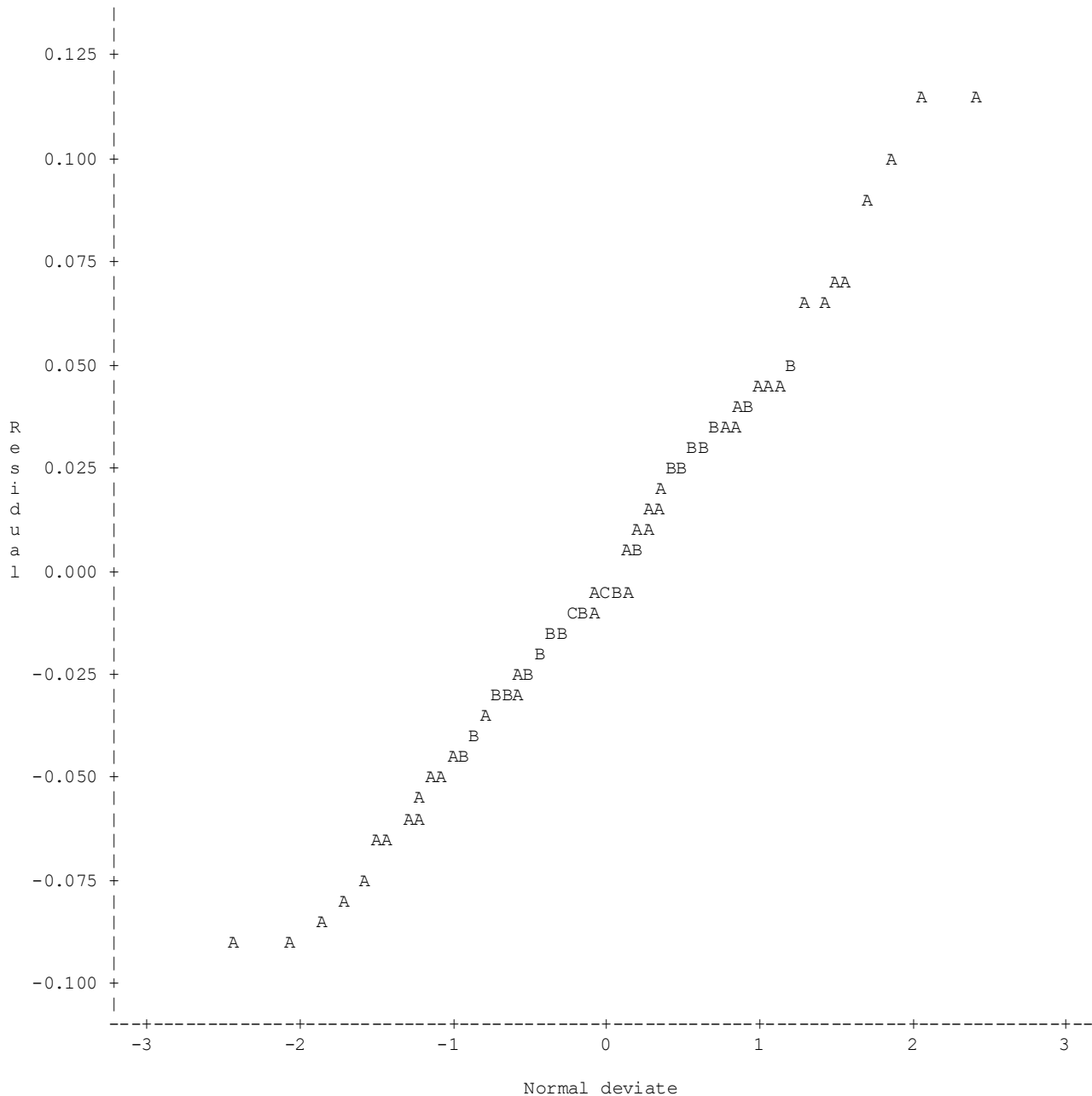
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Proc MIXED analysis of LOG Electrical Stair PTT

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.984 : P-value= 0.434)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



NOTE: 11 obs had missing values.

SAS output 6.2 Electrical Stair PTT (mA) change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Electrical Stair PTT
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaElecStairPTT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske- Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	73
Subjects	1
Max Obs Per Subject	92

Number of Observations

Number of Observations Read	92
Number of Observations Used	81
Number of Observations Not Used	11

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-44.84812379	
1	2	-96.07309002	0.00001049
2	1	-96.07430104	0.00000001

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.004190
Treatment*SubjectNr	0.01348
etime*SubjectNr	0.002290
Residual	0.004128

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Proc MIXED analysis of LOG Electrical Stair PTT
Change from baseline

Fit Statistics

-2 Res Log Likelihood	-96.1
AIC (smaller is better)	-88.1
AICC (smaller is better)	-87.5
BIC (smaller is better)	-86.5

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	51.23	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	7.92	0.03	0.8759
etime	3	27	0.53	0.6684
Occasion	1	8.35	0.34	0.5765
Treatment*etime	3	27	1.00	0.4097
preElecStairPTT	1	11.2	0.74	0.4086

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		0.08844	0.04249	16	2.08	0.0538	0.05
Treatment	Paracetamol		0.09708	0.04414	15.9	2.20	0.0430	0.05
Treatment*etime	Placebo	1:08:00	0.08351	0.04710	23.9	1.77	0.0890	0.05
Treatment*etime	Placebo	2:08:00	0.08410	0.04804	25.4	1.75	0.0921	0.05
Treatment*etime	Placebo	3:08:00	0.08287	0.04804	25.4	1.73	0.0966	0.05
Treatment*etime	Placebo	5:08:00	0.1033	0.04804	25.4	2.15	0.0413	0.05
Treatment*etime	Paracetamol	1:08:00	0.05937	0.04921	24.4	1.21	0.2392	0.05
Treatment*etime	Paracetamol	2:08:00	0.1016	0.04932	24.4	2.06	0.0502	0.05
Treatment*etime	Paracetamol	3:08:00	0.1261	0.04932	24.4	2.56	0.0172	0.05
Treatment*etime	Paracetamol	5:08:00	0.1012	0.04932	24.4	2.05	0.0509	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.00165	0.1785
Treatment	Paracetamol		0.003443	0.1907
Treatment*etime	Placebo	1:08:00	-0.01372	0.1807
Treatment*etime	Placebo	2:08:00	-0.01476	0.1830
Treatment*etime	Placebo	3:08:00	-0.01598	0.1817
Treatment*etime	Placebo	5:08:00	0.004418	0.2021
Treatment*etime	Paracetamol	1:08:00	-0.04211	0.1609
Treatment*etime	Paracetamol	2:08:00	-0.00009	0.2033
Treatment*etime	Paracetamol	3:08:00	0.02439	0.2278
Treatment*etime	Paracetamol	5:08:00	-0.00045	0.2029

Delta Electrical Stair AUC (mA*%)**SAS output 7.1 Delta Electrical Stair AUC (mA*%)**

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Proc MIXED analysis of Delta Electrical Stair AUC

Model Information

Data Set	WORK.MIX
Dependent Variable	dElecStairAUC
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:21 2:21 3:21 5:21
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	94

Number of Observations

Number of Observations Read	94
Number of Observations Used	94
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1215.64724487	
1	3	1211.64050235	0.00006266
2	1	1211.60503302	0.00000089
3	1	1211.60456008	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-10125
Treatment*SubjectNr	25280
etime*SubjectNr	-2237.08
Residual	61020

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Proc MIXED analysis of Delta Electrical Stair AUC

Fit Statistics

-2 Res Log Likelihood	1211.6
AIC (smaller is better)	1219.6
AICC (smaller is better)	1220.1
BIC (smaller is better)	1221.5

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	4.04	0.2569

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	6.73	0.05	0.8349
etime	3	32.8	0.23	0.8771
Occasion	1	6.89	1.42	0.2728
Treatment*etime	3	33.6	1.08	0.3708
predElecStairAUC	1	10.6	6.77	0.0253

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	17.9511	82.8323	6.73	0.22	0.8349	0.05	-179.51	215.42

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-199.93	49.9349	15.3	-4.00	0.0011	0.05
Treatment	Paracetamol		-181.98	50.7337	16.1	-3.59	0.0024	0.05
Treatment*etime	Placebo	1:21:00	-178.95	78.5331	62.3	-2.28	0.0261	0.05
Treatment*etime	Placebo	2:21:00	-224.20	78.5331	62.3	-2.85	0.0058	0.05
Treatment*etime	Placebo	3:21:00	-227.98	78.5331	62.3	-2.90	0.0051	0.05
Treatment*etime	Placebo	5:21:00	-168.59	78.5331	62.3	-2.15	0.0357	0.05
Treatment*etime	Paracetamol	1:21:00	-252.97	78.5377	62.4	-3.22	0.0020	0.05
Treatment*etime	Paracetamol	2:21:00	-120.20	78.5377	62.4	-1.53	0.1310	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-306.16	-93.7037
Treatment	Paracetamol		-289.47	-74.4923
Treatment*etime	Placebo	1:21:00	-335.92	-21.9826
Treatment*etime	Placebo	2:21:00	-381.17	-67.2326
Treatment*etime	Placebo	3:21:00	-384.94	-71.0076
Treatment*etime	Placebo	5:21:00	-325.56	-11.6243
Treatment*etime	Paracetamol	1:21:00	-409.95	-95.9969
Treatment*etime	Paracetamol	2:21:00	-277.18	36.7781

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Proc MIXED analysis of Delta Electrical Stair AUC

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	3:21:00	-112.11	78.5377	62.4	-1.43	0.1584	0.05
Treatment*etime	Paracetamol	5:21:00	-242.63	86.2217	69.1	-2.81	0.0064	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	3:21:00	-269.08	44.8697
Treatment*etime	Paracetamol	5:21:00	-414.64	-70.6305

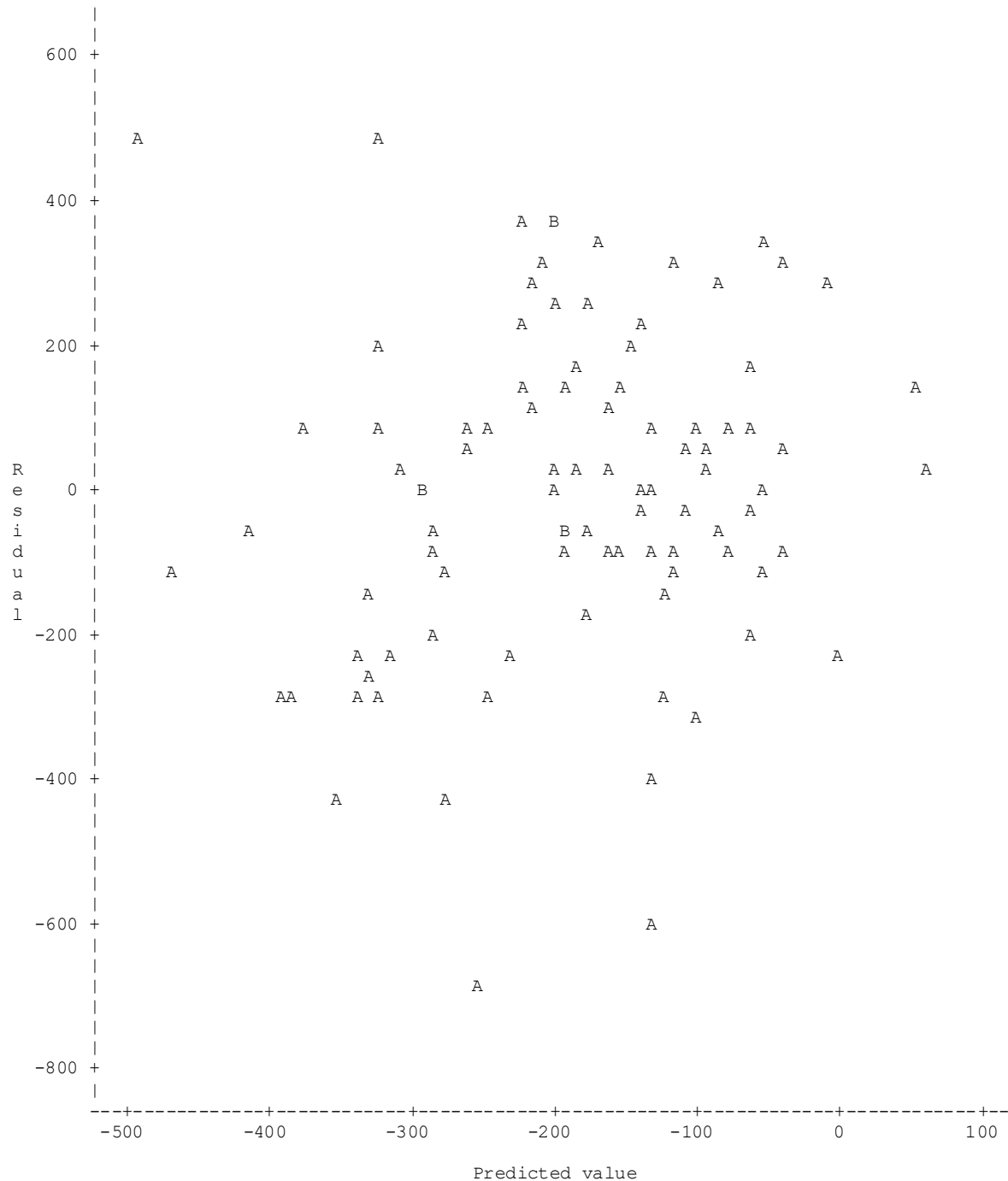
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Delta Electrical Stair AUC

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



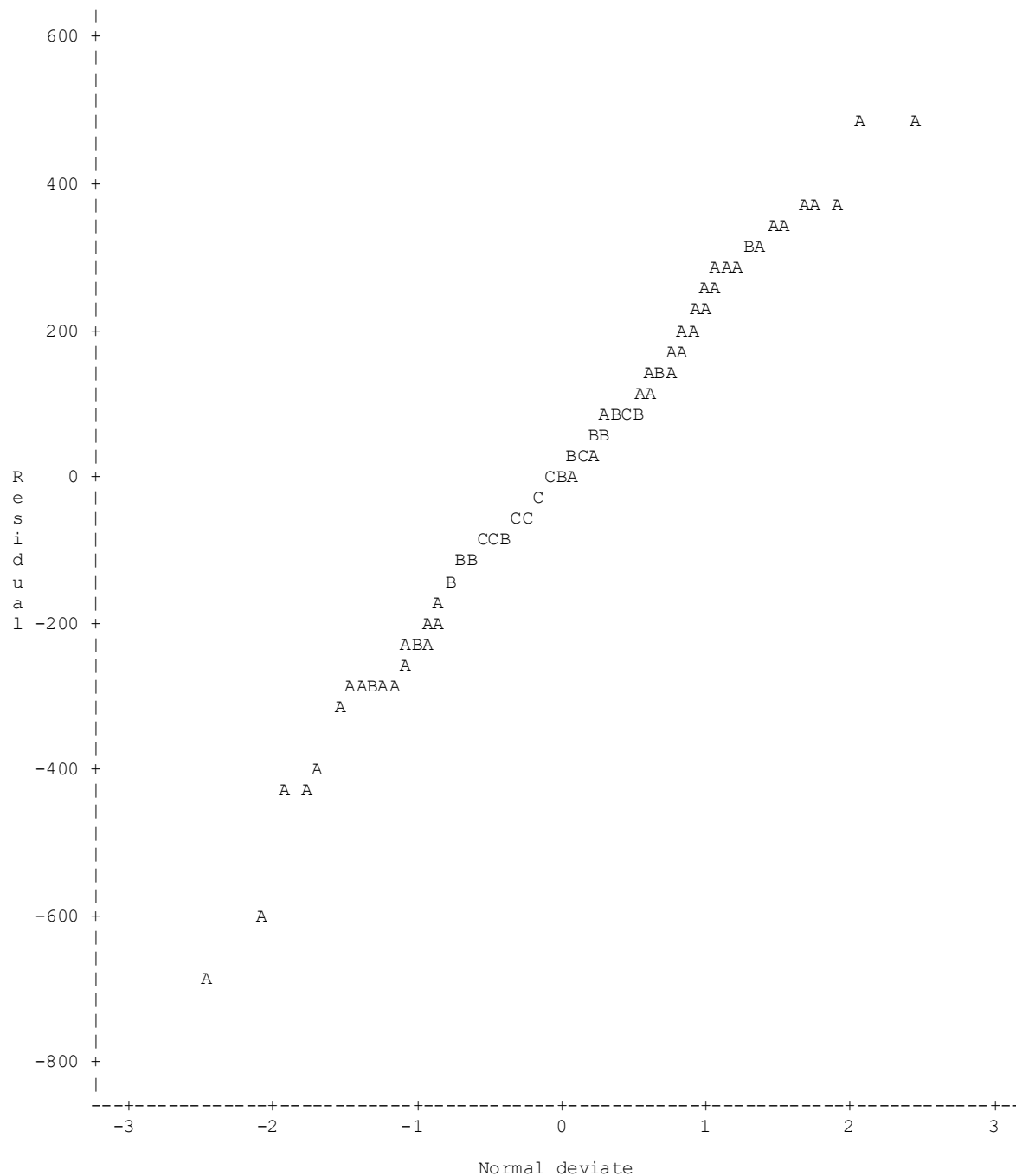
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Proc MIXED analysis of Delta Electrical Stair AUC

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.986 : P-value= 0.434)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 7.2 Delta Electrical Stair AUC (mA*%) change from baseline

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Proc MIXED analysis of Delta Electrical Stair AUC
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltadElecStairAUC
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:21 2:21 3:21 5:21
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	94

Number of Observations

Number of Observations Read	94
Number of Observations Used	94
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1215.64724487	
1	3	1211.64050235	0.00006266
2	1	1211.60503302	0.00000089
3	1	1211.60456008	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-10125
Treatment*SubjectNr	25280
etime*SubjectNr	-2237.08
Residual	61020

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Proc MIXED analysis of Delta Electrical Stair AUC
Change from baseline

Fit Statistics

-2 Res Log Likelihood	1211.6
AIC (smaller is better)	1219.6
AICC (smaller is better)	1220.1
BIC (smaller is better)	1221.5

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	4.04	0.2569

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	6.73	0.05	0.8349
etime	3	32.8	0.23	0.8771
Occasion	1	6.89	1.42	0.2728
Treatment*etime	3	33.6	1.08	0.3708
predElecStairAUC	1	10.6	20.67	0.0009

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		48.2807	49.9349	15.3	0.97	0.3486	0.05
Treatment	Paracetamol		66.2318	50.7337	16.1	1.31	0.2101	0.05
Treatment*etime	Placebo	1:21:00	69.2599	78.5331	62.3	0.88	0.3812	0.05
Treatment*etime	Placebo	2:21:00	24.0099	78.5331	62.3	0.31	0.7608	0.05
Treatment*etime	Placebo	3:21:00	20.2349	78.5331	62.3	0.26	0.7975	0.05
Treatment*etime	Placebo	5:21:00	79.6182	78.5331	62.3	1.01	0.3146	0.05
Treatment*etime	Paracetamol	1:21:00	-4.7634	78.5377	62.4	-0.06	0.9518	0.05
Treatment*etime	Paracetamol	2:21:00	128.01	78.5377	62.4	1.63	0.1082	0.05
Treatment*etime	Paracetamol	3:21:00	136.10	78.5377	62.4	1.73	0.0880	0.05
Treatment*etime	Paracetamol	5:21:00	5.5757	86.2217	69.1	0.06	0.9486	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-57.9455	154.51
Treatment	Paracetamol		-41.2547	173.72
Treatment*etime	Placebo	1:21:00	-87.7082	226.23
Treatment*etime	Placebo	2:21:00	-132.96	180.98
Treatment*etime	Placebo	3:21:00	-136.73	177.20
Treatment*etime	Placebo	5:21:00	-77.3499	236.59
Treatment*etime	Paracetamol	1:21:00	-161.74	152.21
Treatment*etime	Paracetamol	2:21:00	-28.9654	284.99
Treatment*etime	Paracetamol	3:21:00	-20.8738	293.08
Treatment*etime	Paracetamol	5:21:00	-166.43	177.58

Delta Electrical Stair PDT (mA)**SAS output 8.1 Delta Electrical Stair PDT (mA)**

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Proc MIXED analysis of Delta Electrical Stair PDT

Model Information

Data Set	WORK.MIX
Dependent Variable	dElecStairPDT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:21 2:21 3:21 5:21
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	94

Number of Observations

Number of Observations Read	94
Number of Observations Used	94
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	465.53107896	
1	2	464.01275925	0.00000026
2	1	464.01271912	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-0.5535
Treatment*SubjectNr	1.6790
etime*SubjectNr	-0.4246
Residual	9.9081

Fit Statistics

-2 Res Log Likelihood	464.0
AIC (smaller is better)	472.0

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Proc MIXED analysis of Delta Electrical Stair PDT

Fit Statistics

AICC (smaller is better)	472.5
BIC (smaller is better)	474.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	1.52	0.6780

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.02	0.13	0.7308
etime	3	31.5	0.42	0.7418
Occasion	1	9.44	0.15	0.7038
Treatment*etime	3	32.9	0.17	0.9170
predElecStairPDT	1	18.3	6.06	0.0240

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	0.3030	0.8537	9.02	0.35	0.7308	0.05	-1.6278	2.2338

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		1.5124	0.5448	18.8	2.78	0.0121	0.05
Treatment	Paracetamol		1.8154	0.5569	19.9	3.26	0.0039	0.05
Treatment*etime	Placebo	1:21:00	1.6603	0.9431	77.7	1.76	0.0823	0.05
Treatment*etime	Placebo	2:21:00	1.0936	0.9431	77.7	1.16	0.2498	0.05
Treatment*etime	Placebo	3:21:00	1.3603	0.9431	77.7	1.44	0.1532	0.05
Treatment*etime	Placebo	5:21:00	1.9353	0.9431	77.7	2.05	0.0435	0.05
Treatment*etime	Paracetamol	1:21:00	1.2071	0.9434	77.7	1.28	0.2045	0.05
Treatment*etime	Paracetamol	2:21:00	1.7488	0.9434	77.7	1.85	0.0676	0.05
Treatment*etime	Paracetamol	3:21:00	1.6738	0.9434	77.7	1.77	0.0800	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		0.3712	2.6536
Treatment	Paracetamol		0.6533	2.9775
Treatment*etime	Placebo	1:21:00	-0.2174	3.5381
Treatment*etime	Placebo	2:21:00	-0.7841	2.9714
Treatment*etime	Placebo	3:21:00	-0.5174	3.2381
Treatment*etime	Placebo	5:21:00	0.05755	3.8131
Treatment*etime	Paracetamol	1:21:00	-0.6712	3.0855
Treatment*etime	Paracetamol	2:21:00	-0.1296	3.6271
Treatment*etime	Paracetamol	3:21:00	-0.2046	3.5521

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Proc MIXED analysis of Delta Electrical Stair PDT

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	5:21:00	2.6319	1.0425	79.7	2.52	0.0136	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	5:21:00	0.5572	4.7066

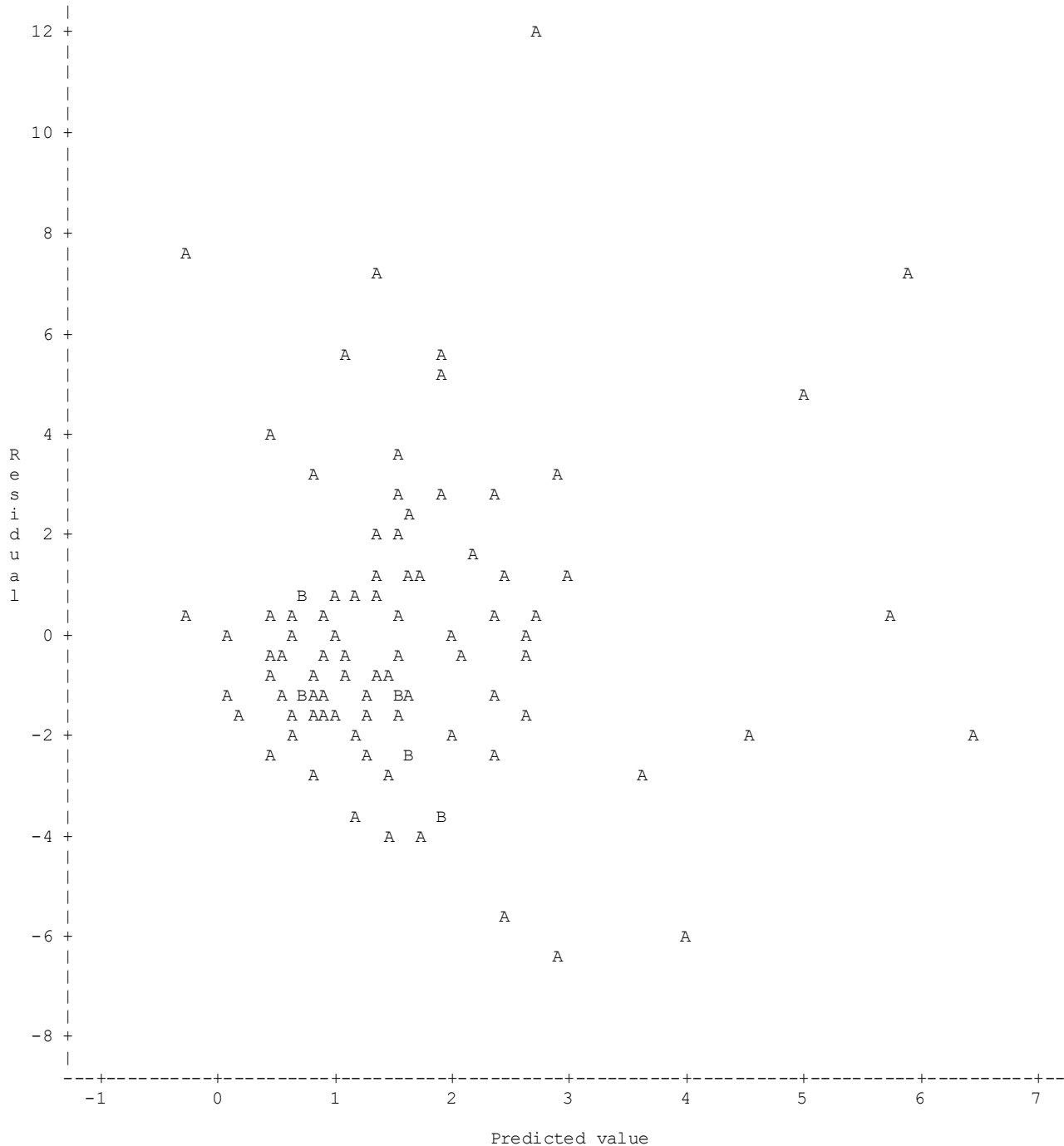
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Proc MIXED analysis of Delta Electrical Stair PDT

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



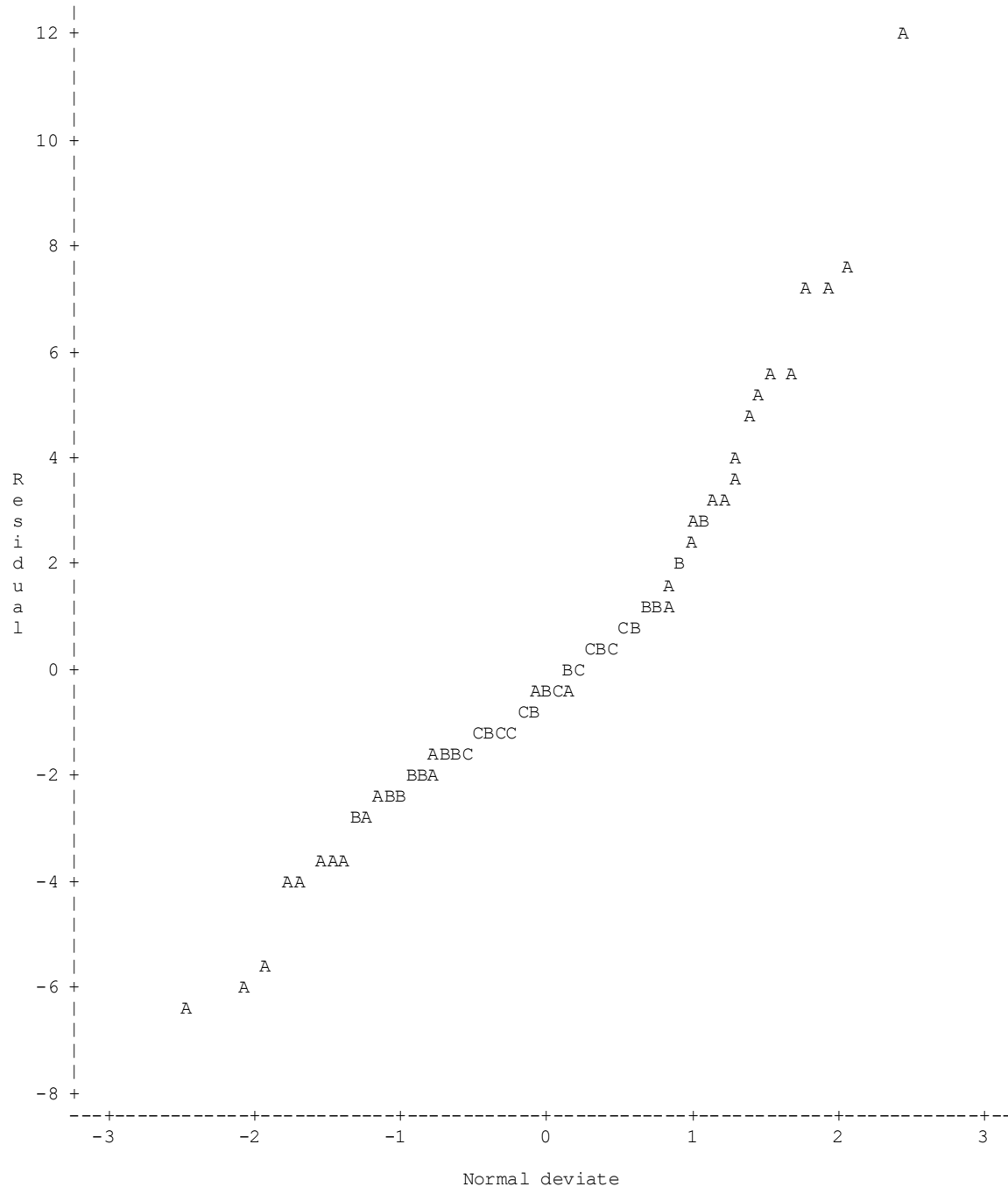
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Proc MIXED analysis of Delta Electrical Stair PDT

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.922 : P-value=<0.001)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 8.2 Delta Electrical Stair PDT (mA) change from baseline

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Proc MIXED analysis of Delta Electrical Stair PDT
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltadElecStairPDT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:21 2:21 3:21 5:21
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	94

Number of Observations

Number of Observations Read	94
Number of Observations Used	94
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	465.53107896	
1	2	464.01275925	0.00000026
2	1	464.01271912	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-0.5535
Treatment*SubjectNr	1.6790
etime*SubjectNr	-0.4246
Residual	9.9081

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Proc MIXED analysis of Delta Electrical Stair PDT
Change from baseline

Fit Statistics

-2 Res Log Likelihood	464.0
AIC (smaller is better)	472.0
AICC (smaller is better)	472.5
BIC (smaller is better)	474.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	1.52	0.6780

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.02	0.13	0.7308
etime	3	31.5	0.42	0.7418
Occasion	1	9.44	0.15	0.7038
Treatment*etime	3	32.9	0.17	0.9170
predElecStairPDT	1	18.3	23.78	0.0001

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-0.4387	0.5448	18.8	-0.81	0.4308	0.05
Treatment	Paracetamol		-0.1357	0.5569	19.9	-0.24	0.8100	0.05
Treatment*etime	Placebo	1:21:00	-0.2908	0.9431	77.7	-0.31	0.7587	0.05
Treatment*etime	Placebo	2:21:00	-0.8574	0.9431	77.7	-0.91	0.3661	0.05
Treatment*etime	Placebo	3:21:00	-0.5908	0.9431	77.7	-0.63	0.5329	0.05
Treatment*etime	Placebo	5:21:00	-0.01575	0.9431	77.7	-0.02	0.9867	0.05
Treatment*etime	Paracetamol	1:21:00	-0.7439	0.9434	77.7	-0.79	0.4328	0.05
Treatment*etime	Paracetamol	2:21:00	-0.2023	0.9434	77.7	-0.21	0.8308	0.05
Treatment*etime	Paracetamol	3:21:00	-0.2773	0.9434	77.7	-0.29	0.7696	0.05
Treatment*etime	Paracetamol	5:21:00	0.6809	1.0425	79.7	0.65	0.5156	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-1.5799	0.7025
Treatment	Paracetamol		-1.2978	1.0265
Treatment*etime	Placebo	1:21:00	-2.1685	1.5870
Treatment*etime	Placebo	2:21:00	-2.7352	1.0203
Treatment*etime	Placebo	3:21:00	-2.4685	1.2870
Treatment*etime	Placebo	5:21:00	-1.8935	1.8620
Treatment*etime	Paracetamol	1:21:00	-2.6223	1.1344
Treatment*etime	Paracetamol	2:21:00	-2.0806	1.6761
Treatment*etime	Paracetamol	3:21:00	-2.1556	1.6011
Treatment*etime	Paracetamol	5:21:00	-1.3938	2.7556

Delta Electrical Stair PTT (mA)**SAS output 9.1 Delta Electrical Stair PTT (mA)**

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Proc MIXED analysis of Delta Electrical Stair PTT

Model Information

Data Set	WORK.MIX
Dependent Variable	dElecStairPTT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:21 2:21 3:21 5:21
Occasion	2	1 2
SubjectNr	10	2 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	70
Subjects	1
Max Obs Per Subject	87

Number of Observations

Number of Observations Read	87
Number of Observations Used	79
Number of Observations Not Used	8

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	361.98984792	
1	2	360.01659787	0.00000003
2	1	360.01659489	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.8262
Treatment*SubjectNr	-0.1976
etime*SubjectNr	0.3158
Residual	6.5389

Fit Statistics

-2 Res Log Likelihood	360.0
AIC (smaller is better)	368.0

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Proc MIXED analysis of Delta Electrical Stair PTT

Fit Statistics

AICC (smaller is better)	368.6
BIC (smaller is better)	369.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	1.97	0.5780

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.57	0.79	0.3993
etime	3	27.3	0.89	0.4577
Occasion	1	10.2	0.01	0.9347
Treatment*etime	3	27.1	1.55	0.2244
predElecStairPTT	1	16.3	0.31	0.5850

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	-0.5049	0.5692	8.57	-0.89	0.3993	0.05	-1.8023	0.7926

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		1.7539	0.4910	14.3	3.57	0.0030	0.05
Treatment	Paracetamol		1.2491	0.4986	14.9	2.51	0.0244	0.05
Treatment*etime	Placebo	1:21:00	1.3639	0.8690	63.1	1.57	0.1215	0.05
Treatment*etime	Placebo	2:21:00	1.9439	0.8690	63.1	2.24	0.0288	0.05
Treatment*etime	Placebo	3:21:00	1.8939	0.8690	63.1	2.18	0.0330	0.05
Treatment*etime	Placebo	5:21:00	1.8139	0.8690	63.1	2.09	0.0409	0.05
Treatment*etime	Paracetamol	1:21:00	2.1761	0.8690	63.1	2.50	0.0149	0.05
Treatment*etime	Paracetamol	2:21:00	1.2661	0.8690	63.1	1.46	0.1501	0.05
Treatment*etime	Paracetamol	3:21:00	-0.5439	0.8690	63.1	-0.63	0.5337	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		0.7030	2.8049
Treatment	Paracetamol		0.1856	2.3126
Treatment*etime	Placebo	1:21:00	-0.3726	3.1004
Treatment*etime	Placebo	2:21:00	0.2074	3.6804
Treatment*etime	Placebo	3:21:00	0.1574	3.6304
Treatment*etime	Placebo	5:21:00	0.07745	3.5504
Treatment*etime	Paracetamol	1:21:00	0.4396	3.9126
Treatment*etime	Paracetamol	2:21:00	-0.4704	3.0026
Treatment*etime	Paracetamol	3:21:00	-2.2804	1.1926

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Proc MIXED analysis of Delta Electrical Stair PTT

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	5:21:00	2.0979	0.9251	64	2.27	0.0267	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	5:21:00	0.2498	3.9460

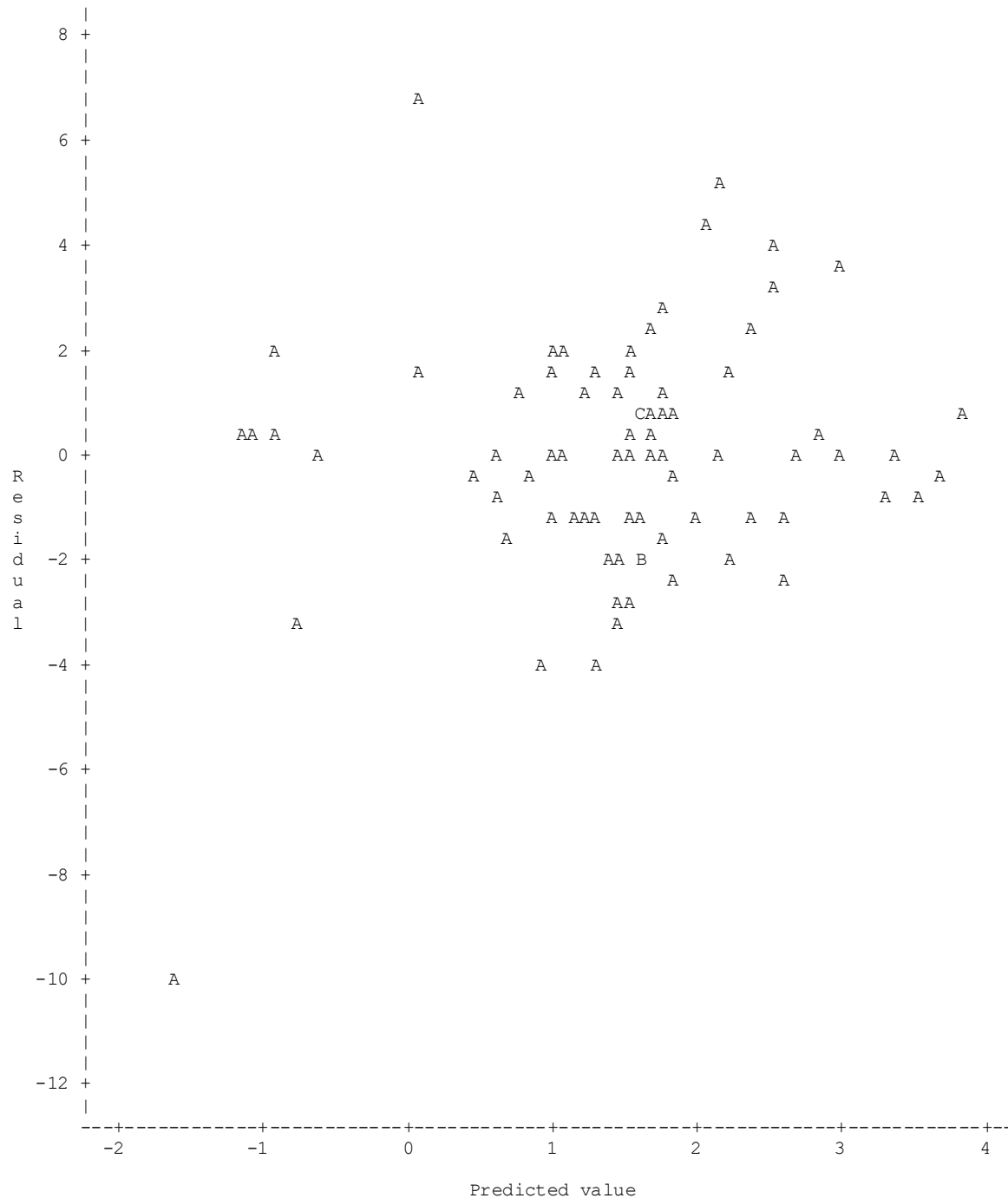
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Proc MIXED analysis of Delta Electrical Stair PTT

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



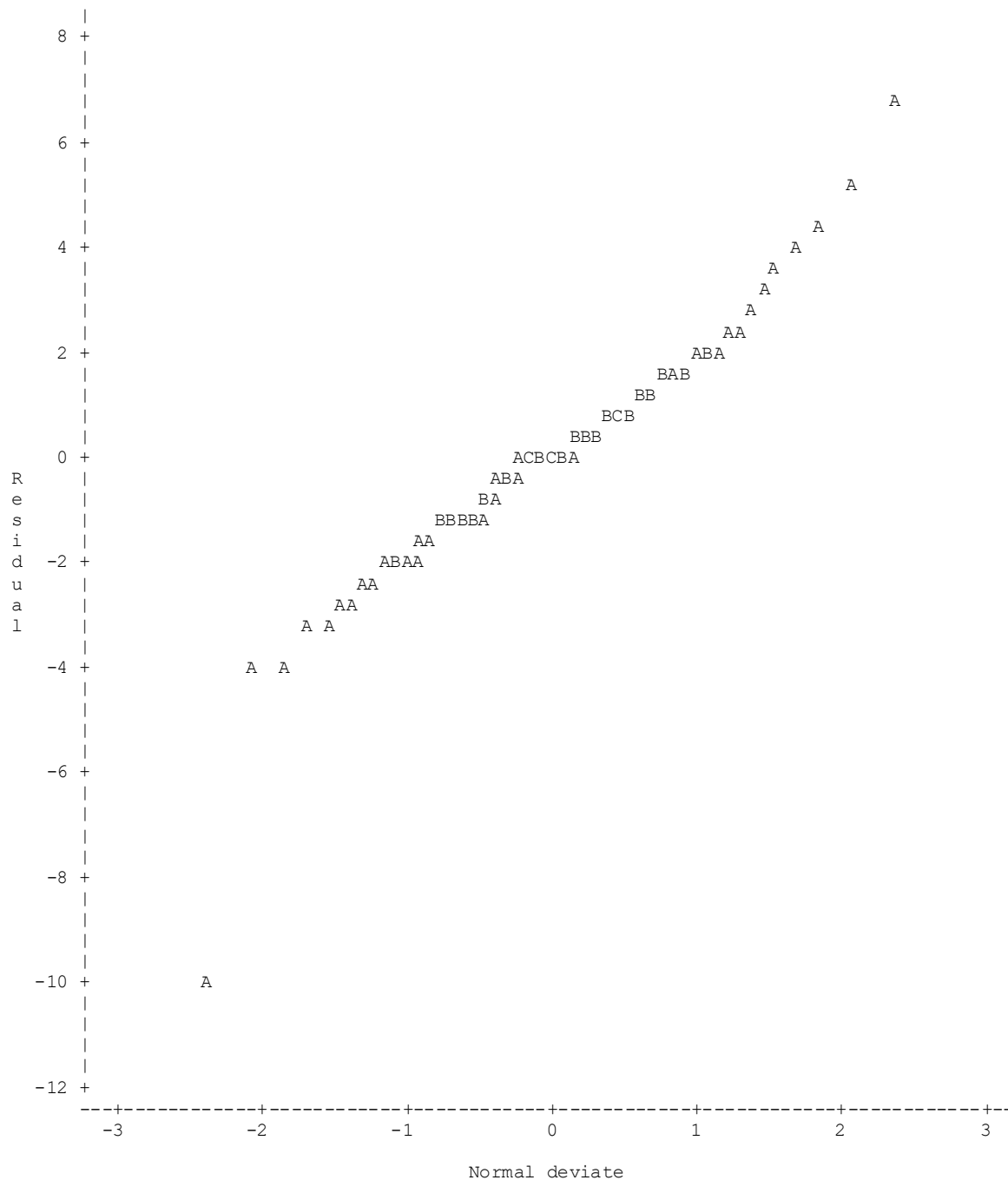
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Proc MIXED analysis of Delta Electrical Stair PTT

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.937 : P-value=<0.001)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



NOTE: 8 obs had missing values.

