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TITLE: Treating Intractable Post-Amputation Phantom Limb Pain With Ambulatory Continuous Peripheral Nerve Blocks

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13. SUPPLEMENTARY NOTES

14. ABSTRACT (brief – 200 words appro•.) of most significant finding during the research period.

This is a randomized, double-masked, placebo-controlled clinical trial. The results will not be available until the completion of enrollment and unmasking of treatment groups. Therefore, there are no results/findings to report at this juncture as we are still completing enrollment.

The tasks of the no-cost extension Year 6 encompassed finishing recruiting and enrollment as well as continuing data collection:

- 144 subjects enrolled to date for all centers—this is the full compliment of subjects—no further subjects will be recruited
- 58 subjects provided crossover treatment
- Amputee support group outreach, prosthetics groups outreach, and clinic outreach conducted and concluded
- Data collection and analysis concluded for enrolled subjects
- Manuscript—draft #1—completed and in the revision stage
- Since we must keep the HRPO open if we are to re-analyze the data—which might be requested by the target medical journal—we have requested an additional no-cost extension year through December 24, 2020

15. SUBJECT TERMS

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Introduction:

This project is a randomized, double-masked, placebo-controlled, simultaneous parallel and crossover, human-subjects clinical trial to determine if ambulatory continuous peripheral nerve block (CPNB) is an effective treatment for intractable phantom limb pain following a traumatic limb amputation. There is currently no reliable treatment for phantom limb pain, which resolves in only 16% of cases. This is a multicenter trial at five collaborating sites: Walter Reed National Military Medical Center, Naval Medical Center San Diego, Veterans Affairs Palo Alto, Cleveland Clinic, and the University of California, San Diego. Subjects will have an e•isting upper or lower amputation and e•perience phantom limb pain at least 3 times each week for the previous 8 weeks. They will be randomized to receive one of two study solutions in a double-masked manner: either a local anesthetic (ropivacaine 0.5%) or placebo (normal saline). Catheters will be removed after 6 days of at-home infusion. Although not required, each subject has the option to return for the alternative treatment 4-16 weeks later (crossover infusion). The primary endpoint will be the difference in average phantom pain intensity at baseline and 4 weeks following the initial infusion as measured with the Numeric Rating Scale between treatment groups for the initial infusion. Secondary endpoints will involve intra- and inter-subject comparisons of additional measures of pain and health-related quality-of-life. This trial has a strong potential to identify the first reliably effective treatment for intractable phantom limb pain following a traumatic limb amputation.

Body:

Revised SOW (submitted with NCE request):

Funding Year:	**2013**			**2014**	**2015**	**2016-19**	**2020**
Months (Within Year):	**1-4**	**5-8**	**9-12**				
Register study on clinicaltrials.gov	x						
Initiate DSMB meetings	x						
DSMB meetings (every 6 months)		x	x	x	x	x	
Report to medical monitor (every month)		x	x	x	x	x	
Finalize protocol and study forms	x						
Hire/train research coordinators	x	x	x				
Site visits and training by UCSD coordinator	x						
Submit study to individual IRBs and USAMRMC	x	x					
Site visits and training by Principal Investigator		x					

Prepare data-entry platform at UCSD	x						
Send database letters (following IRB approval)		x	x	x	x	x	
Educate clinic contacts for referrals		x	x				
Order and prepare equipment	x	x					
Amputee support group outreach			x	x	x	x	
Advertising study in publications/websites			x	x	x	x	
Patient enrollment (following IRB approval)			x	x	x	x	
Interim analyses (at 25%, 50%, 75% enrollment)					x	x	
Quality assurance			x	x	x	x	
Data collection & entry (Day 1 to Month 12)			x	x	x	x	
Data cleaning and final statistical analysis						x	
Abstract preparation							x
Full-length manuscript preparation							x
IRB closures at all enrolling centers							x
Final report to USAMRMC							x
Uploading results to ClinicalTrials.gov							x
Results sent to all enrolled subjects							x

DSMB: Data Safety Monitoring Board

UCSD: University of California San Diego

IRB: Institutional Review Board

USAMRMC: United States Army Medical Research and Materiel Command

Key Research Accomplishments:

We have completed enrollment with a total of 144 subjects, cleaning and uploading of the complete data set, analysis of the data set and drafting of the first draft of the manuscript.