SAS output 9.2 Delta Electrical Stair PTT (mA) change from baseline

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Proc MIXED analysis of Delta Electrical Stair PTT
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltadElecStairPTT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:21 2:21 3:21 5:21
Occasion	2	1 2
SubjectNr	10	2 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	70
Subjects	1
Max Obs Per Subject	87

Number of Observations

Number of Observations Read	87
Number of Observations Used	79
Number of Observations Not Used	8

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	361.98984792	
1	2	360.01659787	0.00000003
2	1	360.01659489	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.8262
Treatment*SubjectNr	-0.1976
etime*SubjectNr	0.3158
Residual	6.5389

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Proc MIXED analysis of Delta Electrical Stair PTT
Change from baseline

Fit Statistics

-2 Res Log Likelihood	360.0
AIC (smaller is better)	368.0
AICC (smaller is better)	368.6
BIC (smaller is better)	369.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	1.97	0.5780

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.57	0.79	0.3993
etime	3	27.3	0.89	0.4577
Occasion	1	10.2	0.01	0.9347
Treatment*etime	3	27.1	1.55	0.2244
predElecStairPTT	1	16.3	33.51	<.0001

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-0.2714	0.4910	14.3	-0.55	0.5890	0.05
Treatment	Paracetamol		-0.7762	0.4986	14.9	-1.56	0.1405	0.05
Treatment*etime	Placebo	1:21:00	-0.6614	0.8690	63.1	-0.76	0.4494	0.05
Treatment*etime	Placebo	2:21:00	-0.08138	0.8690	63.1	-0.09	0.9257	0.05
Treatment*etime	Placebo	3:21:00	-0.1314	0.8690	63.1	-0.15	0.8803	0.05
Treatment*etime	Placebo	5:21:00	-0.2114	0.8690	63.1	-0.24	0.8086	0.05
Treatment*etime	Paracetamol	1:21:00	0.1508	0.8690	63.1	0.17	0.8628	0.05
Treatment*etime	Paracetamol	2:21:00	-0.7592	0.8690	63.1	-0.87	0.3856	0.05
Treatment*etime	Paracetamol	3:21:00	-2.5692	0.8690	63.1	-2.96	0.0044	0.05
Treatment*etime	Paracetamol	5:21:00	0.07261	0.9251	64	0.08	0.9377	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-1.3223	0.7795
Treatment	Paracetamol		-1.8398	0.2873
Treatment*etime	Placebo	1:21:00	-2.3979	1.0751
Treatment*etime	Placebo	2:21:00	-1.8179	1.6551
Treatment*etime	Placebo	3:21:00	-1.8679	1.6051
Treatment*etime	Placebo	5:21:00	-1.9479	1.5251
Treatment*etime	Paracetamol	1:21:00	-1.5857	1.8873
Treatment*etime	Paracetamol	2:21:00	-2.4957	0.9773
Treatment*etime	Paracetamol	3:21:00	-4.3057	-0.8327
Treatment*etime	Paracetamol	5:21:00	-1.7755	1.9207

Pressure AUC (kPa*%)**SAS output 10.1 Pressure AUC (kPa*%)**

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Proc MIXED analysis of Pressure AUC

Model Information

Data Set	WORK.MIX
Dependent Variable	PressureAUC
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1406.73391501	
1	2	1380.37245047	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-43514
Treatment*SubjectNr	284381
etime*SubjectNr	39399
Residual	192746

Fit Statistics

-2 Res Log Likelihood	1380.4
AIC (smaller is better)	1388.4
AICC (smaller is better)	1388.9

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Proc MIXED analysis of Pressure AUC

Fit Statistics

BIC (smaller is better) 1390.3

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	26.36	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	10	4.03	0.0726
etime	3	33	2.56	0.0715
Occasion	1	10.1	1.33	0.2758
Treatment*etime	3	33	0.19	0.9035
prePressureAUC	1	11.8	157.63	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	-476.53	237.47	10	-2.01	0.0726	0.05	-1005.63	52.5653

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		6732.93	158.59	19.7	42.46	<.0001	0.05
Treatment	Paracetamol		6256.40	158.59	19.7	39.45	<.0001	0.05
Treatment*etime	Placebo	1:13:00	6996.86	199.15	44.5	35.13	<.0001	0.05
Treatment*etime	Placebo	2:13:00	6643.33	199.15	44.5	33.36	<.0001	0.05
Treatment*etime	Placebo	3:13:00	6634.64	199.15	44.5	33.32	<.0001	0.05
Treatment*etime	Placebo	5:13:00	6656.88	199.15	44.5	33.43	<.0001	0.05
Treatment*etime	Paracetamol	1:13:00	6494.54	199.15	44.5	32.61	<.0001	0.05
Treatment*etime	Paracetamol	2:13:00	6253.80	199.15	44.5	31.40	<.0001	0.05
Treatment*etime	Paracetamol	3:13:00	6190.96	199.15	44.5	31.09	<.0001	0.05
Treatment*etime	Paracetamol	5:13:00	6086.28	199.15	44.5	30.56	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		6401.84	7064.02
Treatment	Paracetamol		5925.31	6587.49
Treatment*etime	Placebo	1:13:00	6595.65	7398.08
Treatment*etime	Placebo	2:13:00	6242.11	7044.54
Treatment*etime	Placebo	3:13:00	6233.42	7035.85
Treatment*etime	Placebo	5:13:00	6255.66	7058.09
Treatment*etime	Paracetamol	1:13:00	6093.32	6895.75
Treatment*etime	Paracetamol	2:13:00	5852.59	6655.02
Treatment*etime	Paracetamol	3:13:00	5789.75	6592.18
Treatment*etime	Paracetamol	5:13:00	5685.06	6487.50

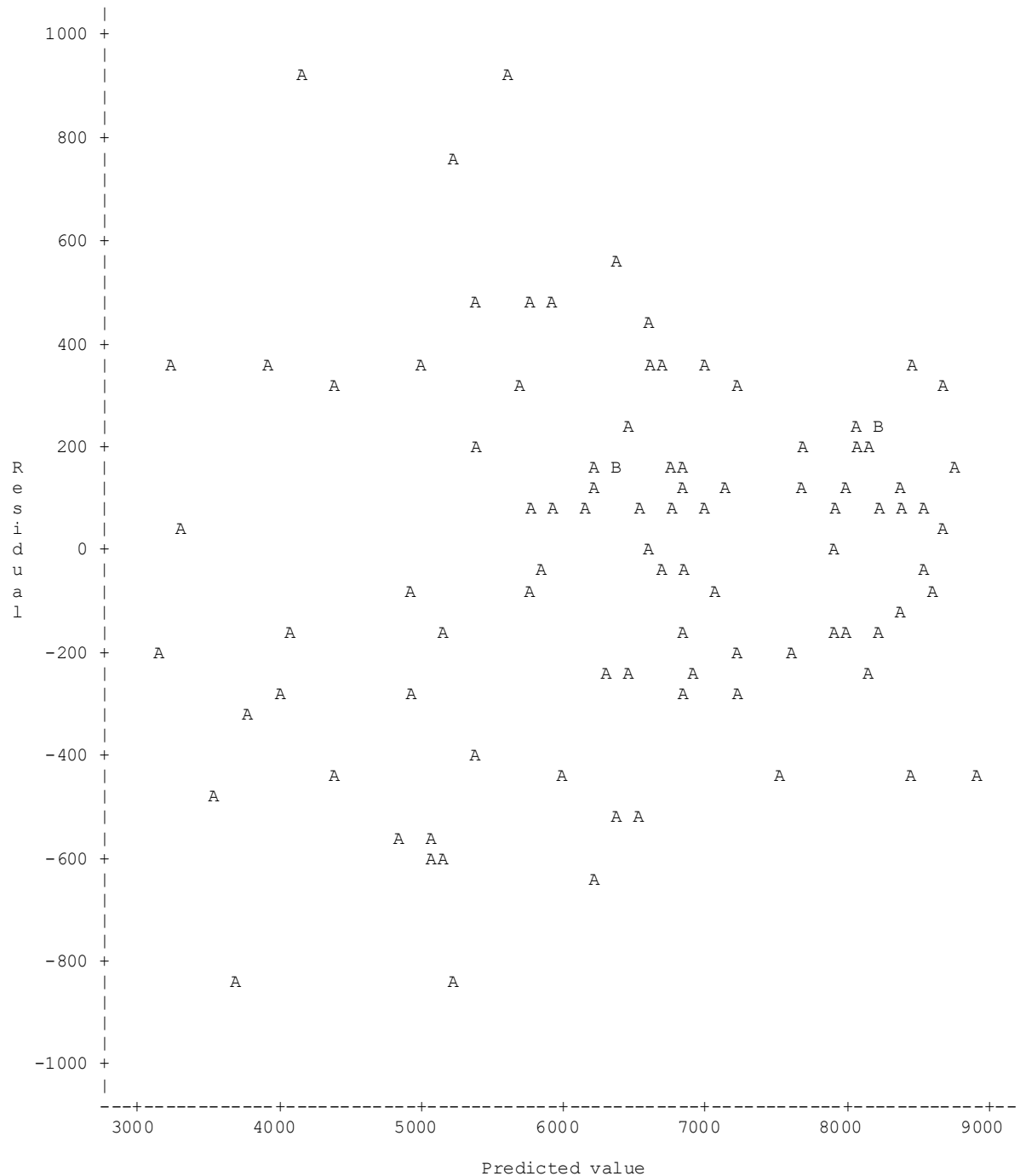
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Proc MIXED analysis of Pressure AUC

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



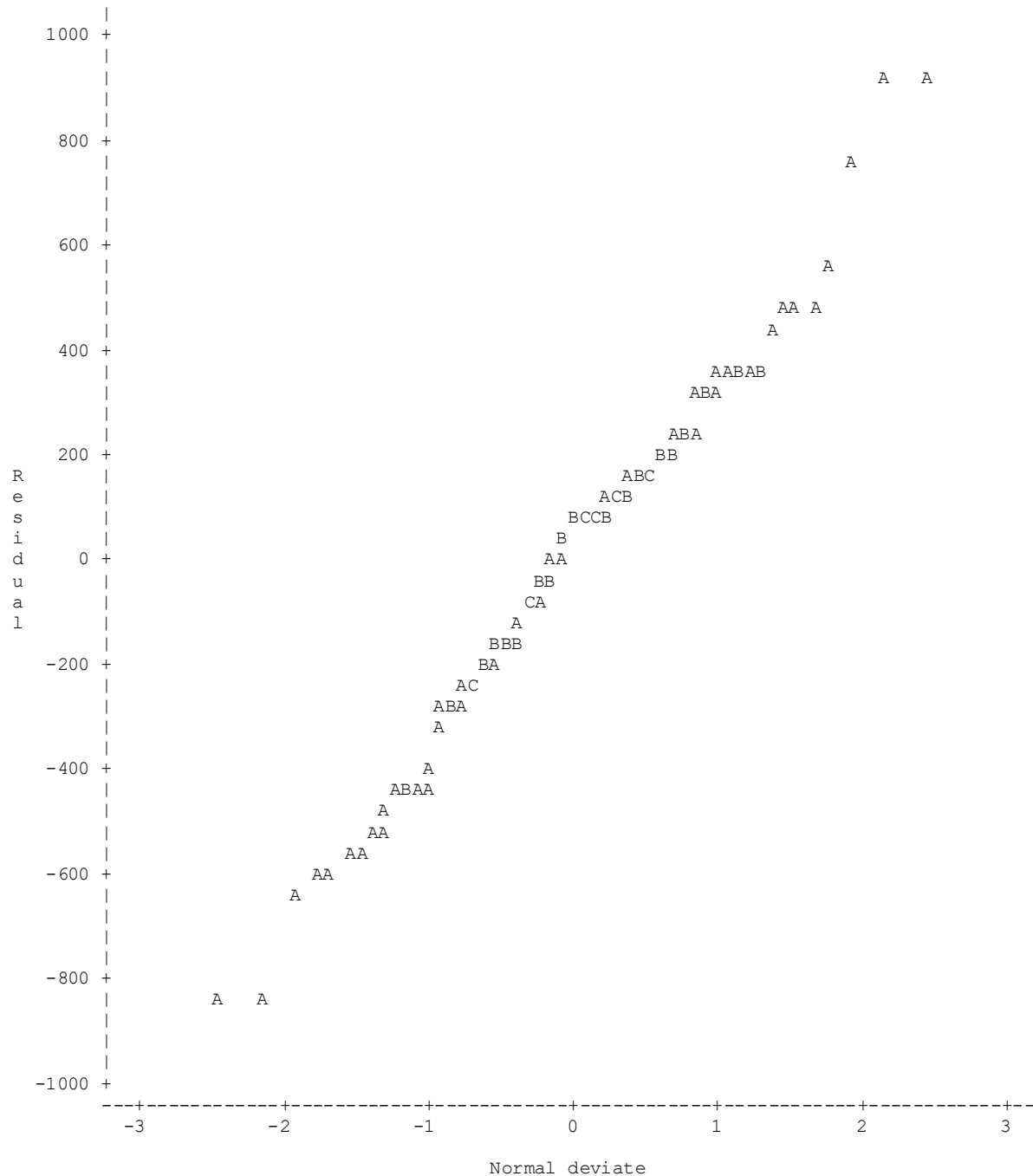
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Proc MIXED analysis of Pressure AUC

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.986 : P-value= 0.430)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 10.2 Pressure AUC (kPa*%) change from baseline

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Proc MIXED analysis of Pressure AUC
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaPressureAUC
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1406.73391501	
1	2	1380.37245047	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-43514
Treatment*SubjectNr	284381
etime*SubjectNr	39399
Residual	192746

Fit Statistics

-2 Res Log Likelihood	1380.4
AIC (smaller is better)	1388.4

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Proc MIXED analysis of Pressure AUC
Change from baseline

Fit Statistics

AICC (smaller is better) 1388.9
BIC (smaller is better) 1390.3

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	26.36	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	10	4.03	0.0726
etime	3	33	2.56	0.0715
Occasion	1	10.1	1.33	0.2758
Treatment*etime	3	33	0.19	0.9035
prePressureAUC	1	11.8	0.03	0.8594

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-125.34	158.59	19.7	-0.79	0.4387	0.05
Treatment	Paracetamol		-601.87	158.59	19.7	-3.80	0.0012	0.05
Treatment*etime	Placebo	1:13:00	138.60	199.15	44.5	0.70	0.4901	0.05
Treatment*etime	Placebo	2:13:00	-214.94	199.15	44.5	-1.08	0.2863	0.05
Treatment*etime	Placebo	3:13:00	-223.63	199.15	44.5	-1.12	0.2675	0.05
Treatment*etime	Placebo	5:13:00	-201.39	199.15	44.5	-1.01	0.3174	0.05
Treatment*etime	Paracetamol	1:13:00	-363.73	199.15	44.5	-1.83	0.0745	0.05
Treatment*etime	Paracetamol	2:13:00	-604.46	199.15	44.5	-3.04	0.0040	0.05
Treatment*etime	Paracetamol	3:13:00	-667.30	199.15	44.5	-3.35	0.0016	0.05
Treatment*etime	Paracetamol	5:13:00	-771.99	199.15	44.5	-3.88	0.0003	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-456.43	205.75
Treatment	Paracetamol		-932.96	-270.78
Treatment*etime	Placebo	1:13:00	-262.62	539.81
Treatment*etime	Placebo	2:13:00	-616.15	186.28
Treatment*etime	Placebo	3:13:00	-624.85	177.59
Treatment*etime	Placebo	5:13:00	-602.60	199.83
Treatment*etime	Paracetamol	1:13:00	-764.94	37.4868
Treatment*etime	Paracetamol	2:13:00	-1005.68	-203.25
Treatment*etime	Paracetamol	3:13:00	-1068.52	-266.09
Treatment*etime	Paracetamol	5:13:00	-1173.20	-370.77

Pressure PDT (kPa)**SAS output 11.1 Pressure PDT (kPa)**

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Proc MIXED analysis of LOG Pressure PDT

Model Information

Data Set	WORK.MIX
Dependent Variable	PressurePDT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	50.86078020	
1	2	42.26099421	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.000281
Treatment*SubjectNr	0.02264
etime*SubjectNr	0.005574
Residual	0.05094

Fit Statistics

-2 Res Log Likelihood	42.3
AIC (smaller is better)	50.3
AICC (smaller is better)	50.8

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Proc MIXED analysis of LOG Pressure PDT

Fit Statistics

BIC (smaller is better) 52.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	8.60	0.0351

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.81	4.29	0.0656
etime	3	33	3.24	0.0343
Occasion	1	11.6	1.03	0.3310
Treatment*etime	3	33	3.22	0.0352
prePressurePDT	1	13.4	105.89	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	0.1609	0.07766	9.81	2.07	0.0656	0.05	-0.01257	0.3344

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		2.7019	0.05587	20	48.36	<.0001	0.05
Treatment	Paracetamol		2.8628	0.05587	20	51.24	<.0001	0.05
Treatment*etime	Placebo	1:13:00	2.7374	0.08157	65.3	33.56	<.0001	0.05
Treatment*etime	Placebo	2:13:00	2.6525	0.08157	65.3	32.52	<.0001	0.05
Treatment*etime	Placebo	3:13:00	2.6509	0.08157	65.3	32.50	<.0001	0.05
Treatment*etime	Placebo	5:13:00	2.7668	0.08157	65.3	33.92	<.0001	0.05
Treatment*etime	Paracetamol	1:13:00	2.6581	0.08157	65.3	32.59	<.0001	0.05
Treatment*etime	Paracetamol	2:13:00	2.8980	0.08157	65.3	35.53	<.0001	0.05
Treatment*etime	Paracetamol	3:13:00	2.8395	0.08157	65.3	34.81	<.0001	0.05
Treatment*etime	Paracetamol	5:13:00	3.0555	0.08157	65.3	37.46	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		2.5853	2.8184
Treatment	Paracetamol		2.7462	2.9793
Treatment*etime	Placebo	1:13:00	2.5745	2.9003
Treatment*etime	Placebo	2:13:00	2.4896	2.8153
Treatment*etime	Placebo	3:13:00	2.4880	2.8138
Treatment*etime	Placebo	5:13:00	2.6039	2.9296
Treatment*etime	Paracetamol	1:13:00	2.4952	2.8210
Treatment*etime	Paracetamol	2:13:00	2.7351	3.0609
Treatment*etime	Paracetamol	3:13:00	2.6766	3.0024
Treatment*etime	Paracetamol	5:13:00	2.8926	3.2184

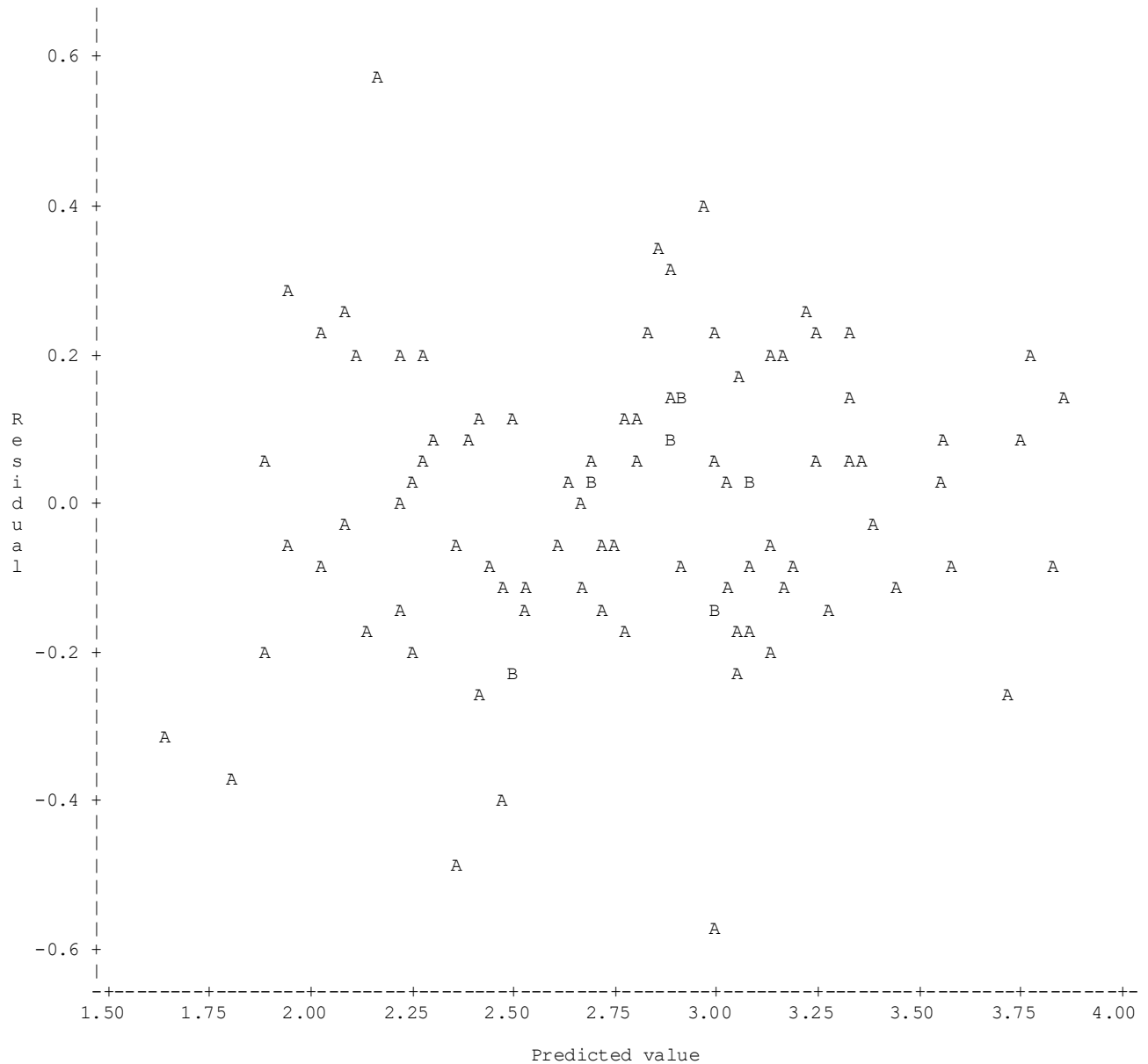
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Pressure PDT

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



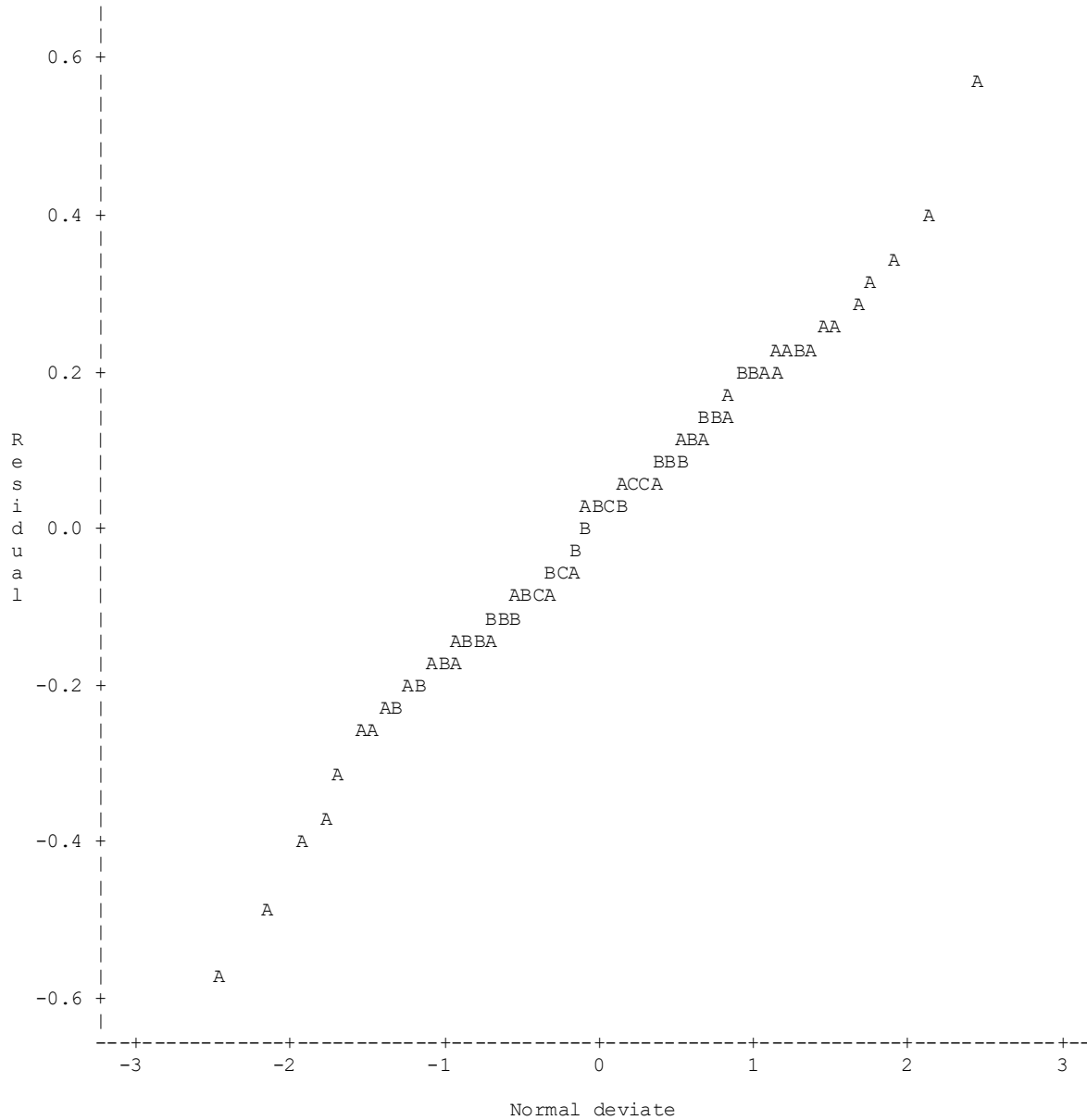
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Proc MIXED analysis of LOG Pressure PDT

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.990 : P-value= 0.672)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 11.2 Pressure PDT (kPa) change from baseline

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Proc MIXED analysis of LOG Pressure PDT
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaPressurePDT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	50.86078020	
1	2	42.26099421	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.000281
Treatment*SubjectNr	0.02264
etime*SubjectNr	0.005574
Residual	0.05094

Fit Statistics

-2 Res Log Likelihood	42.3
AIC (smaller is better)	50.3

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Proc MIXED analysis of LOG Pressure PDT
Change from baseline

Fit Statistics

AICC (smaller is better)	50.8
BIC (smaller is better)	52.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	8.60	0.0351

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.81	4.29	0.0656
etime	3	33	3.24	0.0343
Occasion	1	11.6	1.03	0.3310
Treatment*etime	3	33	3.22	0.0352
prePressurePDT	1	13.4	5.37	0.0368

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		0.1078	0.05587	20	1.93	0.0679	0.05
Treatment	Paracetamol		0.2687	0.05587	20	4.81	0.0001	0.05
Treatment*etime	Placebo	1:13:00	0.1434	0.08157	65.3	1.76	0.0835	0.05
Treatment*etime	Placebo	2:13:00	0.05839	0.08157	65.3	0.72	0.4767	0.05
Treatment*etime	Placebo	3:13:00	0.05685	0.08157	65.3	0.70	0.4883	0.05
Treatment*etime	Placebo	5:13:00	0.1727	0.08157	65.3	2.12	0.0381	0.05
Treatment*etime	Paracetamol	1:13:00	0.06407	0.08157	65.3	0.79	0.4350	0.05
Treatment*etime	Paracetamol	2:13:00	0.3039	0.08157	65.3	3.73	0.0004	0.05
Treatment*etime	Paracetamol	3:13:00	0.2455	0.08157	65.3	3.01	0.0037	0.05
Treatment*etime	Paracetamol	5:13:00	0.4614	0.08157	65.3	5.66	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.00873	0.2244
Treatment	Paracetamol		0.1522	0.3853
Treatment*etime	Placebo	1:13:00	-0.01954	0.3062
Treatment*etime	Placebo	2:13:00	-0.1045	0.2213
Treatment*etime	Placebo	3:13:00	-0.1060	0.2197
Treatment*etime	Placebo	5:13:00	0.009806	0.3356
Treatment*etime	Paracetamol	1:13:00	-0.09882	0.2270
Treatment*etime	Paracetamol	2:13:00	0.1410	0.4668
Treatment*etime	Paracetamol	3:13:00	0.08258	0.4084
Treatment*etime	Paracetamol	5:13:00	0.2985	0.6243

Pressure PTT (kPa)**SAS output 12.1 Pressure PTT (kPa)**

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Proc MIXED analysis of LOG Pressure PTT

Model Information

Data Set	WORK.MIX
Dependent Variable	PressurePTT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1.52000808	
1	2	-48.54212771	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.003449
Treatment*SubjectNr	0.02661
etime*SubjectNr	0.006394
Residual	0.009605

Fit Statistics

-2 Res Log Likelihood	-48.5
AIC (smaller is better)	-40.5
AICC (smaller is better)	-40.0

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Proc MIXED analysis of LOG Pressure PTT

Fit Statistics

BIC (smaller is better) -38.6

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	50.06	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.83	0.22	0.6460
etime	3	33	0.43	0.7315
Occasion	1	9.73	0.57	0.4684
Treatment*etime	3	33	0.21	0.8886
prePressurePTT	1	11.8	104.65	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	0.03320	0.07008	9.83	0.47	0.6460	0.05	-0.1233	0.1897

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		3.7511	0.05345	19.6	70.18	<.0001	0.05
Treatment	Paracetamol		3.7843	0.05345	19.6	70.80	<.0001	0.05
Treatment*etime	Placebo	1:13:00	3.7109	0.06210	34.2	59.75	<.0001	0.05
Treatment*etime	Placebo	2:13:00	3.7609	0.06210	34.2	60.56	<.0001	0.05
Treatment*etime	Placebo	3:13:00	3.7583	0.06210	34.2	60.52	<.0001	0.05
Treatment*etime	Placebo	5:13:00	3.7744	0.06210	34.2	60.78	<.0001	0.05
Treatment*etime	Paracetamol	1:13:00	3.7676	0.06210	34.2	60.67	<.0001	0.05
Treatment*etime	Paracetamol	2:13:00	3.7772	0.06210	34.2	60.82	<.0001	0.05
Treatment*etime	Paracetamol	3:13:00	3.7967	0.06210	34.2	61.13	<.0001	0.05
Treatment*etime	Paracetamol	5:13:00	3.7958	0.06210	34.2	61.12	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		3.6395	3.8628
Treatment	Paracetamol		3.6727	3.8960
Treatment*etime	Placebo	1:13:00	3.5847	3.8370
Treatment*etime	Placebo	2:13:00	3.6347	3.8871
Treatment*etime	Placebo	3:13:00	3.6321	3.8844
Treatment*etime	Placebo	5:13:00	3.6483	3.9006
Treatment*etime	Paracetamol	1:13:00	3.6415	3.8938
Treatment*etime	Paracetamol	2:13:00	3.6510	3.9034
Treatment*etime	Paracetamol	3:13:00	3.6705	3.9228
Treatment*etime	Paracetamol	5:13:00	3.6696	3.9220

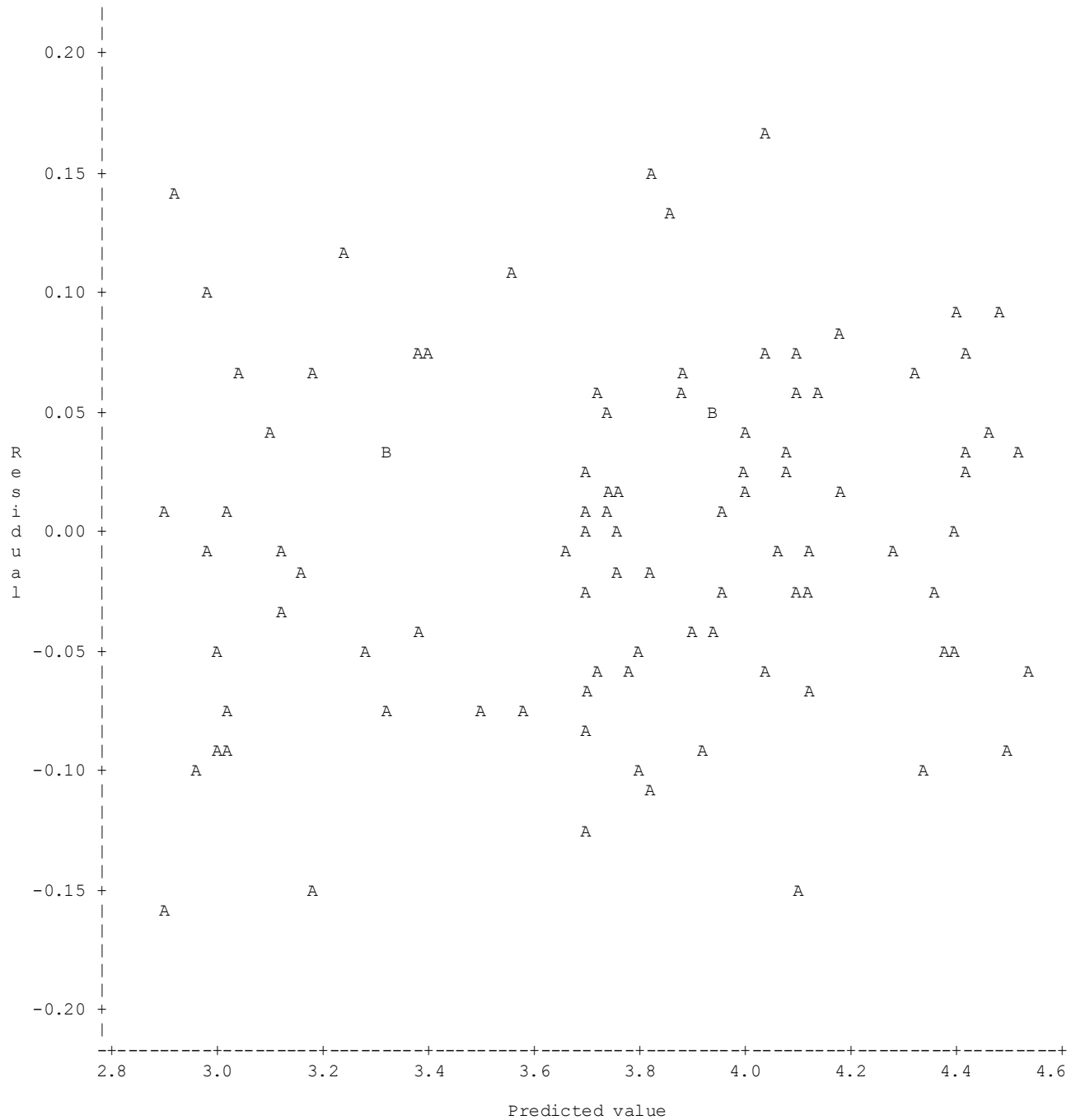
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Pressure PTT

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



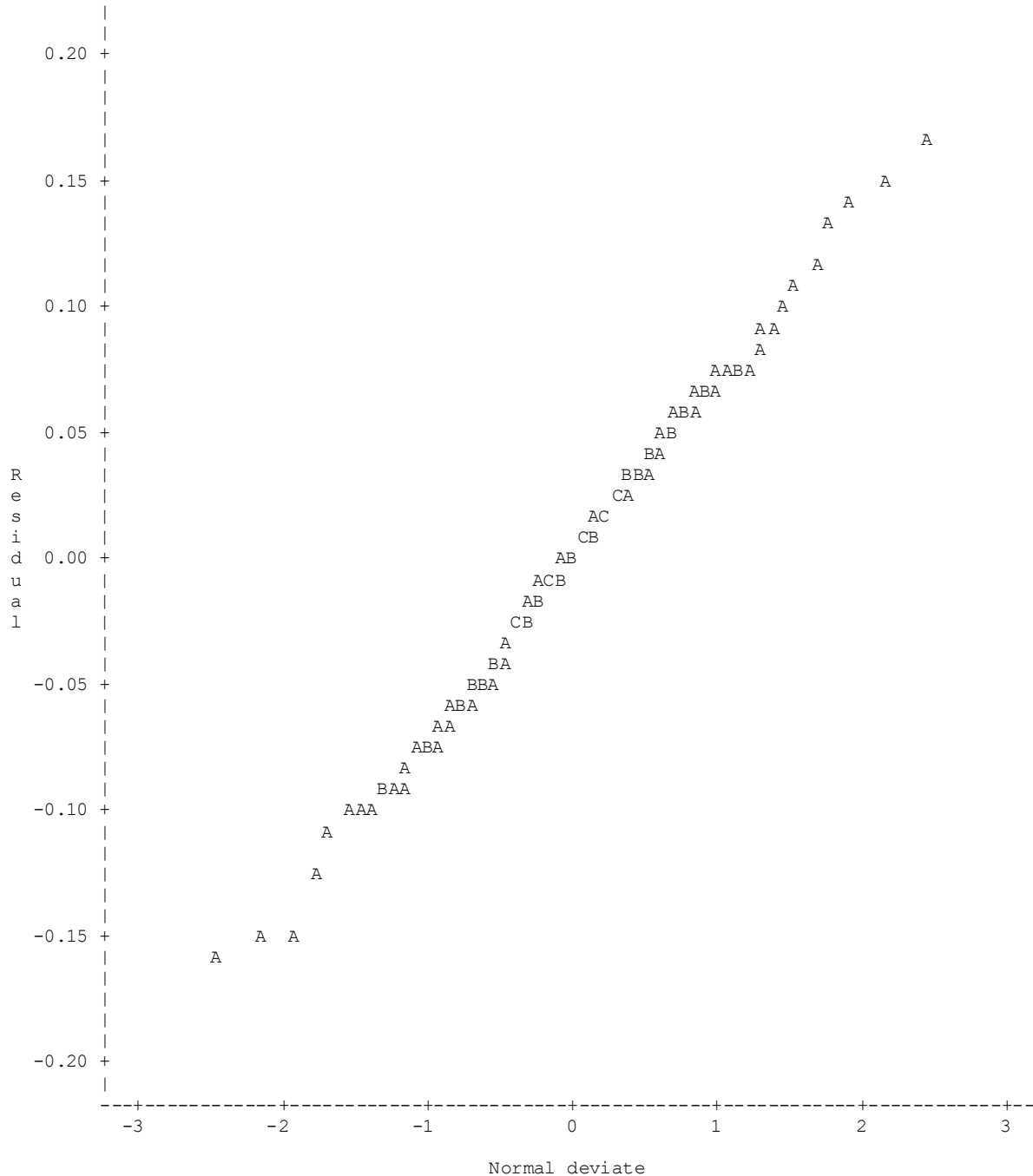
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Pressure PTT

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.993 : P-value= 0.889)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 12.2 Pressure PTT (kPa) change from baseline

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Proc MIXED analysis of LOG Pressure PTT
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaPressurePTT
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1.52000808	
1	2	-48.54212771	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.003449
Treatment*SubjectNr	0.02661
etime*SubjectNr	0.006394
Residual	0.009605

Fit Statistics

-2 Res Log Likelihood	-48.5
AIC (smaller is better)	-40.5

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Proc MIXED analysis of LOG Pressure PTT
Change from baseline

Fit Statistics

AICC (smaller is better) -40.0
BIC (smaller is better) -38.6

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	50.06	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.83	0.22	0.6460
etime	3	33	0.43	0.7315
Occasion	1	9.73	0.57	0.4684
Treatment*etime	3	33	0.21	0.8886
prePressurePTT	1	11.8	1.68	0.2197

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		0.05971	0.05345	19.6	1.12	0.2775	0.05
Treatment	Paracetamol		0.09291	0.05345	19.6	1.74	0.0979	0.05
Treatment*etime	Placebo	1:13:00	0.01946	0.06210	34.2	0.31	0.7559	0.05
Treatment*etime	Placebo	2:13:00	0.06951	0.06210	34.2	1.12	0.2708	0.05
Treatment*etime	Placebo	3:13:00	0.06685	0.06210	34.2	1.08	0.2893	0.05
Treatment*etime	Placebo	5:13:00	0.08302	0.06210	34.2	1.34	0.1901	0.05
Treatment*etime	Paracetamol	1:13:00	0.07623	0.06210	34.2	1.23	0.2280	0.05
Treatment*etime	Paracetamol	2:13:00	0.08579	0.06210	34.2	1.38	0.1761	0.05
Treatment*etime	Paracetamol	3:13:00	0.1052	0.06210	34.2	1.69	0.0992	0.05
Treatment*etime	Paracetamol	5:13:00	0.1044	0.06210	34.2	1.68	0.1019	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.05194	0.1714
Treatment	Paracetamol		-0.01874	0.2046
Treatment*etime	Placebo	1:13:00	-0.1067	0.1456
Treatment*etime	Placebo	2:13:00	-0.05666	0.1957
Treatment*etime	Placebo	3:13:00	-0.05933	0.1930
Treatment*etime	Placebo	5:13:00	-0.04316	0.2092
Treatment*etime	Paracetamol	1:13:00	-0.04995	0.2024
Treatment*etime	Paracetamol	2:13:00	-0.04039	0.2120
Treatment*etime	Paracetamol	3:13:00	-0.02094	0.2314
Treatment*etime	Paracetamol	5:13:00	-0.02181	0.2305

Heat PDT (C)**SAS output 13.1 Heat PDT (C)**

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of LOG Heat PDT

Model Information

Data Set	WORK.MIX
Dependent Variable	QST_heat_thr
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:03 2:03 3:03 5:03
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-253.22040513	
1	2	-297.93379192	0.00000003
2	1	-297.93379918	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.000722
Treatment*SubjectNr	0.000858
etime*SubjectNr	-0.00016
Residual	0.001057

Fit Statistics

-2 Res Log Likelihood	-297.9
AIC (smaller is better)	-289.9

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Proc MIXED analysis of LOG Heat PDT

Fit Statistics

AICC (smaller is better)	-289.4
BIC (smaller is better)	-288.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	44.71	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.98	3.15	0.1096
etime	3	33	0.68	0.5734
Occasion	1	10.1	0.10	0.7535
Treatment*etime	3	33	0.19	0.8997
preQST_heat_thr	1	19.9	23.52	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	0.02429	0.01368	8.98	1.78	0.1096	0.05	-0.00667	0.05525

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		3.7061	0.01226	17.9	302.31	<.0001	0.05
Treatment	Paracetamol		3.7304	0.01226	17.9	304.29	<.0001	0.05
Treatment*etime	Placebo	1:03:00	3.7074	0.01436	32.4	258.21	<.0001	0.05
Treatment*etime	Placebo	2:03:00	3.7094	0.01436	32.4	258.35	<.0001	0.05
Treatment*etime	Placebo	3:03:00	3.7073	0.01436	32.4	258.21	<.0001	0.05
Treatment*etime	Placebo	5:03:00	3.7004	0.01436	32.4	257.73	<.0001	0.05
Treatment*etime	Paracetamol	1:03:00	3.7366	0.01436	32.4	260.25	<.0001	0.05
Treatment*etime	Paracetamol	2:03:00	3.7353	0.01436	32.4	260.16	<.0001	0.05
Treatment*etime	Paracetamol	3:03:00	3.7231	0.01436	32.4	259.31	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		3.6803	3.7319
Treatment	Paracetamol		3.7046	3.7562
Treatment*etime	Placebo	1:03:00	3.6782	3.7366
Treatment*etime	Placebo	2:03:00	3.6801	3.7386
Treatment*etime	Placebo	3:03:00	3.6781	3.7366
Treatment*etime	Placebo	5:03:00	3.6711	3.7296
Treatment*etime	Paracetamol	1:03:00	3.7073	3.7658
Treatment*etime	Paracetamol	2:03:00	3.7060	3.7645
Treatment*etime	Paracetamol	3:03:00	3.6939	3.7524

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Proc MIXED analysis of LOG Heat PDT

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	5:03:00	3.7267	0.01436	32.4	259.56	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	5:03:00	3.6975	3.7559

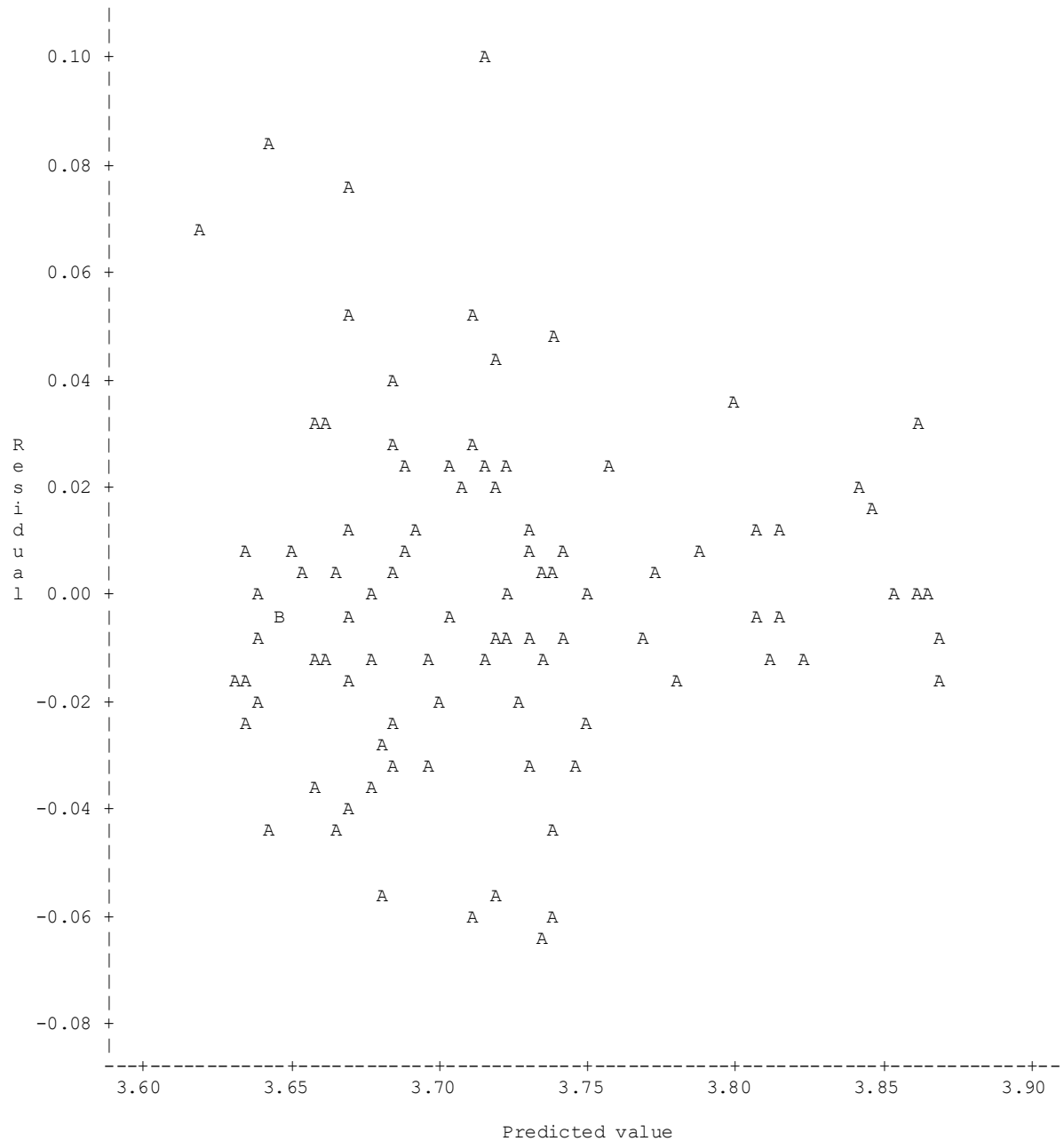
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Proc MIXED analysis of LOG Heat PDT

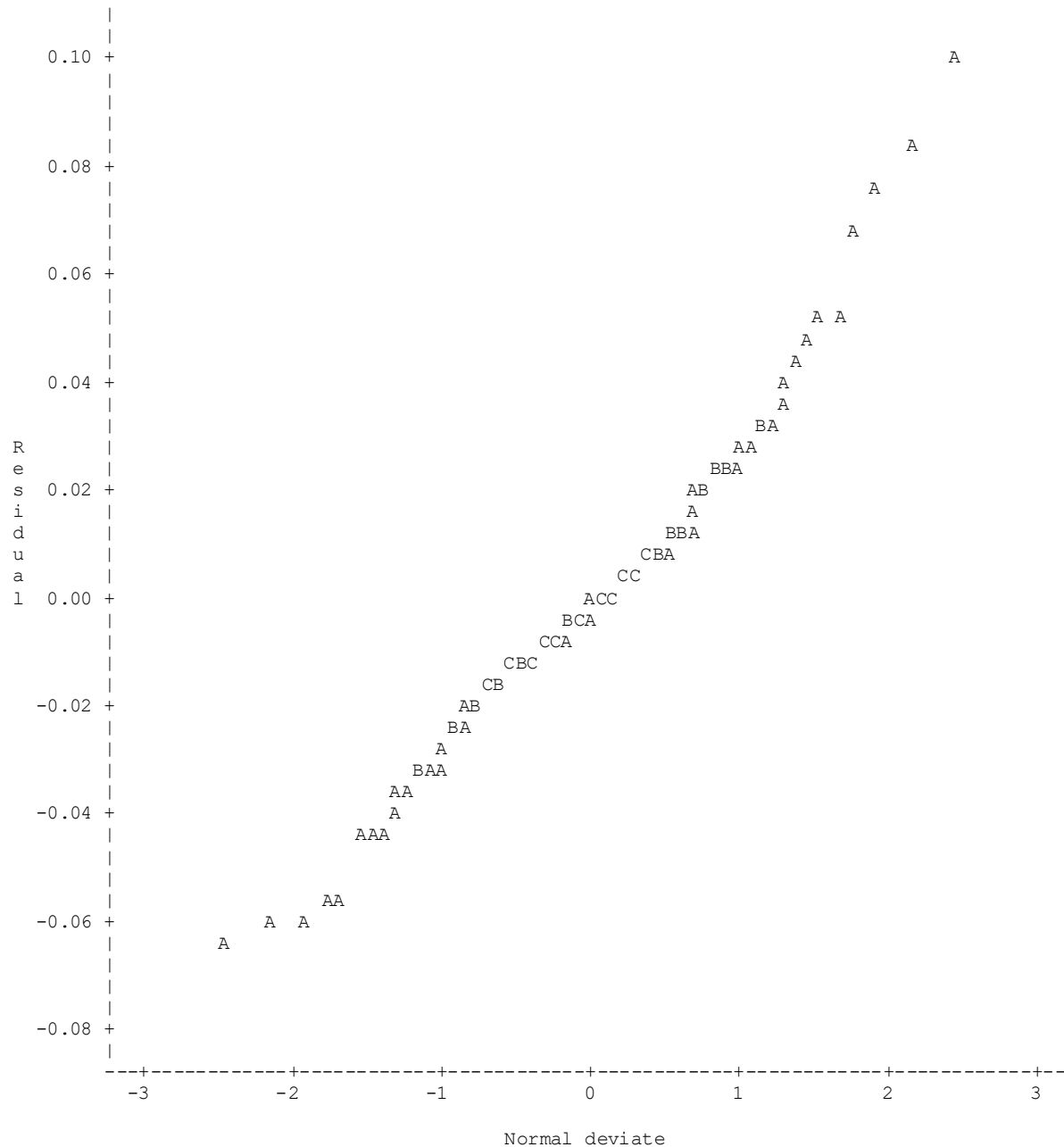
Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



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Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.971 : P-value= 0.032)
Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 13.2 Heat PDT (C) change from baseline

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Proc MIXED analysis of LOG Heat PDT
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaQST_heat_thr
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:03 2:03 3:03 5:03
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-253.22040513	
1	2	-297.93379192	0.00000003
2	1	-297.93379918	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.000722
Treatment*SubjectNr	0.000858
etime*SubjectNr	-0.00016
Residual	0.001057

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Proc MIXED analysis of LOG Heat PDT
Change from baseline

Fit Statistics

-2 Res Log Likelihood	-297.9
AIC (smaller is better)	-289.9
AICC (smaller is better)	-289.4
BIC (smaller is better)	-288.0

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	44.71	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.98	3.15	0.1096
etime	3	33	0.68	0.5734
Occasion	1	10.1	0.10	0.7535
Treatment*etime	3	33	0.19	0.8997
preQST_heat_thr	1	19.9	6.39	0.0201

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-0.01395	0.01226	17.9	-1.14	0.2703	0.05
Treatment	Paracetamol		0.01035	0.01226	17.9	0.84	0.4098	0.05
Treatment*etime	Placebo	1:03:00	-0.01268	0.01436	32.4	-0.88	0.3837	0.05
Treatment*etime	Placebo	2:03:00	-0.01071	0.01436	32.4	-0.75	0.4612	0.05
Treatment*etime	Placebo	3:03:00	-0.01272	0.01436	32.4	-0.89	0.3824	0.05
Treatment*etime	Placebo	5:03:00	-0.01969	0.01436	32.4	-1.37	0.1798	0.05
Treatment*etime	Paracetamol	1:03:00	0.01649	0.01436	32.4	1.15	0.2590	0.05
Treatment*etime	Paracetamol	2:03:00	0.01519	0.01436	32.4	1.06	0.2978	0.05
Treatment*etime	Paracetamol	3:03:00	0.003082	0.01436	32.4	0.21	0.8314	0.05
Treatment*etime	Paracetamol	5:03:00	0.006618	0.01436	32.4	0.46	0.6479	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.03972	0.01182
Treatment	Paracetamol		-0.01542	0.03612
Treatment*etime	Placebo	1:03:00	-0.04191	0.01655
Treatment*etime	Placebo	2:03:00	-0.03994	0.01853
Treatment*etime	Placebo	3:03:00	-0.04195	0.01652
Treatment*etime	Placebo	5:03:00	-0.04892	0.009547
Treatment*etime	Paracetamol	1:03:00	-0.01274	0.04573
Treatment*etime	Paracetamol	2:03:00	-0.01404	0.04443
Treatment*etime	Paracetamol	3:03:00	-0.02615	0.03231
Treatment*etime	Paracetamol	5:03:00	-0.02261	0.03585

Heat PTT (C)**SAS output 14.1 Heat PTT (C)**

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Proc MIXED analysis of LOG Heat PTT

Model Information

Data Set	WORK.MIX
Dependent Variable	QST_heat_tol
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:03 2:03 3:03 5:03
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-355.40906200	
1	2	-409.07143461	0.00034345
2	1	-409.18056192	0.00001849
3	1	-409.18610352	0.00000019
4	1	-409.18615687	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.000259
Treatment*SubjectNr	0.000316
etime*SubjectNr	-0.00001
Residual	0.000240

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Proc MIXED analysis of LOG Heat PTT

Fit Statistics

-2 Res Log Likelihood	-409.2
AIC (smaller is better)	-401.2
AICC (smaller is better)	-400.7
BIC (smaller is better)	-399.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	53.78	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	3.42	0.02	0.8946
etime	3	33	2.58	0.0703
Occasion	1	4.09	0.13	0.7389
Treatment*etime	3	33	1.47	0.2414
preQST_heat_tol	1	15.7	14.18	0.0017

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	-0.00113	0.007941	3.42	-0.14	0.8946	0.05	-0.02473	0.02246

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		3.8495	0.007260	13.2	530.20	<.0001	0.05
Treatment	Paracetamol		3.8484	0.007260	13.2	530.05	<.0001	0.05
Treatment*etime	Placebo	1:03:00	3.8506	0.008185	21	470.42	<.0001	0.05
Treatment*etime	Placebo	2:03:00	3.8588	0.008185	21	471.42	<.0001	0.05
Treatment*etime	Placebo	3:03:00	3.8500	0.008185	21	470.34	<.0001	0.05
Treatment*etime	Placebo	5:03:00	3.8388	0.008185	21	468.97	<.0001	0.05
Treatment*etime	Paracetamol	1:03:00	3.8489	0.008185	21	470.21	<.0001	0.05
Treatment*etime	Paracetamol	2:03:00	3.8516	0.008185	21	470.54	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		3.8339	3.8652
Treatment	Paracetamol		3.8327	3.8641
Treatment*etime	Placebo	1:03:00	3.8336	3.8676
Treatment*etime	Placebo	2:03:00	3.8418	3.8758
Treatment*etime	Placebo	3:03:00	3.8330	3.8670
Treatment*etime	Placebo	5:03:00	3.8217	3.8558
Treatment*etime	Paracetamol	1:03:00	3.8318	3.8659
Treatment*etime	Paracetamol	2:03:00	3.8345	3.8686

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Proc MIXED analysis of LOG Heat PTT

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	3:03:00	3.8446	0.008185	21	469.68	<.0001	0.05
Treatment*etime	Paracetamol	5:03:00	3.8486	0.008185	21	470.18	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	3:03:00	3.8276	3.8616
Treatment*etime	Paracetamol	5:03:00	3.8316	3.8656

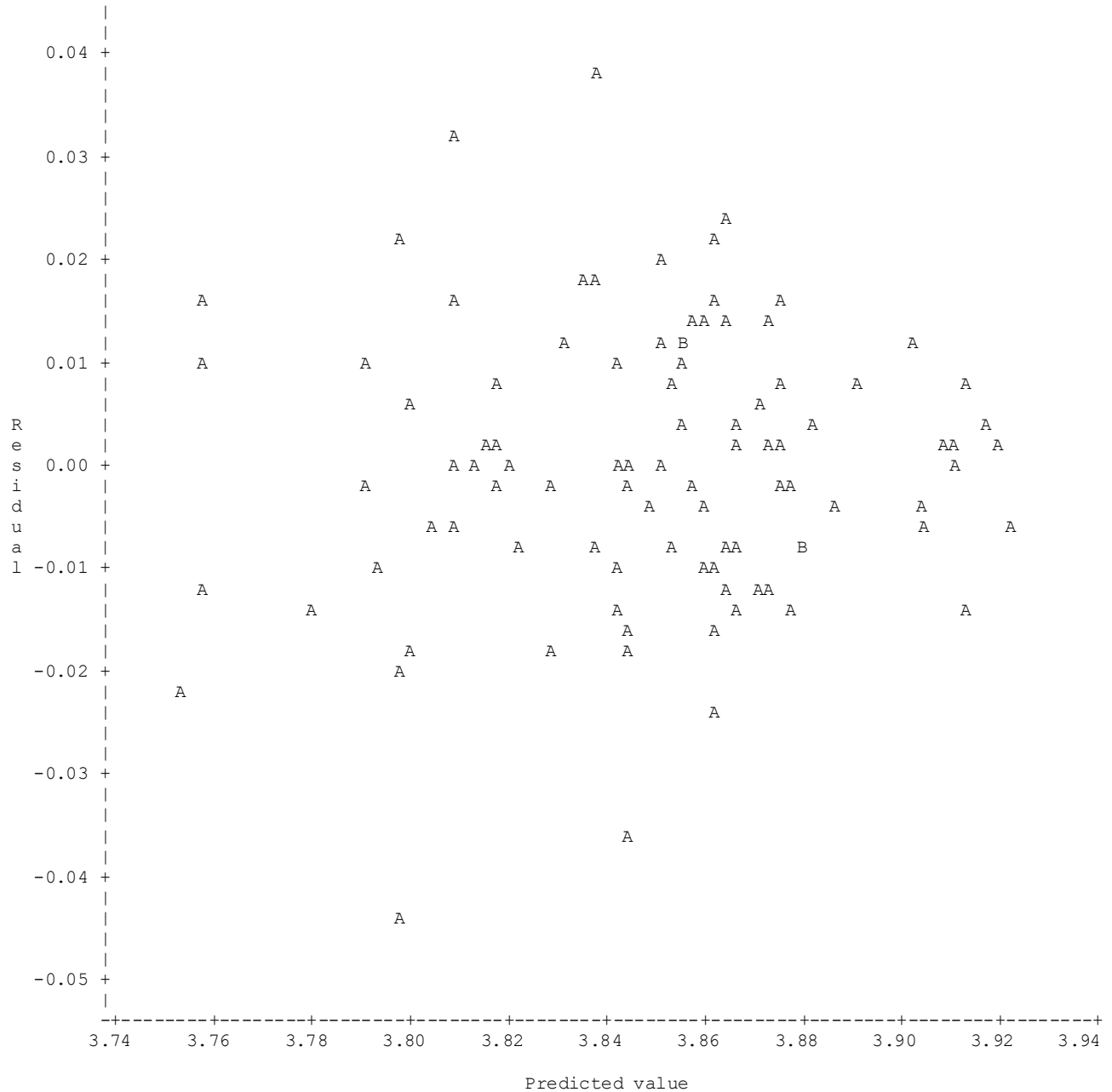
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Proc MIXED analysis of LOG Heat PTT

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



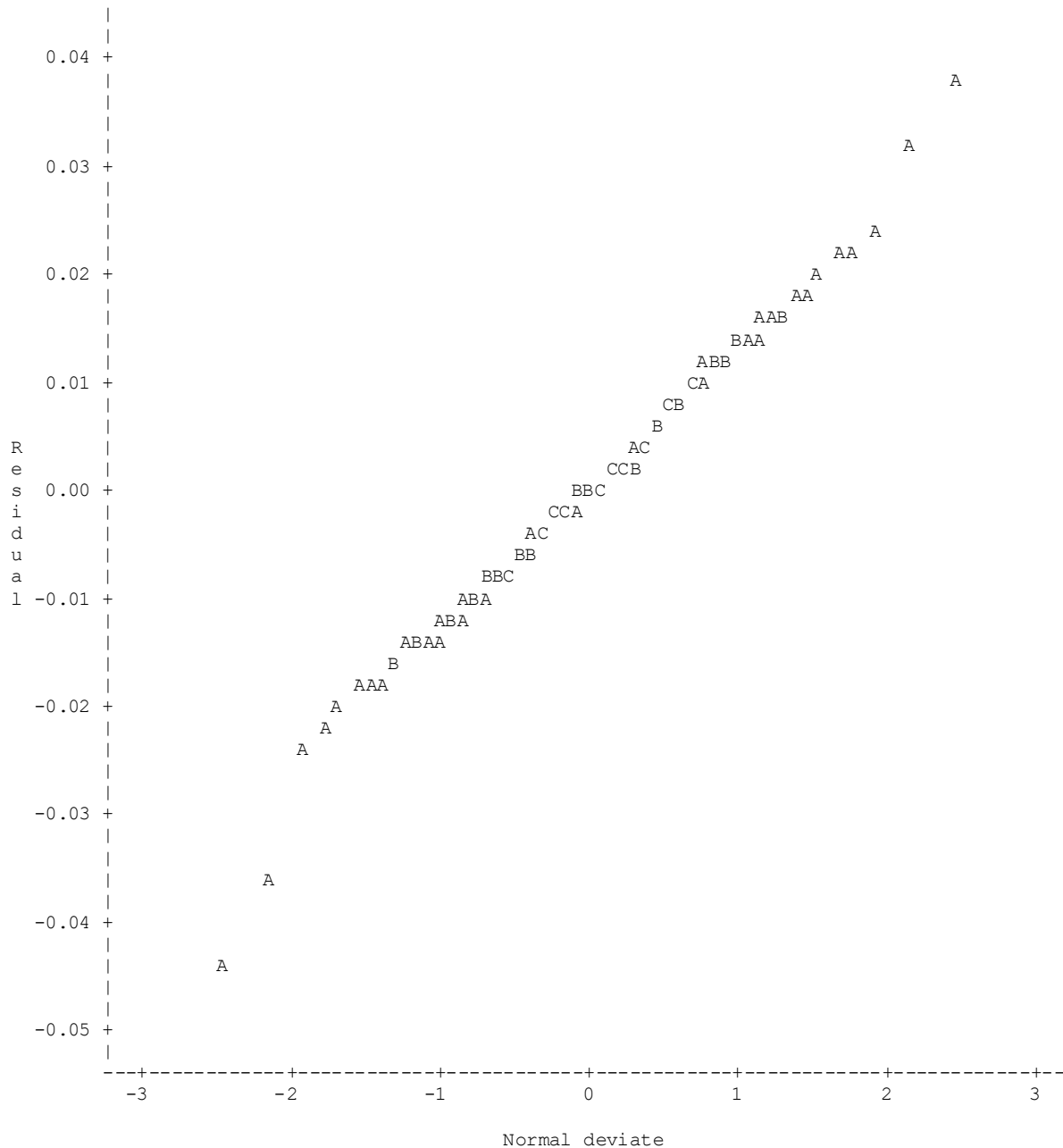
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Proc MIXED analysis of LOG Heat PTT

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.986 : P-value= 0.427)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 14.2 Heat PTT (C) change from baseline

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Proc MIXED analysis of LOG Heat PTT
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaQST_heat_tol
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kacker-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:03 2:03 3:03 5:03
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-355.40906200	
1	2	-409.07143461	0.00034345
2	1	-409.18056192	0.00001849
3	1	-409.18610352	0.00000019
4	1	-409.18615687	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.000259
Treatment*SubjectNr	0.000316
etime*SubjectNr	-0.00001
Residual	0.000240

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Proc MIXED analysis of LOG Heat PTT
Change from baseline

Fit Statistics

-2 Res Log Likelihood	-409.2
AIC (smaller is better)	-401.2
AICC (smaller is better)	-400.7
BIC (smaller is better)	-399.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	53.78	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	3.42	0.02	0.8946
etime	3	33	2.58	0.0703
Occasion	1	4.09	0.13	0.7389
Treatment*etime	3	33	1.47	0.2414
preQST_heat_tol	1	15.7	4.65	0.0469

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		0.003353	0.007260	13.2	0.46	0.6518	0.05
Treatment	Paracetamol		0.002221	0.007260	13.2	0.31	0.7645	0.05
Treatment*etime	Placebo	1:03:00	0.004393	0.008185	21	0.54	0.5971	0.05
Treatment*etime	Placebo	2:03:00	0.01262	0.008185	21	1.54	0.1379	0.05
Treatment*etime	Placebo	3:03:00	0.003806	0.008185	21	0.46	0.6468	0.05
Treatment*etime	Placebo	5:03:00	-0.00741	0.008185	21	-0.91	0.3754	0.05
Treatment*etime	Paracetamol	1:03:00	0.002672	0.008185	21	0.33	0.7473	0.05
Treatment*etime	Paracetamol	2:03:00	0.005376	0.008185	21	0.66	0.5184	0.05
Treatment*etime	Paracetamol	3:03:00	-0.00159	0.008185	21	-0.19	0.8476	0.05
Treatment*etime	Paracetamol	5:03:00	0.002426	0.008185	21	0.30	0.7698	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.01231	0.01901
Treatment	Paracetamol		-0.01344	0.01788
Treatment*etime	Placebo	1:03:00	-0.01263	0.02142
Treatment*etime	Placebo	2:03:00	-0.00440	0.02965
Treatment*etime	Placebo	3:03:00	-0.01322	0.02083
Treatment*etime	Placebo	5:03:00	-0.02443	0.009609
Treatment*etime	Paracetamol	1:03:00	-0.01435	0.01969
Treatment*etime	Paracetamol	2:03:00	-0.01165	0.02240
Treatment*etime	Paracetamol	3:03:00	-0.01861	0.01543
Treatment*etime	Paracetamol	5:03:00	-0.01460	0.01945

Sensory after Cold

SAS output 15.1 Sensory after Cold

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Proc MIXED analysis of Sensory after Cold

Model Information

Data Set	WORK.MIX
Dependent Variable	Sensorycold
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	87

Number of Observations

Number of Observations Read	87
Number of Observations Used	87
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	7.22597400	
1	2	-32.33515611	0.00000539
2	1	-32.33563097	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-0.00709
Treatment*SubjectNr	0.03878
etime*SubjectNr	-0.00034
Residual	0.01736

Fit Statistics

-2 Res Log Likelihood	-32.3
AIC (smaller is better)	-24.3

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Proc MIXED analysis of Sensory after Cold

Fit Statistics

AICC (smaller is better)	-23.8
BIC (smaller is better)	-22.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	39.56	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.6	0.73	0.4166
etime	3	30	0.93	0.4377
Occasion	1	8.75	0.56	0.4746
Treatment*etime	3	30.1	0.97	0.4213
preSensoryCold	1	9.28	159.33	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	-0.07600	0.08906	8.6	-0.85	0.4166	0.05	-0.2789	0.1269

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		1.0065	0.05733	17.2	17.56	<.0001	0.05
Treatment	Paracetamol		0.9305	0.05745	17.3	16.20	<.0001	0.05
Treatment*etime	Placebo	1:16:00	1.0024	0.06669	30.4	15.03	<.0001	0.05
Treatment*etime	Placebo	2:16:00	1.0106	0.06669	30.4	15.15	<.0001	0.05
Treatment*etime	Placebo	3:16:00	1.0602	0.06669	30.4	15.90	<.0001	0.05
Treatment*etime	Placebo	5:16:00	0.9528	0.06669	30.4	14.29	<.0001	0.05
Treatment*etime	Paracetamol	1:16:00	0.9758	0.06832	32.7	14.28	<.0001	0.05
Treatment*etime	Paracetamol	2:16:00	0.9320	0.06667	30.4	13.98	<.0001	0.05
Treatment*etime	Paracetamol	3:16:00	0.9072	0.06667	30.4	13.61	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		0.8857	1.1274
Treatment	Paracetamol		0.8095	1.0515
Treatment*etime	Placebo	1:16:00	0.8662	1.1385
Treatment*etime	Placebo	2:16:00	0.8745	1.1468
Treatment*etime	Placebo	3:16:00	0.9241	1.1964
Treatment*etime	Placebo	5:16:00	0.8167	1.0889
Treatment*etime	Paracetamol	1:16:00	0.8367	1.1148
Treatment*etime	Paracetamol	2:16:00	0.7959	1.0681
Treatment*etime	Paracetamol	3:16:00	0.7711	1.0433

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Proc MIXED analysis of Sensory after Cold

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	5:16:00	0.9072	0.06667	30.4	13.61	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	5:16:00	0.7711	1.0433

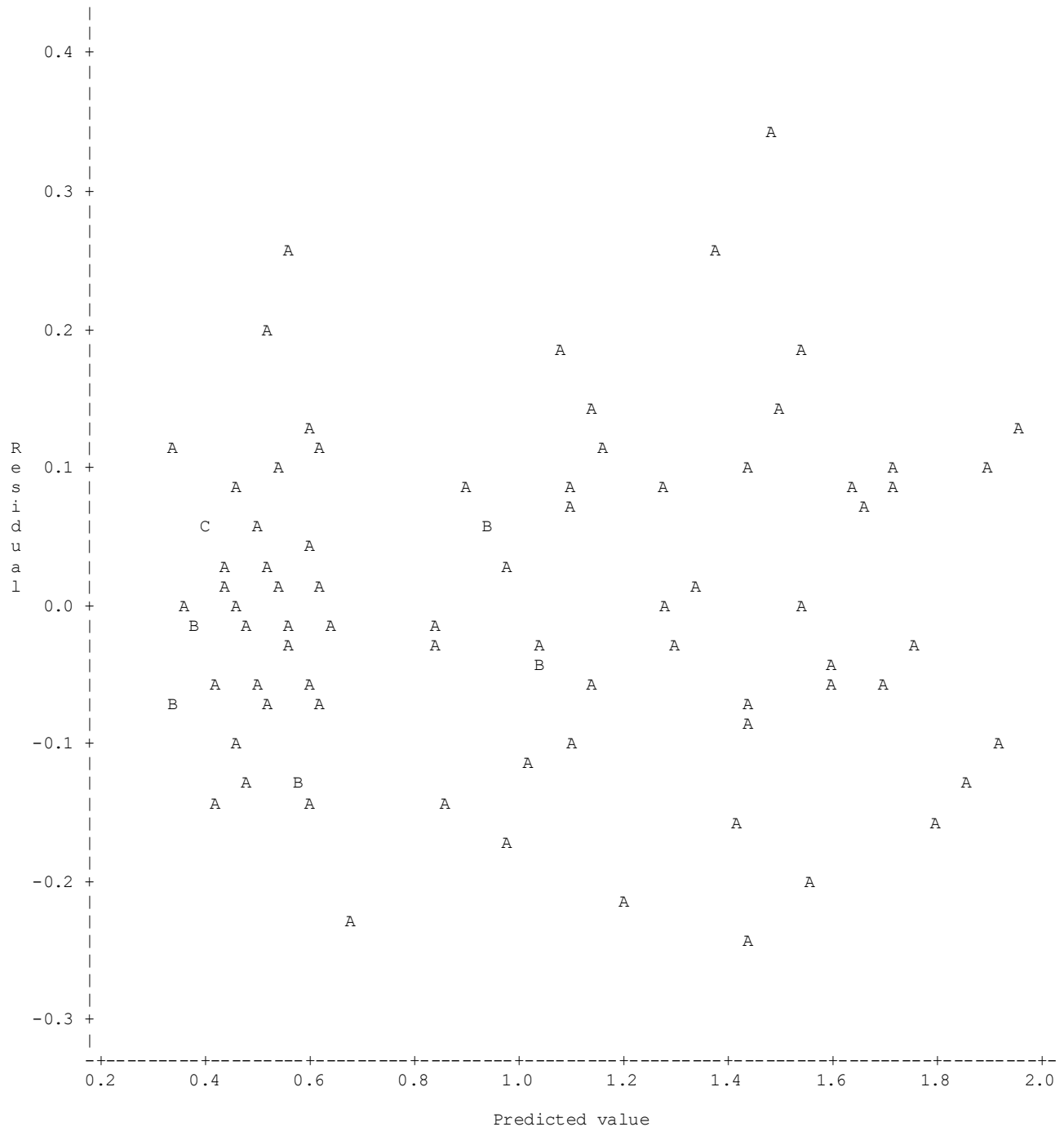
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Proc MIXED analysis of Sensory after Cold

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



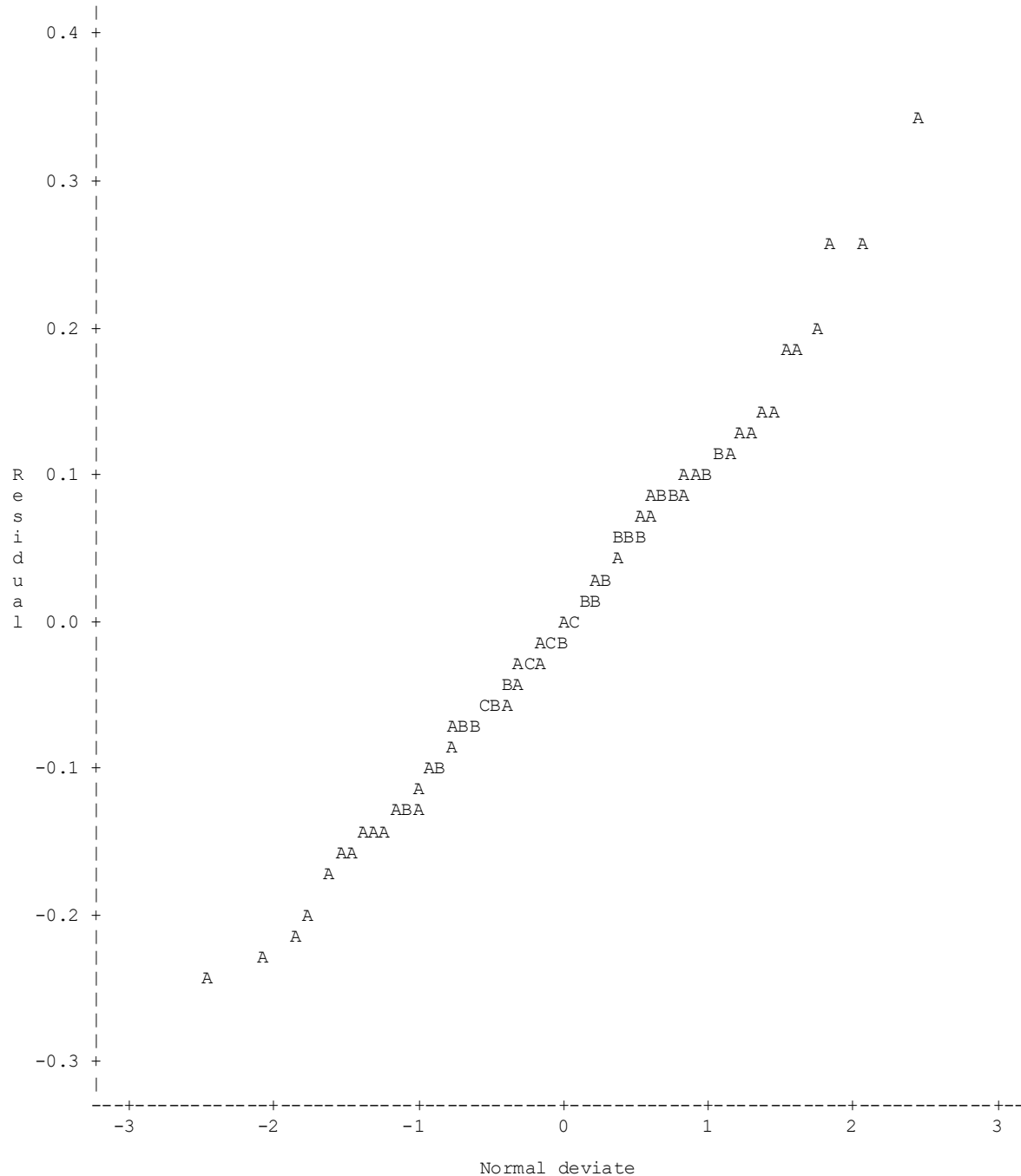
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after Cold

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.990 : P-value= 0.765)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 15.2 Sensory after Cold change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after Cold
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaSensoryCold
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	87

Number of Observations

Number of Observations Read	87
Number of Observations Used	87
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	7.22597400	
1	2	-32.33515611	0.00000539
2	1	-32.33563097	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-0.00709
Treatment*SubjectNr	0.03878
etime*SubjectNr	-0.00034
Residual	0.01736

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after Cold
Change from baseline

Fit Statistics

-2 Res Log Likelihood	-32.3
AIC (smaller is better)	-24.3
AICC (smaller is better)	-23.8
BIC (smaller is better)	-22.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	39.56	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.6	0.73	0.4166
etime	3	30	0.93	0.4377
Occasion	1	8.75	0.56	0.4746
Treatment*etime	3	30.1	0.97	0.4213
preSensoryCold	1	9.28	0.27	0.6171

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		0.002332	0.05733	17.2	0.04	0.9680	0.05
Treatment	Paracetamol		-0.07366	0.05745	17.3	-1.28	0.2166	0.05
Treatment*etime	Placebo	1:16:00	-0.00180	0.06669	30.4	-0.03	0.9786	0.05
Treatment*etime	Placebo	2:16:00	0.006464	0.06669	30.4	0.10	0.9234	0.05
Treatment*etime	Placebo	3:16:00	0.05605	0.06669	30.4	0.84	0.4072	0.05
Treatment*etime	Placebo	5:16:00	-0.05139	0.06669	30.4	-0.77	0.4469	0.05
Treatment*etime	Paracetamol	1:16:00	-0.02840	0.06832	32.7	-0.42	0.6803	0.05
Treatment*etime	Paracetamol	2:16:00	-0.07222	0.06667	30.4	-1.08	0.2872	0.05
Treatment*etime	Paracetamol	3:16:00	-0.09702	0.06667	30.4	-1.46	0.1559	0.05
Treatment*etime	Paracetamol	5:16:00	-0.09702	0.06667	30.4	-1.46	0.1559	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.1185	0.1232
Treatment	Paracetamol		-0.1947	0.04736
Treatment*etime	Placebo	1:16:00	-0.1379	0.1343
Treatment*etime	Placebo	2:16:00	-0.1297	0.1426
Treatment*etime	Placebo	3:16:00	-0.08008	0.1922
Treatment*etime	Placebo	5:16:00	-0.1875	0.08474
Treatment*etime	Paracetamol	1:16:00	-0.1674	0.1106
Treatment*etime	Paracetamol	2:16:00	-0.2083	0.06387
Treatment*etime	Paracetamol	3:16:00	-0.2331	0.03908
Treatment*etime	Paracetamol	5:16:00	-0.2331	0.03908

Affective after Cold

SAS output 16.1 Affective after Cold

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after Cold

Model Information

Data Set	WORK.MIX
Dependent Variable	Affectivecold
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	87

Number of Observations

Number of Observations Read	87
Number of Observations Used	87
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-75.13949512	
1	2	-76.21193697	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-0.00136
Treatment*SubjectNr	0.002359
etime*SubjectNr	0.000183
Residual	0.01484

Fit Statistics

-2 Res Log Likelihood	-76.2
AIC (smaller is better)	-68.2
AICC (smaller is better)	-67.7

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after Cold

Fit Statistics

BIC (smaller is better) -66.6

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	1.07	0.7837

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.95	1.12	0.3167
etime	3	30.3	0.07	0.9778
Occasion	1	9.02	2.49	0.1490
Treatment*etime	3	30.3	0.31	0.8148
preAffectiveCold	1	9.28	1101.04	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	0.03559	0.03356	8.95	1.06	0.3167	0.05	-0.04039	0.1116

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		0.2871	0.02085	16.5	13.77	<.0001	0.05
Treatment	Paracetamol		0.3227	0.02112	17.2	15.28	<.0001	0.05
Treatment*etime	Placebo	1:16:00	0.2985	0.03820	72.9	7.81	<.0001	0.05
Treatment*etime	Placebo	2:16:00	0.2758	0.03820	72.9	7.22	<.0001	0.05
Treatment*etime	Placebo	3:16:00	0.2758	0.03820	72.9	7.22	<.0001	0.05
Treatment*etime	Placebo	5:16:00	0.2985	0.03820	72.9	7.81	<.0001	0.05
Treatment*etime	Paracetamol	1:16:00	0.3238	0.04033	74	8.03	<.0001	0.05
Treatment*etime	Paracetamol	2:16:00	0.3451	0.03820	72.9	9.03	<.0001	0.05
Treatment*etime	Paracetamol	3:16:00	0.3224	0.03820	72.9	8.44	<.0001	0.05
Treatment*etime	Paracetamol	5:16:00	0.2996	0.03820	72.9	7.84	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		0.2430	0.3312
Treatment	Paracetamol		0.2782	0.3672
Treatment*etime	Placebo	1:16:00	0.2224	0.3746
Treatment*etime	Placebo	2:16:00	0.1996	0.3519
Treatment*etime	Placebo	3:16:00	0.1996	0.3519
Treatment*etime	Placebo	5:16:00	0.2224	0.3746
Treatment*etime	Paracetamol	1:16:00	0.2434	0.4042
Treatment*etime	Paracetamol	2:16:00	0.2689	0.4212
Treatment*etime	Paracetamol	3:16:00	0.2462	0.3985
Treatment*etime	Paracetamol	5:16:00	0.2235	0.3758

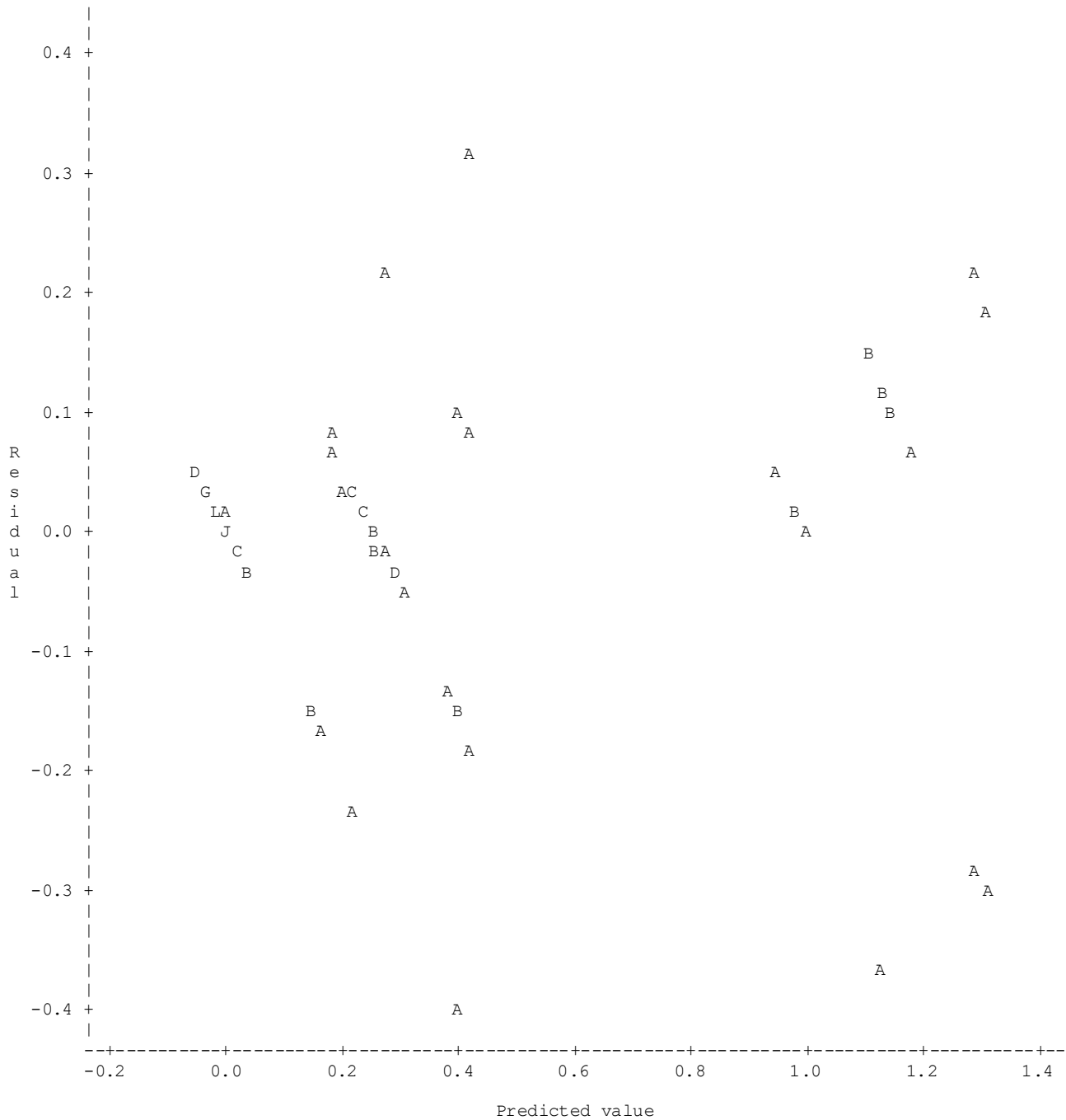
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after Cold

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



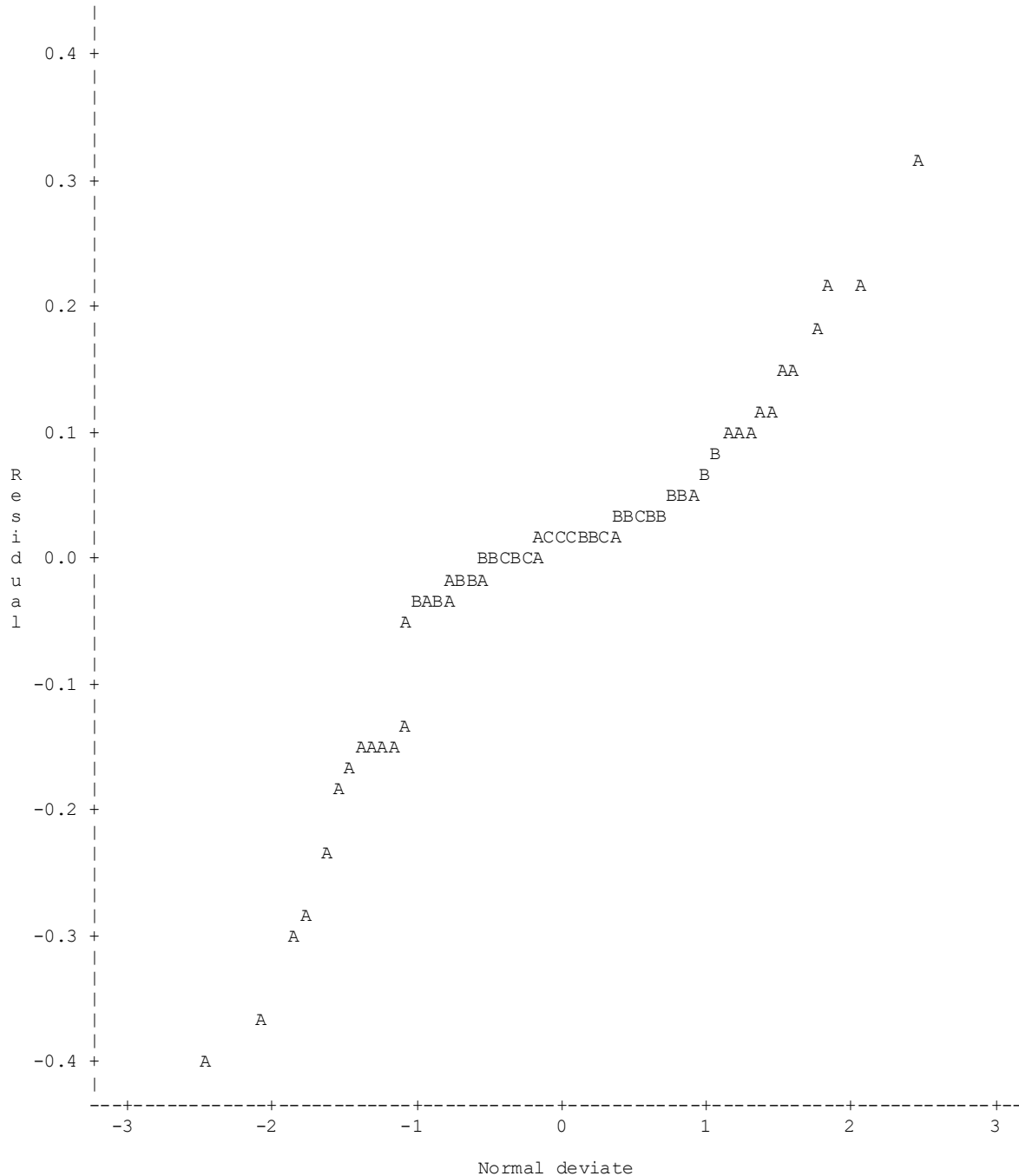
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after Cold

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.861 : P-value=<0.001)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 16.2 Affective after Cold change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after Cold
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaAffectiveCold
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	87

Number of Observations

Number of Observations Read	87
Number of Observations Used	87
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-75.13949512	
1	2	-76.21193697	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-0.00136
Treatment*SubjectNr	0.002359
etime*SubjectNr	0.000183
Residual	0.01484

Fit Statistics

-2 Res Log Likelihood	-76.2
AIC (smaller is better)	-68.2

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after Cold
Change from baseline

Fit Statistics

AICC (smaller is better) -67.7
BIC (smaller is better) -66.6

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	1.07	0.7837

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.95	1.12	0.3167
etime	3	30.3	0.07	0.9778
Occasion	1	9.02	2.49	0.1490
Treatment*etime	3	30.3	0.31	0.8148
preAffectiveCold	1	9.28	8.54	0.0164

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-0.05771	0.02085	16.5	-2.77	0.0134	0.05
Treatment	Paracetamol		-0.02211	0.02112	17.2	-1.05	0.3095	0.05
Treatment*etime	Placebo	1:16:00	-0.04634	0.03820	72.9	-1.21	0.2289	0.05
Treatment*etime	Placebo	2:16:00	-0.06907	0.03820	72.9	-1.81	0.0747	0.05
Treatment*etime	Placebo	3:16:00	-0.06907	0.03820	72.9	-1.81	0.0747	0.05
Treatment*etime	Placebo	5:16:00	-0.04634	0.03820	72.9	-1.21	0.2289	0.05
Treatment*etime	Paracetamol	1:16:00	-0.02103	0.04033	74	-0.52	0.6035	0.05
Treatment*etime	Paracetamol	2:16:00	0.000255	0.03820	72.9	0.01	0.9947	0.05
Treatment*etime	Paracetamol	3:16:00	-0.02247	0.03820	72.9	-0.59	0.5582	0.05
Treatment*etime	Paracetamol	5:16:00	-0.04520	0.03820	72.9	-1.18	0.2406	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.1018	-0.01363
Treatment	Paracetamol		-0.06663	0.02241
Treatment*etime	Placebo	1:16:00	-0.1225	0.02978
Treatment*etime	Placebo	2:16:00	-0.1452	0.007054
Treatment*etime	Placebo	3:16:00	-0.1452	0.007054
Treatment*etime	Placebo	5:16:00	-0.1225	0.02978
Treatment*etime	Paracetamol	1:16:00	-0.1014	0.05933
Treatment*etime	Paracetamol	2:16:00	-0.07588	0.07639
Treatment*etime	Paracetamol	3:16:00	-0.09861	0.05366
Treatment*etime	Paracetamol	5:16:00	-0.1213	0.03093

MPQ VAS after Cold (mm)**SAS output 17.1 MPQ VAS after Cold (mm)**

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after Cold

Model Information

Data Set	WORK.MIX
Dependent Variable	MPQcold
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	95

Number of Observations

Number of Observations Read	95
Number of Observations Used	95
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	584.16142327	
1	2	564.44364651	0.00000012
2	1	564.44362165	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-2.0144
Treatment*SubjectNr	18.7866
etime*SubjectNr	-5.4787
Residual	27.8092

Fit Statistics

-2 Res Log Likelihood	564.4
AIC (smaller is better)	572.4

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after Cold

Fit Statistics

AICC (smaller is better)	572.9
BIC (smaller is better)	574.4

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	19.72	0.0002

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	10	1.61	0.2331
etime	3	32.2	0.79	0.5096
Occasion	1	10.1	1.18	0.3030
Treatment*etime	3	32.8	2.39	0.0869
preMPQcold	1	10.3	778.38	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	2.6333	2.0750	10	1.27	0.2331	0.05	-1.9898	7.2564

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		42.9068	1.3650	19.5	31.43	<.0001	0.05
Treatment	Paracetamol		45.5401	1.3701	19.7	33.24	<.0001	0.05
Treatment*etime	Placebo	1:16:00	44.1964	1.8053	50.5	24.48	<.0001	0.05
Treatment*etime	Placebo	2:16:00	41.2964	1.8053	50.5	22.88	<.0001	0.05
Treatment*etime	Placebo	3:16:00	40.6630	1.8053	50.5	22.52	<.0001	0.05
Treatment*etime	Placebo	5:16:00	45.4714	1.8053	50.5	25.19	<.0001	0.05
Treatment*etime	Paracetamol	1:16:00	45.0622	1.8634	54.1	24.18	<.0001	0.05
Treatment*etime	Paracetamol	2:16:00	47.0717	1.8055	50.5	26.07	<.0001	0.05
Treatment*etime	Paracetamol	3:16:00	45.7217	1.8055	50.5	25.32	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		40.0546	45.7590
Treatment	Paracetamol		42.6796	48.4007
Treatment*etime	Placebo	1:16:00	40.5713	47.8214
Treatment*etime	Placebo	2:16:00	37.6713	44.9214
Treatment*etime	Placebo	3:16:00	37.0380	44.2881
Treatment*etime	Placebo	5:16:00	41.8463	49.0964
Treatment*etime	Paracetamol	1:16:00	41.3265	48.7979
Treatment*etime	Paracetamol	2:16:00	43.4461	50.6972
Treatment*etime	Paracetamol	3:16:00	42.0961	49.3472

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Proc MIXED analysis of MPQ VAS after Cold

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	5:16:00	44.3050	1.8055	50.5	24.54	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	5:16:00	40.6794	47.9306

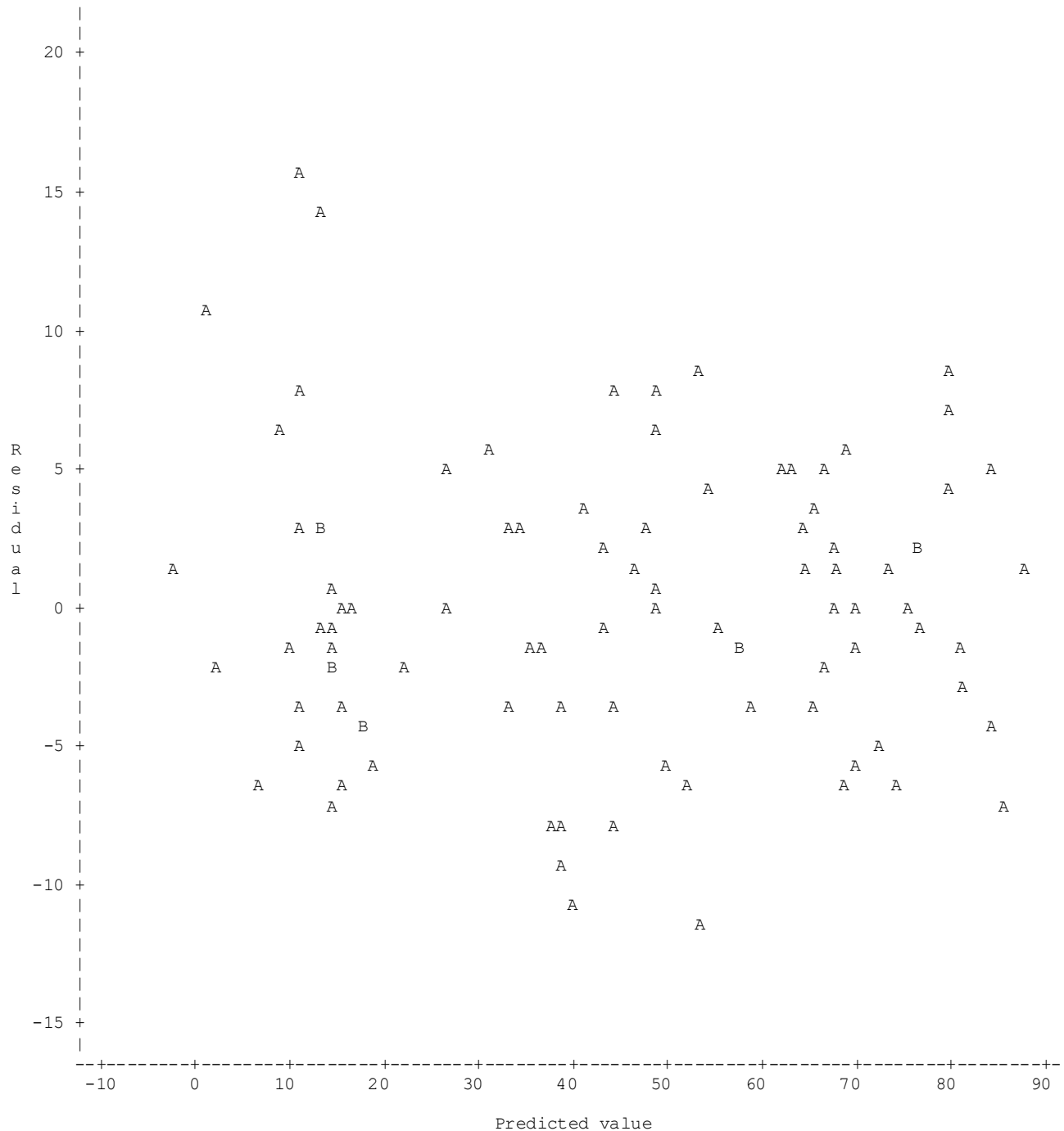
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

30SEP2014 10:28 Page: 4

Proc MIXED analysis of MPQ VAS after Cold

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



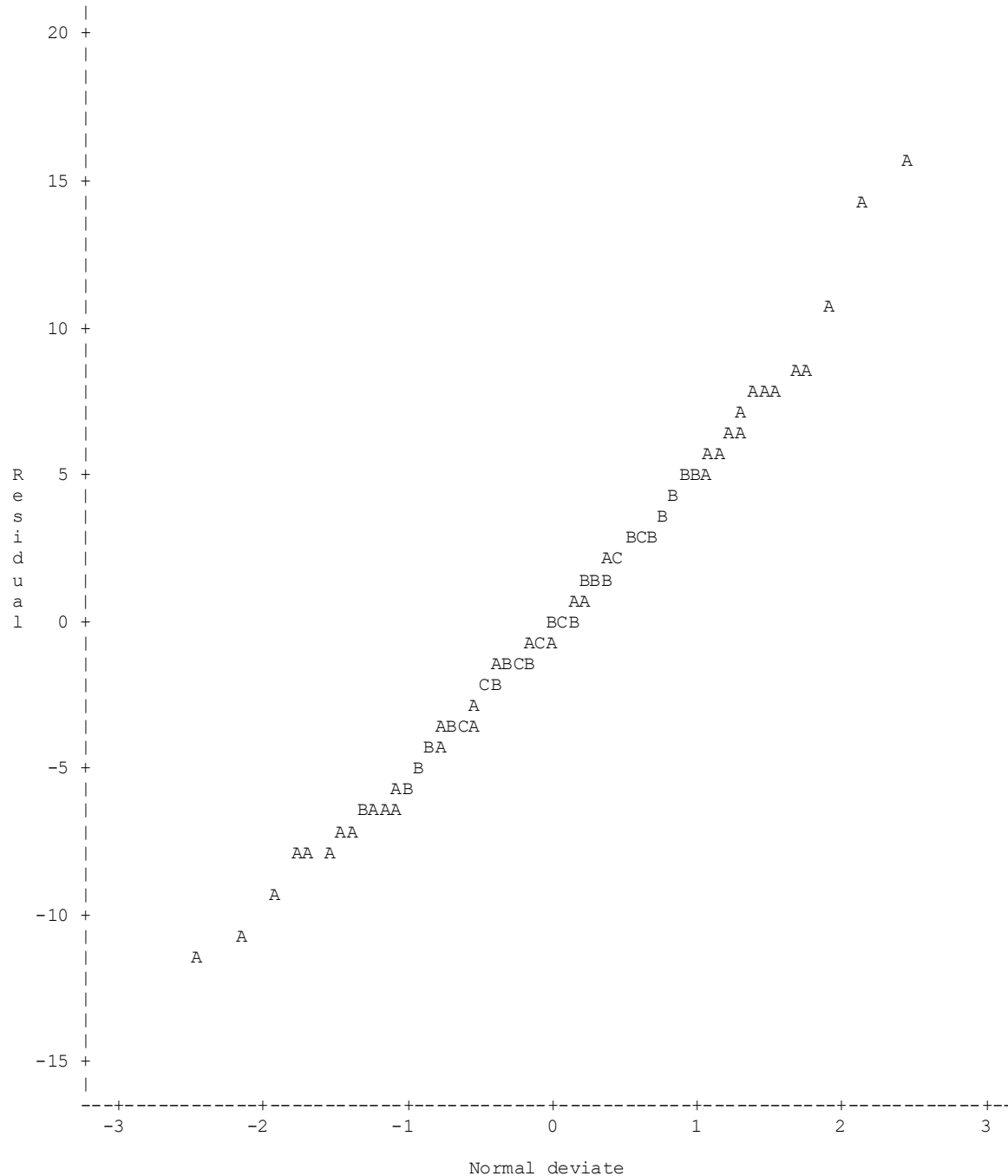
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after Cold