Reportable Outcomes:

ABSTRACT RESULTS:
Pretreatment phantom pain scores were similar in both groups, with a median [quartiles] of **5.0** [4.0, 7.0] for each. After one month (three weeks after treatment ended), pain severity

decreased by **2.0** [0, 4.0] points in those given local anesthetic and **0** [0.5, 2.0] in those given placebo (P<0.001). Patients who received active treatment had a higher (improved) global impression of change and less pain-induced physical and emotional dysfunction, but no difference in depression. For subjects who received only the first infusion and no confounding crossover, the median change in phantom limb pain at 6 months was -**3.0** [-5.0, 0] vs. -**1.5** [-5.0, 0] for the placebo group, whereas there was little residual benefit at 12 months.

COMPLETE RESULTS SECTION:

Between December 16, 2013, and October 16, 2018, a total of 144 patients were enrolled from 4 hospitals and all perineural catheters were inserted per protocol. For both study groups, phantom limb pain fell from a median [quartiles] of 5.0 [3.0, 7.0] immediately prior to the initial single-injection lidocaine bolus to 0 [0, 2.0] 20 minutes following the bolus. Residual limb pain similarly fell to 0 [0, 0] for all participants. Patients were subsequently randomized to either active treatment with a ropivacaine (n=71) or normal saline placebo (n=73) 6-day infusion. Of baseline characteristics, only pain's interference with sleep was imbalanced between the two randomized groups with an ASD of 0.36 (> imbalance criterion of 0.33), and so was adjusted for in all analyses. One patient began her infusion but withdrew from the study on the day following catheter insertion and was included in all analyses per the intent-to-treat protocol.

Primary end point. Pretreatment average phantom pain scores were similar in both groups, with a median [quartiles] of **5.0** [4.0, 7.0] for each. After one month (three weeks after treatment ended), pain in patients randomized to active treatment decreased to **3.0** [0, 5.5], while pain in patients given the placebo were relatively unchanged at **5.0** [3.0, 6.5], P=0.008 (**Figure 2**). This was a decrease by **2.0** [0, 4.0] points in those given local anesthetic and **0** [0.5, 2.0] in those given placebo (P<0.001).

Regarding calculations involving missing data, at this same time point average phantom pain severity was a mean (SD) of 3.0 (2.9) for active treatment and 4.5 (2.6) for patients who had received placebo, with an estimated difference in means (95% CI) of -1.3 (-2.2, -0.4) using last observation carried forward; *P* = 0.003). Nearly identical results were obtained using multiple imputation (difference in means (95% CI) of -1.4 (-2.4, -0.5); P=0.002). The nonparametric Hodges-Lehman estimator gave a very similar result as well, with median difference (95% CI) of -1.4 (-2.8, -0.1), P=0.008. There was a corresponding change from baseline of -2.4 (3.0) and -0.9 (2.3) for active and placebo, respectively, with difference in means (95% CI) of -1.3 (-2.3, -0.39), *P* = 0.005.

Secondary end points at 1 month. Using the 1-7 Global Impression of Change Scale, subjects who had received active treatment rated their phantom pain as a median of **5** ("improved") [4, 7] versus **4** ("no change") [4, 5] for placebo subjects with an estimated median difference (95% CI) of 0 (0, 1), P=0.007 (Aim 2A). Similarly, subjects who had received active treatment had less pain-induced physical and emotional dysfunction, with a median Brief Pain Inventory interference subscale of **11** [0, 38] versus **28** [4, 45], median difference (95% CI) of -8 (-17, 0), P=0.024 (Aim 2B). No difference was found on the Beck Depression Inventory (Aim 2C), with subjects receiving active treatment reporting a median of **9** [3, 19] vs. **14** [5, 23] for placebo [mean difference (CI) of -2.5 (-5.5, 0.5); P = 0.095].

As described in Methods, type I error was controlled at 5% across the above primary and secondary endpoints using parallel gatekeeping. Using that approach, the significance criterion for each test remained at the nominal 0.044 (adjusting for interim monitoring) since each of the first 3 of 4 sequential tests was statistically significant.

Tertiary end points. Descriptively assessed (*no testing done* other than the above-reported results at 28 days), phantom and residual limb *pain* as well as pain's *interference* with physical

and emotional functioning appeared lower in the active treatment group at nearly all time points both during (Day 1) and following (Days 7-28) the initial infusion**.** Correspondingly, participants who had received active treatment appeared to experience a lower *frequency* of phantom and residual limb pain as well as non-painful phantom *sensations* both during (Day 1) and following (Day 28) the infusion**.**

Treatment effect heterogeneity. There was little evidence of treatment effect heterogeneity across levels of most of the selected baseline (pre-randomization) variables, except for amputation side of study limb (interaction P=0.071) and residual limb pain 20 min following intervention (interaction P=0.090). Treatment effect also did not differ by etiology (traumatic versus surgical amputation, P=0.546 (not displayed). Significant interaction was claimed if P value < 0.10.