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.987 : P-value= 0.485)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 17.2 MPQ VAS after Cold (mm) change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

30SEP2014 10:28 Page: 1

Proc MIXED analysis of MPQ VAS after Cold
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaMPQcold
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske- Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:16 2:16 3:16 5:16
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	95

Number of Observations

Number of Observations Read	95
Number of Observations Used	95
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	584.16142327	
1	2	564.44364651	0.00000012
2	1	564.44362165	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-2.0144
Treatment*SubjectNr	18.7866
etime*SubjectNr	-5.4787
Residual	27.8092

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

30SEP2014 10:28 Page: 2

Proc MIXED analysis of MPQ VAS after Cold
Change from baseline

Fit Statistics

-2 Res Log Likelihood	564.4
AIC (smaller is better)	572.4
AICC (smaller is better)	572.9
BIC (smaller is better)	574.4

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	19.72	0.0002

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	10	1.61	0.2331
etime	3	32.2	0.79	0.5096
Occasion	1	10.1	1.18	0.3030
Treatment*etime	3	32.8	2.39	0.0869
preMPQcold	1	10.3	0.78	0.3983

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-2.3237	1.3650	19.5	-1.70	0.1046	0.05
Treatment	Paracetamol		0.3096	1.3701	19.7	0.23	0.8236	0.05
Treatment*etime	Placebo	1:16:00	-1.0342	1.8053	50.5	-0.57	0.5693	0.05
Treatment*etime	Placebo	2:16:00	-3.9342	1.8053	50.5	-2.18	0.0340	0.05
Treatment*etime	Placebo	3:16:00	-4.5675	1.8053	50.5	-2.53	0.0146	0.05
Treatment*etime	Placebo	5:16:00	0.2408	1.8053	50.5	0.13	0.8944	0.05
Treatment*etime	Paracetamol	1:16:00	-0.1683	1.8634	54.1	-0.09	0.9284	0.05
Treatment*etime	Paracetamol	2:16:00	1.8411	1.8055	50.5	1.02	0.3127	0.05
Treatment*etime	Paracetamol	3:16:00	0.4911	1.8055	50.5	0.27	0.7867	0.05
Treatment*etime	Paracetamol	5:16:00	-0.9255	1.8055	50.5	-0.51	0.6105	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-5.1759	0.5285
Treatment	Paracetamol		-2.5509	3.1701
Treatment*etime	Placebo	1:16:00	-4.6592	2.5909
Treatment*etime	Placebo	2:16:00	-7.5592	-0.3091
Treatment*etime	Placebo	3:16:00	-8.1925	-0.9425
Treatment*etime	Placebo	5:16:00	-3.3842	3.8659
Treatment*etime	Paracetamol	1:16:00	-3.9041	3.5674
Treatment*etime	Paracetamol	2:16:00	-1.7845	5.4667
Treatment*etime	Paracetamol	3:16:00	-3.1345	4.1167
Treatment*etime	Paracetamol	5:16:00	-4.5511	2.7001

Sensory after ES

SAS output 18.1 Sensory after ES

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after ES

Model Information

Data Set	WORK.MIX
Dependent Variable	Sensorystair
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	88

Number of Observations

Number of Observations Read	88
Number of Observations Used	88
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	26.92887627	
1	2	-33.97708730	0.00000067
2	1	-33.97714671	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.01284
Treatment*SubjectNr	0.03570
etime*SubjectNr	0.002811
Residual	0.01255

Fit Statistics

-2 Res Log Likelihood	-34.0
AIC (smaller is better)	-26.0

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after ES

Fit Statistics

AICC (smaller is better)	-25.4
BIC (smaller is better)	-24.4

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	60.91	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	7.77	0.07	0.8023
etime	3	30	2.74	0.0609
Occasion	1	8.43	0.76	0.4082
Treatment*etime	3	30	1.97	0.1403
preSensoryStair	1	11.7	50.31	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	-0.02187	0.08440	7.77	-0.26	0.8023	0.05	-0.2175	0.1737

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		1.1576	0.06912	16.8	16.75	<.0001	0.05
Treatment	Paracetamol		1.1358	0.06912	16.8	16.43	<.0001	0.05
Treatment*etime	Placebo	1:08:00	1.1907	0.07632	24.6	15.60	<.0001	0.05
Treatment*etime	Placebo	2:08:00	1.2403	0.07632	24.6	16.25	<.0001	0.05
Treatment*etime	Placebo	3:08:00	1.1411	0.07632	24.6	14.95	<.0001	0.05
Treatment*etime	Placebo	5:08:00	1.0585	0.07632	24.6	13.87	<.0001	0.05
Treatment*etime	Paracetamol	1:08:00	1.1564	0.07632	24.6	15.15	<.0001	0.05
Treatment*etime	Paracetamol	2:08:00	1.1564	0.07632	24.6	15.15	<.0001	0.05
Treatment*etime	Paracetamol	3:08:00	1.0986	0.07632	24.6	14.39	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		1.0117	1.3036
Treatment	Paracetamol		0.9898	1.2817
Treatment*etime	Placebo	1:08:00	1.0334	1.3480
Treatment*etime	Placebo	2:08:00	1.0830	1.3976
Treatment*etime	Placebo	3:08:00	0.9838	1.2984
Treatment*etime	Placebo	5:08:00	0.9012	1.2157
Treatment*etime	Paracetamol	1:08:00	0.9991	1.3137
Treatment*etime	Paracetamol	2:08:00	0.9991	1.3137
Treatment*etime	Paracetamol	3:08:00	0.9413	1.2559

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Proc MIXED analysis of Sensory after ES

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	5:08:00	1.1316	0.07632	24.6	14.83	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	5:08:00	0.9743	1.2889

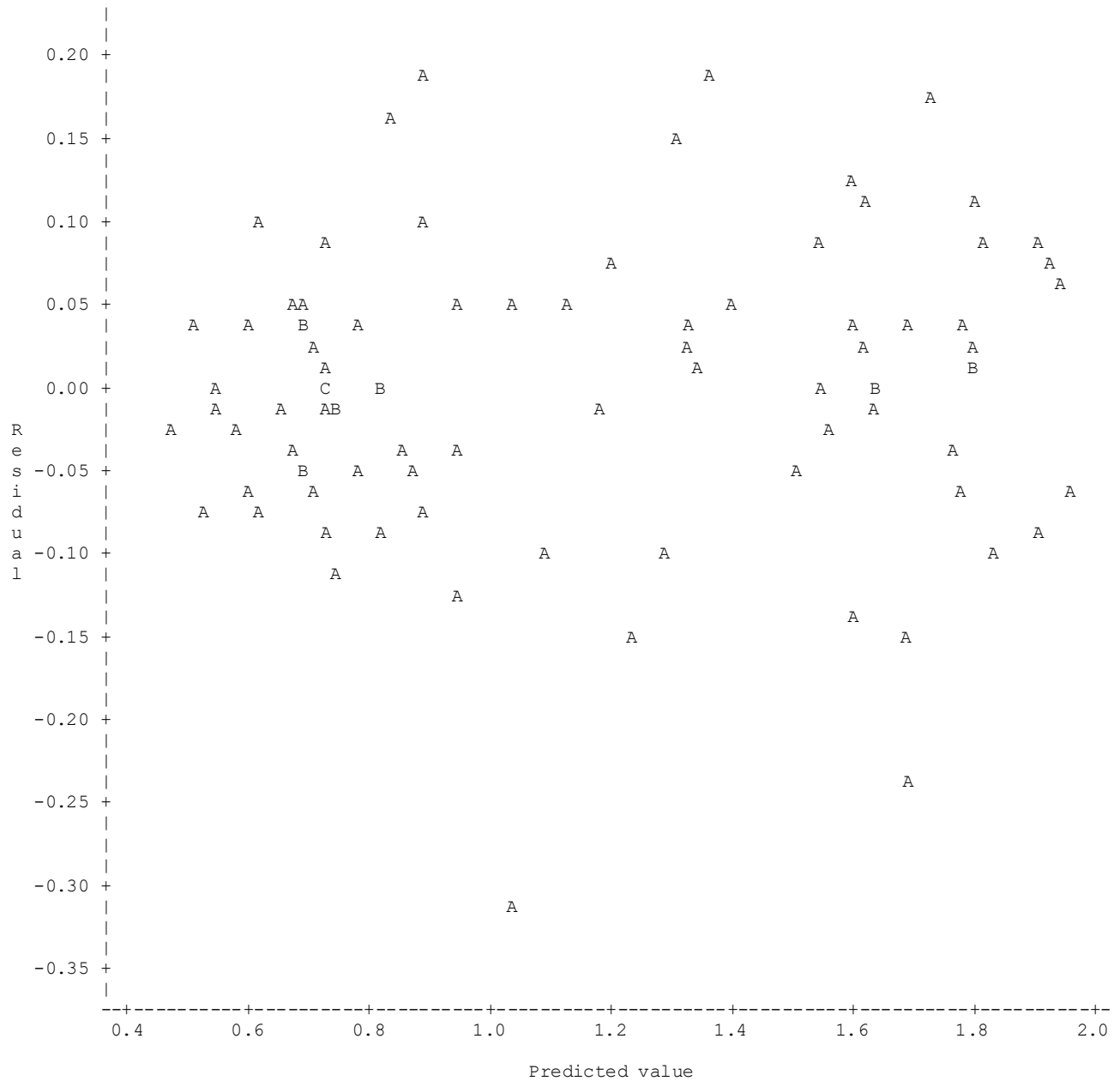
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after ES

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



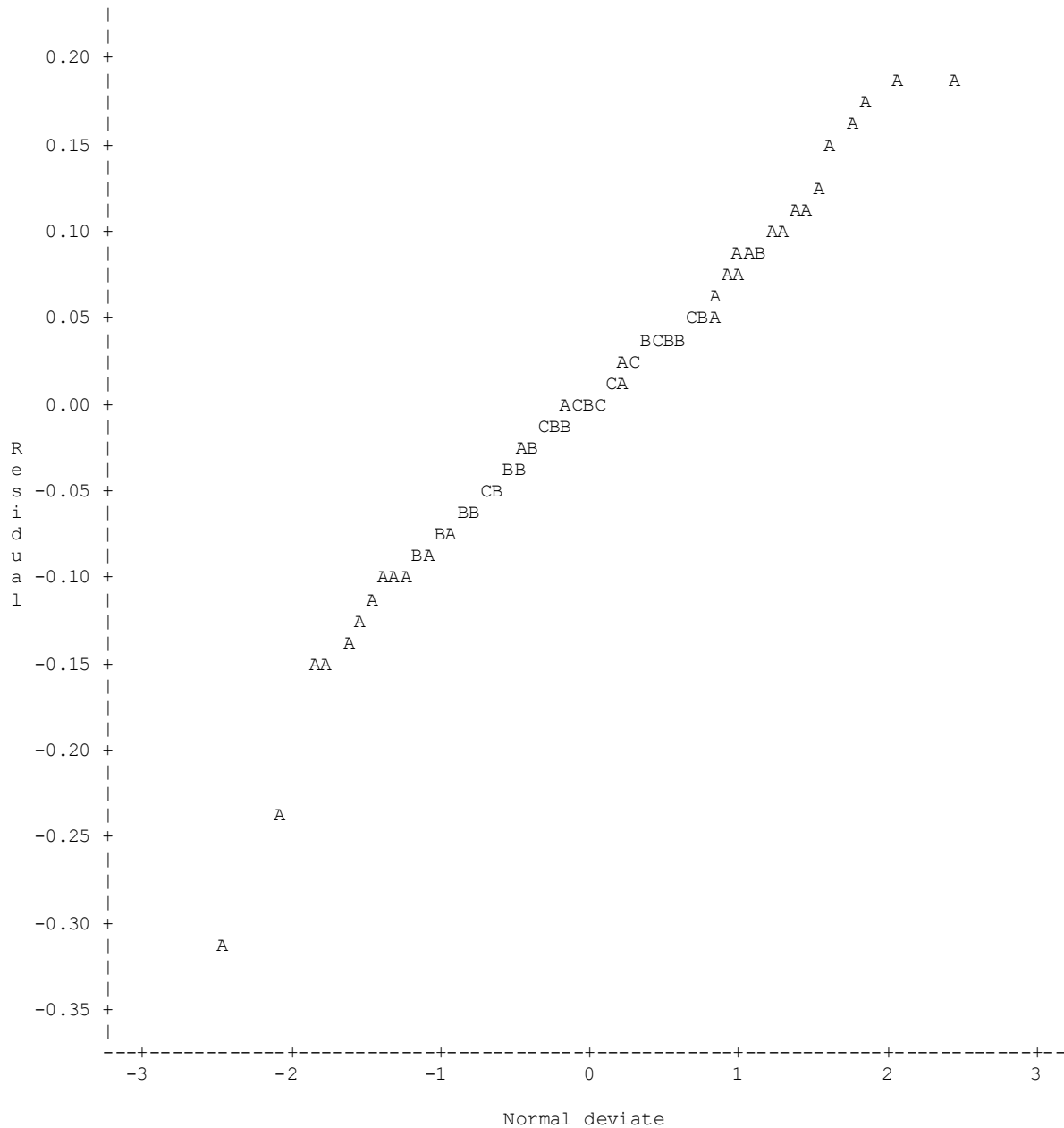
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after ES

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.973 : P-value= 0.062)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 18.2 Sensory after ES change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after ES
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaSensoryStair
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	88

Number of Observations

Number of Observations Read	88
Number of Observations Used	88
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	26.92887627	
1	2	-33.97708730	0.00000067
2	1	-33.97714671	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.01284
Treatment*SubjectNr	0.03570
etime*SubjectNr	0.002811
Residual	0.01255

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after ES
Change from baseline

Fit Statistics

-2 Res Log Likelihood	-34.0
AIC (smaller is better)	-26.0
AICC (smaller is better)	-25.4
BIC (smaller is better)	-24.4

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	60.91	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	7.77	0.07	0.8023
etime	3	30	2.74	0.0609
Occasion	1	8.43	0.76	0.4082
Treatment*etime	3	30	1.97	0.1403
preSensoryStair	1	11.7	0.00	0.9543

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-0.08617	0.06912	16.8	-1.25	0.2296	0.05
Treatment	Paracetamol		-0.1080	0.06912	16.8	-1.56	0.1366	0.05
Treatment*etime	Placebo	1:08:00	-0.05311	0.07632	24.6	-0.70	0.4930	0.05
Treatment*etime	Placebo	2:08:00	-0.00353	0.07632	24.6	-0.05	0.9635	0.05
Treatment*etime	Placebo	3:08:00	-0.1027	0.07632	24.6	-1.35	0.1906	0.05
Treatment*etime	Placebo	5:08:00	-0.1853	0.07632	24.6	-2.43	0.0228	0.05
Treatment*etime	Paracetamol	1:08:00	-0.08738	0.07632	24.6	-1.14	0.2632	0.05
Treatment*etime	Paracetamol	2:08:00	-0.08738	0.07632	24.6	-1.14	0.2632	0.05
Treatment*etime	Paracetamol	3:08:00	-0.1452	0.07632	24.6	-1.90	0.0688	0.05
Treatment*etime	Paracetamol	5:08:00	-0.1122	0.07632	24.6	-1.47	0.1543	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.2321	0.05978
Treatment	Paracetamol		-0.2540	0.03791
Treatment*etime	Placebo	1:08:00	-0.2104	0.1042
Treatment*etime	Placebo	2:08:00	-0.1608	0.1538
Treatment*etime	Placebo	3:08:00	-0.2600	0.05459
Treatment*etime	Placebo	5:08:00	-0.3426	-0.02805
Treatment*etime	Paracetamol	1:08:00	-0.2447	0.06991
Treatment*etime	Paracetamol	2:08:00	-0.2447	0.06991
Treatment*etime	Paracetamol	3:08:00	-0.3025	0.01206
Treatment*etime	Paracetamol	5:08:00	-0.2695	0.04512

Affective after ES

SAS output 19.1 Affective after ES

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after ES

Model Information

Data Set	WORK.MIX
Dependent Variable	Affectivestair
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	88

Number of Observations

Number of Observations Read	88
Number of Observations Used	88
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-8.50642983	
1	2	-48.05662842	0.00001462
2	1	-48.05805799	0.00000002
3	1	-48.05805960	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.02004
Treatment*SubjectNr	0.004750
etime*SubjectNr	0.002841
Residual	0.01316

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after ES

Fit Statistics

-2 Res Log Likelihood	-48.1
AIC (smaller is better)	-40.1
AICC (smaller is better)	-39.5
BIC (smaller is better)	-38.5

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	39.55	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	7.78	0.53	0.4880
etime	3	30	1.75	0.1788
Occasion	1	8.23	3.73	0.0886
Treatment*etime	3	30	0.49	0.6948
preAffectiveStair	1	12.1	51.76	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	-0.02798	0.03844	7.78	-0.73	0.4880	0.05	-0.1171	0.06110

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		0.3293	0.05120	11.1	6.43	<.0001	0.05
Treatment	Paracetamol		0.3013	0.05120	11.1	5.89	0.0001	0.05
Treatment*etime	Placebo	1:08:00	0.4032	0.06093	21.6	6.62	<.0001	0.05
Treatment*etime	Placebo	2:08:00	0.3350	0.06093	21.6	5.50	<.0001	0.05
Treatment*etime	Placebo	3:08:00	0.2896	0.06093	21.6	4.75	0.0001	0.05
Treatment*etime	Placebo	5:08:00	0.2896	0.06093	21.6	4.75	0.0001	0.05
Treatment*etime	Paracetamol	1:08:00	0.3241	0.06093	21.6	5.32	<.0001	0.05
Treatment*etime	Paracetamol	2:08:00	0.3241	0.06093	21.6	5.32	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		0.2168	0.4419
Treatment	Paracetamol		0.1888	0.4139
Treatment*etime	Placebo	1:08:00	0.2767	0.5297
Treatment*etime	Placebo	2:08:00	0.2085	0.4615
Treatment*etime	Placebo	3:08:00	0.1630	0.4161
Treatment*etime	Placebo	5:08:00	0.1630	0.4161
Treatment*etime	Paracetamol	1:08:00	0.1976	0.4506
Treatment*etime	Paracetamol	2:08:00	0.1976	0.4506

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Proc MIXED analysis of Affective after ES

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	3:08:00	0.2786	0.06093	21.6	4.57	0.0002	0.05
Treatment*etime	Paracetamol	5:08:00	0.2786	0.06093	21.6	4.57	0.0002	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	3:08:00	0.1521	0.4051
Treatment*etime	Paracetamol	5:08:00	0.1521	0.4051

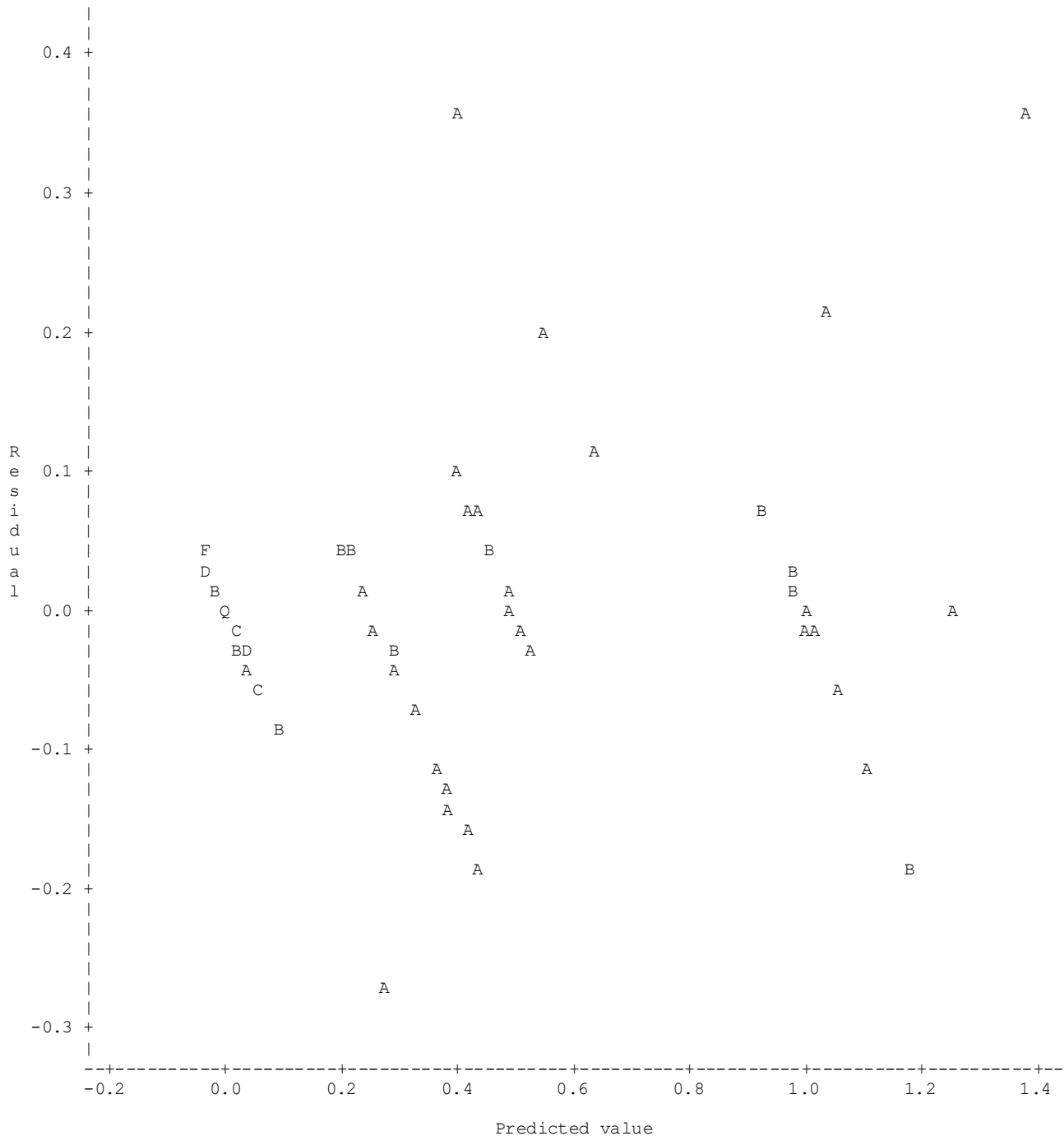
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after ES

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



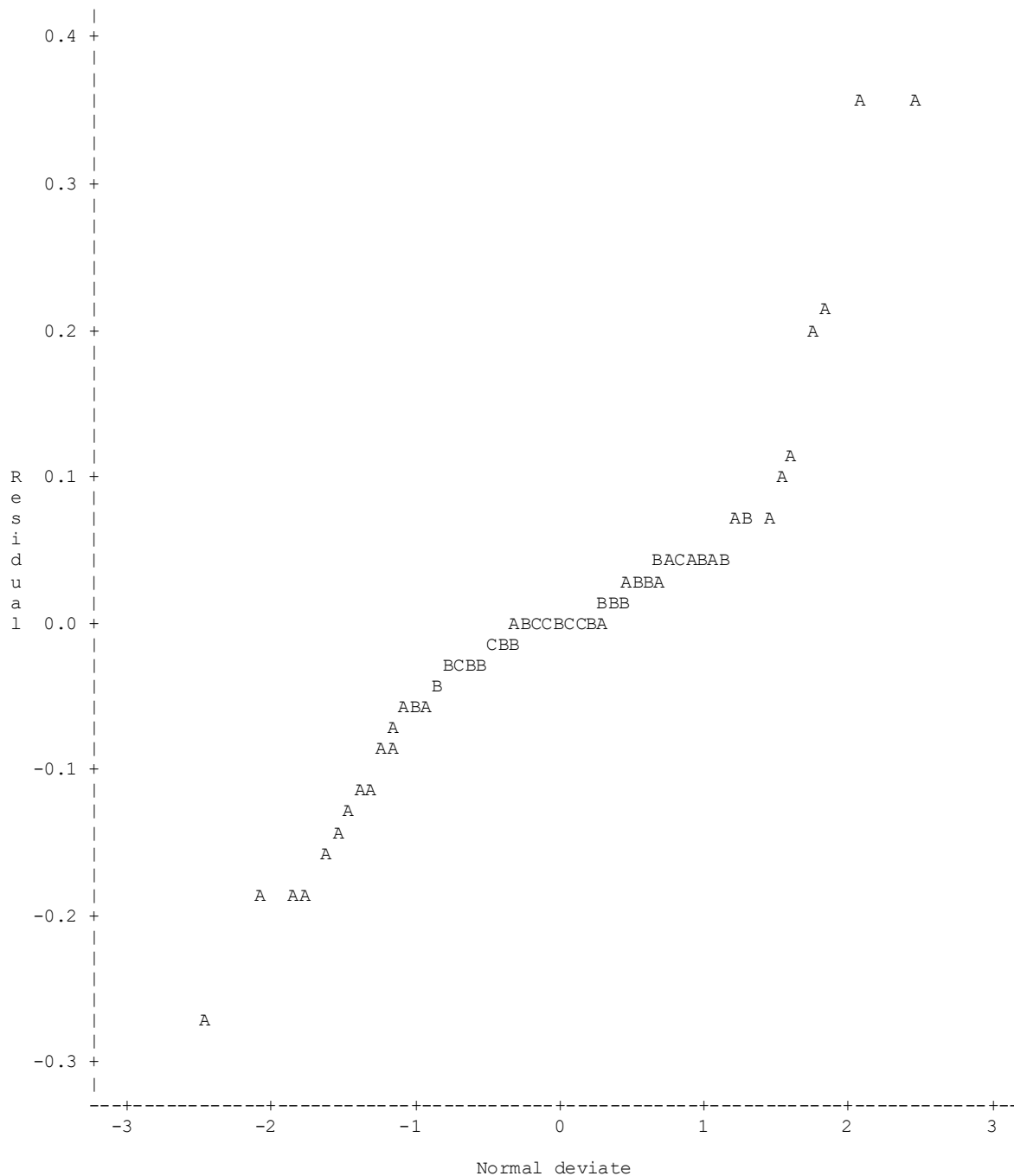
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after ES

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.849 : P-value=<0.001)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 19.2 Affective after ES change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after ES
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaAffectiveStair
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	88

Number of Observations

Number of Observations Read	88
Number of Observations Used	88
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-8.50642983	
1	2	-48.05662842	0.00001462
2	1	-48.05805799	0.00000002
3	1	-48.05805960	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.02004
Treatment*SubjectNr	0.004750
etime*SubjectNr	0.002841
Residual	0.01316

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after ES
Change from baseline

Fit Statistics

-2 Res Log Likelihood	-48.1
AIC (smaller is better)	-40.1
AICC (smaller is better)	-39.5
BIC (smaller is better)	-38.5

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	39.55	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	7.78	0.53	0.4880
etime	3	30	1.75	0.1788
Occasion	1	8.23	3.73	0.0886
Treatment*etime	3	30	0.49	0.6948
preAffectiveStair	1	12.1	2.46	0.1426

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-0.00021	0.05120	11.1	-0.00	0.9968	0.05
Treatment	Paracetamol		-0.02820	0.05120	11.1	-0.55	0.5928	0.05
Treatment*etime	Placebo	1:08:00	0.07365	0.06093	21.6	1.21	0.2399	0.05
Treatment*etime	Placebo	2:08:00	0.005469	0.06093	21.6	0.09	0.9293	0.05
Treatment*etime	Placebo	3:08:00	-0.03999	0.06093	21.6	-0.66	0.5186	0.05
Treatment*etime	Placebo	5:08:00	-0.03999	0.06093	21.6	-0.66	0.5186	0.05
Treatment*etime	Paracetamol	1:08:00	-0.00547	0.06093	21.6	-0.09	0.9293	0.05
Treatment*etime	Paracetamol	2:08:00	-0.00547	0.06093	21.6	-0.09	0.9293	0.05
Treatment*etime	Paracetamol	3:08:00	-0.05092	0.06093	21.6	-0.84	0.4125	0.05
Treatment*etime	Paracetamol	5:08:00	-0.05092	0.06093	21.6	-0.84	0.4125	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.1128	0.1124
Treatment	Paracetamol		-0.1408	0.08437
Treatment*etime	Placebo	1:08:00	-0.05287	0.2002
Treatment*etime	Placebo	2:08:00	-0.1210	0.1320
Treatment*etime	Placebo	3:08:00	-0.1665	0.08653
Treatment*etime	Placebo	5:08:00	-0.1665	0.08653
Treatment*etime	Paracetamol	1:08:00	-0.1320	0.1210
Treatment*etime	Paracetamol	2:08:00	-0.1320	0.1210
Treatment*etime	Paracetamol	3:08:00	-0.1774	0.07559
Treatment*etime	Paracetamol	5:08:00	-0.1774	0.07559

MPQ VAS after ES (mm)**SAS output 20.1 MPQ VAS after ES (mm)**

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after ES

Model Information

Data Set	WORK.MIX
Dependent Variable	MPQstair
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kacker-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	630.74112692	
1	2	605.80877217	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	6.7887
Treatment*SubjectNr	24.0143
etime*SubjectNr	5.7322
Residual	26.3023

Fit Statistics

-2 Res Log Likelihood	605.8
AIC (smaller is better)	613.8
AICC (smaller is better)	614.3

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after ES

Fit Statistics

BIC (smaller is better) 615.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	24.93	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	10.3	2.47	0.1462
etime	3	33	1.05	0.3834
Occasion	1	9.98	1.08	0.3243
Treatment*etime	3	33	0.04	0.9910
preMPQstair	1	10.6	202.26	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	3.5777	2.2755	10.3	1.57	0.1462	0.05	-1.4743	8.6297

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		37.0653	1.8039	19.1	20.55	<.0001	0.05
Treatment	Paracetamol		40.6430	1.8039	19.1	22.53	<.0001	0.05
Treatment*etime	Placebo	1:08:00	38.1841	2.2927	44.8	16.65	<.0001	0.05
Treatment*etime	Placebo	2:08:00	38.1591	2.2927	44.8	16.64	<.0001	0.05
Treatment*etime	Placebo	3:08:00	35.8757	2.2927	44.8	15.65	<.0001	0.05
Treatment*etime	Placebo	5:08:00	36.0424	2.2927	44.8	15.72	<.0001	0.05
Treatment*etime	Paracetamol	1:08:00	41.8493	2.2927	44.8	18.25	<.0001	0.05
Treatment*etime	Paracetamol	2:08:00	41.5826	2.2927	44.8	18.14	<.0001	0.05
Treatment*etime	Paracetamol	3:08:00	39.0243	2.2927	44.8	17.02	<.0001	0.05
Treatment*etime	Paracetamol	5:08:00	40.1159	2.2927	44.8	17.50	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		33.2913	40.8393
Treatment	Paracetamol		36.8690	44.4170
Treatment*etime	Placebo	1:08:00	33.5659	42.8022
Treatment*etime	Placebo	2:08:00	33.5409	42.7772
Treatment*etime	Placebo	3:08:00	31.2575	40.4939
Treatment*etime	Placebo	5:08:00	31.4242	40.6606
Treatment*etime	Paracetamol	1:08:00	37.2311	46.4675
Treatment*etime	Paracetamol	2:08:00	36.9644	46.2008
Treatment*etime	Paracetamol	3:08:00	34.4061	43.6425
Treatment*etime	Paracetamol	5:08:00	35.4978	44.7341

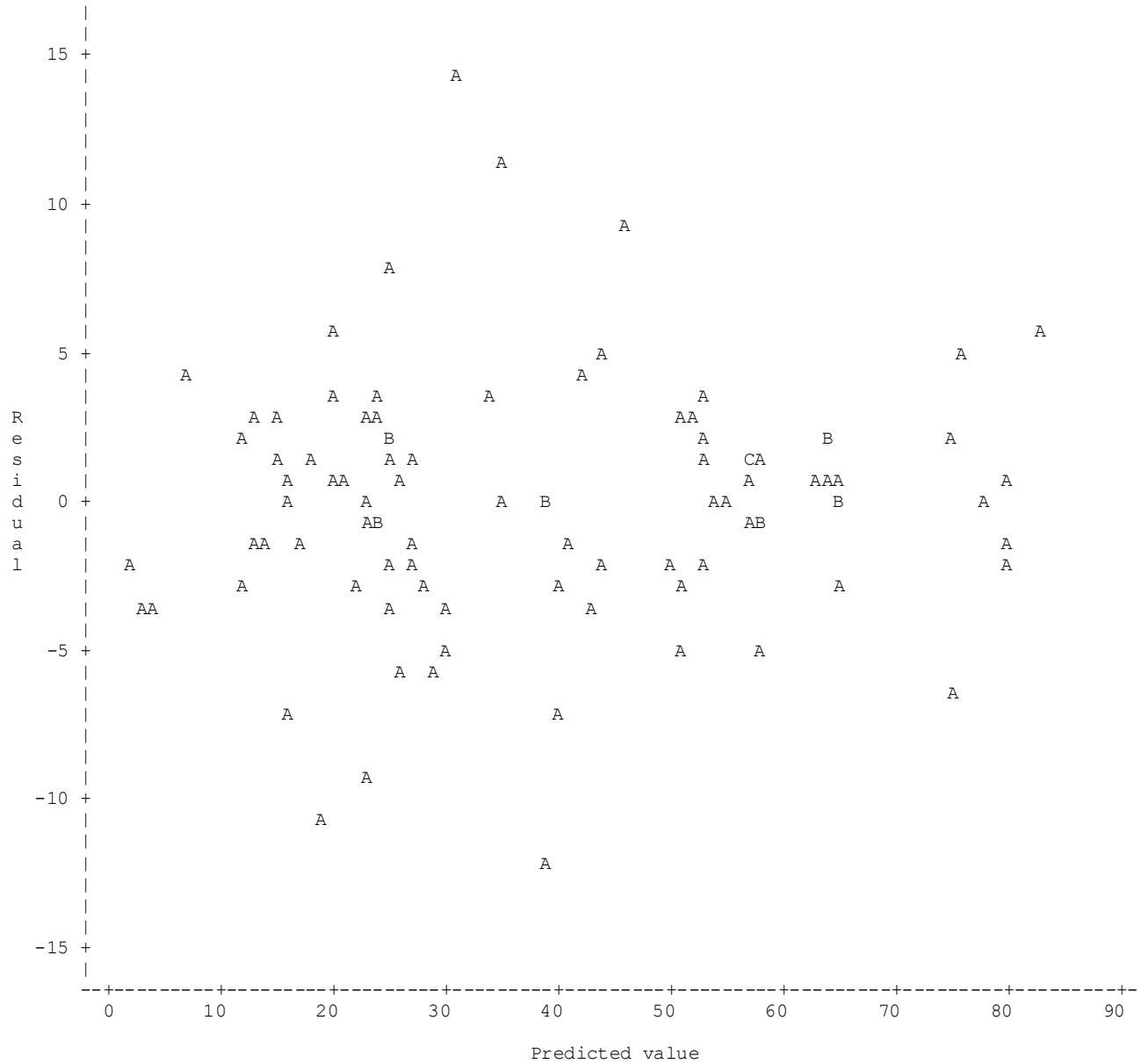
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after ES

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



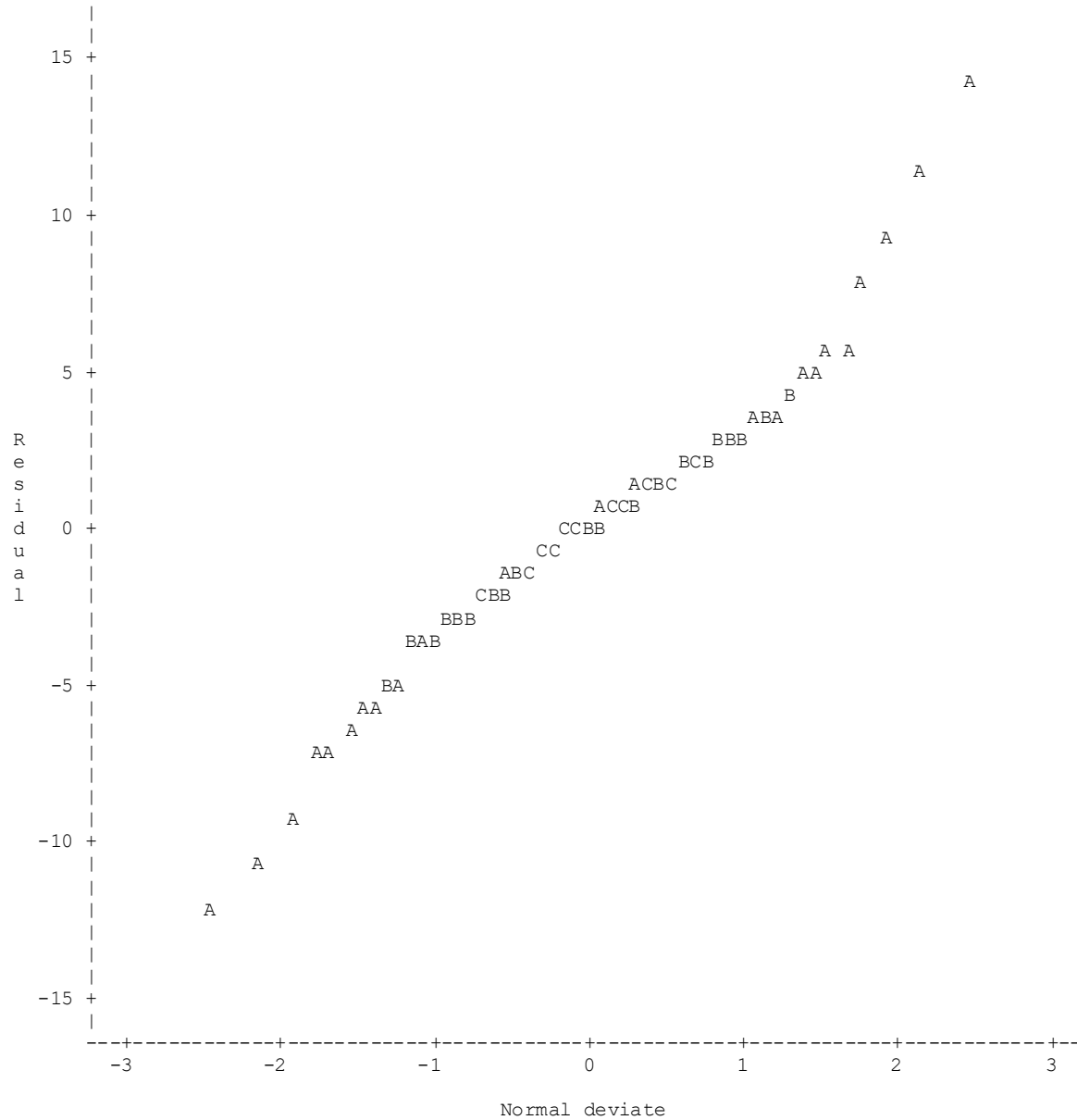
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Proc MIXED analysis of MPQ VAS after ES

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.962 : P-value= 0.007)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 20.2 MPQ VAS after ES (mm) change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after ES
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaMPQstair
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:08 2:08 3:08 5:08
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	630.74112692	
1	2	605.80877217	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	6.7887
Treatment*SubjectNr	24.0143
etime*SubjectNr	5.7322
Residual	26.3023

Fit Statistics

-2 Res Log Likelihood	605.8
AIC (smaller is better)	613.8

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Proc MIXED analysis of MPQ VAS after ES
Change from baseline

Fit Statistics

AICC (smaller is better) 614.3
BIC (smaller is better) 615.7

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	24.93	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	10.3	2.47	0.1462
etime	3	33	1.05	0.3834
Occasion	1	9.98	1.08	0.3243
Treatment*etime	3	33	0.04	0.9910
preMPQstair	1	10.6	0.12	0.7339

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-3.2180	1.8039	19.1	-1.78	0.0903	0.05
Treatment	Paracetamol		0.3597	1.8039	19.1	0.20	0.8441	0.05
Treatment*etime	Placebo	1:08:00	-2.0993	2.2927	44.8	-0.92	0.3648	0.05
Treatment*etime	Placebo	2:08:00	-2.1243	2.2927	44.8	-0.93	0.3591	0.05
Treatment*etime	Placebo	3:08:00	-4.4076	2.2927	44.8	-1.92	0.0609	0.05
Treatment*etime	Placebo	5:08:00	-4.2409	2.2927	44.8	-1.85	0.0709	0.05
Treatment*etime	Paracetamol	1:08:00	1.5659	2.2927	44.8	0.68	0.4981	0.05
Treatment*etime	Paracetamol	2:08:00	1.2993	2.2927	44.8	0.57	0.5737	0.05
Treatment*etime	Paracetamol	3:08:00	-1.2591	2.2927	44.8	-0.55	0.5856	0.05
Treatment*etime	Paracetamol	5:08:00	-0.1674	2.2927	44.8	-0.07	0.9421	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-6.9920	0.5560
Treatment	Paracetamol		-3.4143	4.1337
Treatment*etime	Placebo	1:08:00	-6.7175	2.5189
Treatment*etime	Placebo	2:08:00	-6.7425	2.4939
Treatment*etime	Placebo	3:08:00	-9.0258	0.2106
Treatment*etime	Placebo	5:08:00	-8.8591	0.3772
Treatment*etime	Paracetamol	1:08:00	-3.0522	6.1841
Treatment*etime	Paracetamol	2:08:00	-3.3189	5.9175
Treatment*etime	Paracetamol	3:08:00	-5.8772	3.3591
Treatment*etime	Paracetamol	5:08:00	-4.7856	4.4508

Sensory after Pressure

SAS output 21.1 Sensory after Pressure

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after Pressure

Model Information

Data Set	WORK.MIX
Dependent Variable	Sensorypress
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	88

Number of Observations

Number of Observations Read	88
Number of Observations Used	88
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-6.84607907	
1	2	-19.94382354	0.00000003
2	1	-19.94382600	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-0.00473
Treatment*SubjectNr	0.01999
etime*SubjectNr	0.001897
Residual	0.02305

Fit Statistics

-2 Res Log Likelihood	-19.9
AIC (smaller is better)	-11.9

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Proc MIXED analysis of Sensory after Pressure

Fit Statistics

AICC (smaller is better)	-11.4
BIC (smaller is better)	-10.4

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	13.10	0.0044

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.68	0.06	0.8057
etime	3	30	1.13	0.3514
Occasion	1	9.31	3.11	0.1108
Treatment*etime	3	30	1.65	0.1985
preSensoryPress	1	9.23	285.46	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	-0.01742	0.06871	8.68	-0.25	0.8057	0.05	-0.1737	0.1389

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		0.9240	0.04432	17.2	20.85	<.0001	0.05
Treatment	Paracetamol		0.9066	0.04432	17.2	20.46	<.0001	0.05
Treatment*etime	Placebo	1:13:00	1.0128	0.06054	49.3	16.73	<.0001	0.05
Treatment*etime	Placebo	2:13:00	0.9467	0.06054	49.3	15.64	<.0001	0.05
Treatment*etime	Placebo	3:13:00	0.8641	0.06054	49.3	14.27	<.0001	0.05
Treatment*etime	Placebo	5:13:00	0.8723	0.06054	49.3	14.41	<.0001	0.05
Treatment*etime	Paracetamol	1:13:00	0.8797	0.06054	49.3	14.53	<.0001	0.05
Treatment*etime	Paracetamol	2:13:00	0.9458	0.06054	49.3	15.62	<.0001	0.05
Treatment*etime	Paracetamol	3:13:00	0.9293	0.06054	49.3	15.35	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		0.8306	1.0174
Treatment	Paracetamol		0.8132	1.0000
Treatment*etime	Placebo	1:13:00	0.8912	1.1345
Treatment*etime	Placebo	2:13:00	0.8251	1.0684
Treatment*etime	Placebo	3:13:00	0.7424	0.9857
Treatment*etime	Placebo	5:13:00	0.7507	0.9940
Treatment*etime	Paracetamol	1:13:00	0.7581	1.0014
Treatment*etime	Paracetamol	2:13:00	0.8242	1.0675
Treatment*etime	Paracetamol	3:13:00	0.8077	1.0509

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Proc MIXED analysis of Sensory after Pressure

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	5:13:00	0.8715	0.06054	49.3	14.39	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	5:13:00	0.7498	0.9931

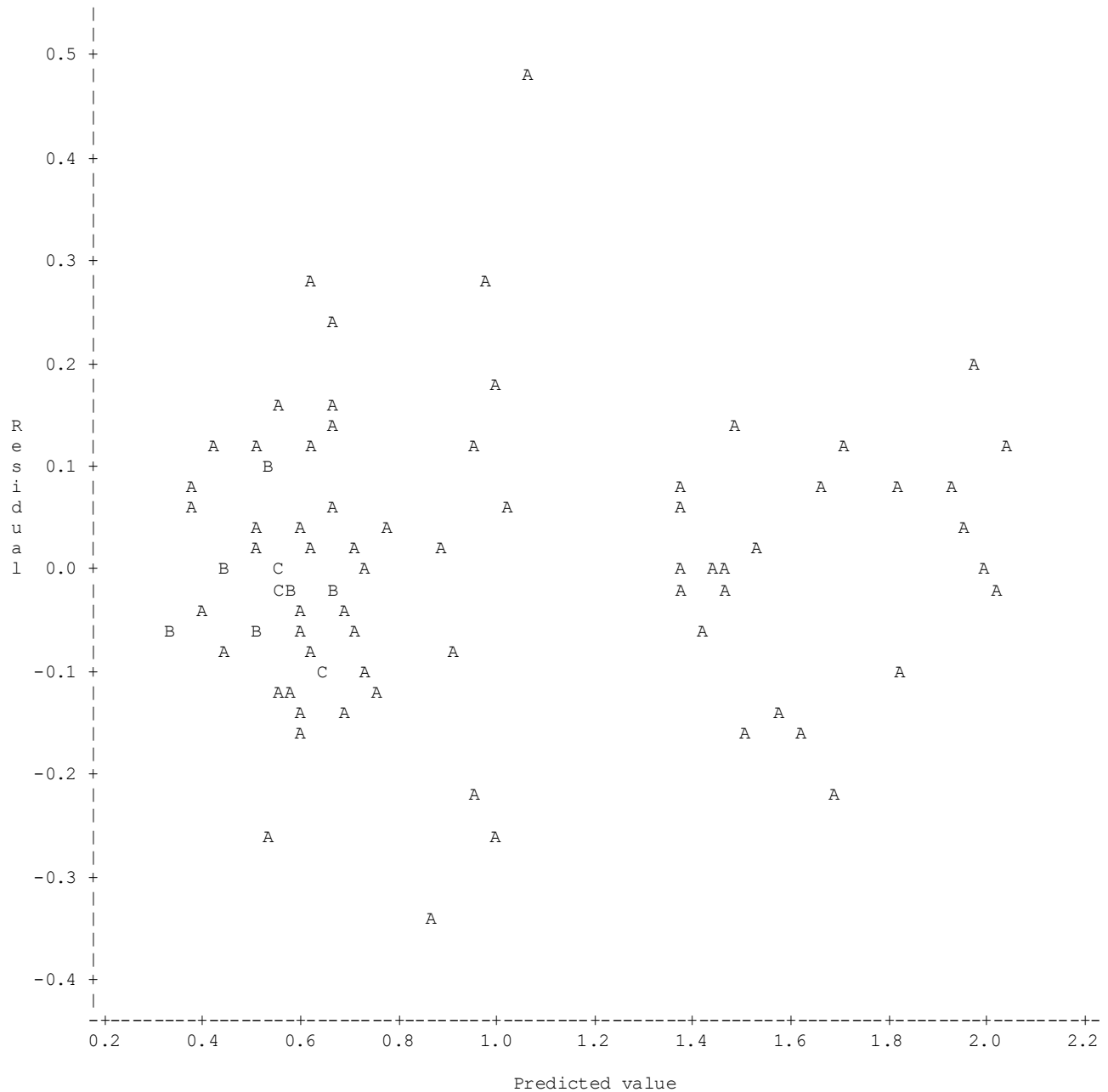
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after Pressure