Crossover treatment effect. For the N=65 patients who participated in the crossover phase, the baseline characteristics were compared between patients whose initial randomization was active (N=25) versus placebo (N=40). Active treatment was significantly better than placebo on 28-day phantom limb pain intensity, with an estimated within-patient mean difference of -0.94 (95.6% CI: -1.61, -0.27; P = 0.007). The period by treatment interaction P-value of 0.87 suggests that there was no evidence of differential carryover effect. Significant reductions were also found for the pain interference total score and the Global Impression of Change score**.** These results are generalizable to patients like those who chose to receive the crossover, which may differ from the main trial population.

The variability in the individual causal effects of active versus placebo as measured by the standard deviation of the individual treatment effects was 2.7. As well, active treatment had a larger reduction from baseline in average phantom limb pain intensity with a mean (95% CI) of -1.45 (-2.3, -0.63), P<0.001.

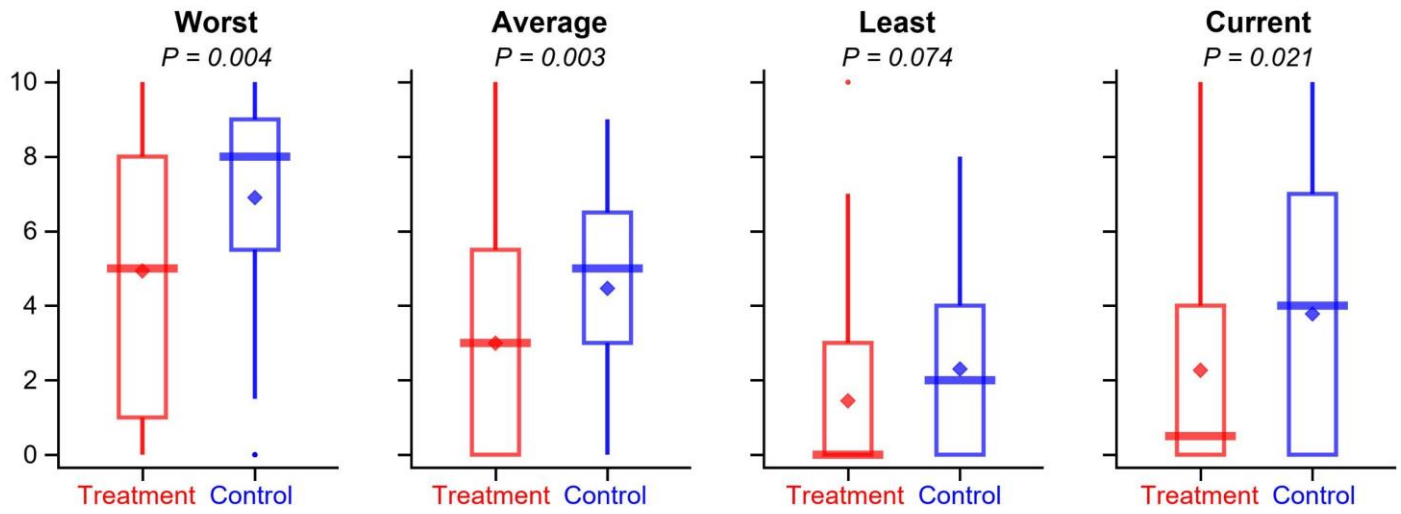
Outcomes at 6 and 12 months post randomization. The crossover treatment administered 0-2 weeks following the measurement of the primary end point was optional, resulting in selection bias on patients who did not cross over. Therefore, 6- and 12-month results comparing initial active and placebo assignment by crossover status is reported descriptively only.

Conclusion:
A 6-day continuous peripheral nerve block reduced phantom limb pain as well as physical and emotional dysfunction for at least a month.