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



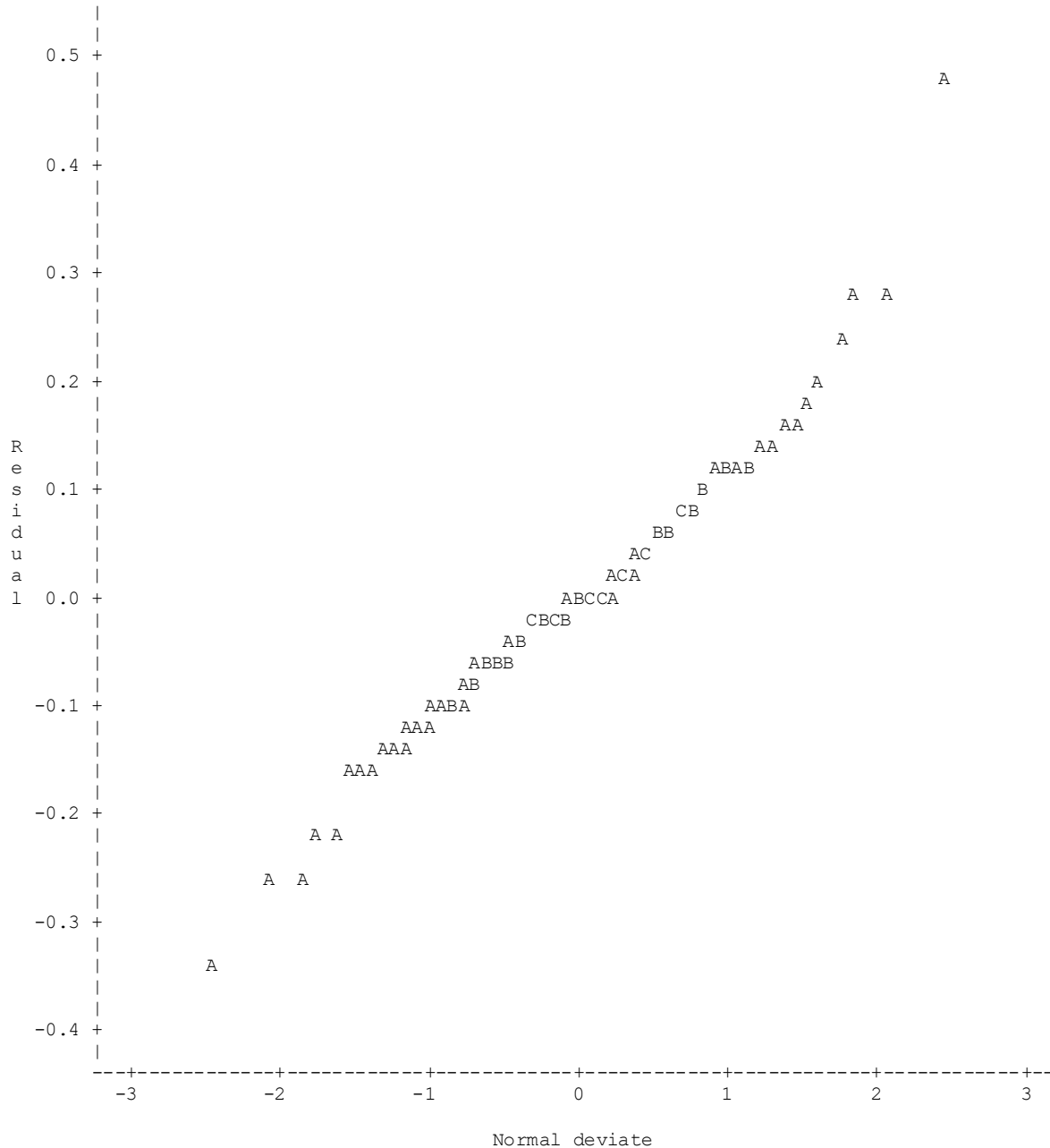
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Proc MIXED analysis of Sensory after Pressure

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.974 : P-value= 0.074)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 21.2 Sensory after Pressure change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after Pressure
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaSensoryPress
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske- Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	88

Number of Observations

Number of Observations Read	88
Number of Observations Used	88
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-6.84607907	
1	2	-19.94382354	0.00000003
2	1	-19.94382600	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-0.00473
Treatment*SubjectNr	0.01999
etime*SubjectNr	0.001897
Residual	0.02305

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Sensory after Pressure
Change from baseline

Fit Statistics

-2 Res Log Likelihood	-19.9
AIC (smaller is better)	-11.9
AICC (smaller is better)	-11.4
BIC (smaller is better)	-10.4

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	13.10	0.0044

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	8.68	0.06	0.8057
etime	3	30	1.13	0.3514
Occasion	1	9.31	3.11	0.1108
Treatment*etime	3	30	1.65	0.1985
preSensoryPress	1	9.23	10.15	0.0107

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-0.04294	0.04432	17.2	-0.97	0.3460	0.05
Treatment	Paracetamol		-0.06037	0.04432	17.2	-1.36	0.1907	0.05
Treatment*etime	Placebo	1:13:00	0.04590	0.06054	49.3	0.76	0.4519	0.05
Treatment*etime	Placebo	2:13:00	-0.02021	0.06054	49.3	-0.33	0.7399	0.05
Treatment*etime	Placebo	3:13:00	-0.1029	0.06054	49.3	-1.70	0.0956	0.05
Treatment*etime	Placebo	5:13:00	-0.09459	0.06054	49.3	-1.56	0.1246	0.05
Treatment*etime	Paracetamol	1:13:00	-0.08722	0.06054	49.3	-1.44	0.1560	0.05
Treatment*etime	Paracetamol	2:13:00	-0.02111	0.06054	49.3	-0.35	0.7288	0.05
Treatment*etime	Paracetamol	3:13:00	-0.03764	0.06054	49.3	-0.62	0.5370	0.05
Treatment*etime	Paracetamol	5:13:00	-0.09549	0.06054	49.3	-1.58	0.1211	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.1363	0.05047
Treatment	Paracetamol		-0.1538	0.03304
Treatment*etime	Placebo	1:13:00	-0.07574	0.1675
Treatment*etime	Placebo	2:13:00	-0.1419	0.1014
Treatment*etime	Placebo	3:13:00	-0.2245	0.01878
Treatment*etime	Placebo	5:13:00	-0.2162	0.02705
Treatment*etime	Paracetamol	1:13:00	-0.2089	0.03442
Treatment*etime	Paracetamol	2:13:00	-0.1427	0.1005
Treatment*etime	Paracetamol	3:13:00	-0.1593	0.08400
Treatment*etime	Paracetamol	5:13:00	-0.2171	0.02615

Affective after Pressure

SAS output 22.1 Affective after Pressure

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Proc MIXED analysis of Affective after Pressure

Model Information

Data Set	WORK.MIX
Dependent Variable	Affectivepress
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	88

Number of Observations

Number of Observations Read	88
Number of Observations Used	88
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-63.58142719	
1	2	-104.73533395	0.00156487
2	1	-104.96381975	0.00019400
3	1	-104.99011537	0.00000466
4	1	-104.99070326	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.008119
Treatment*SubjectNr	0.001376
etime*SubjectNr	0.007765
Residual	0.003599

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Proc MIXED analysis of Affective after Pressure

Fit Statistics

-2 Res Log Likelihood	-105.0
AIC (smaller is better)	-97.0
AICC (smaller is better)	-96.4
BIC (smaller is better)	-95.4

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	41.41	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	6.45	0.46	0.5212
etime	3	30	1.03	0.3945
Occasion	1	6.45	2.74	0.1457
Treatment*etime	3	30	2.30	0.0972
preAffectivePress	1	15.9	81.90	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	0.01448	0.02135	6.45	0.68	0.5212	0.05	-0.03689	0.06585

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		0.1547	0.03364	8.32	4.60	0.0016	0.05
Treatment	Paracetamol		0.1692	0.03364	8.32	5.03	0.0009	0.05
Treatment*etime	Placebo	1:13:00	0.1774	0.04367	21.6	4.06	0.0005	0.05
Treatment*etime	Placebo	2:13:00	0.1547	0.04367	21.6	3.54	0.0019	0.05
Treatment*etime	Placebo	3:13:00	0.1092	0.04367	21.6	2.50	0.0205	0.05
Treatment*etime	Placebo	5:13:00	0.1774	0.04367	21.6	4.06	0.0005	0.05
Treatment*etime	Paracetamol	1:13:00	0.2089	0.04367	21.6	4.78	<.0001	0.05
Treatment*etime	Paracetamol	2:13:00	0.1180	0.04367	21.6	2.70	0.0131	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		0.07762	0.2318
Treatment	Paracetamol		0.09210	0.2462
Treatment*etime	Placebo	1:13:00	0.08676	0.2681
Treatment*etime	Placebo	2:13:00	0.06403	0.2454
Treatment*etime	Placebo	3:13:00	0.01858	0.1999
Treatment*etime	Placebo	5:13:00	0.08676	0.2681
Treatment*etime	Paracetamol	1:13:00	0.1183	0.2996
Treatment*etime	Paracetamol	2:13:00	0.02738	0.2087

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Proc MIXED analysis of Affective after Pressure

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	3:13:00	0.1635	0.04367	21.6	3.74	0.0012	0.05
Treatment*etime	Paracetamol	5:13:00	0.1862	0.04367	21.6	4.26	0.0003	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	3:13:00	0.07283	0.2541
Treatment*etime	Paracetamol	5:13:00	0.09556	0.2769

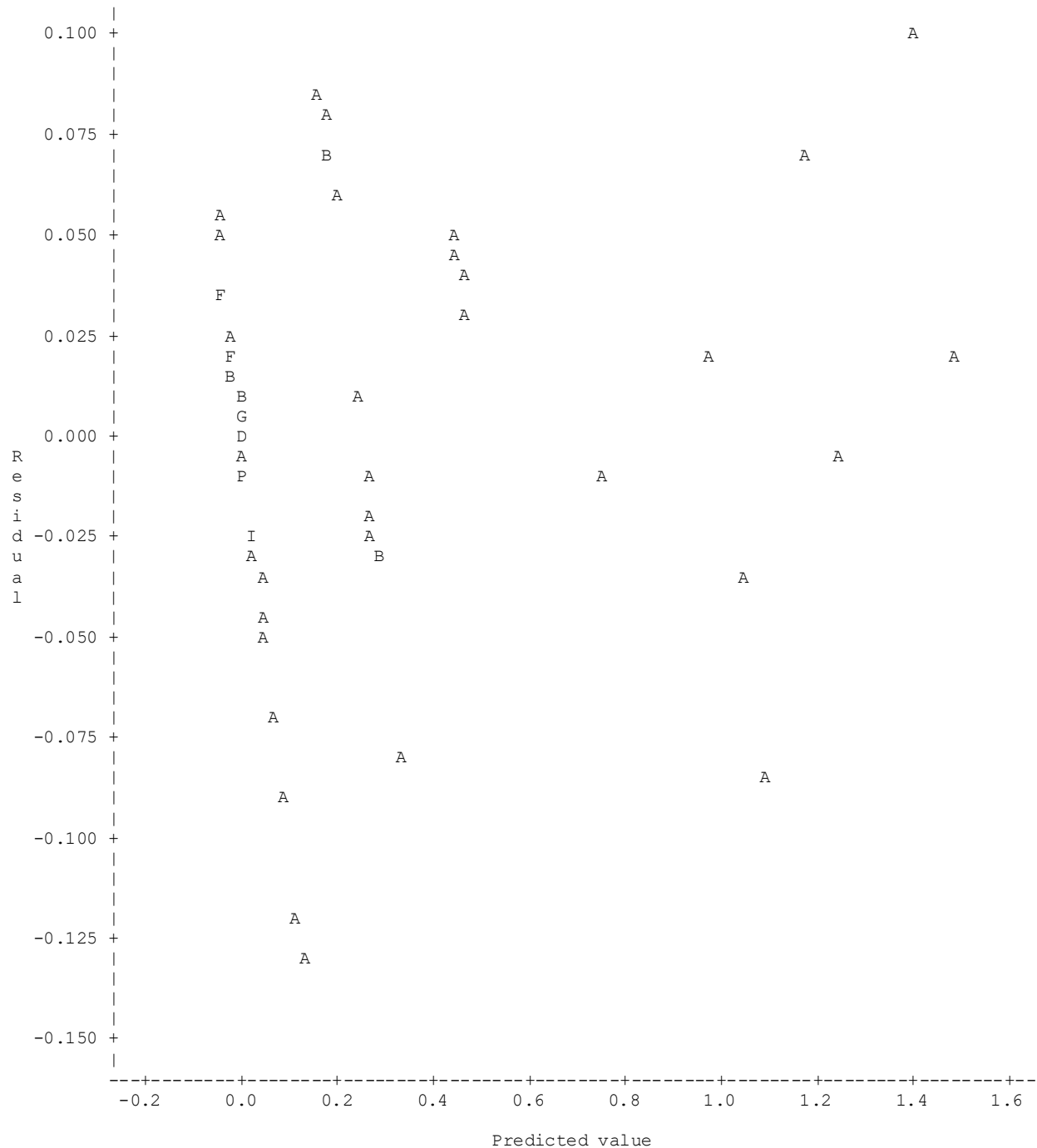
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Proc MIXED analysis of Affective after Pressure

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



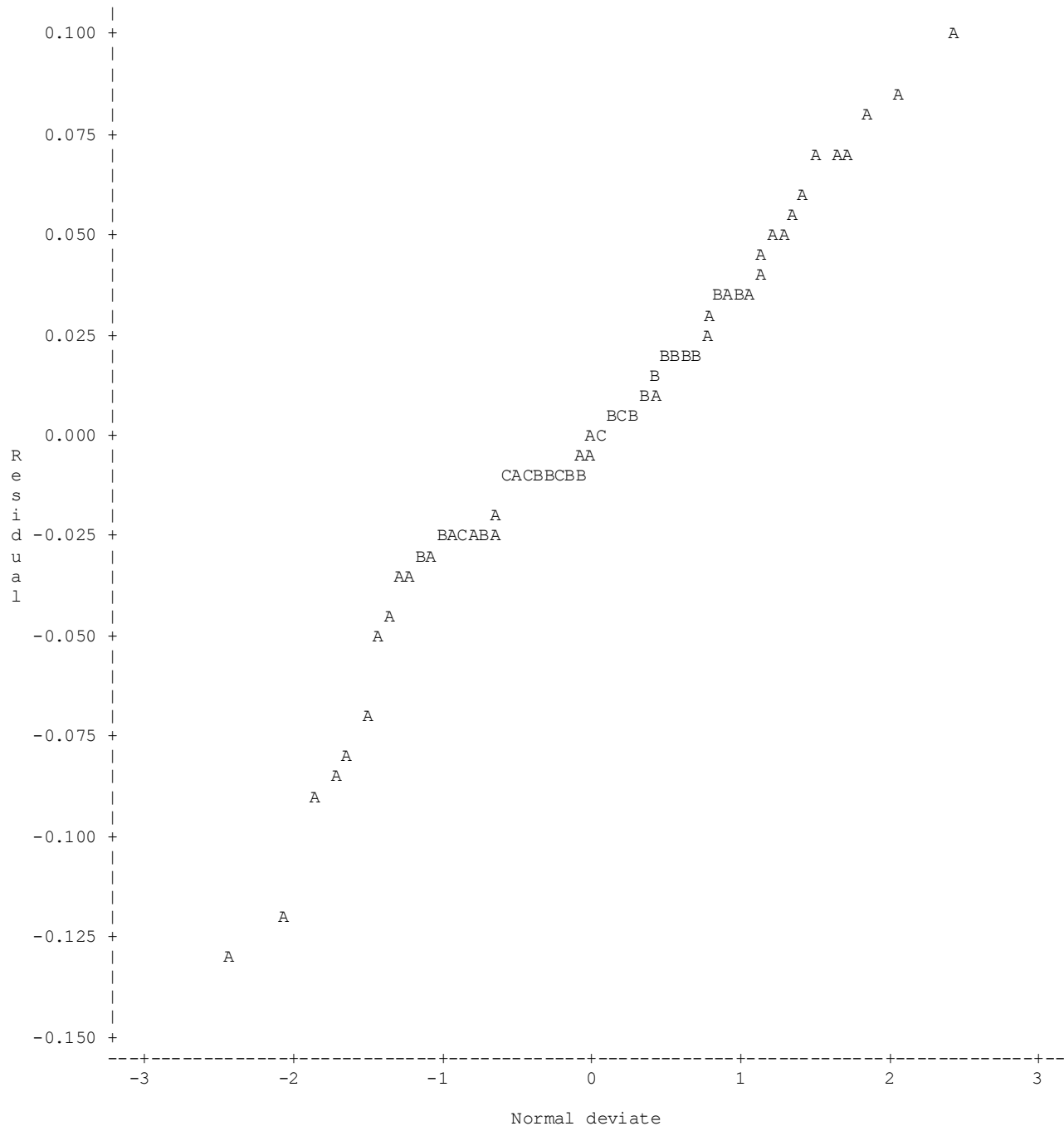
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Proc MIXED analysis of Affective after Pressure

Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.954 : P-value= 0.004)

Plot of Resid*rankres. Legend: A = 1 obs, B = 2 obs, etc.



SAS output 22.2 Affective after Pressure change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after Pressure
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaAffectivePress
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske- Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	11	2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	77
Subjects	1
Max Obs Per Subject	88

Number of Observations

Number of Observations Read	88
Number of Observations Used	88
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	-63.58142719	
1	2	-104.73533395	0.00156487
2	1	-104.96381975	0.00019400
3	1	-104.99011537	0.00000466
4	1	-104.99070326	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	0.008119
Treatment*SubjectNr	0.001376
etime*SubjectNr	0.007765
Residual	0.003599

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of Affective after Pressure
Change from baseline

Fit Statistics

-2 Res Log Likelihood	-105.0
AIC (smaller is better)	-97.0
AICC (smaller is better)	-96.4
BIC (smaller is better)	-95.4

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	41.41	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	6.45	0.46	0.5212
etime	3	30	1.03	0.3945
Occasion	1	6.45	2.74	0.1457
Treatment*etime	3	30	2.30	0.0972
preAffectivePress	1	15.9	9.23	0.0079

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-0.08394	0.03364	8.32	-2.50	0.0362	0.05
Treatment	Paracetamol		-0.06946	0.03364	8.32	-2.06	0.0715	0.05
Treatment*etime	Placebo	1:13:00	-0.06122	0.04367	21.6	-1.40	0.1752	0.05
Treatment*etime	Placebo	2:13:00	-0.08394	0.04367	21.6	-1.92	0.0679	0.05
Treatment*etime	Placebo	3:13:00	-0.1294	0.04367	21.6	-2.96	0.0073	0.05
Treatment*etime	Placebo	5:13:00	-0.06122	0.04367	21.6	-1.40	0.1752	0.05
Treatment*etime	Paracetamol	1:13:00	-0.02969	0.04367	21.6	-0.68	0.5038	0.05
Treatment*etime	Paracetamol	2:13:00	-0.1206	0.04367	21.6	-2.76	0.0115	0.05
Treatment*etime	Paracetamol	3:13:00	-0.07515	0.04367	21.6	-1.72	0.0996	0.05
Treatment*etime	Paracetamol	5:13:00	-0.05242	0.04367	21.6	-1.20	0.2430	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-0.1610	-0.00688
Treatment	Paracetamol		-0.1465	0.007603
Treatment*etime	Placebo	1:13:00	-0.1519	0.02944
Treatment*etime	Placebo	2:13:00	-0.1746	0.006715
Treatment*etime	Placebo	3:13:00	-0.2201	-0.03874
Treatment*etime	Placebo	5:13:00	-0.1519	0.02944
Treatment*etime	Paracetamol	1:13:00	-0.1204	0.06097
Treatment*etime	Paracetamol	2:13:00	-0.2113	-0.02994
Treatment*etime	Paracetamol	3:13:00	-0.1658	0.01551
Treatment*etime	Paracetamol	5:13:00	-0.1431	0.03824

MPQ VAS after Pressure (mm)**SAS output 23.1 MPQ VAS after Pressure (mm)**

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after Pressure

Model Information

Data Set	WORK.MIX
Dependent Variable	MPQpress
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	610.31918621	
1	2	553.18080084	0.00004894
2	1	553.17059977	0.00000039
3	1	553.17052275	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-24.7160
Treatment*SubjectNr	59.5606
etime*SubjectNr	-4.5582
Residual	20.5761

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after Pressure

Fit Statistics

-2 Res Log Likelihood	553.2
AIC (smaller is better)	561.2
AICC (smaller is better)	561.7
BIC (smaller is better)	563.1

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	57.15	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.93	2.63	0.1359
etime	3	33	2.68	0.0626
Occasion	1	9.9	1.00	0.3410
Treatment*etime	3	33	1.75	0.1755
preMPQpress	1	10.1	958.54	<.0001

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Placebo - Paracetamol	5.3401	3.2903	9.93	1.62	0.1359	0.05	-1.9982	12.6784

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		32.2727	1.8022	13.8	17.91	<.0001	0.05
Treatment	Paracetamol		37.6128	1.8022	13.8	20.87	<.0001	0.05
Treatment*etime	Placebo	1:13:00	32.9977	2.0613	23.1	16.01	<.0001	0.05
Treatment*etime	Placebo	2:13:00	31.6477	2.0613	23.1	15.35	<.0001	0.05
Treatment*etime	Placebo	3:13:00	31.0477	2.0613	23.1	15.06	<.0001	0.05
Treatment*etime	Placebo	5:13:00	33.3977	2.0613	23.1	16.20	<.0001	0.05
Treatment*etime	Paracetamol	1:13:00	39.3440	2.0613	23.1	19.09	<.0001	0.05
Treatment*etime	Paracetamol	2:13:00	39.4440	2.0613	23.1	19.14	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		28.4020	36.1433
Treatment	Paracetamol		33.7421	41.4834
Treatment*etime	Placebo	1:13:00	28.7347	37.2606
Treatment*etime	Placebo	2:13:00	27.3847	35.9106
Treatment*etime	Placebo	3:13:00	26.7847	35.3106
Treatment*etime	Placebo	5:13:00	29.1347	37.6606
Treatment*etime	Paracetamol	1:13:00	35.0811	43.6069
Treatment*etime	Paracetamol	2:13:00	35.1811	43.7069

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Proc MIXED analysis of MPQ VAS after Pressure

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment*etime	Paracetamol	3:13:00	36.2357	2.0613	23.1	17.58	<.0001	0.05
Treatment*etime	Paracetamol	5:13:00	35.4273	2.0613	23.1	17.19	<.0001	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment*etime	Paracetamol	3:13:00	31.9727	40.4986
Treatment*etime	Paracetamol	5:13:00	31.1644	39.6903

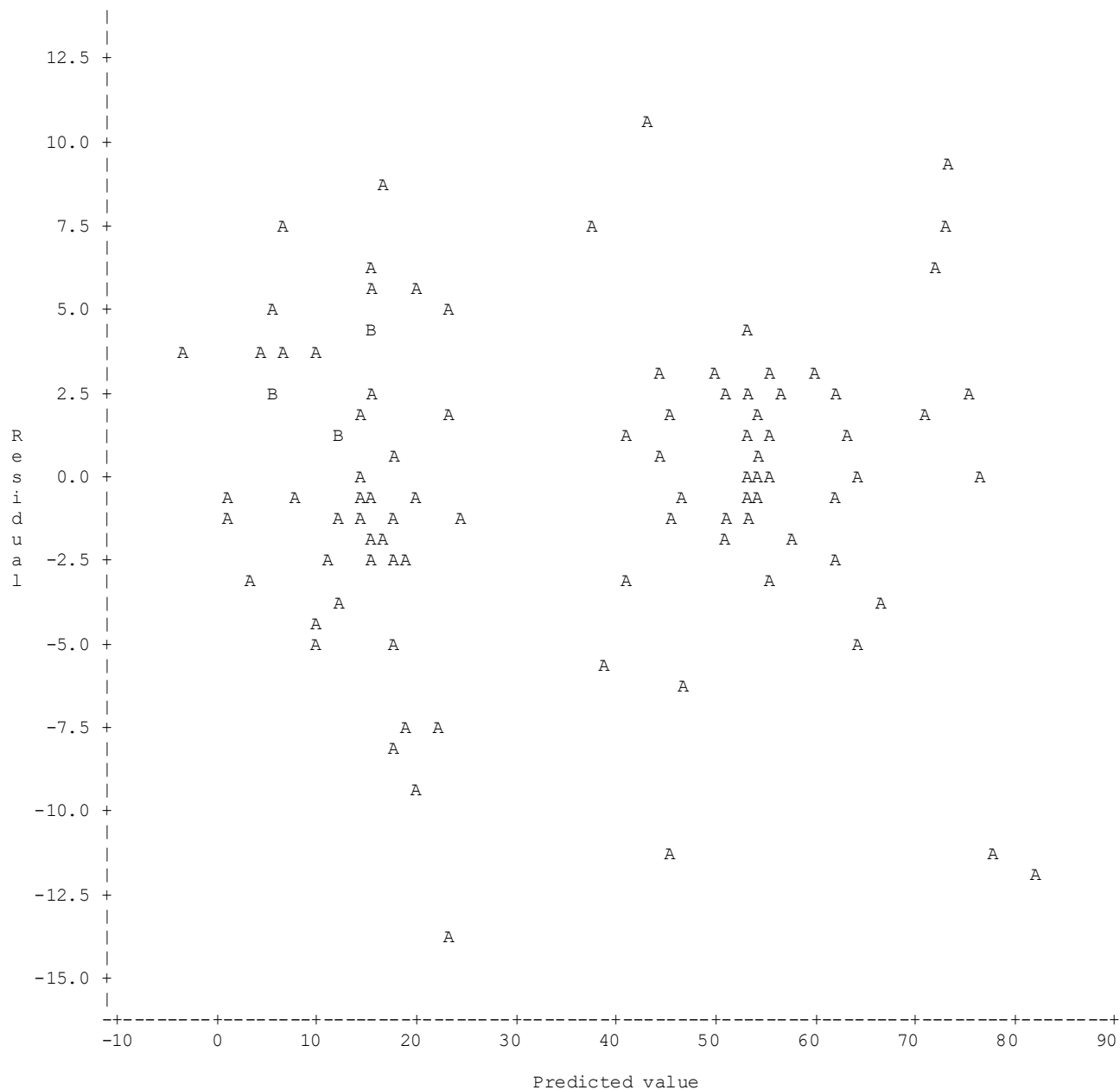
g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after Pressure

Residuals vs Predicted values

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



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Normal probability plot for residuals
(Shapiro-Wilk Test Statistic = 0.973 : P-value= 0.045)

[illegible]

SAS output 23.2 MPQ VAS after Pressure (mm) change from baseline

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after Pressure
Change from baseline

Model Information

Data Set	WORK.MIX
Dependent Variable	deltaMPQpress
Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Prasad-Rao-Jeske- Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
Treatment	2	Placebo Paracetamol
etime	4	1:13 2:13 3:13 5:13
Occasion	2	1 2
SubjectNr	12	1 2 3 4 5 6 7 8 9 10 11 12

Dimensions

Covariance Parameters	4
Columns in X	18
Columns in Z	84
Subjects	1
Max Obs Per Subject	96

Number of Observations

Number of Observations Read	96
Number of Observations Used	96
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	610.31918621	
1	2	553.18080084	0.00004894
2	1	553.17059977	0.00000039
3	1	553.17052275	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
SubjectNr	-24.7160
Treatment*SubjectNr	59.5606
etime*SubjectNr	-4.5582
Residual	20.5761

g:\2011\CHDR1117\Stats\Analysis\2014_09_30\CHDR1117_PD_DataA.sas

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Proc MIXED analysis of MPQ VAS after Pressure
Change from baseline

Fit Statistics

-2 Res Log Likelihood	553.2
AIC (smaller is better)	561.2
AICC (smaller is better)	561.7
BIC (smaller is better)	563.1

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	57.15	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treatment	1	9.93	2.63	0.1359
etime	3	33	2.68	0.0626
Occasion	1	9.9	1.00	0.3410
Treatment*etime	3	33	1.75	0.1755
preMPQpress	1	10.1	3.00	0.1136

Least Squares Means

Effect	Treatment	Time (hh:mm)	Estimate	Standard Error	DF	t Value	Pr > t	Alpha
Treatment	Placebo		-4.2440	1.8022	13.8	-2.35	0.0339	0.05
Treatment	Paracetamol		1.0961	1.8022	13.8	0.61	0.5529	0.05
Treatment*etime	Placebo	1:13:00	-3.5190	2.0613	23.1	-1.71	0.1012	0.05
Treatment*etime	Placebo	2:13:00	-4.8690	2.0613	23.1	-2.36	0.0270	0.05
Treatment*etime	Placebo	3:13:00	-5.4690	2.0613	23.1	-2.65	0.0142	0.05
Treatment*etime	Placebo	5:13:00	-3.1190	2.0613	23.1	-1.51	0.1438	0.05
Treatment*etime	Paracetamol	1:13:00	2.8273	2.0613	23.1	1.37	0.1833	0.05
Treatment*etime	Paracetamol	2:13:00	2.9273	2.0613	23.1	1.42	0.1689	0.05
Treatment*etime	Paracetamol	3:13:00	-0.2810	2.0613	23.1	-0.14	0.8927	0.05
Treatment*etime	Paracetamol	5:13:00	-1.0893	2.0613	23.1	-0.53	0.6022	0.05

Least Squares Means

Effect	Treatment	Time (hh:mm)	Lower	Upper
Treatment	Placebo		-8.1146	-0.3734
Treatment	Paracetamol		-2.7745	4.9667
Treatment*etime	Placebo	1:13:00	-7.7819	0.7439
Treatment*etime	Placebo	2:13:00	-9.1319	-0.6061
Treatment*etime	Placebo	3:13:00	-9.7319	-1.2061
Treatment*etime	Placebo	5:13:00	-7.3819	1.1439
Treatment*etime	Paracetamol	1:13:00	-1.4356	7.0903
Treatment*etime	Paracetamol	2:13:00	-1.3356	7.1903
Treatment*etime	Paracetamol	3:13:00	-4.5439	3.9819
Treatment*etime	Paracetamol	5:13:00	-5.3523	3.1736

SAS Syntax

Analysis

```

*****;
*****;
* PROJECT NUMBER      :CHDR1117                                     *;
* AUTHOR              :M. de Kam                                   *;
* SAS VERSION         :9.1.3                                       *;
* SPONSOR             :CHDR                                         *;
* SHORT TITEL         :Effects paracetamol nociceptive pain        *;
* PURPOSE             :Statistical analysis of PD measurements     *;
* DATA FILE(S) USED  :CHDR1117_PDdata_2014_09_30.txt             *;
* DATE                :2014_09_30                                   *;
* VERSION             :1.1                                          *;
* CHANGES TO PREV.   :QST_heat variables added                   *;
* EXCL. DATA FILE:   :NA, no data to be excluded based on the BDR *;
*****;
*****;
* THIS FILE HAS TO BE SAVED IN A DIRECTORY WITHIN STATS/ANALYSIS/ THAT IS NAMED AS THE VERSION *;
* DATE: YYYY_MM_DD                                         *;
*****;

*****;
* G   =General                                           *;
* L   =Listing                                           *;
* IG  =Individual graphs                                *;
* STG =Summary table and graph                          *;
* A   =Analysis                                           *;
* RO  =Raw output                                         *;
*****;

***DATES-----;

/*DATE OF VERSION*/
%let dateV=2014_09_30;

/*DATE OF PROMASYS EXPORT*/
%let dateE=2014_09_30;

/*DATE OF VALIDATION */
%let dateVal=2014_09_30;

/*The validation can have a different date than the latest version, as not every version change*/
/*generates a new validation report (only if changes to the analysis data have been made compared*/
/*to the former version)*/
/*NB Within the directory stats/analysis/ there has to be a directory named with the date of the*/
/*validation*/

***OPTIONS-----;
/*hexadecimal code for CHDR colours*/
%let green=CX84BD00;
%let blue=CX009FE3;
%let red=CXE6007E;

/*document settings*/
%let linesizeP=100;
%let pagesizeP=68;
%let linesizeL=150;
%let pagesizeL=45;
%let linelen=100;
%let startpos=10;
%let pages=1;
%let pbpos=60;

missing U H L M;
options center linesize=&linesizeP pagesize=&pagesizeP number nodate pageno=1 missing=' '
formchar='|---|+|---+|=|<>' nofmtterr;

***DATE MACRO VARIABLES-----;
data _null_;
call symput('today',put(date(),yymmdd10.));
call symput('Bigtoday',left(put(date(),worddate18.)));

```

```

run;

***STUDY SPECIFIC MACRO VARIABLES-----;
%let statistician=M.L. de Kam; /*e.g. E.S. Klaassen*/
%let protocol=CHDR1117;
%let year=2011;
%let ana=PD;
/*these can be used further down in the script, but, if they are not used, empty notes have to*/
/*exist for the script to run*/
%let note1=;
%let note2=;

/*NAME OF THE RAW DATA FILE*/
*****;
%let file=&protocol._PDData_&dateE;
*****;

%let dirlocbase=g:\&year\&protocol\Stats\Analysis\;
%let dirloc=g:\&year\&protocol\Stats\Analysis\&DateV\;
%let dirlocval=g:\&year\&protocol\Stats\Analysis\&DateVal\;

%let dirlocL=&dirlocbase.Listings\;
%let dirlocT=&dirlocbase.Tables\;
%let dirlocG=&dirlocbase.Graphs\;
%let dirlocDfG=&dirlocbase.DataForGraphs\;
%let dirlocRO=&dirlocbase.RawOutput\;

***IF MACROS ARE VALIDATED DO;
/*%let macroloc=g:\stats\sassource\code\;*/
***ELSE DO;
%let macroloc=&dirlocbase;

%let root=&dirloc;
%let sasfile=&protocol._&ana._Analysis;

%let RI1=Prof. A.F. Cohen, MD, PhD, FFPM;
%let RI2=Prof. J.M.A. van Gerven, MD, PhD;
%let RI3=Prof. J. Burggraaf, MD, PhD;
%let RI4=G.J. Groeneveld MD, PhD;

%let RI="&RI4"; /*see above*/
%let CI="L. Schrier, P. Okkerse";
%let St="&statistician, MSc";
%let SpID="NA";
%let SpN="CHDR";
%let RTit="Effects of paracetamol on nociceptive pain in adolescents.";
%let STit="Effects paracetamol nociceptive pain ";
%let StAT="Statistical appendix: Analysis of pharmacodynamic parameters";
%let Author="&statistician, MSc";
%let Reviewer="E.S. Klaassen, MSc";

***LOCATIONS-----;
libname trt "G:\stats\random\&year\";
libname data "&dirloc";
libname ana "&dirlocRO";

***DATA: RAW DATA FILE-----;
%include "&dirloc.&file..sas";

***GENERAL STUDY SPECIFIC MACROS-----;
%include "&dirloc.&protocol._&ana._MacrosG.sas";

***GENERAL STUDY SPECIFIC DDE MACROS-----;
%include "&dirloc.&protocol._&ana._MacrosDDE.sas";

***GENERAL STUDY SPECIFIC DATA MANIPULATIONS-----;
%include "&dirloc.&protocol._&ana._DataG.sas";

***START THE WORD DOCUMENT FROM TEMPLATE-----;
%DDEStartAppTemplt (file=&protocol._&ana._stats_output_&today,
RespInvestigator=&RI
,CoInvestigator=&CI
,Statistician=&St
,ProtocolID="&protocol"
,SponsorID= &SpID
,SponsorName= &SpN
,ReportTitle= &RTit
,ShortTitle= &STit

```

```

,ProtocolDate= "&today"
,StatAppTitle= &StAT);

****DESCRIPTION OF THE ANALYSIS-----;
%DDEInsertHeader1 (name=Description of the analysis);
%DDEInsertFileNH (file=&dirloc.StatsDesc&protocol..docx);

***SAVING LOG-----;
%G_clr (clr=General);

***LISTINGS-----;

***GENERAL LISTING MACRO;
%include "&macroloc.MacroL.sas";
***STUDY SPECIFIC DATA MANIPULATIONS AND FORMATTING FOR LISTINGS;
%include "&dirloc.&protocol._&ana._DataL.sas";

***LOOP LISTINGS;
%macro doL (a1=, a2=);
%local i;
%do i=&a1 %to &a2 ;
%DDEInsertHeader2 (name=Listing /*16.2.6. ICH numbering*/&i &&lab&i &&unit&i);
%L(file= Listing, listvar1=&&var&i, namel=&&lab&i, listunit1=&&unit&i, flag1=N, by4=gendersid,
formatby4=width=7 "Gender");
%DDEInsertFileNH (file=&dirlocL.listing&&var&i...lst);
%end;
%mend doL;

***CREATING LISTINGS;

/*ICH paragraph title*/
%DDEInsertHeader1 (name=Individual pharmacodynamic response data);
/*Efficacy is the official ICH term, but we hardly ever do real efficacy*/

/*If a note is required the text is automatically inserted between two lines at the bottom*/
/*of the listing. Two lines can be added without extra programming*/
%let note1="M = Missing H = Maximum score reached";
%let note2=;
%doL (a1=1, a2=1);
%doL (a1=2, a2=14);

%let note1="M = Missing";
%doL (a1=15, a2=15);
%doL (a1=16, a2=23);

***SAVING LOG;
%G_clr (clr=Listings);

****INDIVIDUAL GRAPHS-----;

***GENERAL INDIVIDUAL GRAPHS MACRO;
%include "&macroloc.MacroIG.sas";
***STUDY SPECIFIC DATA MANIPULATIONS AND FORMATTING FOR INDIVIDUAL GRAPHS;
%include "&dirloc.&protocol._&ana._DataIG.sas";

***LOOP INDIVIDUAL GRAPHS;
%macro doIG (b1=, b2=);
%local i;
%do i=&b1 %to &b2 ;
%DDEInsertHeader2 (name=Individual plots /*16.2.6. ICH numbering*/&i &&lab&i &&unit&i);
%if &&sort&i=RP %then %do;
%IG( file=Igraphs, ylvar=&&var&i, orientation=P, nrow=3);
%end;
%if &&sort&i=SN %then %do;
%IG( file=Igraphs,x1var=treatment, x2var=&&var&i, by1=, ylvar=&&var&i);
%end;
%end;
%mend doIG;

***CREATING INDIVIDUAL GRAPHS;

/*ICH paragraph title, though individual graphs are not in the guidelines ;-)*
%DDEInsertHeader1 (name=Individual pharmacodynamic/*efficacy*/ response plots);

%doIG (b1=1, b2=1);
%doIG (b1=2, b2=6);

```

```

%do IG (b1=7, b2=10);
%do IG (b1=11, b2=15);
%do IG (b1=16, b2=20);
%do IG (b1=21, b2=23);

***SAVING LOG;
%G_clr (clr=Individual Graphs);

***SUMMARY TABLE AND GRAPH-----;

***GENERAL SUMMARY TABLE AND GRAPH MACRO;
%include "&macroloc.MacroSTG.sas";
***STUDY SPECIFIC DATA MANIPULATIONS AND FORMATTING FOR SUMMARY TABLE AND GRAPH;
%include "&dirloc.&protocol._ana._DataSTG.sas";

***LOOP SUMMARY TABLE AND GRAPH;
%macro doSTG (c1=, c2=);
%local i;
%do i=&c1 %to &c2 ;
  %if &&sort&i=RP %then %do;
    %STG (file=summary, yvar=&&var&i , name=&&lab&i, unit=&&unit&i,ndec=&&dec&i, log=&&log&i,
      colour=Y,
      %if &&log&i =1 %then %do; orientation=L %end;
      %else %do; orientation=P %end;);
  %end;
  %if &&sort&i=SN %then %do;
    %STG (file=summary, yvar=&&var&i ,xvar=, name=&&lab&i, unit=&&unit&i,ndec=&&dec&i, colour=Y
      /*formatbar= coutline=black*/);
  %end;
%end;
%mend doSTG;

***CREATING SUMMARY TABLE AND GRAPH;

/*ICH paragraph title*/
%DDEInsertHeader1 (name=Summary pharmacodynamic/*efficacy*/ response table and graph);

/*Headings with ICH numbering are made in the DDE macro in &protocol_PD_DataSTG*/

/*If a note is required the text is automatically inserted between two lines at the bottom*/
/*of the listing. Two lines can be added without extra programming*/
%let notel=;
%let note2=;

%doSTG (c1=1, c2=1);
%doSTG (c1=2, c2=2);
%doSTG (c1=3, c2=8);
%doSTG (c1=9, c2=23);

***SAVING LOG;
%G_clr (clr=Summaries);

***ANALYSIS-----;

***GENERAL ANALYSIS MACRO;
%include "&macroloc.MacroA.sas";
***STUDY SPECIFIC DATA MANIPULATIONS AND FORMATTING FOR ANALYSIS;
%include "&dirloc.&protocol._ana._DataA.sas";

%macro doA (d1=, d2=);
%local i;
%do i=&d1 %to &d2 ;
  %DDEInsertHeader2 (name=&&lab&i &&unit&i);
  %if &&sort&i=RP or &&sort&i=RN %then %do;
    %A (file=analysis, var=&&var&i, name=&&lab&i, ndec=&&dec&i, unit=&&unit&i,
      xvar=etime , by1=Treatment, by2=,precov=&&precov&i, log=&&log&i, up=&&up&i, down=&&down&i);
  %end;
  %if &&sort&i=SP or &&sort&i=SN %then %do;
    %A (file=analysis, var=&&var&i, name=&&lab&i, ndec=&&dec&i, unit=&&unit&i,
      xvar=, by1=Treatment,by2=,precov=&&precov&i, log=&&log&i);
  %end;
%end;
%mend doA;

/*ICH paragraph title*/

```



```

%DDEInsertHeader1 (name=Analysis results pharmacodynamic response table%str(, ) LSM table and
graphs);

/*Headings with ICH numbering are made in the DDE macro in script &protocol_PD_DataAnalysis*/

/*If a note is required the text is automatically inserted between two lines at the bottom*/
/*of the listing. Two lines can be added without extra programming*/
%let note1=;
%let note2=;

%doA (d1=1, d2=1);
%doA (d1=2, d2=2);
%doA (d1=3, d2=3);
%doA (d1=4, d2=4);
%doA (d1=5, d2=5);
%doA (d1=6, d2=6);
%doA (d1=7, d2=7);
%doA (d1=8, d2=8);
%doA (d1=9, d2=9);
%doA (d1=10, d2=10);
%doA (d1=11, d2=11);
%doA (d1=12, d2=12);
%doA (d1=13, d2=13);
%doA (d1=14, d2=18);
%doA (d1=19, d2=23);

***SAVING LOG;
%G_clr (clr=Analysis);

***RTF SUMMARY TABLE-----;
%include "&dirloc.&protocol._&ana._RTFSummary.sas";

***SAVING LOG;
%G_clr (clr=RTFtable);

***ADDING UNEDITED SAS OUTPUT-----;
%macro doRO (e1=, e2=);
%local i;
%do i=&e1 %to &e2 ;
%DDEInsertHeader2 (name=&&lab&i &&unit&i);
%DDEInsertHeader3 (name=SAS output /*16.2.6. ICH numbering*/&i..1 &&lab&i &&unit&i);
%DDEInsertFileNH (file=&dirlocRO.SASanalysis&&var&i...ana);
/*Change from baseline*/
%if &&sort&i=RP or &&sort&i=SP %then %do;
%DDEInsertHeader3 (name=SAS output /*16.2.6.*&i..2 &&lab&i &&unit&i change from baseline);
%DDEInsertFileNH (file=&dirlocRO.SASanalysisdelta&&var&i...ana);
%end;
%end;
%mend doRO;
%DDEInsertHeader1 (name=Unedited SAS output);
%doRO (e1=1, e2=2);
%doRO (e1=3, e2=10);
%doRO (e1=11, e2=23);

***SAVING LOG;
%G_clr (clr=RawOutput);

***ADDING SYNTAX-----;
%DDEInsertHeader1 (name=SAS Syntax);

%DDEInsertFile (label=Analysis, file=&dirloc.&protocol._PD_Analysis1.1.sas );
%DDEInsertFile (label=Raw data for analysis , file=&dirloc.&protocol._PDData_&dateE...sas );
%DDEInsertFile (label=General macros, file=&dirloc.&protocol._PD_MacrosG.sas );
%DDEInsertFile (label=DDE macros, file=&dirloc.&protocol._PD_MacrosDDE.sas );
%DDEInsertFile (label=General data manipulations, file=&dirloc.&protocol._PD_DataG.sas );
%DDEInsertFile (label=Listings, file=&dirloc.&protocol._PD_DataL.sas );
%DDEInsertFile (label=Macro Listings, file=&dirlocbase.MacroL.sas );
%DDEInsertFile (label=Individual plots, file=&dirloc.&protocol._PD_DataIG.sas );
%DDEInsertFile (label=Macro Individual plots, file=&dirlocbase.MacroIG.sas );
%DDEInsertFile (label=Summaries, file=&dirloc.&protocol._PD_DataSTG.sas );
%DDEInsertFile (label=Macro Summaries, file=&dirlocbase.MacroSTG.sas );
%DDEInsertFile (label=Analysis, file=&dirloc.&protocol._PD_DataA.sas );
%DDEInsertFile (label=Macro Analysis, file=&dirlocbase.MacroA.sas );

%DDEBackspace;

```

```
%DDESaveWord;

***SAVING LOG;
%G_clr (clr=Syntax);

***TO COMPARE THE ORIGINAL DATA FILE TO THE ANALYSIS FILE-----;

/*NB!! first close the word document with the statistical output before running this*/
/*Creates a new document with the result of the proc compare*/
%include "&dirloc.&protocol._PD_Validation.sas";
%validation(by=occasion);

***SAVING LOG;
%G_clr (clr=Compare);
```

Raw data for analysis

```

/* SAS import procedure G:\2011\CHDR1117\STATS\Analysis\2014_09_29\CHDR1117_PDdata_2014_09_30.sas as
on 30/09/2014 09:59:30 */
/* Generated by Promasys v7.1.0 */

%LET FOLDER=G:\2011\CHDR1117\STATS\Analysis\2014_09_30\;
%LET DATASET=CHDR1117_PDdata_2014_09_30;

OPTIONS COMPRESS=CHAR;
MISSING U M H L;

PROC FORMAT;
Value $Treatment
    "Paracetamol"="2 capsules of 500 mg paracetamol po"
    "Placebo"="2 capsules of matching placebo po";
RUN;

DATA &DATASET;
INFILE "&FOLDER.CHDR1117_PDdata_2014_09_30.TXT" DLM="|" LRECL=32767 MISSEVER DSD FIRSTOBS=2
ENCODING="UTF-16";

INFORMAT Protocol $15.;
INFORMAT SubjectNr 5.;
INFORMAT GenderSID $7.;
INFORMAT Occasion 3.;
INFORMAT Timetable $12.;
INFORMAT Treatment $12.;
INFORMAT ProtTime TIME12.;
INFORMAT ExpDelta 9.;
INFORMAT ActDelta 9.;
INFORMAT ActClock DATETIME18.;
INFORMAT ActClock_Date DATE9.;
INFORMAT ActClock_Time TIME8.;
INFORMAT ActClock_StringValue $32.;
INFORMAT Activity $12.;
INFORMAT ColdAUC BEST10.;
INFORMAT ColdPDT BEST10.;
INFORMAT ColdPTT BEST10.;
INFORMAT ElecStairAUC BEST10.;
INFORMAT ElecStairPDT BEST10.;
INFORMAT ElecStairPTT BEST10.;
INFORMAT MPQ_SF01 BEST10.;
INFORMAT MPQ_SF02 BEST10.;
INFORMAT MPQ_SF03 BEST10.;
INFORMAT MPQ_SF04 BEST10.;
INFORMAT MPQ_SF05 BEST10.;
INFORMAT MPQ_SF06 BEST10.;
INFORMAT MPQ_SF07 BEST10.;
INFORMAT MPQ_SF08 BEST10.;
INFORMAT MPQ_SF09 BEST10.;
INFORMAT MPQ_SF10 BEST10.;
INFORMAT MPQ_SF11 BEST10.;
INFORMAT MPQ_SF12 BEST10.;
INFORMAT MPQ_SF13 BEST10.;
INFORMAT MPQ_SF14 BEST10.;
INFORMAT MPQ_SF15 BEST10.;
INFORMAT MPQ_SF_PPI BEST10.;
INFORMAT MPQ_SF_VAS BEST10.;
INFORMAT PressureAUC BEST10.;
INFORMAT PressurePDT BEST10.;
INFORMAT PressurePTT BEST10.;
INFORMAT QST_heat_thr BEST10.;
INFORMAT QST_heat_tol BEST10.;

FORMAT Protocol $15.;
FORMAT SubjectNr 5.;
FORMAT GenderSID $7.;
FORMAT Occasion 3.;
FORMAT Timetable $12.;
FORMAT Treatment Treatment.;
FORMAT ProtTime TIME12.;
FORMAT ExpDelta 9.;
FORMAT ActDelta 9.;
FORMAT ActClock DATETIME18.;
FORMAT ActClock_Date DATE9.;
FORMAT ActClock_Time TIME8.;