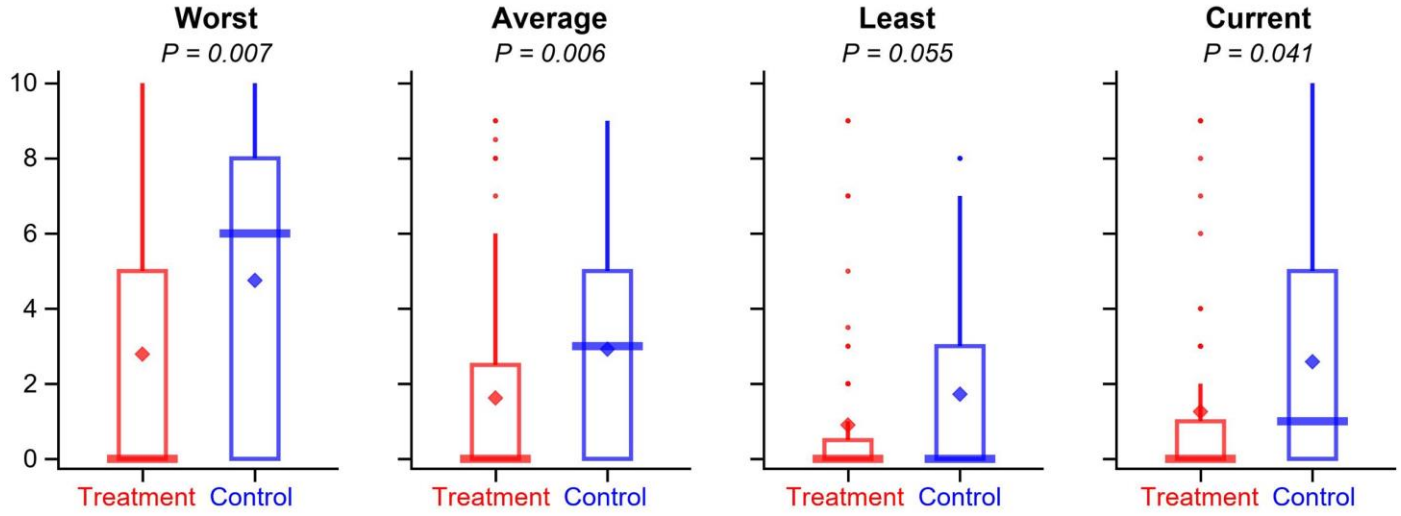
References:
Non-applicable

Appendices:
Figures…

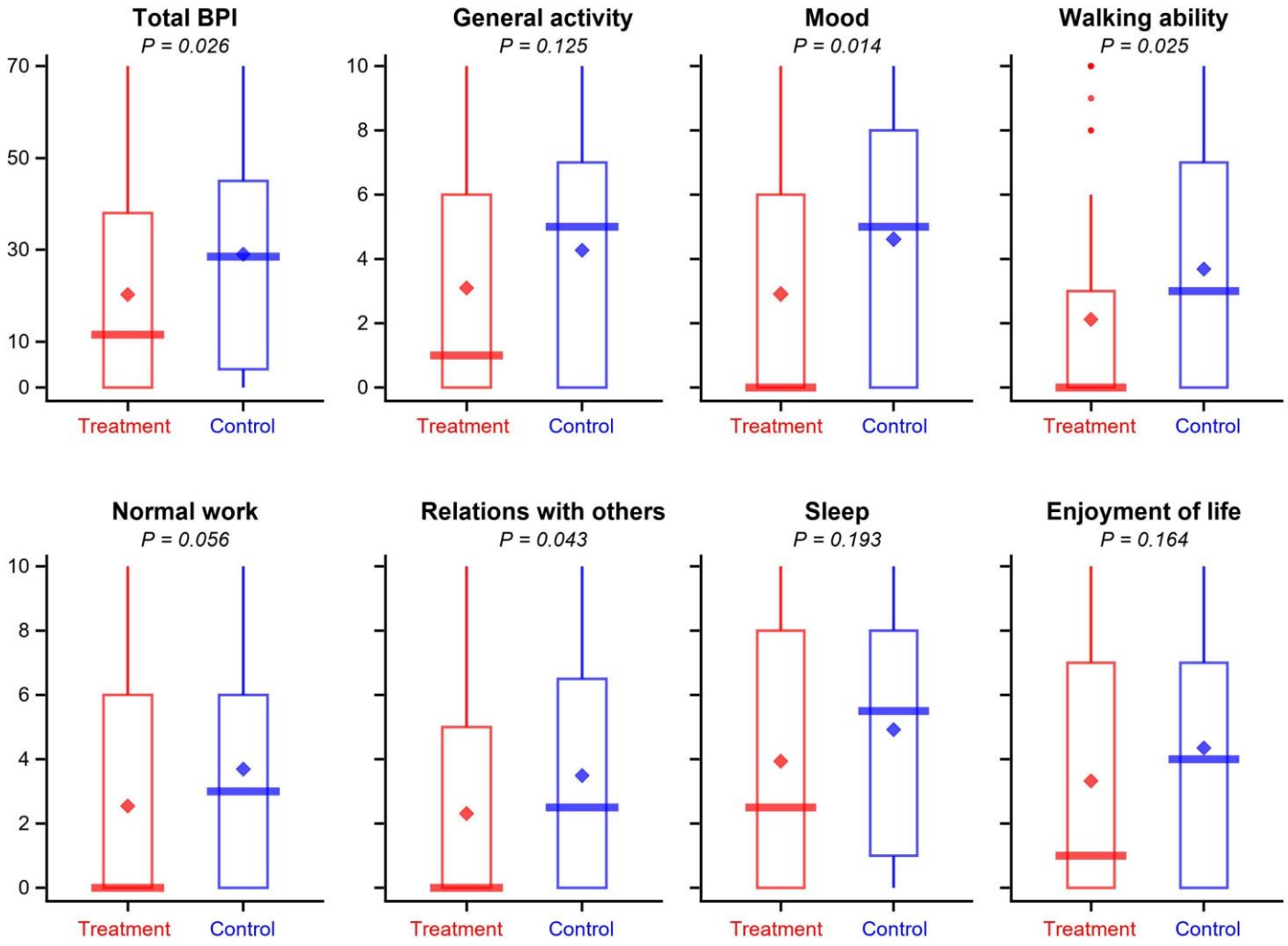
Phantom Limb Pain

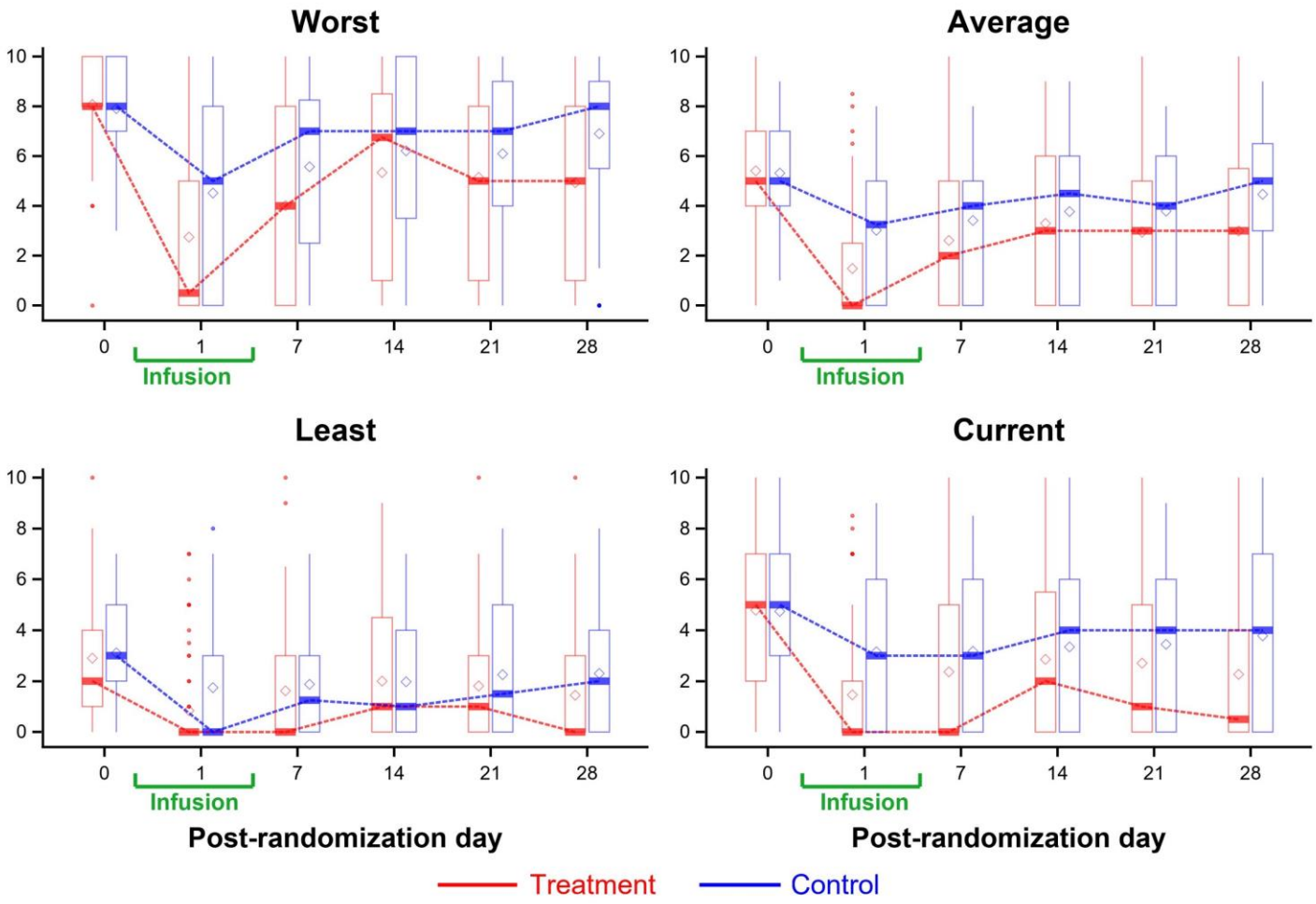