```

```
FORMAT ActClock_StringValue $32.;
FORMAT Activity $12.;
FORMAT ColdAUC 7.1;
FORMAT ColdPDT 4.1;
FORMAT ColdPTT 5.1;
FORMAT ElecStairAUC 7.1;
FORMAT ElecStairPDT 4.1;
FORMAT ElecStairPTT 4.1;
FORMAT MPQ_SF01 2.0;
FORMAT MPQ_SF02 2.0;
FORMAT MPQ_SF03 2.0;
FORMAT MPQ_SF04 2.0;
FORMAT MPQ_SF05 2.0;
FORMAT MPQ_SF06 2.0;
FORMAT MPQ_SF07 2.0;
FORMAT MPQ_SF08 2.0;
FORMAT MPQ_SF09 2.0;
FORMAT MPQ_SF10 2.0;
FORMAT MPQ_SF11 2.0;
FORMAT MPQ_SF12 2.0;
FORMAT MPQ_SF13 2.0;
FORMAT MPQ_SF14 2.0;
FORMAT MPQ_SF15 2.0;
FORMAT MPQ_SF_PPI 2.0;
FORMAT MPQ_SF_VAS 5.1;
FORMAT PressureAUC 7.1;
FORMAT PressurePDT 5.1;
FORMAT PressurePTT 5.1;
FORMAT QST_heat_thr 4.1;
FORMAT QST_heat_tol 4.1;
```

```
INPUT
Protocol
SubjectNr
GenderSID
Occasion
Timetable
Treatment
ProtTime
ExpDelta
ActDelta
ActClock
ActClock_Date
ActClock_Time
ActClock_StringValue
Activity
ColdAUC
ColdPDT
ColdPTT
ElecStairAUC
ElecStairPDT
ElecStairPTT
MPQ_SF01
MPQ_SF02
MPQ_SF03
MPQ_SF04
MPQ_SF05
MPQ_SF06
MPQ_SF07
MPQ_SF08
MPQ_SF09
MPQ_SF10
MPQ_SF11
MPQ_SF12
MPQ_SF13
MPQ_SF14
MPQ_SF15
MPQ_SF_PPI
MPQ_SF_VAS
PressureAUC
PressurePDT
PressurePTT
QST_heat_thr
QST_heat_tol ;
```

```
LABEL Protocol="Protocol ID";
LABEL SubjectNr="Subject Nr";
LABEL GenderSID="Gender of Subject";
```

```
LABEL Occasion="Occasion number";
LABEL Timetable="Timetable name";
LABEL Treatment="Treatment";
LABEL ProtTime="Protocol Time";
LABEL ExpDelta="Expected delta-time (min)";
LABEL ActDelta="Actual delta time (min)";
LABEL ActClock="Actual clock date-time";
LABEL ActClock_Date="Actual clock (date part)";
LABEL ActClock_Time="Actual clock (time part)";
LABEL ActClock_StringValue="Actual clock (string value)";
LABEL Activity="Activity name";
LABEL ColdAUC="Cold Area Under the Curve (Time vs eVAS)";
LABEL ColdPDT="Cold Pain Detection Threshold (seconds)";
LABEL ColdPTT="Cold Pain Tolerance Threshold (seconds)";
LABEL ElecStairAUC="Electrical Stair Area Under the Curve (Intensity vs eVAS)";
LABEL ElecStairPDT="Electrical Stair Pain Detection Threshold (seconds)";
LABEL ElecStairPTT="Electrical Stair Pain Tolerance Threshold (seconds)";
LABEL MPQ_SF01="McGill Pain: Throbbing";
LABEL MPQ_SF02="McGill Pain: Shooting";
LABEL MPQ_SF03="McGill Pain: Stabbing";
LABEL MPQ_SF04="McGill Pain: Sharp";
LABEL MPQ_SF05="McGill Pain: Cramping";
LABEL MPQ_SF06="McGill Pain: Gnawing";
LABEL MPQ_SF07="McGill Pain: Hot-Burning";
LABEL MPQ_SF08="McGill Pain: Aching";
LABEL MPQ_SF09="McGill Pain: Heavy";
LABEL MPQ_SF10="McGill Pain: Tender";
LABEL MPQ_SF11="McGill Pain: Splitting";
LABEL MPQ_SF12="McGill Pain: Tiring-Exhausting";
LABEL MPQ_SF13="McGill Pain: Sickening";
LABEL MPQ_SF14="McGill Pain: Fearful";
LABEL MPQ_SF15="McGill Pain: Punishing-Cruel";
LABEL MPQ_SF_PPI="McGill Pain: Present Pain Intensity";
LABEL MPQ_SF_VAS="McGill Pain: VAS (mm)";
LABEL PressureAUC="Pressure Pain Area Under the Curve (Intensity vs eVAS) (kPa.%)";
LABEL PressurePDT="Pressure Pain Detection Threshold (kPa)";
LABEL PressurePTT="Pressure Pain Tolerance Threshold (kPa)";
LABEL QST_heat_thr="QST heat pain threshold (C)";
LABEL QST_heat_tol="QST heat pain tolerance (C)";
```

```
RUN;
```

General macros

```
%Macro G_clr (clr=);
/*save the log to a permanent file, overwriting if necessary;*/
dm 'log; file "&dirloc.log &clr &sysdate9..log" replace';
/*Clear the log window;*/
DM "log; clear; ";
%mend G_clr;

%macro G_header (root=,sasfile=);
/* generates a title statement with correct length to specify the sas-file*/
/* producing the output and the date and time of production plus a page number*/
/* Portrait*/
%global instringP;
options pagesize=&pagesizeP linesize=&linesizeP;
data _null_;
length ins %eval(&linesizeP-25);
ins="&root&sasfile..sas";
call symput ('instringP', ins);
run;
title1 "&instringP &sysdate9 &systime Page:    ";
/*custom titles start at title3 */
title2;
%mend G_header;
%macro G_headerLS (root=,sasfile=);
/* generates a title statement with correct length (150) to specify the sas-file*/
/* producing the output and the date and time of production plus a page number*/
/* Landscape*/
%global instringL;
options pagesize=&pagesizeL linesize=&linesizeL;
data _null_;
length ins %eval(&linesizeL-25);
ins="&root&sasfile..sas";
call symput ('instringL', ins);
run;
title1 "&instringL &sysdate9 &systime Page:    ";
/*custom titles start at title3 */
title2;
%mend G_headerLS;
%macro G_dummy (dumlinesize);
/* read the dummy listing and measure headline length*/
%global linelen;
%global startpos;
data length;
length headline $200;
infile "&dirloc.reportdummy.lst" ;
input @ "-" headline @@;
pos=index(headline,"-----");
if pos>0 then do; output; stop;
end;
run;
data length;
set length;
le=length(headline);
s=&dumlinesize-le;
/*if output is centered with s the starting position of the line can be calculated*/
start=0.5*s;
%if "&statistician"="M.L. de Kam" %then %do;
pbpos=le+start-22;
%end;
%if "&statistician"="E.S. Klaassen" %then %do;
pbpos=le+start-24;
%end;
%if "&statistician" ne "M.L. de Kam" and "&statistician" ne "E.S. Klaassen" %then %do;
pbpos=le+start-25;
%end;
call symput ("linelen",trim(left(put(le,8)))));
call symput ("startpos",trim(left(put(start,8)))));
call symput ("pbpos",trim(left(put(pbpos,8)))));
run;
%mend G_dummy;

%macro G_j;
/*creates dummy output the first time a proc report is run, to count the number of pages for*/
/*page x of y line*/
%if &j=1 %then %do;
data &reportfile;
```

```

set &reportfile;
dummy=0;
run;
proc printto file="&dirloc.reportdummy.lst" new; run;
%end;
%mend G_j;

%macro G_pages;
%let notestatement1=;
%let notestatement2=;
%let notestatement3=;
%let notestatement4=;
%let notestatement5=;
%let notestatement6=;
%let notestatement7=;
%if %length(&note1)>0 %then %do;
%let notestatement1=%nrstr(if symget('page') ne symget ('pages') then pagetext1=&note1; else
pagetext1=" ");
%let notestatement2=%nrstr(LINE @&startpos pagetext1 $100.);
%let notestatement5=%nrstr(LINE @&startpos uline $200. );
%let notestatement6=%nrstr(LINE @&startpos &note1);
%end;
%if %length(&note2)>0 %then %do;
%let notestatement3=%nrstr(if symget('page') ne symget ('pages') then pagetext3=&note2; else
pagetext3=" ");
%let notestatement4=%nrstr(LINE @&startpos pagetext3 $100.);
%let notestatement7=%nrstr(LINE @&startpos &note2);
%end;

%if "&pages" ne "1" or &j=1 %then %do;
compute after _page_;
call execute('%let page = %eval(&page. + 1);');
if symget('page') ne symget ('pages') then
uline=repeat('-',&linelen);
else
uline=repeat(' ',&linelen);
if symget('page') ne symget ('pages') then
pagetext=compbl('Page '||symget('page')||' of '||symget ('pages'));
else
pagetext=compbl(' ');
if symget('page') ne symget ('pages') then
pagetext2="Produced by &statistician";
else
pagetext2=" ";
&notestatement1;
&notestatement3;
LINE @&startpos uline $200. ;
&notestatement2;
&notestatement4;
&notestatement5 ;
Line @&startpos pagetext $15. @&pbpos pagetext2 $25.;
endcomp;
%end;
compute after dummy;
uline=repeat('-',&linelen);
pagetext=compbl('Page '||symget('pages')||' of '||symget ('pages'));
LINE @&startpos uline $200. ;
&notestatement6;
&notestatement7;
&notestatement5 ;
Line @&startpos pagetext $15. @&pbpos "Produced by &statistician";
endcomp;
%mend G_pages;

%macro G_yaxis;
/*automatically calculates the order for the y-axis*/
/*in a more sophisticated way than SAS itself*/
%global autoyaxis;
data x;
set x;
delta=(upper-lower)/5;
scale=10*floor(log10(delta));
sdelta=delta/scale;
r1=scale*ceil(sdelta);
r2=scale*2*(ceil(sdelta/2));
r5=scale*5*(ceil(sdelta/5));
l1=floor(lower/r1)*r1;
l2=floor(lower/r2)*r2;

```

```
l5=floor(lower/r5)*r5;
u1=ceil(upper/r1)*r1;
u2=ceil(upper/r2)*r2;
u5=ceil(upper/r5)*r5;
n1 = abs(5-(u1-l1)/r1);
n2 = abs(5-(u2-l2)/r2);
n5 = abs(5-(u5-l5)/r5);
from = l5;
to = u5;
by = r5;
if n2 < n5 then do;
    from = l2;
    to = u2;
    by = r2;
if n1 < n2 then do;
    from = l1;
    to = u1;
    by = r1;
end;
end;
call symput("autoyaxis","order = (" || trim(left(put(from,best6.))) ||
" to " || trim(left(put(to,best6.))) || " by " || trim(left(put(by,best6.))) || ")");
run;
%mend G_yaxis;
```


DDE macros

```

/*****
**
** Launch the Word application and
** define a DDE system doublet with
** filename SAS2WORD pointing to it
**
*****/
%macro DDEStartWord (file=FirstAttempt);
options noxsync noxwait xmin;
filename sas2word dde 'winword|system';
data _null_;
  length fid rc start stop time 8;
  fid=fopen('sas2word','s');
  if (fid le 0) then do;
    rc=system('start winword');
    start=datetime();
    stop=start+60;
    do while (fid le 0);
      fid=fopen('sas2word','s');
      time=datetime();
      if (time ge stop) then fid=1;
    end;
  end;
  rc=fclose(fid);
run;
data _null_;
  file sas2word;
  put "[ChDefaultDir ""&dirloc"",0]";
  put "[FileSaveAs.Name=""&file""]";
  put '[AppMinimize]';
run;
data _null_;
file sas2word;
  put '[FormatStyle .Name = "Plain Text", .Define]';
  put '[FormatDefineStyleFont .Font="Courier New" .Points = "8"]';
  put '[FileSave]';
run;
%mend DDEStartWord;

/*****
**
** Insert table of contents
**
*****/
%macro DDEInsertToc;
data _null_;
  file sas2word;
*insert page numbers;
  put '[EndOfDocument]';
  put '[InsertPageNumbers.Type=1,.Position=4]';
*generates a table of contents;
  *put '[StartOfDocument]';
  put '[InsertPara]';
  put '[Insert "Table of Contents"]';
  put '[ParaUp,1]';
  put '[FormatFont.Font="Arial",.Points="14",.bold=1]';
  put '[ParaDown,0]';
  put '[InsertPara]';
  put '[InsertPara]';
  put '[InsertTableofContents]';
  put '[InsertPageBreak]';
run;
%mend DDEInsertToc;
*Start statistical appendix template;
/*****
/*starts the CHDR statistical appendix template and */
/*fills in the required fields */
*****/

%macro DDEStartAppTemplt (file=StatsApp,
RespInvestigator=
,CoInvestigator=
,Statistician=
,Author= " "

```

```

,Reviewer= " "
,ProtocolID=
,SponsorID=
,SponsorName=
,ReportTitle=
,ShortTitle=
,ProtocolDate=
,StatAppTitle=
,Standard=Y);

options noxsync noxwait xmin;
filename sas2word dde 'winword\system';
data _null_;
  length fid rc start stop time 8;
  fid=fopen('sas2word','s');
  if (fid le 0) then do;
    rc=system('start winword');
    start=datetime();
    stop=start+60;
    do while (fid le 0);
      fid=fopen('sas2word','s');
      time=datetime();
      if (time ge stop) then fid=1;
    end;
  end;
  rc=fclose(fid);
run;
data _null_;
  file sas2word;
  put '[FileClose 2]';
%if &standard=Y %then %do;
  put "[FileNew.Template=""g:\Stats\SASSource\Statistical appendix grid.dotx""]";
  put "[ChDefaultDir ""&dirloc"",0]";
  put "[FileSaveAs.Name=""&file"",.Format=0]";
  put '[AppMinimize]';
  run;
  filename RespInve dde "winword|&dirloc&file..doc!RespInvestigator" notab;
  filename CoInvest dde "winword|&dirloc&file..doc!CoInvestigator" notab;
  filename Statisti dde "winword|&dirloc&file..doc!Statistician" notab;
  filename Authorst dde "winword|&dirloc&file..doc!Author" notab;
  filename Reviewer dde "winword|&dirloc&file..doc!Reviewer" notab;
  filename ProtocID dde "winword|&dirloc&file..doc!ProtocolID" notab;
  filename SponsoID dde "winword|&dirloc&file..doc!SponsorID" notab;
  filename SponsNam dde "winword|&dirloc&file..doc!SponsorName" notab;
  filename RepTitle dde "winword|&dirloc&file..doc!ReportTitle" notab;
  filename ShrtTitl dde "winword|&dirloc&file..doc!ShortTitle" notab;
  filename ProtDate dde "winword|&dirloc&file..doc!ProtocolDate" notab;
  filename SApTitle dde "winword|&dirloc&file..doc!StatAppTitle" notab;
%end;
%if &standard=V %then %do;
  put "[FileNew.Template=""g:\Stats\SASSource\Statistical appendix sign.dotx""]";
  put "[ChDefaultDir ""&dirlocval"",0]";
  put "[FileSaveAs.Name=""&file"",.Format=0]";
  put '[AppMinimize]';
  run;
  filename RespInve dde "winword|&dirlocval&file..doc!RespInvestigator" notab;
  filename CoInvest dde "winword|&dirlocval&file..doc!CoInvestigator" notab;
  filename Statisti dde "winword|&dirlocval&file..doc!Statistician" notab;
  filename Authorst dde "winword|&dirlocval&file..doc!Author" notab;
  filename Reviewer dde "winword|&dirlocval&file..doc!Reviewer" notab;
  filename ProtocID dde "winword|&dirlocval&file..doc!ProtocolID" notab;
  filename SponsoID dde "winword|&dirlocval&file..doc!SponsorID" notab;
  filename SponsNam dde "winword|&dirlocval&file..doc!SponsorName" notab;
  filename RepTitle dde "winword|&dirlocval&file..doc!ReportTitle" notab;
  filename ShrtTitl dde "winword|&dirlocval&file..doc!ShortTitle" notab;
  filename ProtDate dde "winword|&dirlocval&file..doc!ProtocolDate" notab;
  filename SApTitle dde "winword|&dirlocval&file..doc!StatAppTitle" notab;
%end;

data _null_;
file RespInve;
put &RespInvestigator;
file CoInvest;
put &CoInvestigator;
file Statisti;
put &Statistician;
file Authorst;
put &Author;

```

```

file Reviewer;
put &Reviewer;
file ProtocID;
put &ProtocolID;
file SponsoID;
put &SponsorID;
file SponsNam;
put &SponsorName;
file RepTitle;
put &ReportTitle;
file ShrtTitl;
put &ShortTitle;
file ProtDate;
put &ProtocolDate;
file SApTitle;
put &StatAppTitle;
run;

data _null_;
file sas2word;
/*redefines the plain text style to change the font to 8 point courier*/
put '[FormatStyle .Name = "Plain Text", .Define]';
put '[FormatDefineStyleFont .Font="Courier New" .Points = "8"]';
put '[ViewNormal]';
put '[FileSave]';
run;
%mend DDEStartAppTemplt;

%macro DDEStartAppTempltPower (file=StatsApp,
RespInvestigator= "Prof. A.F. Cohen, MD, PhD, FFPM"
/*"G.J. Groeneveld MD, PhD"*/
/*"J.M.A. van Gerven, MD, PhD"*/
/*"J. Burggraaf, MD, PhD"*/
,CoInvestigator=" "
,Statistician= "M.L. de Kam"
,ProtocolID= "CHDRXXXX"
,SponsorName= " "
,ProtocolDate= " "
,StatAppTitle="Power calculation");

options noxsync noxwait xmin;
filename sas2word dde 'winword|system';
data _null_;
length fid rc start stop time 8;
fid=fopen('sas2word','s');
if (fid le 0) then do;
rc=system('start winword');
start=datetime();
stop=start+60;
do while (fid le 0);
fid=fopen('sas2word','s');
time=datetime();
if (time ge stop) then fid=1;
end;
end;
rc=fclose(fid);
run;
data _null_;
file sas2word;
put '[FileClose 2]';
put '[FileNew.Template=""g:\Stats\Powercalculations\Statistical appendix power.dotx""]';
put '[ChDefaultDir ""&dirloc"", 0]';
put '[FileSaveAs.Name=""&file"", .Format=0]';
/* put '[FileSaveAs.Name=""&file""]; */
put '[AppMinimize]';
run;
filename RespInve dde "winword|&dirloc&file..doc!RespInvestigator" notab;
filename CoInvest dde "winword|&dirloc&file..doc!CoInvestigator" notab;
filename Statisti dde "winword|&dirloc&file..doc!Statistician" notab;
filename ProtocID dde "winword|&dirloc&file..doc!ProtocolID" notab;
filename SponsNam dde "winword|&dirloc&file..doc!SponsorName" notab;
filename ProtDate dde "winword|&dirloc&file..doc!ProtocolDate" notab;
filename SApTitle dde "winword|&dirloc&file..doc!StatAppTitle" notab;

data _null_;
file RespInve;
put &RespInvestigator;
file CoInvest;

```

```

put &CoInvestigator;
file Statisti;
put &Statistician;
file ProtocID;
put &ProtocolID;
file SponsNam;
put &SponsorName;
file ProtDate;
put &ProtocolDate;
file SApTitle;
put &StatAppTitle;
run;

data _null_;
file sas2word;
/*redefines the plain text style to change the font to 8 point courier*/
put '[FormatStyle .Name = "Plain Text", .Define]';
put '[FormatDefineStyleFont .Font="Courier New" .Points = "8"]';
put '[ViewNormal]';
put '[FileSave]';
run;
%mend DDEStartAppTempltPower;
*Header;
/*****/
/**/
/** Insert a Header 1 **/
/**/
/*****/
%macro DDEInsertHeader1 (name= );
data _null_;
file sas2word;
put '[EndOfDocument]';
put "[Insert "&name""]";
put '[ParaUp,1]';
put '[FormatStyle.Name = "Heading 1", .Apply]';
put '[ParaDown,0]';
put '[InsertPara]';
run;
%mend DDEInsertHeader1;

/*****/
/**/
/** Insert a Header 2 **/
/**/
/*****/
%macro DDEInsertHeader2 (name= );
data _null_;
file sas2word;
put '[EndOfDocument]';
put "[Insert "&name""]";
put '[ParaUp,1]';
put '[FormatStyle.Name = "Heading 2", .Apply]';
put '[ParaDown,0]';
put '[InsertPara]';
run;
%mend DDEInsertHeader2;

/*****/
/**/
/** Insert a Header 3 **/
/**/
/*****/
%macro DDEInsertHeader3 (name= );
data _null_;
file sas2word;
put '[EndOfDocument]';
put "[Insert "&name""]";
put '[ParaUp,1]';
put '[FormatStyle.Name = "Heading 3", .Apply]';
put '[ParaDown,0]';
put '[InsertPara]';
run;
%mend DDEInsertHeader3;
*File;
*With heading;
/*****/
/**/
/** Inserts a file with a heading **/
/**/

```

```

/*****/
%macro DDEInsertFile (label=, file= );
data _null_;
  file sas2word;
  put '[EndOfDocument]';
  put "[Insert "&label""]";
  put '[ParaUp,1]';
  put '[FormatStyle.Name = "Heading 3", .Apply]';
  put '[ParaDown,0]';
  put '[InsertPara]';
  put '[InsertPara]';
  put "[InsertFile.Name="&file"", .ConfirmConversions=0]";
  put '[EndOfDocument]';
  put '[InsertPageBreak]';
run;
%mend DDEInsertFile;

*File;
*Without heading;
/*****/
/**
/** Inserts a file without a heading
/**
/**
/*****/
%macro DDEInsertFileNH (file= );
data _null_;
  file sas2word;
  put '[EndOfDocument]';
/* put '[FormatDefineStyleFont .Font="Courier New" .Points = "7" ]';*/
  put '[InsertPara]';
  put "[InsertFile.Name="&file"", .ConfirmConversions=0]";
  put '[EndOfDocument]';
  put '[InsertPageBreak]';
run;
%mend DDEInsertFileNH;

/*****/
/**
/** Insert Individual Graphs and scale
/**
/** Portrait layout
/**
/**
/*****/
%macro DDEInsertIndGraphP (name=, file= ,outliers=0, marker=);
data _null_;
  file sas2word;
  put '[EndOfDocument]';
%if %length(&name) > 0 %then %do;
  put "[Insert ""Individual graphs of &name"""]";
  put '[ParaUp,1]';
  put '[FormatStyle.Name = "Heading 3", .Apply]';
  put '[ParaDown,0]';
%end;
  put '[InsertPara]';
%if %length(&marker) > 0 %then %do;
  put "[Insert ""&marker"""]";
  put '[ParaUp,1]';
  put '[FormatFont.Font="Arial", .Points="10"]';
  put '[LeftPara]';
  put '[ParaDown,0]';
%end;
  put '[InsertPara]';
  put '[InsertPara]';
  put "[InsertPicture.Name="&file""]";
  put '[CharLeft 1,1]';
  put '[FormatPicture.ScaleX="200%", .ScaleY="200%"]';
  put '[CharRight 1,0]';
  put '[InsertPara]';
/* put '[InsertPageBreak]';*/
run;
%mend DDEInsertIndGraphP;
/*****/
/**
/** Insert Individual Graphs and scale
/**
/** Landscape layout
/**
/**
/*****/

```

```

%macro DDEInsertIndGraphL (name=, file= ,outliers=0, marker=);
data _null_;
  file sas2word;
  put '[EndOfDocument]';
%if %length(&name) > 0 %then %do;
  put "[Insert ""Individual graphs of &name""]";
  put '[ParaUp,1]';
  put '[FormatStyle.Name = "Heading 3", .Apply]';
  put '[ParaDown,0]';
%end;
  put '[InsertPara]';
%if %length(&marker) > 0 %then %do;
  put "[Insert ""&marker""]";
  put '[ParaUp,1]';
  put '[FormatFont.Font="Arial",.Points="10"]';
  put '[LeftPara]';
  put '[ParaDown,0]';
%end;
  put '[InsertPara]';
  put '[InsertPara]';
  put "[InsertPicture.Name=""&file""]";
  put '[CharLeft 1,1]';
  put '[FormatPicture.ScaleX="220%",.ScaleY="220%"]';
  put '[CharRight 1,0]';
  put '[InsertPara]';
/* put '[InsertPageBreak]';*/
run;
%mend DDEInsertIndGraphL;

%macro DDEInsertText0 (name= );
data _null_;
  file sas2word;
  put '[EndOfDocument]';
  put '[InsertPara]';
  put "[Insert ""&name""]";
  put '[ParaUp,1]';
  put '[FormatStyle.Name = "Plain Text", .Apply]';
  put '[ParaDown,0]';
  put '[InsertPara]';
  put '[InsertPara]';
run;
%mend DDEInsertText0;

%macro DDEInsertText1 (text1=, text2=);
data _null_;
  file sas2word;
  put '[EndOfDocument]';
  put "[Insert ""&text1""]";
  put '[ParaUp,1]';
  put '[FormatStyle.Name = "Plain style", .Apply]';
  put '[CenterPara]';
  put '[ParaDown,0]';
  put '[InsertPara]';
  put '[InsertPara]';
  put "[Insert ""&text2""]";
  put '[ParaUp,1]';
  put '[FormatStyle.Name = "Plain style", .Apply]';
  put '[CenterPara]';
  put '[ParaDown,0]';
  put '[InsertPara]';
run;
%mend DDEInsertText1;

%macro DDEInsertText2 (name= );
data _null_;
  file sas2word;
  put '[EndOfDocument]';
  put "[Insert ""&name""]";
  put '[ParaUp,1]';
  put '[FormatStyle.Name = "Plain Text", .Apply]';
  put '[ParaDown,0]';
  put '[InsertPageBreak]';
run;
%mend DDEInsertText2;

*Average graph;
/*****
**/

```

```

/** Insert Average Graphs and scale      **/
/**                                     **/
/*****/

%macro DDEInsertAvgGraph (label=, file=
                        ,sub1=);

data _null_;
  file sas2word;
  put '[EndOfDocument]';
%if %length(&label) > 0 %then %do;
  put "[Insert "&label""]";
  put '[ParaUp,1]';
  put '[FormatStyle.Name = "Heading 3", .Apply]';
/* put '[FormatFont.Font = "Arial", .Points="12"]'; */
  put '[ParaDown,0]';
  put '[InsertPara]';
%end;
%if %length(&sub1) > 0 %then %do;
  put "[Insert "&sub1""]";
  put '[ParaUp,1]';
  put '[FormatFont.Font="Arial", .Points="10"]';
  put '[LeftPara]';
  put '[ParaDown,0]';
  put '[InsertPara]';
%end;
/* put '[InsertPara]'; */
  put "[InsertPicture.Name="&file""]";
  put '[CharLeft 1,1]';
  put '[FormatPicture.ScaleX="150%", .ScaleY="150%"]';
  put '[CharRight 1,0]';
  put '[InsertPara]';
run;
%mend DDEInsertAvgGraph;

*Removes pagebreak;
/*****/
/**                                     **/
/** Remove pagebreak **/
/**                                     **/
/*****/
%macro DDEBackspace;
data _null_;
  file sas2word;
  *removes last page break;
  put '[CharLeft 1,1]';
  put '[EditCut]';
  put '[InsertPara]';
run;
%mend DDEBackspace;

*Save document;
/*****/
/**                                     **/
/** Save the document only **/
/**                                     **/
/*****/
%macro DDESaveWord;
data _null_;
  file sas2word;
  put '[UpdateTableofContents]';
  put '[UpdateFormfields]';
  put '[FilePrintPreview]';
  put '[ViewPage]';
  put '[UnprotectDocument]';
  put '[FileSave]';
run;
%mend DDESaveWord;

*Save document and close Word;
/*****/
/**                                     **/
/** Save and close the document, kill **/
/** Word too ... **/
/**                                     **/
/*****/
%macro DDEEndWord;
data _null_;
  file sas2word;

```

```

    *removes last page break;
    put '[CharLeft 1,1]';
/*  put '[EditCut]';*/
    put '[FileSave]';
    put '[FileClose 2]';
    put '[FileExit 2]';
run;
%mend DDEEndWord;

%macro DDEInsertFileRTF (file= );
data _null_;
    file sas2word;
    put '[EndOfDocument]';
    put '[InsertPara]';
    put "[InsertFile.Name=\"%file\", .ConfirmConversions=0]";
    put '[ParaUp,0]';
    put '[ParaUp,1]';
    put '[FormatStyle.Name = "Table RTF", .Apply]';
    put '[EndOfDocument]';
    put '[InsertPageBreak]';
run;
%mend DDEInsertFileRTF;

/**/

%macro DDEInsertPageBreak ;
data _null_;
    file sas2word;
    put '[EndOfDocument]';
    put '[InsertPageBreak]';
run;
%mend DDEInsertPageBreak;

%macro DDEInsertSectionBreak ;
data _null_;
    file sas2word;
    put '[EndOfDocument]';
    put '[InsertSectionBreak]';
run;
%mend DDEInsertSectionBreak;

%macro DDEToggleLayout;
data _null_;
    file sas2word;
    put '[CharLeft 1,1]';
    put '[EditCut]';
    put '[InsertSectionBreak]';
    put '[TogglePortrait]';
    put '[ViewHeader]';
    put '[ToggleHeaderFooterLink]';
    put '[CloseViewHeaderFooter]';
    put '[ViewFooter]';
    put '[ToggleHeaderFooterLink]';
    put '[CloseViewHeaderFooter]';
run;
%mend DDEToggleLayout;

%macro DDEToggleLayoutStart;
data _null_;
    file sas2word;
    put '[EndOfDocument]';
    put '[InsertSectionBreak]';
    put '[TogglePortrait]';
    put '[ViewHeader]';
    put '[ToggleHeaderFooterLink]';
    put '[CloseViewHeaderFooter]';
    put '[ViewFooter]';
    put '[ToggleHeaderFooterLink]';
    put '[CloseViewHeaderFooter]';
run;
%mend DDEToggleLayoutStart;

%macro DDEStartProtection;
data _null_;
    file sas2word;
    put '[ProtectDocument]';

```



```
run;  
%mend DDEstartProtection;
```

General data manipulations

```
%let sasfile=&protocol._DataG;

****INFORMATION ON THE PARAMETERS;
proc contents data=&file (drop=Protocol--activity) out=pars0
(keep=NAME LABEL FORMATL formatD) noprint;
run;
data pars;
retain NAME FORMATL format formatD LABEL;
set pars0;
format=trim(left(formatL))||"."||trim(left(formatD));
run;

***TXT FILE: CAN BE USED TO MAKE THE PARS FILE;
data _null_;
set PARS;
file "&dirloc.var&protocol..txt";
put (_all_) ('|') /('09'x)*/;
run;

***MAKING MACRO VARIABLES FOR LOOPS;

/*****
/
/*SORT      sort=RP, SP, RN, SN = repeated with pre value, single with pre value, repeated no
*/
/*          pre value, single no pre value
*/
/*PRECOV    precov=1 or 0, 1= pre value as covariate, 0 not
*/
/*NDEC      ndec=number of decimals in the original datafile. Decimals for summary stats are
adjusted*/
/*          in the macro
*/
/*LOG       log=1 or 0, 1=log transform, 0 not
*/
/*UP DOWN   up and down are controlling the treatment with the error bars up and down,
*/
/*          only used to overrule the automatic calculation
*/
/*YAXIS     yaxis1/2/3, xaxis1/2/3 can be used for specific axis formatting to overrule the
automatic*/
/*          calculation, for average graph, LSM and LSM change from baseline graph
*/
/*****/

data Pars;
INFILE datalines delimiter='|' dsd TRUNCOVER;
length num $2 sort $2 precov $1 PMSvar $16 name $60 UNIT $25 format $9 ndec$1 log $1 up$1 down$1
yaxis1 $30 xaxis1 $30 yaxis2 $30 xaxis2 $30 yaxis3 $30 xaxis3 $30;
input num $ sort $ precov $ PMSvar $ name $ UNIT $ format $ ndec $ log $ up $ down $
yaxis1 $ xaxis1 $ yaxis2 $ xaxis2 $ yaxis3 $ xaxis3 $;
/*see ParsVariables.docx file in "G:/stats/sassource/code*/
datalines;
1|RP|1|ColdAAC          |Cold AAC          |(s*)      |7.1 | 1|0
2|RP|1|ColdPDT          |Cold PDT          |(s)       |5.1 | 1|1
3|RP|1|ColdPTT          |Cold PTT          |(s)       |5.1 | 1|1
4|RP|1|ElecStairAUC     |Electrical Stair AUC |(mA*)    |7.1 | 1|0
5|RP|1|ElecStairPDT     |Electrical Stair PDT |(mA)     |4.1 | 1|1
6|RP|1|ElecStairPTT     |Electrical Stair PTT |(mA)     |4.1 | 1|1|2|1
7|RP|1|dElecStairAUC    |Delta Electrical Stair AUC |(mA*)    |8.1 | 1|0|2|1
8|RP|1|dElecStairPDT    |Delta Electrical Stair PDT |(mA)     |8.2 | 2|0
9|RP|1|dElecStairPTT    |Delta Electrical Stair PTT |(mA)     |8.2 | 2|0|1|2
10|RP|1|PressureAUC     |Pressure AUC      |(kPa*)   |7.1 | 1|0
11|RP|1|PressurePDT     |Pressure PDT      |(kPa)    |5.1 | 1|1
12|RP|1|PressurePTT     |Pressure PTT      |(kPa)    |5.1 | 1|1
13|RP|1|QST_heat_thr    |Heat PDT          |(C)      |5.1 | 1|1
14|RP|1|QST_heat_tol    |Heat PTT          |(C)      |5.1 | 1|1
15|RP|1|SensoryCold     |Sensory after Cold |          |8.2 | 2|0
16|RP|1|AffectiveCold   |Affective after Cold |          |8.2 | 2|0
17|RP|1|MPQcold         |MPQ VAS after Cold |(mm)     |8.1 | 1|0
18|RP|1|SensoryStair     |Sensory after ES  |          |8.2 | 2|0
19|RP|1|AffectiveStair  |Affective after ES |          |8.2 | 2|0
20|RP|1|MPQstair        |MPQ VAS after ES  |(mm)     |8.1 | 1|0
```

```

21|RP|1|SensoryPress |Sensory after Pressure | | 18.2 | 2|0
22|RP|1|AffectivePress|Affective after Pressure | | 18.2 | 2|0
23|RP|1|MPQpress |MPQ VAS after Pressure | (mm) | 18.1 | 1|0
;
run;
/*16|RP|1|PPIcold |MPQ PPI after Cold | | 18.1 | 1|0*/
/*20|RP|1|PPIstair |MPQ PPI after ES | | 18.1 | 1|0*/
/*24|RP|1|PPIpress |MPQ PPI after Pressure | | 18.1 | 1|0*/

data _null_;
set pars end=last;
call symput('var' ||trim(left(put(_n_,8))),trim(PMSvar));
call symput('sort' ||trim(left(put(_n_,8))),trim(sort)) ;
call symput('precov' ||trim(left(put(_n_,8))),trim(precov));
call symput('lab' ||trim(left(put(_n_,8))),trim(name)) ;
call symput('unit' ||trim(left(put(_n_,8))),trim(unit)) ;
call symput('fmt' ||trim(left(put(_n_,8))),trim(format));
call symput('dec' ||trim(left(put(_n_,8))),trim(ndec)) ;
call symput('log' ||trim(left(put(_n_,8))),trim(log)) ;
call symput('up' ||trim(left(put(_n_,8))),trim(up)) ;
call symput('down' ||trim(left(put(_n_,8))),trim(down)) ;
call symput('yaxis1' ||trim(left(put(_n_,8))),trim(yaxis1));
call symput('xaxis1' ||trim(left(put(_n_,8))),trim(xaxis1));
call symput('yaxis2' ||trim(left(put(_n_,8))),trim(yaxis2));
call symput('xaxis2' ||trim(left(put(_n_,8))),trim(xaxis2));
call symput('yaxis3' ||trim(left(put(_n_,8))),trim(yaxis3));
call symput('xaxis3' ||trim(left(put(_n_,8))),trim(xaxis3));
if last then call symput('nlast',trim(left(put(_n_,8))));
run;

***STUDY SPECIFIC FORMATS-----;
proc format ;
value trtf 0="?" 1="Placebo" 2="Paracetamol";
run;
/*NB: in file &protocol._&ana._DataSTG and &protcol._&ana._DataA an extra format (treatmentf) has */
/*to be made */

***TREATMENT HANDLING-----;

data PDtrt (rename=(trt=Treatment));
set &file;
if treatment="Placebo" then trt=1;
if treatment="Paracetamol" then trt=2;
drop treatment;
/*CHECK THE TRT FORMAT ABOVE WITH THIS CODE CAREFULLY*/
format trt trtf.;
run;

***MACRO VARIABLES TREATMENT -----;

/*making macro variables trt1 to trtn with correct naming as in format*/
/*use if &by1=treatment*/
proc sort data=pdtrt out=trtnames (keep=treatment) nodupkey;
by treatment;
run;
data _null_;
set trtnames end=last;
trtfmt=put(treatment, trtf.);
call symput('trt' ||trim(left(put(_n_,8))),trim(trtfmt));
if last then call symput('ntrt',trim(left(put(_n_,8))));
run;

***GENERAL DATA MANIPULATIONS-----;
/*calculations*/
data PD1;
set PDtrt;

/*calculation of the area above the curve of the cold pressor test*/
ColdAAC=12000-ColdAUC;
format ColdAAC 7.1;

/*The MPQ_SF has been measured after the different pain inducing methods and are actually
measuring*/
/*something different after each different activity*/
if activity = "PainESTstair" then MPQstair =MPQ_SF_VAS;
if activity = "PainESTBurst" then MPQburst =MPQ_SF_VAS;
if activity = "PainPressure" then MPQpress =MPQ_SF_VAS;
if activity = "PainCold" then MPQcold =MPQ_SF_VAS;

```

```

if activity = "PainESTstair" then PPIstair =MPQ_SF_PPI;
if activity = "PainPressure" then PPIpress =MPQ_SF_PPI;
if activity = "PainCold" then PPIcold =MPQ_SF_PPI;
/**/

/*Calculation of the sensory and affective component of the MPQ*/
Sensory=(MPQ_SF01+MPQ_SF02+MPQ_SF03+MPQ_SF04+MPQ_SF05+MPQ_SF06+MPQ_SF07+MPQ_SF08+MPQ_SF09+MPQ_SF10+MPQ_SF11)/11;
if MPQ_SF01=.M or MPQ_SF02=.M or MPQ_SF03=.M or MPQ_SF04=.M or MPQ_SF05=.M or MPQ_SF06=.M or MPQ_SF07=.M or MPQ_SF08=.M or MPQ_SF09=.M or MPQ_SF10=.M or MPQ_SF11=.M then Sensory=.M;
Affective=(MPQ_SF12+MPQ_SF13+MPQ_SF14+MPQ_SF15)/4;
if MPQ_SF12=.M or MPQ_SF13=.M or MPQ_SF14=.M or MPQ_SF15=.M then Affective=.M;

if activity = "PainESTstair" then Sensorystair =Sensory;
if activity = "PainPressure" then Sensorypress =Sensory;
if activity = "PainCold" then Sensorycold =Sensory;
if activity = "PainGrill" then Sensorygrill =Sensory;
if activity = "PainESTstair" then Affectivestair =Affective;
if activity = "PainPressure" then Affectivepress =Affective;
if activity = "PainCold" then Affectivecold =Affective;

format Sensorystair sensorypress sensorycold
affectivestair affectivepress affectivecold 6.1;
run;
/**/

/*****
/*calculation of the diffuse noxious inhibitory control*/
*****/

/*getting the expdeltas for the ESTstair activity*/
proc sort data=pd1 (where=(activity="PainESTstair"))
out=stairtimes (keep=activity expdelta) nodupkeys;
by occasion expdelta;
run;
/*taking only the even or odd expdeltas respectively*/
data stairtime2;
set stairtimes;
if mod(_N_,2) = 0 then output;
rename expdelta=expdelta2;
run;
data stairtime1;
set stairtimes;
if mod(_N_,2) ne 0 then output;
run;
/*to calculate the difference between time1 and time 2 of the painESTstair*/
data diff;
merge stairtime1 stairtime2;
diff=expdelta2-expdelta;
run;
proc sort data=diff out=diff nodupkey;
by diff;
run;
/*CHECK if there is only one diff, if not, blame the project leader and think of a fancy
solution*/
data _null_;
set diff;
call symput('diff',trim(diff));
run;
/*CHECK IF THE SECOND ELECSTAIR MEASURE IS WITHIN 5 MINUTES OF THE PAINCOLD MEASURE*/
proc sort data=pd1 (where=(activity="PainESTstair"))
out=stairacttimes (keep=subjectnr occasion activity expdelta actdelta) ;
by subjectnr occasion expdelta;
run;
proc sort data=pd1 (where=(activity="PainCold"))
out=coldacttimes (keep=subjectnr occasion expdelta activity actdelta) ;
by subjectnr occasion expdelta;
run;
/*taking only the even actdeltas respectively*/
data stairacttime2;
set stairacttimes;
if mod(_N_,2) = 0 then output;
rename actdelta=actdelta2;
run;
data acttimes (keep=subjectnr occasion expdelta flag);
merge stairacttime2 coldacttimes (drop=expdelta);
delta=actdelta2 -actdelta;
flag=0;

```

```

if delta>5 then flag=1;
if flag=1;
run;

/*only times before cold pain test adjusted for time difference*/
data es1;
set pd1;
keep subjectnr occasion expdelta ElecStairAUC ElecStairPDT ElecStairPTT activity;
if activity="PainESTstair" and not missing (expdelta);
run;
data es2;
set es1;
if mod(_N_,2) ne 0 then output;
rename ElecStairAUC=ElecStairAUC1;
rename ElecStairPDT=ElecStairPDT1;
rename ElecStairPTT=ElecStairPTT1;
run;
data es1;
set es2;
expdelta=expdelta+&diff;
run;

/*merge the first times back on the total file and calculate the difference*/
/*merge the acttimes file with flags for times > 5 minutes after cold test on too*/
proc sort data=pd1;
by subjectnr occasion expdelta;
run;
proc sort data=es1;
by subjectnr occasion expdelta;
run;
proc sort data=acttimes;
by subjectnr occasion expdelta;
run;
data pd2;
merge pd1 es1 acttimes;
by subjectnr occasion expdelta;

if ElecStairAUC ne . then do;
  dElecStairAUC=ElecStairAUC-ElecStairAUC1;
end;
if (ElecStairAUC=.M or ElecStairAUC1=.M) and ElecStairAUC1 ne . then dElecStairAUC=.M;
if (ElecStairAUC=.H or ElecStairAUC1=.H) and ElecStairAUC1 ne . then dElecStairAUC=.H;
if (ElecStairAUC=.L or ElecStairAUC1=.L) and ElecStairAUC1 ne . then dElecStairAUC=.L;
if (ElecStairAUC=.U or ElecStairAUC1=.U) and ElecStairAUC1 ne . then dElecStairAUC=.U;
if flag=1 then dElecStairAUC=.M;
/*removing the second, after the cold test, electrical stair and MPQ scores*/
if dElecStairAUC ne . then do;
  ElecStairAUC=.;
  SensoryStair=.;
  AffectiveStair=.;
  MPQstair=.;
  PPIstair=.;
end;

if ElecStairPDT ne . then do;
  dElecStairPDT=ElecStairPDT-ElecStairPDT1;
end;
if (ElecStairPDT=.M or ElecStairPDT1=.M) and ElecStairPDT1 ne . then dElecStairPDT=.M;
if (ElecStairPDT=.H or ElecStairPDT1=.H) and ElecStairPDT1 ne . then dElecStairPDT=.H;
if (ElecStairPDT=.L or ElecStairPDT1=.L) and ElecStairPDT1 ne . then dElecStairPDT=.L;
if (ElecStairPDT=.U or ElecStairPDT1=.U) and ElecStairPDT1 ne . then dElecStairPDT=.U;
if flag=1 then dElecStairPDT=.M;
/*removing the second, after the cold test, electrical stair*/
if dElecStairPDT ne . then ElecStairPDT=.;

if ElecStairPTT ne . then do;
  dElecStairPTT=ElecStairPTT-ElecStairPTT1;
end;
if (ElecStairPTT=.M or ElecStairPTT1=.M) and ElecStairPTT1 ne . then dElecStairPTT=.M;
if (ElecStairPTT=.H or ElecStairPTT1=.H) and ElecStairPTT1 ne . then dElecStairPTT=.H;
if (ElecStairPTT=.L or ElecStairPTT1=.L) and ElecStairPTT1 ne . then dElecStairPTT=.L;
if (ElecStairPTT=.U or ElecStairPTT1=.U) and ElecStairPTT1 ne . then dElecStairPTT=.U;
/*removing the second, after the cold test, electrical stair*/
if flag=1 then dElecStairPTT=.M;
if dElecStairPTT ne . then ElecStairPTT=.;
run;
/*****
/*
end
*/

```

```
/****** /

%macro labels;
%local i;
data PD3;
retain Protocol SubjectNr Occasion Treatment;
set PD2;

/*to get rid of screening and follow up occasions*/
if occasion not in (0,99);

/*Label by variables correctly*/
Label treatment ="Treatment";
label SubjectNr="Subject";
label Occasion="Visit";

/*Label variable correctly according to pars file names*/
%do i=1 %to &nlast;
  label &&var&i="&&lab&i &&unit&i";
%end;

/*Make time variables correct and label correctly*/
length etime 8;
length atime 8;
etime=expdelta*60;
atime=actdelta*60;
if actdelta=.M then atime=.M;
format etime atime time6.;
label etime="Time (hh:mm)";
label atime="Actual time (hh:mm)";
label Actclock_Date="Date";
label Actclock_Time="Time (hh:mm)";
format actclock_time time6.;

run;
%mend labels;
%labels;
***PREPARED FILE;
/*to be used in other data manipulation files as start file*/
%let prepfile=PD3;
```