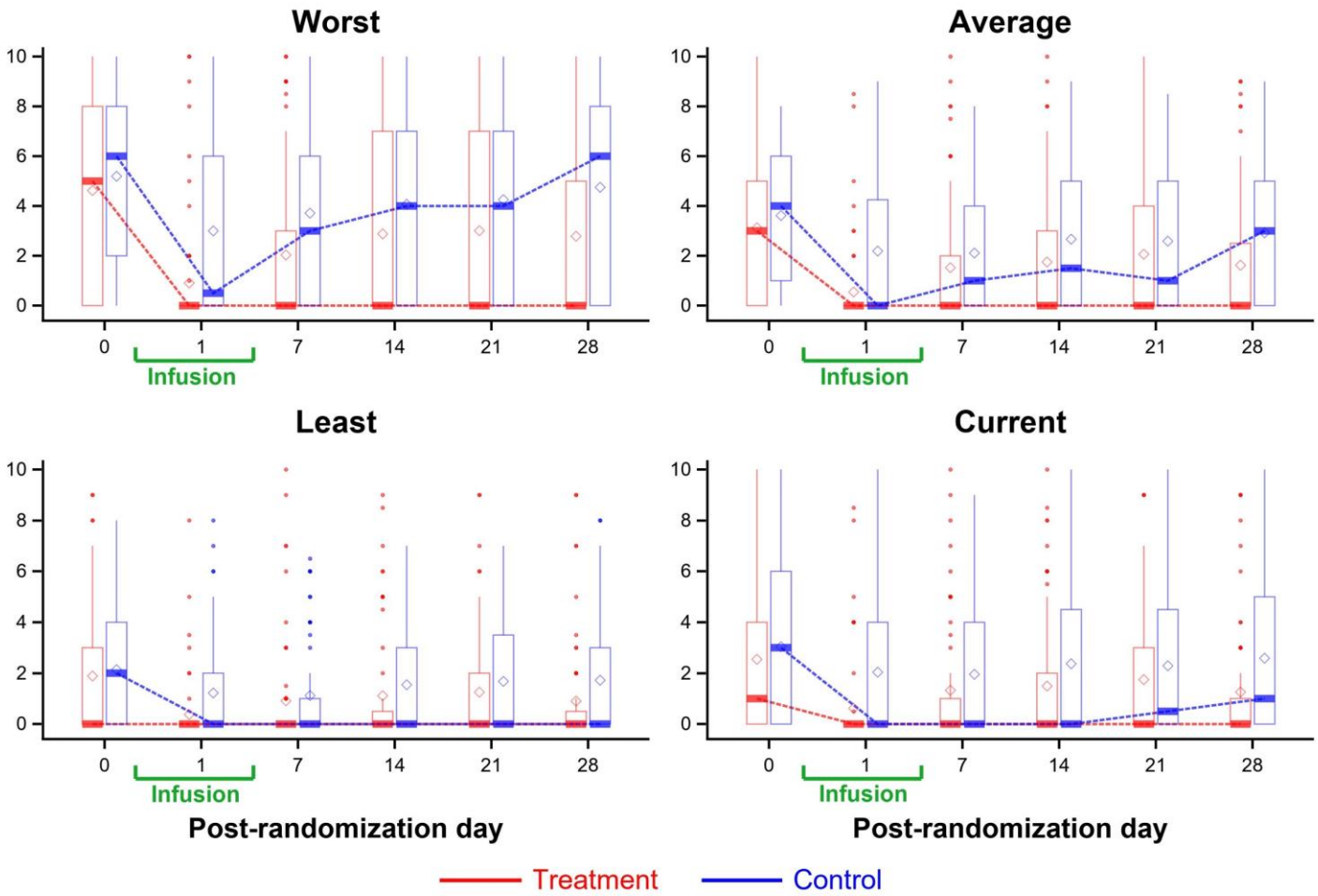
Residual Limb Pain

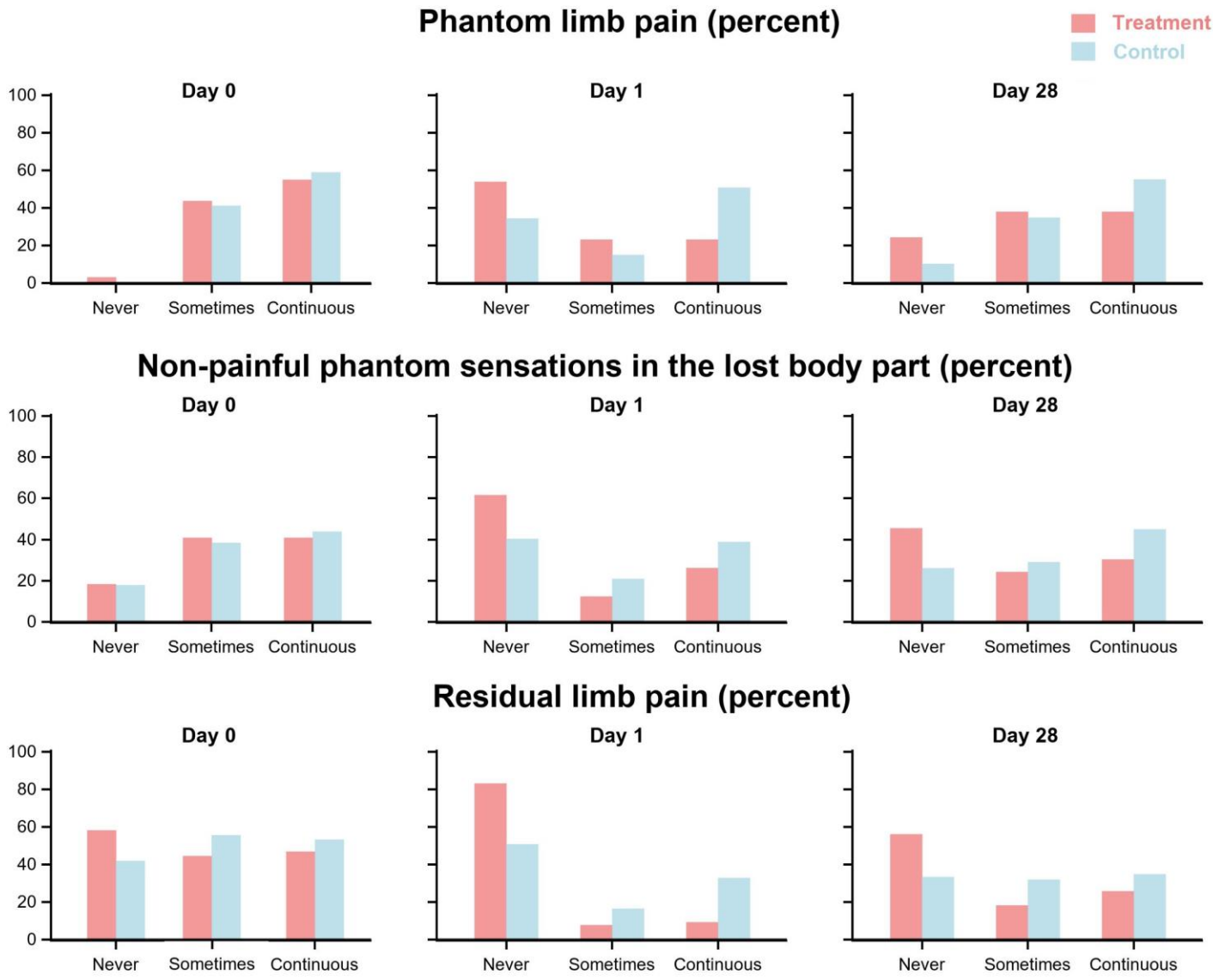


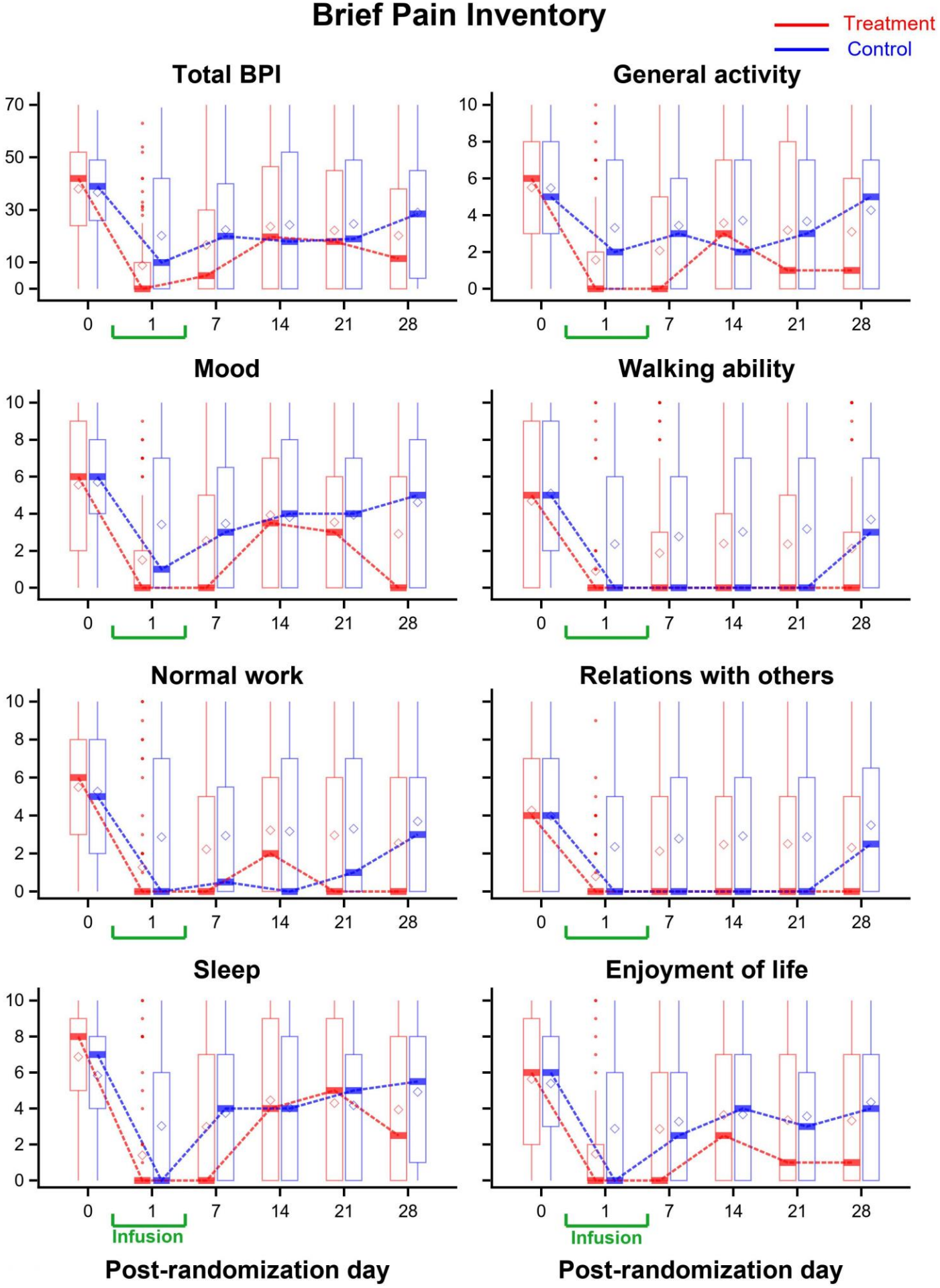
Brief Pain Inventory




Phantom Limb Pain
Worst
Average
Least
Current
10
8
6
4
2
0
0
1
7
14
21
28
Infusion
Post-randomization day
Treatment
Control


Residual Limb Pain
Worst
Average
Least
Current
10
8
6
4
2
0
0
1
7
14
21
28
Infusion
Post-randomization day
Treatment
Control


Phantom limb pain (percent)
Treatment
Control
Day 0
Day 1
Day 28
100
80
60
40
20
0
Never
Sometimes
Continuous
Non-painful phantom sensations in the lost body part (percent)
Residual limb pain (percent)


Brief Pain Inventory
Treatment
Control
Total BPI
General activity
Mood
Walking ability
Normal work
Relations with others
Sleep
Enjoyment of life
Infusion
Infusion
Post-randomization day
Post-randomization day