Listings

```

/*****DATAMANIPULATION CODE TO RUN MACRO LISTING*****/

/*****
/* Macro Listing makes a listing of one to five variables with 5 possible by variables, and 4
/* possible time variables.
/* Orientation can be portrait or landscape.
/* It needs macros G_dummy, G_j, G_pages, to be found in &protocol_PD_MacrosG.sas
/* and L_titles to be found in &protocol_&ana.DataL.sas.
/* It needs macro variables linesizep or linesizel, pagesizep or pagesizel and dirlocL,
/* to store the output.
/* It generates an output with the listing called listing&var.lst.
/* Written by M. de Kam, october 2013.
*****/

/*Macro vars:
file          = SAS data file                      standard "Listing"

listvar1      = first variable
name1         = variable label
listunit1     = unit of first variable
formatlistvar1 = general formatting first variable  standard "Width=14 center"  can remain empty
listvar2      = second variable                    can remain empty
name2         = full name of second variable        can remain empty
listunit2     = unit of second variable             can remain empty
formatlistvar2 = general formatting second variable  standard "Width=14 center"  can remain empty
listvar3      = third variable                     can remain empty
name3         = full name of third variable         can remain empty
listunit3     = unit of third variable              can remain empty
formatlistvar3 = general formatting third variable   standard "Width=14 center"  can remain empty
listvar4      = fourth variable                    can remain empty
name4         = full name of fourth variable        can remain empty
listunit4     = unit of fourth variable             can remain empty
formatlistvar4 = general formatting fourth variable  standard "Width=14 center"  can remain empty
listvar5      = fifth variable                     can remain empty
name5         = full name of fourth variable        can remain empty
listunit5     = unit of fourth variable             can remain empty
formatlistvar5 = general formatting fifth variable   standard "Width=14 center"  can remain empty

by1           = first by variable                  standard "Subjectnr"
formatby1     = formatting first by variable        standard "Width=7 center"   can remain empty
by2           = second by variable                  standard "Occasion"         can remain empty
formatby2     = formatting second by variable       standard "Width=5 center"   can remain empty
by3           = third by variable                   standard "Treatment"        can remain empty
formatby3     = formatting third by variable        standard "Width=12 flow left" can remain empty
by4           = fourth by variable                  can remain empty
formatby4     = formatting fourth by variable       can remain empty
by5           = fifth by variable                   can remain empty
formatby5     = formatting fifth by variable        can remain empty

time1         = first time variable                 standard "Actclock_Date"    can remain empty
formattime1   = formatting first by variable        standard "Width=9 center"   can remain empty
time2         = second time variable                standard "Actclock_Time"    can remain empty
formattime2   = formatting second by variable       standard "Width=7 center"   can remain empty
time3         = third time variable                 standard "Etime"           can remain empty
formattime3   = formatting third by variable        standard "Width=8 center"   can remain empty
time4         = fourth time variable                standard "Atime"           can remain empty
formattime4   = formatting fourth by variable       standard "Width=8 center"   can remain empty
deltatime     = indicator time1 and time2 being     standard "Y" must be capital
               delta times                          if delta=Y there has to be a
               time1 and time2

flag1         = if Y then flag&var is reported      standard "Y" must be capital
formatflag1   = formatting first flag               can remain empty
flag2         = if Y then flag&var2 is reported     standard "N" must be capital can remain empty
formatflag2   = formatting second flag              can remain empty
flag3         = if Y then flag&var3 is reported     standard "N" must be capital can remain empty
formatflag3   = formatting third flag               can remain empty
flag4         = if Y then flag&var4 is reported     standard "N" must be capital can remain empty
formatflag4   = formatting fourth flag              can remain empty
flag5         = if Y then flag&var5 is reported     standard "N" must be capital can remain empty
formatflag5   = formatting fifth flag               can remain empty

orientation   = table in portrait or landscape     standard "P" must be capital
delete        = removing temporary files           standard "Y" must be capital

```

```

print                = printing the table to an lst file    standard "Y" must be capital
                    (instead of to output window)
*/

%let sasfile=&protocol._PD_DataL;

****PREPARING DATA-----;
%macro L_prelist;
%local i;
data Listing;
set &prepfile;
label etime="Protocol (hh:mm)";
label atime="Actual (hh:mm)";
run;
%do i=1 %to &nlast;
/*if change from baseline values (for example as &var2 in the listing macro) are wanted*/
data pre&&var&i;
set &prepfile;
if &&var&i ne .;
if expdelta <0;
run;
proc means data=pre&&var&i noprint;
by subjectnr occasion;
output out=pre&&var&i (keep=subjectnr occasion pre&&var&i) mean (&&var&i)=pre&&var&i;
run;
proc sort data=pre&&var&i;
by subjectnr occasion;
run;
proc sort data=Listing;
by subjectnr occasion;
run;
data Listing;
merge Listing pre&&var&i;
by subjectnr occasion;
run;
data Listing;
set listing;
d&&var&i=&&var&i-pre&&var&i;
format d&&var&i 8.%eval(&&dec&i+1);
run;
proc datasets lib=work nolist;
delete pre&&var&i;
run;
quit;
%end;
%mend L_prelist;
%L_prelist;

****SORT BY &BY1 TO &BY5 AND &TIME1-----;
proc sort data=listing;
by subjectnr occasion treatment etime ;
run;

****MAKE TITLES AND FOOTNOTES-----;
%macro L_titles;

title3 "Listing &i of dynamic measurements";/*16.2.6.*/
title4 ;
title5 "Safety population";

/*footnotes can be added here or in the macro pages in the &protocol._&ana._MacroG*/
footnotel;
run;

%mend L_titles;

****PRINTING OF THE LISTING IN THE WORD DOCUMENT THROUGH DDE IN THE LISTING LOOP IN
&protocol._&ana._Analysis CODE;

```


Macro Listings

```

/*****
/* Macro Listing makes a listing of one to five variables with 5 possible by variables, and 4
/* possible time variables.
/* Orientation can be portrait or landscape.
/* It needs macros G_dummy, G_j, G_pages, to be found in &protocol_PD_MacrosG.sas
/* and L_titles to be found in &protocol.&ana._DataL.sas.
/* It needs macro variables linesizep or linesizel, pagesizep or pagesizel and dirlocL,
/* to store the output.
/* It generates an output with the listing called listing&var.lst.
/* Written by M. de Kam, october 2013.
*****/

%macro L
  (file                =Listing,
   listvar1            =,
   name1               =,
   listunit1           =,
   formatlistvar1      =,
   listvar2            =,
   name2               =,
   listunit2           =,
   formatlistvar2      =,
   listvar3            =,
   name3               =,
   listunit3           =,
   formatlistvar3      =,
   listvar4            =,
   name4               =,
   listunit4           =,
   formatlistvar4      =,
   listvar5            =,
   name5               =,
   listunit5           =,
   formatlistvar5      =,
   by1                 =SubjectNr,
   formatby1           =,
   by2                 =Occasion,
   formatby2           =,
   by3                 =Treatment,
   formatby3           =,
   by4                 =,
   formatby4           =,
   by5                 =,
   formatby5           =,
   time1               =Actclock_Date,
   formattime1         =,
   time2               =Actclock_Time,
   formattime2         =,
   time3               =Etime,
   formattime3         =,
   time4               =Atime,
   formattime4         =,
   deltetime           =Y,
   flag1               =Y,
   formatflag1         =,
   flag2               =N,
   formatflag2         =,
   flag3               =N,
   formatflag3         =,
   flag4               =N,
   formatflag4         =,
   flag5               =N,
   formatflag5         =,
   orientation         =P,
   delete              =Y,
   print               =Y
  );

  ***DATA CHANGES;
  data local ;
  set &file;
  %if %length(&listvar2)=0 %then %do;
    if &listvar1 ne .;
  %end;
  %if %length(&listvar3)=0 and %length(&listvar2) ne 0 %then %do;

```

```

    if (&listvar1= . and &listvar2= .) then delete;
%end;
%if %length(&listvar4)=0 and %length(&listvar3) ne 0 %then %do;
    if (&listvar1= . and &listvar2= . and &listvar3= .) then delete;
%end;
%if %length(&listvar5)=0 and %length(&listvar4) ne 0 %then %do;
    if (&listvar1= . and &listvar2= . and &listvar3= . and &listvar4= .) then delete;
%end;
%if %length(&listvar5)>0 %then %do;
    if (&listvar1= . and &listvar2= . and &listvar3= . and &listvar4= . and &listvar5 = .) then
delete;
%end;
run;

***LISTING TABLE;

/*The report is run in a macro, which is run twice.*/
/*First to create a dummy table to count the pages.*/
/*This is used to create a page x of y page numbering*/
/*Secondly to run the actual report with page x of y numbering*/
%macro L_report (reportfile=local,printfile="&dirlocL.listing&listvar1..lst");

    /*macro j adds a dummy variable to be used to generate the last line under the table*/
    %G_j;

    %let page=0;
    options pageno=1
    %if &orientation=P %then %do;
        pagesize=&pagesizep linesize=&linesizep;
        %G_header (sasfile=&sasfile, root=&root);
    %end;
    %if &orientation=L %then %do;
        pagesize=&pagesizel linesize=&linesizel;
        %G_headerLS (sasfile=&sasfile, root=&root);
    %end;

    %L_titles;

    %if &j=2 and &print=Y %then %do ;
        proc printto file=&printfile new; run;
    %end;

    proc report data=local headline headskip nowindows split="~" spacing=2;
    column ("--" dummy &by1 &by2 &by3 &by4 &by5 &time1 &time2
    %if &deltatime=Y %then %do;
        ("Time from dosing" "--" &time3 &time4)
    %end;
    %else %do;
        &time3
        &time4
    %end;
    &listvar1
    %if &flag1=Y %then %do; flag&listvar1 %end;
    &listvar2
    %if &flag2=Y %then %do; flag&listvar2 %end;
    &listvar3
    %if &flag3=Y %then %do; flag&listvar3 %end;
    &listvar4
    %if &flag4=Y %then %do; flag&listvar4 %end;
    &listvar5
    %if &flag5=Y %then %do; flag&listvar5 %end;
    );
    define dummy/order noprint;
    define &by1/order order=data width=7 center &formatby1;
    %if %length(&by2) GT 0 %then %do;
        define &by2/order order=data width=5 center &formatby2;
    %end;
    %if %length(&by3) GT 0 %then %do;
        define &by3/order order=data left width=12 flow &formatby3 ;
    %end;
    %if %length(&by4) GT 0 %then %do;
        define &by4/order order=data &formatby4;
    %end;
    %if %length(&by5) GT 0 %then %do;
        define &by5/order order=data &formatby5;
    %end;
    %if %length(&time1) GT 0 %then %do;
        define &time1/display width=9 left &formattime1;

```

```

%end;
%if %length(&time2) GT 0 %then %do;
  define &time2/display width=8 left &formattime2;
%end;
%if %length(&time3) GT 0 %then %do;
  define &time3/display width=8 center &formattime3;
%end;
%if %length(&time4) GT 0 %then %do;
  define &time4/display width=8 center &formattime4;
%end;
define &listvar1/display width=14 center "&name1 &listunit1" &formatlistvar1;
%if &flag1=Y %then %do;
  define flag&listvar1/display &formatflag1;
%end;
%if %length(&listvar2)>0 %then %do;
  define &listvar2/display width=14 center "&name2 &listunit2" &formatlistvar2;
  %if &flag2=Y %then %do;
    define flag&listvar2/display &formatflag2;
  %end;
%end;
%if %length(&listvar3)>0 %then %do;
  define &listvar3/display width=14 center "&name3 &listunit3" &formatlistvar3;
  %if &flag3=Y %then %do;
    define flag&listvar3/display &formatflag3;
  %end;
%end;
%if %length(&listvar4)>0 %then %do;
  define &listvar4/display width=14 center "&name4 &listunit4" &formatlistvar4;
  %if &flag4=Y %then %do;
    define flag&listvar4/display &formatflag4;
  %end;
%end;
%if %length(&listvar5)>0 %then %do;
  define &listvar5/display width=14 center "&name5 &listunit5" &formatlistvar5;
  %if &flag5=Y %then %do;
    define flag&listvar5/display &formatflag5;
  %end;
%end;
%if %length(&by5) GT 0 %then %do;
  break after &by5/skip;
%end;
%if %length(&by4) GT 0 and %length(&by5)=0 %then %do;
  break after &by4/skip;
%end;
%if %length(&by3) GT 0 and %length(&by4)=0 %then %do;
  break after &by3/skip;
%end;
%if %length(&by2) GT 0 and %length(&by3)=0 %then %do;
  break after &by2/skip;
%end;
%if %length(&by1) GT 0 and %length(&by2)=0 %then %do;
  break after &by1/skip;
%end;
/*macro pages creates the actual page x of y page numbering*/
%G_pages;
run;
proc printto; run;
/*macro dummy calculates the starting position of the bottom line if output is centered*/
%if &j=1 %then %do;
  %global pages; %let pages=&page.;
  %if &orientation=P %then %do;
    %G_dummy (dumlinesize=&linesizep);
  %end;
  %if &orientation=L %then %do;
    %G_dummy (dumlinesize=&linesizel);
  %end;
%end;
%mend L_report;

%local j;
%do j=1 %to 2;
  %L_report;
%end;

proc printto;
run;

***DELETING OF TEMPORARY FILES;

```

```
%if &delete=Y %then %do;  
  proc datasets lib=work nolist;  
    delete local;  
  run;  
  quit;  
%end;  
  
%mend L;
```

Individual plots

```

/*****
/* Macro Individual graphs makes plots of 3 possible y variables over 2 possible x variables,
/* with 2 possible by variables
/* Orientation can be portrait or landscape
/* It needs a macro IG_PlotNames and IG_Panels that are included in MacroIG.sas
/* It needs a macro G_yaxis to be found in &protocol._ana._MacrosG.sas and IG_Formats and IG_DDE
/* to be found in &protocol._ana._DataIG.sas
/* It generates cgm output files with graphs called &ylvar&i&f..cgm,i=ith variable, f=1 to number
/* of pages. The result is printed to a word document with DDE macros if print=Y
/* Written by M. de Kam, November 2013
*****/

/*Macro vars
file          = SAS filename for data file,          Standard "Igraphs"
xlvar         = variable on x-axis                   Standard "etime"=protocol time
x2var         = second variable on x-axis            Standard "atime"=actual time      can remain empty
ylvar         = variable on y-axis
y2var         = second variable on first yaxis       can remain empty
y3var         = variable on second yaxis             can remain empty
id            = first identifier for plots           Standard "SubjectNr"
labelid       = Y if label is wanted above graphs   Standard "Y" must be capital
                                                    presuming id=SubjectNr
by1           = first by variable appears in graph  Standard "Treatment"           can remain empty
                                                    header without label
labelby1      = Y if label is wanted above graph    Standard "N" must be capital
                                                    presuming by1=Treatment
by2           = extra by variable appears in graph  can remain empty
                                                    header without label
labelby2      = Y if label is wanted above graph    Standard "N" must be capital
sort          = if CO then for missing subject/&by1 combinations an empty graph is
                                                    generated (CO=cross-over studies)
xaxisI        = additional x-axis formatting        can remain empty
yaxisI        = additional y-axis formatting        can remain empty
yaxisI2       = additional second y-axis formatting can remain empty
nrows         = number of rows in the plot-matrix  Standard "3"
ncols         = number of columns in the            Standard calculated as levels
                                                    of by1 variable if by1 is empty
                                                    and ncols not specified then
                                                    ncols=4 (landscape) or ncols=2
                                                    (portrait)
secondyaxis    = Y if second yaxis is wanted: y3var Standard "N" must be capital
                                                    has to be specified
orientation   = portrait or landscape               Standard="P" must be capital
extra         = extra statement in the plot         can remain empty
                                                    statement (e.g reflines)
adjppp        = extra number to adjust the number  Standard=0
                                                    of plots per page (ppp+adjppp)
print         = print output through DDE            Standard="Y" must be capital
delete        = removing of temporaray files        Standard="Y" must be capital
*/

%let sasfile=&protocol._ana._DataIG;

****PREPARING DATA-----;
data igraps ;
set &prepfile;
run;

****MAKE TITLES AND FOOTNOTES-----;

/*used in DDE statement, printed above graph*/
%let marker=Dot: actual time   Circle: protocol time;

/*for the DDE output this creates necessary macrovariables instrngL and instrngP*/
%G_headerLS (sasfile=&sasfile, root=&root);
%G_header (sasfile=&sasfile, root=&root);

/*For the DDE output this creates necessary macrovariables footL and footP*/
/*Length can be adjusted depending on the length of the name of the output producer*/
/*22=M.L. de Kam, 15=Page xx of yy*/
data _null_;
footL=" ";
call symput ('footL',put(footL,$%eval(&linesizeL-22-15).)||"produced by &statistician");
run;

```

```

data _null_;
footP=" ";
call symput ('footP',put(footP,$%eval(&linesizeP-22-15).)||"produced by &statistician");
run;

***FORMATTING GRAPHS-----;
%macro IG_formats;
  options reset=all;
  run;

  options horigin= vorigin= hpos= vpos= htext=3.4pct nodisplay noprompt hsize=12cm vsize=12cm
  gsfname=grafout gsfname=replace goutmode=replace ftext="HWCGM001" target = cgmof97p;
  %if &orientation=L %then %do;
    options device=cgmof97l target=cgmof97l;
  %end;
  %else %do;
    options device=cgmof97p target=cgmof97p ;
  %end;

  axis1 label=(angle=90) width=1 major=(height=-1.5pct) minor=none offset=(4pct) &autoyaxis
    &yaxisI;
  axis2 width=1 major=(height=-1pct) minor=(height=-0.66pct n=1) offset=(4pct) &xaxisI;
  %if &secondyaxis=Y %then %do;
    axis3 label=(angle=270) width=1 major=(height=-1.5pct) minor=none offset=(4pct) &yaxisI2 ;
  %end;
  /*1=x1var*y1var*/
  /*2=x2var*y1var*/
  /*3=x1var*y2var*/
  /*4=x2var*y2var*/
  /*5=x1var*y3var*/
  /*6=x2var*y3var*/
  symbol1 interpol=none value=circle height=4pct c=black mode=include width=1 ;
  symbol2 interpol=join value=dot height=4pct c=black mode=include width=1 ;
  symbol3 interpol=none font=markerE value="U" height=2pct c=black mode=include width=3 ;
  symbol4 interpol=join font=marker value="U" height=2pct c=black mode=include width=3 ;

  %if &secondyaxis=Y %then %do;
    symbol5 interpol=join font=markerE value="C" height=2pct c=black mode=include width=3 ;
    symbol6 interpol=none font=marker value="C" height=2pct c=black mode=include width=3 ;
  %end;
%mend IG_formats;

***DDE OUTPUT-----;
%macro IG_DDE;
%local r;
%do r=1 %to &npanels;
  %if &orientation=L %then %do;
    %DDEInsertText0 (name=&instringL &sysdate9 &system Page: &r );
    %DDEInsertText1 (text1=Individual Plots &i of dynamic measurements,
      text2=Safety population); /*16.2.6. ICH numbering*/
    %DDEInsertIndGraphL (name=,marker=&marker, file=&dirlocG.&y1var&r..cgm);
    %DDEInsertText2 (name= Page: &r of &npanels &footL);
  %end;
  %if &orientation=P %then %do;
    %DDEInsertText0 (name=&instringP &sysdate9 &system Page: &r );
    %DDEInsertText1 (text1=Individual Plots &i of dynamic measurements,
      text2=Safety population); /*16.2.6. ICH numbering*/
    %DDEInsertIndGraphP (name=,marker=&marker, file=&dirlocG.&y1var&r..cgm);
    %DDEInsertText2 (name= Page: &r of &npanels &footP);
  %end;
%end;
%mend IG_DDE;

```

Macro Individual plots

```

/*****
/* Macro Individual graphs makes plots of 3 possible y variables over 2 possible x variables,
/* with 2 possible by variables
/* Orientation can be portrait or landscape
/* It needs a macro IG_PlotNames and IG_Panels that are included in MacroIG.sas
/* It needs a macro G_yaxis to be found in &protocol._&ana._MacrosG.sas and IG_Formats and IG_DDE
/* to be found in &protocol._&ana._DataIG.sas
/* It generates cgm output files with graphs called &ylvar&i&f..cgm,i=ith variable, f=1 to number
/* of pages. The result is printed to a word document with DDE macros if print=Y
/* Written by M. de Kam, November 2013
*****/

%macro IG_PlotNames
  (root=gplot /* root for name
  ,start= /* lowest numeric suffix
  ,num= /* number of plots
  );

%local i j k/*looping variable*/ ;

%do i=&start %to %eval(&start+&num-1);
  %let j=%eval(&i-1);
  %if &i=1 %then %let j=;
  %let k=%eval(&i-&start+1);
  &k:&Root&j /*SAS Code*/
%end;
%mend IG_PlotNames;

%macro IG_panels
  (cols=
  ,rows=
  ,panell=1
  ,xmin=0
  ,xmax=100
  ,ymin=0
  ,ymax=100
  ,xspace=2
  ,yspace=2
  );
  /* the %eval function only returns the integer of a calculated number,
  where the %sysevalf returns the number including the decimals;
  %let xsize=%sysevalf((&xmax-&xmin-(&cols-1)*&xspace)/&cols);
  %let ysize=%sysevalf((&ymax-&ymin-(&rows-1)*&yspace)/&rows);

  %do row=1 %to &rows;
    %let uy=%sysevalf(&ymax-(&ysize+&yspace)*(&row-1));
    %let ly=%sysevalf(&ymax-(&ysize+&yspace)*(&row-1)-&ysize);
    %do col=1 %to &cols;
      %let panel = %sysevalf((&row-1)*&cols+&col+&panell-1);
      %let lx=%sysevalf(&xmin+(&xsize+&xspace)*(&col-1));
      %let rx=%sysevalf(&xmin+(&xsize+&xspace)*(&col-1)+&xsize);
      &panel/llly=&ly uly=&uy llx=&lx lrx=&rx lry=&ly ury=&uy ulx=&lx urx=&rx
    %end;
  %end;

  %PUT NOTE:-Panels &panell - &panel : &xsize % hsize by &ysize % vsize.;

%mend IG_panels;

%macro IG
  ( file=igraphs
  , x1var=etime
  , x2var=atime
  , y1var=
  , y2var=
  , y3var=
  , id=SubjectNr
  , labelid=Y
  , by1=Treatment
  , labelby1=N
  , by2=
  , labelby2=N
  , sort=CO
  , xaxisI=

```

```

    , yaxisI=
    , yaxisI2=
    , nrows=3
    , ncols=
    , secondyaxis=N
    , orientation=P
    , extra=
    , adjppp=0
    , print=Y
    , delete=Y
    );

***DELETING EMPTY ROWS;
data Datafile;
set &file;
%if %length(&y2var) LE 0 and %length(&y3var) LE 0 %then %do;
    if &y1var=. then delete;
%end;
%if %length(&y2var) GT 0 and %length(&y3var) LE 0 %then %do;
    if &y1var=. and &y2var=. then delete;
%end;
%if %length(&y2var) LE 0 and %length(&y3var) GT 0 %then %do;
    if &y1var=. and &y3var=. then delete;
%end;
%if %length(&y2var) GT 0 and %length(&y3var) GT 0 %then %do;
    if &y1var=. and &y2var=. and &y3var=. then delete;
%end;
run;

***CALCULATION OF AUTOMATIC YAXIS;
%if %length(&y2var) LE 0 %then %do;
    proc means data=Datafile noprint;
        output out=x min(&y1var)=lower max(&y1var)=upper;
    run;
%end;
%if %length(&y2var) > 0 %then %do;
    proc means data=Datafile noprint;
        output out=x min(&y1var)=lower max(&y1var)=upper min(&y2var)=lower2 max(&y2var)=upper2;
    run;

    data x;
    set x;
    lower=min(lower,lower2);
    upper=max(upper,upper2);
    run;
%end;

%G_yaxis;

***MACRO VARIABLE NUMBER OF PAGES, ALSO TO BE USED IN DDE MACRO;
%global npanels;

***CALCULATION OF COLUMNS BASED ON BY1;
%if %length(&by1) GT 0 %then %do;
    proc sort data=Datafile out=x (keep = &by1) nodupkeys;
        where not missing(&y1var);
        by &by1;
    run;
    data _null_;
        set x end=last;
        if last then call symput("ncolsG",trim(left(put(_n_,8)))));
    run;
    %if %length(&ncols) LE 0 %then %do;
        %let ncols=&ncolsG;
    %end;
%end;

***NCOLS IF NOT CALCULATED NOR SPECIFIED;
%if %length(&ncols) LE 0 %then %do;
    %if &orientation=L %then %do;
        %let ncols=4;
    %end;
    %if &orientation=P %then %do;
        %let ncols=2;
    %end;
%end;

***CREATING A DATALINE FOR EVERY &ID AND &BY1 COMBINATION IF DATA IS BOOKMARKED AS CROSS-OVER;

```



```

%if &sort=CO %then %do;
  proc sort data=&file out=id (keep=&id) nodupkey;
  by &id;
  run;
  data id;
  set id;
  by &id;
  do &by1 = 1 to &ncolsG;
  output;
  end;
  run;
  proc sort data=datafile;
  by &id &by1;
  run;
  data datafile;
  merge datafile id;
  by &id &by1;
  run;
%end;

***SORTING FOR GRAPHS;
proc sort data=Datafile;
by &id &by1 &by2 &x1var;
run;

***MACRO WITH FORMATTING SPECIFICATIONS;
%IG_formats;

***CREATING GRAPHS;
proc gplot uniform gout=Datafile data=Datafile;
plot &y1var*&x1var
%if %length(&x2var) GT 0 %then %do; &y1var*&x2var %end;
%if %length(&y2var) GT 0 %then %do; &y2var*&x1var %end;
%if %length(&y2var) GT 0 and %length(&x2var) GT 0 %then %do; &y2var*&x2var %end;
/ vaxis=axis1 haxis=axis2 noframe overlay &extra;
by &id &by1 &by2;
%if &labelid=N %then %do;
  label &id='00'x;
%end;
%if %length (&by1)> 0 %then %do;
  %if &labelby1=N %then %do;
    label &by1='00'x;
  %end;
%end;
%if %length (&by2)> 0 %then %do;
  %if &labelby2=N %then %do;
    label &by2='00'x;
  %end;
%end;
%if &secondyaxis=Y %then %do;
  plot2 &y3var*&x1var
  %if %length(&x2var) GT 0 %then %do; &y3var*&x2var %end;
  / vaxis=axis3 noframe overlay;
%end;
run;
quit;

***CALCULATING NUMBER OF PLOTS, NUMBER OF PLOTS PER PAGE, TOTAL NUMBER OF PAGES;
proc sort data=Datafile out=x (keep=&id &by1 &by2) nodupkeys;
by &id &by1 &by2;
run;

data _null_;
set x end=last;
if last;
nplots=_N;
ppp=(&nrows * &ncols)+&adjppp; /*plots per page, adjustable with macro variable*/
npanels=ceil(nplots/ppp); /*number of panels*/
call symput("npanels",trim(left(put(npanels,best4.))));
call symput("ppp",trim(left(put(ppp,best4.))));
run;

***DELETING GRAPHS FROM A FORMER RUN;
%local c;
%do c=1 %to &npanels;
  data _null_;
  command1="del &dirlocG.&y1var&c..cgm";
  call system(command1);

```

```
run;
%end;

***RESETTING GOPTIONS FOR GREPLAY;
%if &orientation=L %then %do;
  goptions hsize=25cm vsize=14cm display;
%end;
%else %do;
  goptions hsize=16cm vsize=21cm display;
%end;
%local f;
%do f=1 %to &npanels;
  filename grafout "&dirlocG.&ylvar&f..cgm";
  proc greplay igout=Datafile gout=Datafile tc=tempcat nofs;
    tdef newpan %IG_panels(cols=&ncols,rows=&nrows);
    template newpan;
    treplay %IG_PlotNames(start=%eval((&f-1)*&ppp+1),num=&ppp);
  run;
  quit;
%end;

***MACRO WITH DDE COMMANDS;
%if &print=Y %then %do;
  %IG_DDE;
%end;

***DELETING OF TEMPORARY FILES;
%if &delete=Y %then %do;
  proc datasets lib=work nolist;
    delete datafile x id;
  run;
  quit;
%end;

%mend IG;
```

Summaries

```

/*****
/* Macro SummaryTableGraph makes a summary table and a graph of a y variable, an x variable and
/* 2 possible by variables
/* It needs a macro G_yaxis to be found in &protocol._&ana._MacrosG.sas and a macro STG_report
/* STG_formatsR or STG_formatsS and STG_DDE to be found in &protocol._&ana._DataSTG.sas
/* Orientation of the table can be portrait or landscape
/* If no xvar is defined, the macro returns a column graph
/* If there are two by variables the column graph groups by the second by variable
/* It generates 1st and cgm output files with a table and a graph called tp&file&yvar..1st and
/* avg&file&yvar..cgm and an XLS file called avg&file&yvar..XLS with data to make graphs with
/* other software.
/* The result can be printed to a word document if print=Y
/* Written by M. de Kam, November 2013
*****/

```

```

/*Macro vars
file      = SAS filename for data file,           Standard "Summary"
yvar      = variable on y-axis
name      = variable label (appears on y-axis
           and in title of DDE)
unit      = unit of the yvar
ndec      = number of decimals of the yvar
pdec      = number of decimals wanted for         Standard "1"
           percentage values
by1=      = first by variable for summary, has to be Standard "Treatment"
           numeric and, for the xls export, with
           format &by1.f

```

IF BY2 IS NOT EMPTY A VARIABLE COMBI IS CALCULATED AS (level of &by2-1)*&nby1+(level of &by1)
WHICH NEEDS THE CORRECT FORMAT!! FIRST EVERY LEVEL OF BY1 THEN THE LEVEL OF BY2. IF &BY2 IS EMPTY,
COMBI=&BY1.

```

by2      = second by variable for summary, has to be                can remain empty
           numeric and, for the xls export, with
           format &by2.f
xvar      = variable for the x-axis of the summary                 Standard "etime"           can remain empty
           graph , if empty a column graph is made
sdextradec = number of extra decimals for the SD                 Standard "2"
meanextradec= number of extra decimals for the mean              Standard "1"
log        = can be used in the macro STG_report to
           print geometric mean and CV
orientation = orientation of the summary table,
           portrait or landscape                                Standard "P"
print      = printing the output to files and
           Word thorough DDE                                    Standard "Y" must be capital
up         = &by1/combi number with upper SD bar in
           graph, if empty automatically calculated,
           if up=-1 ALL error bars are shown                    Standard empty
down       = &by1/combi number with lower SD bar in
           graph, if empty automatically calculated              Standard empty
colour     = define colours in macro vars as many as
           there are combis or in case of bargraph
           as many as there are levels of &by1                   Standard "Y" ONLY AFFECTS
           COLOUR OF ERROR BARS
SEerrorbars = SE error bars instead of SD                        Standard "N" must be capital
yaxis1     = additional x-axis formats                           Standard empty
yaxis1     = additional y-axis formats                           Standard empty
legend     = legend yes or no                                    Standard "Y" must be capital
extra      = extra statement in the plot statement
           (e.g reflines)                                       Standard empty
pid        = pattern ID column graph                             Standard "midpoint"
           if there is a &by2 pid can be group or
           subgroup
formatbar  = extra formatting column graph                       can remain empty
delete     = removing temporary files                            Standard "Y" must be capital
*/

```

```

/*CALCULATED SUMMARY STATISTICS*/
/* mean, stddev, stderr, n, nmiss, min, median, max, lclm, uclm, Q1, Q3, Qrange, CV, */
/* geometric mean, geometric CV;*/

```

```
%let sasfile=&protocol._&ana._DataSTG;
```

```

***PREPARING DATA-----;
data summary ;
set &prepfile;

```

```

run;

***EXTRA FORMATS IF &BY2 IS USED-----;
/*variable combi is calculated as &nby2* (NUMBER OF &by1)+(NUMBER OF &by2) -&nby2*/
/*Resulting in the order: every level of by1 by first level of by2,*/
/*every level of by1 by next level of by2 etc.*/
/*ADJUST THE FORMAT TO THIS!!!!*/
proc format;
value combif
1="Placebo Male" 5="Placebo Female"
2="Dose 1 Male" 6="Dose 1 Female"
3="Dose 2 Male" 7="Dose 2 Female"
4="Control Male" 8="Control Female";
run;

***EXTRA FORMATS FOR XLS FILES-----;
/*For macro STG format &by1.f is necessary. If &by2 exists the also make &by2.f*/
/*Variable combi is not used for the xls files*/
proc format ;
value treatmentf 0="?" 1="Placebo" 2="Dose 1" 3="Dose 2" 4="Control" ;
run;

/*for the export file a separate format for &by2 is necessary called &by2f.*/
proc format;
value gendersidf 1="Male" 2="Female";
run;

***TITLES AND FOOTNOTES-----;

/*For the DDE output this creates necessary macro variables footL and footP*/
/*Length can be adjusted depending on the length of the name of the output producer*/
/*22=M.L. de Kam, 15=Page xx of yy*/
data _null_;
footL=" ";
call symput ('footL',put(footL,$%eval(&linesizeL-22-15).)||"produced by &statistician");
run;
data _null_;
footP=" ";
call symput ('footP',put(footP,$%eval(&linesizeP-22-15).)||"produced by &statistician");
run;

***SUMMARY TABLE FORMATTING-----;

%macro STG_report (reportfile=sum, printfile="&dirlocT.tp&file&yvar..lst");
/*macro j adds a dummy variable to be used to generate the last line under the the table*/
%G_j;

%let page=0;
options pageno=1
%if &orientation=P %then %do;
pagesize=&pagesizep linesize=&linesizep;
%G_header (sasfile=&sasfile, root=&root);
%end;
%if &orientation=L %then %do;
pagesize=&pagesizel linesize=&linesizel;
%G_headerLS (sasfile=&sasfile, root=&root);
%end;

title3 "Summary &i of dynamic measurements";/*14.2.*/
title4 ;
title5 "Analysis population";

%if &j=2 and &print=Y %then %do ;
proc printto file=&printfile new; run;
%end;

proc report data=sum headline headskip nowindows split="~" spacing=1 ;
column ("Summary table: &name &unit" "--" dummy
%if %length(&xvar) GT 0 %then %do;
&by1 %if %length(&by2) GT 0 %then %do; &by2 %end; &xvar
%end;
%if %length(&xvar) = 0 %then %do;
&by1 %if %length(&by2) GT 0 %then %do; &by1 %end;
%end;
n&yvar avg&yvar
%if &log=1 %then %do; geom&yvar %end;
sd&yvar sem&yvar cv&yvar
%if &log=1 %then %do; geomcv&yvar %end;

```

```

med&yvar min&yvar max&yvar );
define dummy/order noprint;
define &by1/ order order=internal left width=20 flow ;
%if %length(&by2) GT 0 %then %do;
    define &by2/ order order=internal left width=20 flow ;
%end;
%if %length(&xvar) GT 0 %then %do;
    define &xvar / display width=8 left;
%end;
define avg&yvar/ display format=8.&decmean;
define sd&yvar / display format=8.&decstd;
define sem&yvar/ display format=8.&decstd;
define CV&yvar / display format=6.&dec;
define n&yvar / display format=3.0 width=3;
define min&yvar/ display format=8.&dec ;
define med&yvar/ display format=8.&dec;
define max&yvar/ display format=8.&dec;
%if &log=1 %then %do;
    define geom&yvar /display format=8.&decmean width=9;
    define geomcv&yvar/display format=6.&dec width=9;
%end;
%if %length(&by1) GT 0 and %length(&by2)<= 0 %then %do;
    break after &by1/skip;
%end;
%if %length(&by2) GT 0 %then %do;
    break after &by2/skip;
%end;
/*macro pages creates the actual page x of y page numbering*/
%G_pages;
run;
proc printto; run;

/*macro dummy calculates the starting position of the bottom line if output is centered*/
%if &j=1 %then %do;
    %global pages; %let pages=&page.;
    %if &orientation=P %then %do;
        %G_dummy (dumlinesize=&linesizep);
    %end;
    %if &orientation=L %then %do;
        %G_dummy (dumlinesize=&linesizel);
    %end;
%end;
%mend STG_report;

****IF COLOUR=Y THEN DEFINE THE COLOURS HERE-----;

%let colour1="grey";
%let colour2="red";
%let colour3="green";
%let colour4="blue";
%let colour5="grey";
%let colour6="red";
%let colour7="green";
%let colour8="blue";

****FORMATTING REPEATED MEASURES GRAPHS-----;
%macro STG_formatsR;

****OPTIONS GRAPH;
goptions reset=all;
run;
goptions hsize=21cm vsize=14cm horigin= vorigin= hpos= vpos= htext=2.5pct display noprompt
target = cgmo97p device = cgmo97p gsfname=grafout gsfmde=replace goutmode=replace
ftext="HWCGM01";

****AXES;
axis1 label=(angle=90 ) width=3 major=(height=-1pct) minor=none offset=(4pct, 0pct) &autoyaxis
&yaxis1;
axis2 label=(height=3pct) width=3 major=(height=-1.5pct) minor=none offset=(4pct, 0pct) &xaxis1;

****LEGEND;
legend shape=symbol(3,0.75) value=(j=1) label=("SD error bars") position=(top center outside)
offset=(0,-0.5cm);

****SYMBOLS;
/*circle, square, triangle, diamond. Open and close*/
symbol1 interpol=join font = marker value="W" height=2pct c=&colour1 mode=include width=3;

```

```

symbol2 interpol=join font = marker value="U" height=2pct c=&colour2 mode=include width=3;
symbol3 interpol=join font = marker value="C" height=2pct c=&colour3 mode=include width=3;
symbol4 interpol=join font = marker value="P" height=2pct c=&colour4 mode=include width=3;
symbol5 interpol=join font = markerE value="W" height=2pct c=&colour5 mode=include width=3;
symbol6 interpol=join font = markerE value="U" height=2pct c=&colour6 mode=include width=3;
symbol7 interpol=join font = markerE value="C" height=2pct c=&colour7 mode=include width=3;
symbol8 interpol=join font = markerE value="P" height=2pct c=&colour8 mode=include width=3;

%mend STG_formatsR;
***ALTERNATIVES;
/*symbol1 interpol=join value=dot height=4pct c=&colour1 mode=include width=5;*/
/*symbol2 interpol=join value=square height=4pct c=&colour2 mode=include width=5;*/
/*symbol3 interpol=join value=triangle height=4pct c=&colour3 mode=include width=5;*/
/*symbol4 interpol=join value=diamond height=5pct c=&colour4 mode=include width=5;*/
/*symbol5 interpol=join value=circle height=5pct c=black mode=include width=5;*/

*****FORMATTING SINGLE MEASURES GRAPHS-----;
%macro STG_formatsS;

***OPTIONS;
goptions reset=all;
run;
goptions gunit=pct htext=1.75pct ftext="HWCGM001" hsize=15cm vsize=12cm horigin= vorigin= hpos=
vpos= display noprompt
target = cgmof97p gsfname=grafout gsfmode=replace goutmode=replace device = cgmof97p ;

***AXES;
axis1 label=(' ') value=(height=2) ;
axis2 label=(angle=90 "&name &unit" ) minor=none &autoyaxis;
axis3 label=(' ') nobrackets;

***TITLE;
title1 "SD error bars" j=1 ;

***SYMBOLS;
pattern1 value=x1 c=&colour1 ;
pattern2 value=x1 c=&colour2 ;
pattern3 value=x1 c=&colour3 ;
pattern4 value=x1 c=&colour4 ;
%mend STG_formatsS;

****DDE OUTPUT-----;
%macro STG_DDE;
***PRINT TO WORD DOCUMENT USING DDE;

options pagesize=&pagesizep linesize=&linesizep;
%G_header (sasfile=&sasfile, root=&root);

%if &orientation=L %then %do;
%DDEToggleLayout;
options pagesize=&pagesize1 linesize=&linesize1;
%G_headerLS (sasfile=&sasfile, root=&root);
%end;

%DDEInsertHeader2 (name=&&lab&i &&unit&i);
%DDEInsertHeader3 (name=Summary table &i /*14.2. ICH numbering*/&name &unit);
%DDEInsertFileNH (file=&dirlocT.tp&file&yvar..lst );

%if &orientation=L %then %do;
%DDEToggleLayout;
%end;
%if &log ne 1 %then %do;
%DDEBackspace;
%end;

%DDEInsertHeader3 (name=Summary graph &i/*14.2. ICH numbering*/ &name &unit);
%DDEInsertText0 (name=&inststringP &sysdate9 &stime Page: 1 );
%DDEInsertText1 (text1=Summary graph &i of dynamic measurements,
text2=Analysis population); /*14.2. ICH numbering*/
%DDEInsertAvgGraph (label=, sub1= /*with SD error bars*/, file=&dirlocG.avg&file&yvar..cgm);
%DDEInsertText2 (name= Page: 1 of 1 &footP);

%mend STG_DDE;

```

Macro Summaries

```

/*****
/* Macro SummaryTableGraph makes a summary table and a graph of a y variable, an x variable and
/* 2 possible by variables
/* It needs a macro G_yaxis to be found in &protocol._ana._MacrosG.sas and a macro STG_report
/* STG_formatsR or STG_formatsS and STG_DDE to be found in &protocol._ana._DataSTG.sas
/* Orientation of the table can be portrait or landscape
/* If no xvar is defined, the macro returns a column graph
/* If there are two by variables the column graph groups by the second by variable
/* It generates lst and cgm output files with a table and a graph called tp&file&yvar..lst and
/* avg&file&yvar..cgm and an XLS file called avg&file&yvar..XLS with data to make graphs with
/* other software.
/* The result can be printed to a word document if print=Y
/* Written by M. de Kam, November 2013
*****/

%macro STG (file=Summary
    ,yvar=
    ,name=
    ,unit=
    ,ndec=
    ,pdec=1
    ,by1= Treatment
    ,by2=
    ,xvar= etime
    ,sdextradec=2
    ,meanextradec=1
    ,log=
    ,orientation=P
    ,print=Y
    ,up=
    ,down=
    ,colour=Y
    ,SEerrorbars=N
    ,xaxis1=
    ,yaxis1=
    ,legend=Y
    ,extra=
    ,pid=midpoint
    ,formatbar=
    ,delete=Y
);

****DELETING GRAPH FROM A FORMER RUN;
data _null;
command1="del &dirlocG.avg&file&yvar..cgm";
call system(command1);
run;

****DATA CHANGES;
data local;
set &file;
if &yvar ne .;
run;

****LOG TRANSFORMATION FOR GEOMETRIC MEAN;
data local;
set local;
l&yvar=. ;
if &yvar > 0 then l&yvar=log(&yvar);
if &yvar=.M then l&yvar=.M;
run;

****SORTING;
proc sort data=local;
by &by1 &by2 &xvar;
run;

****SUMMARISING;
proc means data=local noprint ;
by &by1 &by2 &xvar;
var &yvar l&yvar ;
output out=sum mean (&yvar)=avg&yvar stddev (&yvar)=sd&yvar stderr (&yvar)=sem&yvar
n (&yvar)=n&yvar min (&yvar)=min&yvar median (&yvar)=med&yvar max (&yvar)=max&yvar
nmiss (&yvar)=nmiss&yvar lclm (&yvar)=LCL&yvar uclm (&yvar)=UCL&yvar Q1 (&yvar)=Q1&yvar
Q3 (&yvar)=Q3&yvar Qrange (&yvar)=QRange&yvar

```

```

mean (l&yvar)=lgavg&yvar stddev (l&yvar)=lgstd&yvar ;
run;

****PREPARING FOR REPORT;
data sum (drop=_TYPE_ _FREQ_);
set sum ;
/*geometric mean calculation*/
geom&yvar=exp(lgavg&yvar);
/*geometric cv calculation*/
geomcv&yvar=100*sqrt(exp(lgstd&yvar*lgstd&yvar)-1);
/*coefficient of variation calculation*/
cv&yvar=100*sd&yvar/avg&yvar;
label   avg&yvar   ="Mean"
geom&yvar   ="Geometric~Mean"
sd&yvar     ="SD"
n&yvar      ="N"
min&yvar    ="Min"
med&yvar    ="Median"
max&yvar    ="Max"
cv&yvar     ="CV (%)"
geomcv&yvar="Geometric~CV (%)"
sem&yvar    ="SEM"
nmiss&yvar  ="N missing"
lcl&yvar    ="Lower~Limit"
ucl&yvar    ="Upper~Limit"
Q1&yvar     ="First~Quartile"
Q3&yvar     ="Third~Quartile"
QRange&yvar="Interquartile~range"
;
run;

****NUMBER OF DECIMALS FOR SD, MEAN AND PERCENTAGE;
%let decsd=%eval(&ndec+&sdxtrdec);
%let decmean=%eval(&ndec+&meanxtrdec);
%let decp=&pdec;

****SUMMARY TABLE;
/*It is run in a macro, which makes it run twice, first to create a dummy table to count the*/
/* pages which is used to generate to create a page x of y page numbering*/
%local j;
%do j=1 %to 2;
    %STG_report ;
%end;

****EXCEL FILE FOR USE IN OTHER SOFTWARE TO CREATE GRAPHS;
data sumexport;
set sum;
/*to reset seconds to minutes*/
%if %upcase(&xvar)=ETIME %then %do;
    &xvar=&xvar/60;
    format &xvar 6.0;
%end;
/*to make numeric &by variables to strings with their format*/
&by1._string=put(&by1, &by1.f.);
%if %length(&by2) > 0 %then %do;
    &by2._string=put(&by2, &by2.f.);
%end;
%if %length(&by2) > 0 %then %do;
    keep &by1._string &by2._string &xvar avg&yvar sd&yvar sem&yvar;
%end;
%else %do;
    keep &by1._string &xvar avg&yvar sd&yvar sem&yvar;
%end;
run;

proc export data= sumexport
outfile="&dirlocDfG.avg&file&yvar..XLS"
dbms=EXCEL2000 replace;
run;

****LOCAL MACRO VARIABLE;
%local a;

****MACRO VARIABLES WITH NUMBER OF LEVELS OF BY1 AND BY2;
proc sort data=sum out=nby1 nodupkey;
by &by1;
run;
data _null_;

```



```

set nby1 end=last;
if last then call symput('nby1',trim(left(put(_n_,8.))));
run;
%if %length (&by2) ne 0 %then %do;
  proc sort data=sum out=nby2 nodupkey;
  by &by2;
  run;
  data _null_;
  set nby2 end=last;
  if last then call symput('nby2',trim(left(put(_n_,8.))));
  run;
%end;
%if %length (&by2) <=0 %then %do;
  %let nby2=1;
%end;
%let ncombi=%eval(&nby1*&nby2);

****TIMEPROFILE GRAPH;
%if %length(&xvar) > 0 %then %do;

  data sumgraph;
  set sum;
  /*unique combinations of by1 and by2 if both are numeric!*/
  %if %length(&by2) ne 0 %then %do;
    combi=(&by2-1)*&nby1+&by1;
    format combi combif.;
  %end;
  %else %do;
    rename &by1=combi;
  %end;
  run;

  ****AUTOMATIC CREATION OF THE ERROR BARS;
  proc sort data=sumgraph out=bars;
  by &xvar;
  run;

  proc means data=bars noprint;
  by &xvar;
  var avg&yvar;
  output out=bars2 min (avg&yvar)= min max (avg&yvar)=max;
  run;

  data bars3;
  merge bars bars2;
  by &xvar;
  run;

  data bars3;
  set bars3;
  if min=avg&yvar then down=combi;
  if max=avg&yvar then up=combi;
  run;

  proc univariate data=bars3 noprint;
  var down up;
  output out=updown mode=modedown modeup;
  run;

  %if (%length(&up)=0)%then %do;
    data _null_;
    set updown;
    call symput("up",modeup);
    run;
  %end;
  %if (%length(&down)=0)%then %do;
    data _null_;
    set updown;
    call symput("down",modedown);
    run;
  %end;

  ****DEFINING OF THE ERROR BARS;
  data anno;
  length color function $8;
  retain xsys ysys '2' hsys '4' when 'a'
  %if &colour=N %then %do; color 'black' %end;
  size 1;

```

```

set sumgraph;
%if &colour=Y %then %do;
  %do a=1 %to &ncombi;
    if combi=&a then color=&&colour&a;
  %end;
%end;
sdup=avg&yvar + sd&yvar;
sddown=avg&yvar - sd&yvar;
%if &SEerrorbars=Y %then %do;
  sdup=avg&yvar + sem&yvar;
  sddown=avg&yvar - sem&yvar;
%end;

%if &up ne -1 %then %do;
  if combi=&up then do;
    /* Upper tick */
    function='move'; xsys='2'; ysys='2'; x=&xvar; y=sdup; output;
    function='draw'; xsys='7'; ysys='2'; x=-0.5; y=sdup; output;
    function='draw'; xsys='7'; ysys='2'; x=+1; y=sdup; output;
    /* Join value and upper*/
    function='move'; xsys='2'; ysys='2'; x=&xvar; y=avg&yvar; output;
    function='draw'; xsys='2'; ysys='2'; x=&xvar; y=sdup; output;
  end;
  if combi=&down then do;
    /*lower tick*/
    function='move'; xsys='2'; ysys='2'; x=&xvar; y=sddown; output;
    function='draw'; xsys='7'; ysys='2'; x=-0.5; y=sddown; output;
    function='draw'; xsys='7'; ysys='2'; x=+1; y=sddown; output;
    /* Join value and lower */
    function='move'; xsys='2'; ysys='2'; x=&xvar; y=avg&yvar; output;
    function='draw'; xsys='2'; ysys='2'; x=&xvar; y=sddown; output;
  end;
%end;
%if &up=-1 %then %do;
  /* Upper tick */
  function='move'; xsys='2'; ysys='2'; x=&xvar; y=sdup; output;
  function='draw'; xsys='7'; ysys='2'; x=-0.5; y=sdup; output;
  function='draw'; xsys='7'; ysys='2'; x=+1; y=sdup; output;
  /* Join value and upper*/
  function='move'; xsys='2'; ysys='2'; x=&xvar; y=avg&yvar; output;
  function='draw'; xsys='2'; ysys='2'; x=&xvar; y=sdup; output;
  /*lower tick*/
  function='move'; xsys='2'; ysys='2'; x=&xvar; y=sddown; output;
  function='draw'; xsys='7'; ysys='2'; x=-0.5; y=sddown; output;
  function='draw'; xsys='7'; ysys='2'; x=+1; y=sddown; output;
  /* Join value and lower */
  function='move'; xsys='2'; ysys='2'; x=&xvar; y=avg&yvar; output;
  function='draw'; xsys='2'; ysys='2'; x=&xvar; y=sddown; output;
%end;
run;

****AUTOMATIC Y-AXIS;
proc means data=anno noprint;
output out=x min(sddown)=lower max(sdup)=upper ;
run;

%G_yaxis

****LABEL ON THE Y-AXIS;
data sumgraph;
set sumgraph;
label avg&yvar="&name &unit";
run;

****MACRO WITH FORMATTING SPECIFICATIONS;
%STG_formatsR;

****GRAPH;
%if &print=Y %then %do;
  filename grafout "&dirlocG.avg&file&yvar..cgm";
%end;
proc gplot uniform gout=sumgraph data=sumgraph ;
plot avg&yvar*&xvar=combi
/ vaxis=axis1 haxis=axis2 noframe annotate=anno %if &legend=Y %then %do; legend=legend %end;
&extra;
run;
quit;

```

```

%end;

***BAR(COLUMN) GRAPH;
%if (%length(&xvar) = 0) %then %do;

  ***AUTOMATIC CREATION OF THE ERROR BARS;
  data sum3;
  set sum ;
  sdup=avg&yvar+sd&yvar;
  sddown=avg&yvar-sd&yvar;
  %if &SEerrorbars=Y %then %do;
    sdup=avg&yvar + sem&yvar;
    sddown=avg&yvar - sem&yvar;
  %end;
  %if (%length(&by2) ne 0) %then %do;
    rename &by2=group;
  %end;
run;

  ***DEFINING OF THE ERROR BARS;
  data anno;
  length color function $8;
  retain xsys ysys '2' hsys '4' when 'a'
  %if &colour=N %then %do; color 'black' %end;
  size 1;
  set sum3;
  %if &colour=Y %then %do;

    %do a=1 %to &nby1;
      if &by1=&a then color=&&colour&a;
    %end;
  %end;
  if avg&yvar >=0 then do;
    /* Upper tick */
    function='move'; xsys='2'; ysys='2'; midpoint=&by1; y=sdup; output;
    function='draw'; xsys='7'; ysys='2'; x=-2; y=sdup; output;
    function='draw'; xsys='7'; ysys='2'; x=+4; y=sdup; output;
    /* Join upper and lower */
    function='move'; xsys='2'; ysys='2'; midpoint=&by1; y=avg&yvar; output;
    function='draw'; xsys='2'; ysys='2'; midpoint=&by1; y=sdup; output;
  end;
  if avg&yvar <0 then do;
    /* Lower tick */
    function='move'; xsys='2'; ysys='2'; midpoint=&by1; y=sddown; output;
    function='draw'; xsys='7'; ysys='2'; x=-2; y=sddown; output;
    function='draw'; xsys='7'; ysys='2'; x=+4; y=sddown; output;
    /* Join upper and lower */
    function='move'; xsys='2'; ysys='2'; midpoint=&by1; y=avg&yvar; output;
    function='draw'; xsys='2'; ysys='2'; midpoint=&by1; y=sddown; output;
  end;
run;

  ***AUTOMATIC Y-AXIS;
  proc means data=sum3 noprint;
  output out=x min(sddown)=lower max(sdup)=upper min(avg&yvar)= miny max(avg&yvar)= maxy;
run;
  data x;
  set x;
  if miny >=0 then lower=0;
  if maxy <=0 then upper=0;
end;
run;

  %G_yaxis;

  ***MACRO WITH FORMATTING SPECIFICATIONS;
  %STG_formatsS;

  ***GRAPH;
  %if &print=Y %then %do;
    filename grafout "&dirlocG.avg&file&yvar..cgm";
  %end;
  proc gchart data=sum3 ;
  vbar &by1/ noframe anno=anno sumvar=avg&yvar midpoints=
  %do c=1 %to &nby1; &c %end;
  maxis=axis1
  raxis=axis2
  %if (%length(&by2) ne 0) %then %do;

```

```
        group=group
        subgroup=&by1
        gaxis=axis3
    %end;
    patternid=&pid
        &formatbar;
    run;
%end;

****PRINT TO WORD DOCUMENT USING DDE;
%if &print=Y %then %do;
    %STG_DDE;
%end;

%if &delete=Y %then %do;
    proc datasets lib=work nolist;
        delete local sum sumexport sumgraph bars bars2 bars3 sum3 anno x;
    run;
%end;

quit;
%mend STG ;
```

Analysis

```

/*****
/* Macro Analysis does a mixed model analysis of variance with two possible by factors and one
/* repeated factor
/* It needs a macro A_Normplot that is included in MacroA.sas
/* It needs a macro G_yaxis and G_Header to be found in &protocol._ana._MacrosG.sas, a macro
/* A_Model, A_ExtraLSMs, A_AnalysisResults, A_LSMtable, A_formatLSMgraph, A_formatdLSMgraph,
/* A_DDE and A_SummaryRTF to be found in &protocol._ana._DataA.sas
/* It generates ana output files: raw SAS output of the analysis called SAS&file&var..ana,
/* a results file called contrast&file&var..ana, a LSM file called lsm&file&var..anatable, CGM
/* files called lsm&file&var..cgm and deltalsm&file&var..cgm, and XLS files called
/* lsm&file&var..XLS and deltalsm&file&var..XLS with data to make graphs with other software
/* The results can be printed to a word document if print=Y
/* Written by M. de Kam, November 2013
*****/

/*Macro vars:
file      = SAS data file                      Standard "Analysis"
var        = variable
name       = full name of variable
unit      = unit of variable
ndec=     = number of decimals of variable
xvar      = variable for the x-axis of the LSM graph      Should remain empty if no
                                                         LSMs graphs are needed

by1=      = first by variable for analysis, has to be
           numeric and, for the xls export, with
           format &by1.f

IF BY2 IS NOT EMPTY A VARIABLE COMBI IS CALCUALTED AS (level of &by2-1)*&nby1+(level of &by1)
WHICH NEEDS THE CORRECT FORMAT!! FIRST EVERY LEVEL OF BY1 THEN THE LEVEL OF BY2. IF &BY2 IS EMPTY,
COMBI=&BY1.
ONLY USE BY2 IF LSM GRAPHS BY &BY1 AND &BY2 ARE WANTED. IT IS POSSIBLE TO ADD ANOTHER FACTOR TO THE
ANALYSIS IN THE MODEL STATEMENT BUT IF GRAPHS BY &BY2 ARE NOT WANTED, DO NOT ADD THE FACTOR AS &BY2.
THE LSM STATMENT NEEDS THE &BY1*&BY2*&XVAR INTERACTION TO BE ABLE TO MAKE THE GRAPHS.

by2      = second by variable for analysis and used          can remain empty
           for LSM graphs, has to be numeric and,
           for the xls export, with format &by2.f
precov   = if 1 then pre value (prepost=0)
           per subject, &by1 and &by2, as covariate
log       = if 1 the variable is log transformed before
           analysis and back transformed for results
perc     = if Y back transformation of difference to %, Standard "Y" must be
           else to ratio capital
up       = &by1/combi number with upper SD bar in          Standard empty, if empty
           graph                                           automatically calculated
           if up=-1 ALL error bars are shown
down     = &by1/combi number with lower SD bar in          Standard empty, if empty
           graph                                           automatically calculated
colour   = define colours in macro vars as many as        Standard "Y" ONLY AFFECTS
           there are combis                               COLOUR OF ERROR BARS
xaxis2   = additional x-axis formats LSM                  Standard empty
yaxis2   = additional y-axis formats LSM                  Standard empty
xaxis3   = additional x-axis formats delta LSM            Standard empty
yaxis3   = additional y-axis formats delta LSM            Standard empty
legend   = adding legend                                  Standard "Y"
extra    = extra statement in the plot statement          Standard empty
           (e.g reflines) LSM graph
dextra   = extra statement in the plot statement          Standard empty
           (e.g reflines) cfb LSM graph
delete   = removing temporary files                      Standard "Y" must be capital
print    = printing the output to files and               Standard "Y" must be capital
           Word thorough DDE

);*/

%let sasfile=&protocol._ana._DataA;
proc format;
value prepostf 0="Pre" 1="Post";
run;

***PREPARING DATA-----;
data analysis;
set &prepfile;
/*designate pre-values*/
/*necessary if analysis with pre-value covariate is done*/
/*0 if pre-value*/

```

```

prepost=1;
if expdelta < 0 then prepost=0;
format prepost prepostf.;
/*if subjectnr=7 and occasion=2 and expdelta=316 then ColdAAC=.M;*/
/*if subjectnr=10 and occasion=1 and activity="PainCold" then ColdAAC=.M;*/
run;

/*for the proc compare of the database file with the file for analysis*/
%let analysisfile=Analysis;

/*IF &by2 IS NOT EMPTY THEN USE THIS-----;
/*&nby1 AND &nby2 are the number of levels of &by1 and &by2 respectively*/
/*and automatically calculated within the macro*/
/*variable combi is calculated as &nby2*(level of &by1)+(level of &by2)-&nby2*/
/*Resulting in the order: every level of by1 by first level of by2, */
/*every level of by1 by next level of by2 etc.*/

/*ADJUST THE FORMAT TO THIS!!!!*/

proc format;
value genderf 1="Male" 2="Female";
value combif
1="Placebo Male" 5="Placebo Female"
2="Dose 1 Male" 6="Dose 1 Female"
3="Dose 2 Male" 7="Dose 2 Female"
4="Control Male" 8="Control Female";
run;

***EXTRA FORMATS FOR XLS FILES-----;
/*For macro A format &by1.f is necessary. If &by2 exists the also make &by2.f*/
/*Variable combi is not used for the xls files*/
proc format ;
value treatmentf 0="?" 1="Placebo" 2="Paracetamol" ;
run;

/*for the export file a seperate format for &by2 is necessary called &by2f.*/
proc format;
value gendersidf 1="Male" 2="Female";
run;

***TITLES AND FOOTNOTES-----;
/*For the DDE output this creates necessary macro variables footL and footP*/
/*Length can be adjusted depending on the length of the name of the output producer*/
/*22=M.L. de Kam, 15=Page xx of yy*/
data _null_;
footL=" ";
call symput ('footL',put(footL,%eval(&linesizeL-22-15).)||"produced by &statistician");
run;
data _null_;
footP=" ";
call symput ('footP',put(footP,%eval(&linesizeP-22-15).)||"produced by &statistician");
run;

***MODEL-----;
%macro A_model (model=);

/*model=1 is for unchanged values*/
/*model=2 is for change from baseline values*/
/*xvar denotes (time)series*/
/*precov=1 for data with prevalue (on xvar < 0)*/
proc mixed data=mix order=internal nobound ;
%if %length(&xvar)>0 and &precov=1 %then %do;
class &by1 &xvar occasion subjectnr;
%if &model=1 %then %do;
model &var=&by1 &xvar occasion &by1*&xvar pre&var/oupt=pred residual ddfm=KR;
%end;
%if &model=2 %then %do;
model delta&var=&by1 &xvar occasion &by1*&xvar pre&var/oupt=pred residual ddfm=KR;
%end;
random subjectnr subjectnr*&by1 subjectnr*&xvar/type=vc;
lsmeans &by1 &by1*&xvar/cl ;
%end;
%if %length(&xvar)=0 and &precov ne 1 %then %do;
class &by1 occasion subjectnr;
%if &model=1 %then %do;
model &var=&by1 occasion /oupt=pred residual ddfm=KR;

```

```

%end;
%if &model=2 %then %do;
  model delta&var=&by1 occasion /outp=pred residual ddfm=KR;
%end;
random subjectnr /type=vc;;
lsmeans &by1 /cl ;
%end;
/*and of course there are two other combinations possible:*/
/*length(xvar)>0 and precov ne 1 and*/
/*length(xvar)<0 and precov=1*/
%if &model=1 %then %do;
  estimate "&trt1 - &trt2" treatment -1 1 /cl;
ods output estimates=est;
ods output tests3=eff;
ods output lsmeans=lsmeans;
%end;
%if &model=2 %then %do;
  ods output lsmeans=dlsmeans;
%end;
run;

%mend A_model;
****FOR OTHER THEN STANDARD ESTIMATES, LSMS CAN BE CALCULATED IN THIS MACRO -----;
%macro A_extraLSMs;
/*MAKE EMPTY IF NO SPECIAL ESTIMATES ARE PROGRAMMED*/
/*E.G.*/
/* data sublsmeans;*/
/* set lsmeans;*/
/* if effect="treatment*etime";*/
/* if etime < 240*60;*/
/* effect="parttreatment";*/
/* run;*/
/**/
/* proc means data=sublsmeans noprint;*/
/* by treatment effect;*/
/* output out=lsmeanspart mean(estimate)=estimate;*/
/* run;*/
/**/
/* data lsmeans;*/
/* set lsmeans lsmeanspart;*/
/* run;*/
%mend A_extraLSMs;

****TABLE WITH ANALYSIS RESULTS-----;
%macro A_analysisresults;

****DNDEC IS THE NUMBER OF DECIMALS FOR THE ESTIMATE OF THE DIFFERENCE AND THE 95% CI;
%global dndec;
%let dndec=%eval(&dndec+1);
%if &log=1 %then %do;
  /*one decimal for percentages*/
  %if &perc=Y %then %do;
    %let dndec=1;
  %end;
  /*two decimals for ratios*/
  %if &perc ne Y %then %do;
    %let dndec=2;
  %end;
%end;

data effect (keep=label estimate prob x lower upper);
attrib label length= $75;
set eff (rename=(probF=prob)) est (rename=(probt=prob));

****GENERAL EFFECTS;
if upcase(effect)=upcase("&by1") then x=1;
if upcase(effect)=upcase("&by2") then x=2;
if upcase(effect)=upcase("occasion") then x=3;
if upcase(effect)=upcase("&xvar") then x=4;
if upcase(effect)=upcase("&by1*&by2") then x=5;
if upcase(effect)=upcase("&by1*&xvar") then x=6;

if x=1 and upcase(effect)=upcase("treatment") then label="Treatment";
if x=2 and upcase(effect)=upcase("gendersid") then label="Sex";
if x=3 and upcase(effect)=upcase("occasion") then label="Period";
if x=4 and upcase(effect)=upcase("etime") then label="Time";
if x=5 and upcase(effect)=upcase("treatment*gendersid") then label="Treatment by sex";
if x=6 and upcase(effect)=upcase("treatment*etime") then label="Treatment by time";

```

```

if x in (1,2,3,4,5,6) and missing(label)                                then label=effect;

****CONTRASTS;
if label="&trt1 - &trt2" then x=7;
if label="&trt1 - &trt3" then x=8;
if label="&trt1 - &trt4" then x=9;

if not missing(x);
run;

/*LSMs OF THE FIRST &BY1 IN THE CONTRAST*/
data lsm1 (keep=&by1 &by2 LSMtrt1 x);
set lsmeans;
if upcase(effect)=upcase("&by1") and &by1=1 then do;
LSMtrt1=estimate; x=7; output;
LSMtrt1=estimate; x=8; output;
LSMtrt1=estimate; x=9; output;
end;
run;

/*LSMs OF THE SECOND &BY1 IN THE CONTRAST*/
data lsm2 (keep=&by1 &by2 LSMtrt2 x);
set lsmeans;
if upcase(effect)=upcase("&by1") and &by1=2 then do;
LSMtrt2=estimate; x=7; output; end;
if upcase(effect)=upcase("&by1") and &by1=3 then do;
LSMtrt2=estimate; x=8; output; end;
if upcase(effect)=upcase("&by1") and &by1=4 then do;
LSMtrt2=estimate; x=9; output; end;
run;

proc sort data=lsm1;
by x;
proc sort data=lsm2;
by x;
proc sort data=effect;
by x;
run;

data effall (where=(not missing(label)));
merge effect lsm2 lsm1;
by x;
/*% added for log transformed values*/
%if &log=1 and &perc=Y %then %do;
    if x>6 then do;
        estimate_ =put(estimate, 7.1)||"%";
        lower_    =put(lower, 7.1)||"%";
        upper_    =put(upper, 7.1)||"%";
    end;
%end;
%else %do;
    estimate_ =estimate;
    lower_    =lower;
    upper_    =upper;
    format estimate_ upper_ lower_ 8.&dndec;
%end;
run;

/*It is run in a macro, which makes it run twice, first to create a dummy table to count the
pages*/
/*which is used to generate to create a page x of y page numbering*/
%macro A_report_result (reportfile=effall, printfile="&dirlocT.contrast&file&var..ana");

%G_j ;

%let page=0;
options missing=" " pageno=1 pagesize=&pagesizeP linesize=&linesizeP;

%G_header (sasfile=&sasfile, root=&root);

title3 "Analysis results &i of dynamic measurements";/*14.2.*/
title4 ;
title5 "Analysis population";

%if &j=2 and &print=Y %then %do;
    proc printto file=&printfile new; run;
%end;

```



```

proc report data=&reportfile headline headskip nowindows split="~" spacing=1 ;
column (%if &log=1 %then %do; "Analysis results: LOG &name &unit" %end;
      %else %do; "Analysis results: &name &unit" %end;
      "--" dummy x label prob
      %if &log=1 %then %do;
        ("Back Transformed" "--" LSMtrt1 LSMtrt2 estimate_ ("95% CI" "--" lower_ rangv upper_))
      %end;
      %else %do;
        LSMtrt1 LSMtrt2 estimate_ ("95% CI" lower_ rangv upper_)
      %end; );
define dummy /order noprint;
define x /order noprint;
define label /display "Effect/Contrast" width=24 flow left ;
define prob /display "P-value" format=pvalue6.4 width=7;
define LSMtrt1 /display "First LSM~of contrast" format=8.&ndec width=11 center;
define LSMtrt2 /display "Second LSM~of contrast" format=8.&ndec width=11 center;
%if &log=1 and &perc ne Y %then %do;
  define estimate_/display "Ratio of LSMs" width=16 center;
%end;
%else %do;
  define estimate_/display "Estimate~of the~difference" width=16 center;
%end;
define lower_ /display "Lower" width=8;
define upper_ /display "Upper" spacing=1 width=8;
define rangv /computed "" format=$1. spacing=1;
compute rangv /length=1 char;
  if x<7 then rangv=' ';
  else rangv='-';
endcomp;
break after x /skip;
%G_pages;
run;
proc printto; run;
%if &j=1 %then %do; %global pages; %let pages=&page.; %G_dummy (dumlinesize=&linesizeP); %end;
%mend A_report_result;

%local j;
%do j=1 %to 2;
  %A_report_result ;
%end;

options missing=".";
title3;
footnotel;
%mend A_analysisresults;

****TABLE WITH LSMs-----;
%macro A_LSMtable;

proc sort data=lsm out=lsmreport;
by &by1 &by2 &xvar;
run;

/*It is run in a macro, which makes it run twice, first to create a dummy table to count the pages*/
/*which is used to generate to create a page x of y page numbering*/
%macro A_report_LSM (reportfile=lsmreport, printfile="&dirlocT.lsm&file&var..ana");
  %G_j ;

  %let page=0;
  options missing=" " pageno=1 pagesize=&pagesizeP linesize=&linesizeP;

  %G_header (sasfile=&sasfile, root=&root);

  title3 "LSMs table &i of dynamic measurements";/*14.2.*/
  title4 ;
  title5 "Analysis population";

  %if &j=2 and &print=Y %then %do;
    proc printto file=&printfile new; run;
  %end;

proc report data=lsmreport headline headskip nowindows split="~" out=report;
column (%if &log=1 %then %do; "Back transformed Least Squares Means~ &name &unit" %end;
      %else %do; "Least Squares Means~ &name &unit" %end;
      "--" dummy &by1 &by2 %if %length(&xvar) >0 %then %do; &xvar %end;
      %if &log=1 %then %do;
        ("Back Transformed" "--" lsmeans %if &precov=1 %then %do; dlsmeans_ %end;)

```

```

%end;
%else %do;
  lsmeans %if &precov=1 %then %do; dlsmeans_ %end;
%end;
);
define dummy/order noprint;
define &by1/ order order=internal width=24 left flow;
%if %length(&by2) >0 %then %do; define &by2/ order order=internal width=24 left flow; %end;
%if %length(&xvar) >0 %then %do; define &xvar/ display width=10 left; %end;
define lsmeans/ display "LSM" format=8.&ndec width=12 center;
%if &precov=1 %then %do;
  define dlsmeans_/ "LSM change from~baseline" display width=24 center;
%end;
%if %length(&by2) >0 %then %do; break after &by2/skip; %end;
%else %do; break after &by1/skip; %end;
%G_pages;
run;
proc printto; run;
%if &j=1 %then %do; %global pages; %let pages=&page.; %G_dummy (dumlinesize=&linesizeP); %end;
%mend A_report_LSM;

%local j;
%do j=1 %to 2;
  %A_report_LSM ;
%end;

title3;
footnotel;
options missing=".";
%mend A_LSMtable;

****IF COLOUR=Y THEN DEFINE THE COLOURS HERE-----
;

%let colour1="grey";
%let colour2="red";
%let colour3="green";
%let colour4="blue";
%let colour5="grey";
%let colour6="red";
%let colour7="green";
%let colour8="blue";

****FORMATTING LSM GRAPHS-----;
/*graph=1 for LSM graph, graph=2 for change from baseline LSM graphs*/
%macro A_formatlsmgraph (graph=);

****OPTIONS;
goptions reset=all;
run;

goptions hsize=21cm vsize=14cm horigin= vorigin= hpos= vpos= htext=2.5pct display noprompt
target = cgmof97p device = cgmof97p gsfname=grafout gsfmode=replace goutmode=replace
ftext="HWCGM001";

****AXES;
axis1 label=(angle=90 ) width=3 major=(height=-1pct) minor=none offset=(4pct, 0pct) &autoyaxis
%if &graph=2 %then %do; &yaxis2; %end;
%if &graph=3 %then %do; &yaxis3; %end;
;
axis2 label=(height=3pct) width=3 major=(height=-1.5pct) minor=none offset=(4pct, 0pct)
%if &graph=2 %then %do; &xaxis2; %end;
%if &graph=3 %then %do; &xaxis3; %end;
;

****LEGEND;
legend shape=symbol(3,0.75) value=(j=1) label=("95% CI error bars") position=(top center outside)
offset=(0,-0.5cm);

****SYMBOLS;
/*circle, square, triangle, diamond. Open and close*/
symbol1 interpol=join font = marker value="W" height=2pct c=&colour1 mode=include width=3;
symbol2 interpol=join font = marker value="U" height=2pct c=&colour2 mode=include width=3;
symbol3 interpol=join font = marker value="C" height=2pct c=&colour3 mode=include width=3;
symbol4 interpol=join font = marker value="P" height=2pct c=&colour4 mode=include width=3;
symbol5 interpol=join font = markerE value="W" height=2pct c=&colour5 mode=include width=3;
symbol6 interpol=join font = markerE value="U" height=2pct c=&colour6 mode=include width=3;

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symbol7 interpol=join font = markerE value="C" height=2pct c=&colour7 mode=include width=3;
symbol8 interpol=join font = markerE value="P" height=2pct c=&colour8 mode=include width=3;

%mend A_formatlsmgraph;

***DDE OUTPUT-----;
%macro A_DDE;
***PRINT TO WORD DOCUMENT USING DDE;
%DDEInsertHeader3 (name=Analysis results table &i &name &unit);/*14.2.*/
%DDEInsertFileNH (file=&dirlocT.contrast&file&var..ana);

%DDEInsertHeader3 (name=LSMs table &i &name &unit);/*14.2.*/
%DDEInsertFileNH (file=&dirlocT.lsm&file&var..ana);

%if %length(&xvar)>0 %then %do;
%DDEInsertHeader3 (name=LSM graph &i &name &unit);/*14.2.*/
%DDEInsertText0 (name=&instrstringP &sysdate9 &sysstime Page: 1 );
%DDEInsertText1 (text1=LSM graph &i of dynamic measurements,
                 text2=Analysis population); /*14.2.*/
%DDEInsertAvgGraph (label=, sub1= /*with 95% CI error bars*/, file=&dirlocG.lsm&file&var..cgm);
%DDEInsertText2 (name= Page: 1 of 1 &footP);
%if &precov=1 %then %do;
%DDEInsertHeader3 (name=LSM change from baseline graph &i &name &unit);/*14.2.*/
%DDEInsertText0 (name=&instrstringP &sysdate9 &sysstime Page: 1 );
%DDEInsertText1 (text1=LSM change from baseline graph &i of dynamic measurements,
                 text2=Analysis population); /*14.2.*/
%DDEInsertAvgGraph (label=, sub1= /*with 95% CI error bars*/,
file=&dirlocG.deltalsm&file&var..cgm);
%DDEInsertText2 (name= Page: 1 of 1 &footP);
%end;
%end;
%mend A_DDE;

***FOR THE SUMMARY RTF TABLE;
%macro A_summaryRTF ;
/*ODS info to be used for RTF tables*/
ods escapechar='\';

data fl&var (keep=&by1 estimate);
set ana.lsm&file&var;
where upcase(effect)=upcase("&by1");
format &by1 1.;
run;

proc transpose data=fl&var out=fl&var;
var estimate;
id &by1;
idlabel &by1;
run;

/*automatic calculation of the number of contrasts*/
data _null_;
set ana.est&file&var end=last;
if last then call symput('ncontrasts',trim(left(put(_n_,8)))));
run;

data %do a=1 %to &ncontrasts; estimates&a(rename=(result=result&a)) %end;;
set ana.est&file&var;
%if &log=1 %then %do;
ci=' (||put(lower,5.&dndec)||%', '||put(upper,5.&dndec)||%')';
d=put(estimate,5.&dndec)||'%';
%end;
%else %do;
ci=' (||put(lower,5.&dndec)||', '||put(upper,5.&dndec)||')';
d=put(estimate,5.&dndec);
%end;
/*Centering and breaking the output*/
result='\R/RTF"\qc" ' ||d || '\R/RTF"\line" ' || ci || '\R/RTF"\line" ' || " p=" ||
put (probt,Pvalue6.4);
%do a=1 %to &ncontrasts;if _n_=&a then output estimates&a; %end;
run;

data fl&var (drop=_NAME_);
length file $20. variable $100. %do a=1 %to &nby1; s_&a $10. %end;;
merge fl&var %do a=1 %to &ncontrasts; estimates&a (keep = result&a) %end;
ana.eff&file&var (where=( upcase(effect)=upcase("&by1")));
variable="&name &unit";
%do a=1 %to &nby1;

```

```

    s_&a=put(_&a,8.&ndec);
%end;
file="&file";
run;

%if &precov=1 %then %do;
    data f2&var (keep=&by1 estimate);
    set ana.lsm&file.d&var;
    where upcase(effect)=upcase("&by1");
    format &by1 1.;
    run;

    proc transpose data=f2&var out=f2&var;
    var estimate;
    id &by1;
    idlabel &by1;
    run;

    data f2&var (drop= NAME_);
    length variable $100. %do a=1 %to &nby1; ds_&a $10. %end;;
    SET f2&var ;
    variable="&name &unit";
    %do a=1 %to &nby1;
        %if &log=1 %then %do;
            ds_&a=put(_&a,8.&dndec)||"%";
        %end;
        %else %do;
            ds_&a=put(_&a,8.&dndec);
        %end;
    %end;
    %end;
    run;

    data f1&var;
    merge f1&var (where=( upcase(effect)=upcase("&by1"))) f2&var(keep = %do a=1 %to &nby1; ds_&a
%end;);
    run;
%end;
data f1&file&var;
set f1&var;
run;
%mend A_summaryRTF;

proc sort data=pred out=test;
by resid;
run;

```

Macro Analysis

```

/*****
/* Macro Analysis does a mixed model analysis of variance with two possible by factors and one
/* repeated factor
/* It needs a macro A_Normplot that is included in MacroA.sas
/* It needs a macro G_yaxis and G_Header to be found in &protocol._&ana._MacrosG.sas, a macro
/* A_Model, A_ExtraLSMs, A_AnalysisResults, A_LSMtable, A_formatLSMgraph, A_formatdLSMgraph,
/* A_DDE and A_SummaryRTF to be found in &protocol._&ana._DataA.sas
/* It generates ana output files: raw SAS output of the analysis called SAS&file&var..ana,
/* a results file called contrast&file&var..ana, a LSM file called lsm&file&var..anatable, CGM
/* files called lsm&file&var..cgm and deltalsm&file&var..cgm, and XLS files called
/* lsm&file&var..XLS and deltalsm&file&var..XLS with data to make graphs with other software
/* The results can be printed to a word document if print=Y
/* Written by M. de Kam, November 2013
*****/

%macro A(
file=
, var=
, name=
, ndec=
, unit=
, xvar=
, by1=
, by2=
, precov=
, prepost=
, log=
, perc=Y
, up=
, down=
, colour=Y
, xaxis2=
, yaxis2=
, xaxis3=
, yaxis3=
, legend=Y
, extra=
, dextra=
, delete=Y
, print=Y
);

***LOCAL MACRO VARIABLE TO BE USED FOR LOOPS;
%local a;

***REMOVE GRAPHS FROM FORMER RUN;
data _null;
command1="del &dirlocG.lsm&file&var..cgm";
command1="del &dirlocG.deltalsm&file&var..cgm";
command1="del &dirlocDfG.lsm&file&var..XLS";
command1="del &dirlocDfG.deltalsm&file&var..XLS";
call system(command1);
run;

***DATA CHANGES;
data local;
set &file;
where not missing(&var);
run;

***DATA SORTING;
proc sort data=local;
by subjectnr &by1 &by2 &xvar;
run;

***LOG TRANSFORMATION;
%if &log=1 %then %do;
data mix0;
set local;
&var=log(&var);
run;
%end;
%else %do;
data mix0;

```

```

    set local;
    run;
%end;

***ADDING PRE-VALUE AS COVARIATE;
%if &precov=1 %then %do;
    proc means data=mix0 noprint;
        by subjectnr &by1 &by2;
        where prepost=0;
        var &var;
        output out=pre mean(&var)=pre&var;
    run;

    data mix ;
    merge mix0 pre;
    by subjectnr &by1 &by2 ;
    run;

    data mix;
    set mix;
    /*Deleting pre-values used as covariate*/
    where prepost > 0;
    /*Change from baseline*/
    delta&var=&var-pre&var;
    run;
%end;
%else %do;
    data mix;
    set mix0;
    run;
%end;

***MIXED MODEL ANALYSIS;
options pageno=1;
ods noptitle;

/*Unedited SAS output*/
%G_header (sasfile=&sasfile, root=&root);

%if &log=1 %then %do;
    title3 "Proc MIXED analysis of LOG &name";
%end;
%else %do;
    title3 "Proc MIXED analysis of &name";
%end;

%if &print=Y %then %do;
    proc printto file="&dirlocRO.SAS&file&var..ana" new; run;
%end;
***MACRO THAT CONTAINS THE ACTUAL MODEL USED;
%A_model (model=1);

***NORMAL PROBABILITY PLOTS ADDED TO THE RAW OUTPUT;
%A_normplot (file=pred, printres=N);
title3;
proc printto;
run;

***NORMAL PROBABILITY PLOTS IN THE SAS OUTPUT WINDOW FOR CHECK;
%A_normplot (file=pred, printres=N);

***FOR OTHER THEN STANDARD ESTIMATES LSMS CAN BE CALCULATED IN THIS MACRO;
%A_ExtraLSMs;

***BACK TRANSFORMATION;
%if &log=1 %then %do;
    data est;
    set est;
    %if &perc=Y %then %do;
        estimate=(exp(estimate)-1)*100;
        lower=(exp(lower)-1)*100;
        upper=(exp(upper)-1)*100;
    %end;
    %else %do;
        estimate=exp(estimate);
        lower=exp(lower);
        upper=exp(upper);
    %end;
%end;

```

```

run;
data lsmeans;
set lsmeans;
estimate=exp(estimate);
lower=exp(lower);
upper=exp(upper);
run;
%end;

****FOR THE SUMMARY TABLE;
data ana.lsm&file&var;
set lsmeans;
run;
data ana.est&file&var;
set est;
run;
data ana.eff&file&var;
set eff;
run;

****PROC MIXED CHANGE FROM BASELINE, FOR VARIABLES WITH A PRE-VALUE;
%if &precov=1 %then %do;
options pageno=1;
ods noptitle;
%if &log=1 %then %do;
title3 "Proc MIXED analysis of LOG &name";
%end;
%else %do;
title3 "Proc MIXED analysis of &name";
%end;
title4 "Change from baseline";

%if &print=Y %then %do;
proc printto file="&dirlocRO.SAS&file.delta&var..ana" new; run;
%end;
%A_model (model=2);
title3;

****BACK TRANSFORMATION;
%if &log=1 %then %do;
data dlsmeans;
set dlsmeans;
estimate=(exp(estimate)-1)*100;
lower=(exp(lower)-1)*100;
upper=(exp(upper)-1)*100;
run;
%end;

****FOR THE SUMMARY TABLE;
data ana.lsm&file.d&var;
set dlsmeans;
run;
%end;

****RESULTS TABLE WITH STUDY SPECIFIC FORMATTING;
%A_analysisresults;

****TABLE WITH LEAST SQUARE MEANS;
%if &precov=1 %then %do;
/*CHANGE FROM BASELINE LSMS*/
data lsmd (keep=effect &by1 &by2 &xvar dlsmeans);
set dlsmeans;
dlsmeans=estimate;
run;

proc sort data=lsmd;
by effect &by1 &by2 &xvar ;
proc sort data=lsmeans;
by effect &by1 &by2 &xvar;
run;

data lsm0;
merge lsmd lsmeans;
by effect &by1 &by2 &xvar ;
run;

data lsm;
set lsm0;

```

```

lsmeans=estimate;
%if &log=1 %then %do;
  %if &perc=Y %then %do;
    dlsmeans_=put(dlsmeans, 8.&dndec)||"%";
  %end;
  %if &perc ne Y %then %do;
    dlsmeans_=put(dlsmeans, 8.&dndec);
  %end;
%end;
%else %do;
  dlsmeans_=dlsmeans;
  format dlsmeans_ 8.&dndec;
%end;
run;
%end;
%if &precov ne 1 %then %do;
  data lsm;
  set lsmeans;
  lsmeans=estimate;
  run;
%end;

***LSM TABLE WITH STUDY SPECIFIC FORMATTING;
%A_lsmtable;

***MACRO VARIABLES WITH NUMBER OF LEVELS OF BY1 AND BY2;
proc sort data=lsmeans (where=(not missing (&by1))) out=nby1 nodupkey;
by &by1;
run;
data _null_;
set nby1 end=last;
if last then call symput('nby1',trim(left(put(_n_,8)))));
run;
%if %length (&by2) ne 0 %then %do;
  proc sort data=lsmeans (where=(not missing (&by2))) out=nby2 nodupkey;
  by &by2;
  run;
  data _null_;
  set nby2 end=last;
  if last then call symput('nby2',trim(left(put(_n_,8)))));
  run;
%end;
%if %length (&by2) <=0 %then %do;
  %let nby2=1;
%end;
%let ncombi=%eval(&nby1*&nby2);

***LSM GRAPHS;
%if %length(&xvar) > 0 %then %do;
  ***RENAMING AND CREATING COMBI VARIABLE;
  data lsm3;
  set lsmeans;
  %if %length(&by2)>0 %then %do;
    combi=(&by2-1)*&nby1+&by1;
    format combi combif.;
  %end;
  %else %do;
    rename &by1=combi;
  %end;
  lsmeans=estimate;
  /*95% CIs are used as error bars*/
  CIup=upper;
  CIdown=lower;
  if not missing (&by1);
  %if %length (&by2) > 0 %then %do;
    if not missing (&by2);
  %end;
  if not missing (&xvar);
  run;

  ***EXCEL FILE FOR USE IN OTHER SOFTWARE TO CREATE GRAPHS;
  data lsmexport;
  set lsmeans;
  lsmeans=estimate;
  /*to reset seconds to minutes*/
  %if %upcase(&xvar)=ETIME %then %do;
    &xvar=&xvar/60;
    format &xvar 6.0;

```



```

%end;
/*to make numeric &by variables to strings with their format*/
&by1._string=put(&by1, &by1.f.);
%if %length(&by2) > 0 %then %do;
    &by2._string=put(&by2, &by2.f.);
%end;
%if %length(&by2) > 0 %then %do;
    keep &by1._string &by2._string &xvar lsmeans lower upper;
%end;
%else %do;
    keep &by1._string &xvar lsmeans lower upper;
%end;
run;

proc export data= lsmexport
outfile="&dirlocDfG.lsm&file&var..XLS"
dbms=EXCEL2000 replace;
run;

****AUTOMATIC CREATION OF THE ERROR BARS;
proc sort data=lsm3 out=lsmbars;
by &xvar;
run;

proc means data=lsmbars noprint;
by &xvar;
var lsmeans;
output out=lsmbars2 min (lsmeans)= min max (lsmeans)=max;
run;

data lsmbars3;
merge lsmbars lsmbars2;
by &xvar;
run;

data lsmbars3;
set lsmbars3;
if min=lsmeans then down=combi;
if max=lsmeans then up=combi;
run;

proc univariate data=lsmbars3 noprint;
var down up;
output out=updown mode=modedown modeup;
run;

%if (%length(&up)=0) %then %do;
    data _null_;
    set updown;
    call symput("up",modeup);
    run;
%end;
%if (%length(&down)=0) %then %do;
    data _null_;
    set updown;
    call symput("down",modedown);
    run;
%end;

****DEFINING OF THE ERROR BARS;
data anno;
length color function $8;
retain xsys ysys '2' hsys '4' when 'a'
%if &colour=N %then %do; color 'black' %end; size 1;
set lsm3;
%if &colour=Y %then %do;
    %do a=1 %to &ncombi;
        if combi=&a then color=&&colour&a;
    %end;
%end;
/* If only error bars are wanted on highest and lowest combi*/
/* Upper tick */
%if &up ne -1 %then %do;
    if combi=&up then do;
        function='move'; xsys='2'; ysys='2'; x=&xvar; y=Ciup; output;
        function='draw'; xsys='7'; ysys='2'; x=-0.5; y=Ciup; output;
        function='draw'; xsys='7'; ysys='2'; x=+1; y=Ciup; output;
        /* Join value and upper*/

```

```

function='move'; xsys='2'; ysys='2'; x=&xvar; y=lsmeans; output;
function='draw'; xsys='2'; ysys='2'; x=&xvar; y=CIup; output;
end;
/*lower tick*/
if combi=&down then do;
function='move'; xsys='2'; ysys='2'; x=&xvar; y=CIdown; output;
function='draw'; xsys='7'; ysys='2'; x=-0.5; y=CIdown; output;
function='draw'; xsys='7'; ysys='2'; x=+1; y=CIdown; output;
/* Join value and lower */
function='move'; xsys='2'; ysys='2'; x=&xvar; y=lsmeans; output;
function='draw'; xsys='2'; ysys='2'; x=&xvar; y=CIdown; output;
end;
%end;
/* If error bars are wanted on ALL combi*/
%if &up = -1 %then %do;
function='move'; xsys='2'; ysys='2'; x=&xvar; y=CIup; output;
function='draw'; xsys='7'; ysys='2'; x=-0.5; y=CIup; output;
function='draw'; xsys='7'; ysys='2'; x=+1; y=CIup; output;
/* Join value and upper*/
function='move'; xsys='2'; ysys='2'; x=&xvar; y=lsmeans; output;
function='draw'; xsys='2'; ysys='2'; x=&xvar; y=CIup; output;
/*lower tick*/
function='move'; xsys='2'; ysys='2'; x=&xvar; y=CIdown; output;
function='draw'; xsys='7'; ysys='2'; x=-0.5; y=CIdown; output;
function='draw'; xsys='7'; ysys='2'; x=+1; y=CIdown; output;
/* Join value and lower */
function='move'; xsys='2'; ysys='2'; x=&xvar; y=lsmeans; output;
function='draw'; xsys='2'; ysys='2'; x=&xvar; y=CIdown; output;
%end;
run;

****AUTOMATIC Y-AXIS;
proc means data=anno noprint;
output out=x min(CIdown)=lower max(CIup)=upper ;
run;
%G_yaxis;

****MACRO WITH FORMATTING SPECIFICATIONS;
%A_formatlsmgraph (graph=2);

****LABEL ON THE Y-AXIS;
data lsm5;
set lsm3;
label lsmeans="&name &unit";
run;

****GRAPH;
%if &print=Y %then %do;
filename grafout "&dirlocG.lsm&file&var..cgm";
%end;

proc gplot uniform gout=lsm5 data=lsm5 ;
plot lsmeans*&xvar=combi
/ vaxis=axis1 haxis=axis2 noframe annotate=anno
%if &legend=Y %then %do; legend=legend %end; &extra;
run;
quit;

****SAS CHANGE FROM BASELINE GRAPH;
%if &precov=1 %then %do;
****RENAMING AND CREATING COMBI VARIABLE, ADDING ZERO;
data lsmd3;
set dlsmeans;
%if %length(&by2)>0 %then %do;
combi=(&by2-1)*&nby1+&by1;
format combi combif.;
%end;
%else %do;
rename &by1=combi;
%end;
dlsmeans=estimate;
/*95% CIs are used as error bars*/
CIup=upper;
CIdown=lower;
if not missing(&by1);
%if %length(&by2)>0 %then %do;
if not missing(&by2);
%end;

```

```

if not missing (&xvar);
run;
/*adding an artificial zero point*/
data zero;
do combi=1 to &ncombi;
  dlsmeans=0;
  CIup=0;
  CIdown=0;
  &xvar=0;
output;
end;
run;
data lsmd4;
set lsmd3 zero;
run;
proc sort data=lsmd4;
by combi &xvar;
run;

****EXCEL FILE FOR USE IN OTHER SOFTWARE TO CREATE GRAPHS;
data lsmdexport;
set dlsmeans;
dlsmeans=estimate;
%if %upcase(&xvar)=ETIME %then %do;
  &xvar=&xvar/60;
  format &xvar 6.0;
%end;
&by1._string=put(&by1, &by1.f.);
%if %length(&by2) > 0 %then %do;
  &by2._string=put(&by2, &by2.f.);
%end;
%if %length(&by2) > 0 %then %do;
  keep &by1._string &by2._string &xvar dlsmeans lower upper;
%end;
%else %do;
  keep &by1._string &xvar dlsmeans lower upper;
%end;
run;

proc export data=lsmdexport
outfile="&dirlocDfG.deltalsm&file&var..XLS"
dbms=EXCEL2000 replace;
run;

****DEFINING OF THE ERROR BARS;
data danno;
length color function $8;
retain xsys ysys '2' hsys '4' when 'a'
%if &colour=N %then %do; color 'black' %end; size 1;
set lsmd4;
%if &colour=Y %then %do;
  %do a=1 %to &ncombi;
    if combi=&a then color=&&colour&a;
  %end;
%end;
/* If only error bars are wanted on highest and lowest combi*/
/* Upper tick */
%if &up ne -1 %then %do;
  if combi=&up then do;
    function='move'; xsys='2'; ysys='2'; x=&xvar; y=CIup; output;
    function='draw'; xsys='7'; ysys='2'; x=-0.5; y=CIup; output;
    function='draw'; xsys='7'; ysys='2'; x=+1; y=CIup; output;
    /* Join value and upper*/
    function='move'; xsys='2'; ysys='2'; x=&xvar; y=dlsmeans; output;
    function='draw'; xsys='2'; ysys='2'; x=&xvar; y=CIup; output;
  end;
  /*lower tick*/
  if combi=&down then do;
    function='move'; xsys='2'; ysys='2'; x=&xvar; y=CIdown; output;
    function='draw'; xsys='7'; ysys='2'; x=-0.5; y=CIdown; output;
    function='draw'; xsys='7'; ysys='2'; x=+1; y=CIdown; output;
    /* Join value and lower */
    function='move'; xsys='2'; ysys='2'; x=&xvar; y=dlsmeans; output;
    function='draw'; xsys='2'; ysys='2'; x=&xvar; y=CIdown; output;
  end;
%end;
/* If error bars are wanted on ALL combi*/

```

```

%if &up = -1 %then %do;
  function='move'; xsys='2'; ysys='2'; x=&xvar; y=CIup; output;
  function='draw'; xsys='7'; ysys='2'; x=-0.5; y=CIup; output;
  function='draw'; xsys='7'; ysys='2'; x=+1; y=CIup; output;
  /* Join value and upper */
  function='move'; xsys='2'; ysys='2'; x=&xvar; y=dlsmeans; output;
  function='draw'; xsys='2'; ysys='2'; x=&xvar; y=CIup; output;
  /* lower tick */
  function='move'; xsys='2'; ysys='2'; x=&xvar; y=CIdown; output;
  function='draw'; xsys='7'; ysys='2'; x=-0.5; y=CIdown; output;
  function='draw'; xsys='7'; ysys='2'; x=+1; y=CIdown; output;
  /* Join value and lower */
  function='move'; xsys='2'; ysys='2'; x=&xvar; y=dlsmeans; output;
  function='draw'; xsys='2'; ysys='2'; x=&xvar; y=CIdown; output;
%end;
run;

****AUTOMATIC Y-AXIS;
proc means data=danno noprint;
output out=x min(CIdown)=lower max(CIup)=upper ;
run;

%G_yaxis;

****MACRO WITH FORMATTING SPECIFICATIONS;
%A_formatlsmgraph (graph=3);

****LABEL ON THE Y-AXIS;
data lsmd5;
set lsmd4;
%if &log=1 %then %do;
  label dlsmeans="&name &unit: % change";
%end;
%else %do;
  label dlsmeans="&name &unit: change";
%end;
run;

****GRAPH;
%if &print=Y %then %do;
  filename grafout "&dirlocG.deltalsm&file&var..cgm";
%end;
title1; footnote1;

proc gplot uniform gout=lsmd5 data=lsmd5 ;
  plot dlsmeans*&xvar =combi/ vaxis=axis1 haxis=axis2 noframe annotate=danno
%if &legend=Y %then %do; legend=legend %end; &dextra ;
run;
quit;

%end;
%end;

****PRINT TO WORD DOCUMENT USING DDE;
%if &print=Y %then %do;
  %A_DDE;
%end;

****FOR THE SUMMARY RTF TABLE;
%A_SummaryRTF;

****DELETING TEMPORARY FILES;
%if &delete=Y %then %do;
  proc datasets lib=work nolist;
  delete local mix0 pre mix lsmeans est eff
  %do a=1 %to &ncontrasts; estimates&a %end;
  dlsmeans effect effect1 estimate lsm lsm0 lsm1 lsm2 lsm3 lsm5 effall
  lsmreport lsmd lsmd3 lsmd4 lsmd5 lsmbars lsmbars2 lsmbars3 nby1 nby2
  lsmexport lsmdexport updown anno annod x;
run;
%end;
quit;
%mend A;

/*****
/* Macro Normplot generates a characted based residual vs predicted values plot */
/* and a QQ plot of residuals with the Wilks-Shapiro statistic in the title */

```

```
/* **** */
```

```
%macro A_normplot(file=
    ,resid=resid
    ,preds=pred
    ,printres=N);

%local nval pval;
data norm1;
set &file;
    label &preds='Predicted value';
    label &resid='Residual';
run;
title6 'Residuals vs Predicted values';
proc plot data=norm1;
    plot &resid * &preds;
run;
proc univariate data=&file noprint normal;
    var &resid;
    output out=temp normal=n probn=pn;
run;
data _null_;
    set temp;
    call symput('nval',put(n,7.3));
    call symput('pval',put(pn,6.3));
if pn LT 0.001 then call symput('pval',"<0.001");
run;
proc rank data=&file ties=mean normal=blom out=rank1;
    var &resid;
    ranks rankres;
run;
%if &printres=Y %then %do;
    proc print;
    run;
%end;
data norm2;
    set rank1;
    label rankres='Normal deviate';
    label &resid='Residual';
run;
proc plot data=norm2;
    title6 'Normal probability plot for residuals';
    title7 "( Shapiro-Wilk Test Statistic = &nval : P-value=&pval )";
    plot &resid * rankres;
run;
quit;
title6;

%mend A_normplot;
```