

## Non-thrust cervical manipulations reduce short-term pain and decrease systolic blood pressure during intervention in mechanical neck pain: a randomized clinical trial

Emmanuel Yung<sup>a</sup>, Cheongeun Oh<sup>b</sup>, Michael Wong<sup>id</sup><sup>c</sup>, Jason K. Grimes<sup>a</sup>, Erica Mae Barton<sup>c</sup>, Muhammad I. Ali<sup>a</sup> and Allison Breakey<sup>a</sup>

<sup>a</sup>Department of Physical Therapy, Sacred Heart University, Fairfield, CT, USA; <sup>b</sup>Division of Biostatistics, Department of Population Health, New York University School of Medicine, New York, NY, USA; <sup>c</sup>Department of Physical Therapy, Azusa Pacific University, Azusa, CA, USA

### ABSTRACT

**Objectives:** To evaluate the association of resting blood pressure with pain response and evaluate the cardiovascular effects of anterior-to-posterior [AP] versus lateral [LAT] techniques of cervical spine non-thrust manipulation [NTM].

**Methods:** Forty-three (23 females) participants with non-chronic neck pain (mean age 29.00 ± SD 9.09 years) randomly received AP or LAT NTM to the cervical spine. Blood pressure and heart rate were measured before, during, and after the intervention. Disability and pain were measured pre- and post-intervention.

**Results:** Resting systolic blood pressure (SBP) was significantly associated with average pain reduction two days later on univariate and multivariate analyses (coefficients  $-0.029 \pm SD 0.013$ ,  $p = 0.036$ ;  $-0.026 \pm 0.012$ ,  $p = 0.032$ ).

No significant differences existed between AP and LAT NTM groups in disability, pain reduction, and cardiovascular variables. The decrease in 'worst neck pain' rating 2-days post-intervention was clinically significant within the AP (mean  $-2.43 \pm SD 2.66$ ) group. Mixed-effect model ANOVA revealed a significant change in SBP over time (estimate  $-1.94 \pm SD 0.70$ ,  $p = 0.007$ ).

**Discussion:** This spinal NTM study was the first to relate resting SBP with short-term pain reduction, demonstrating SBP-related hypoalgesia. In normotensive individuals with unilateral non-chronic neck pain, each 10 mmHg higher resting SBP was associated with a 0.29-unit decrease in average pain at follow-up when holding baseline pain constant.

AP and LAT NTM equally reduced short-term pain and decreased SBP during-intervention, suggesting SBP-sympathoinhibition. These techniques have previously been shown to be sympatho-excitatory when delivered under different dosage parameters. SBP's mediating and moderating role should be investigated.

"Level of Evidence: 1b."

### KEYWORDS



Mechanical neck pain; blood pressure; sympatho-inhibition; hypoalgesia; dosage

## Introduction

Neck pain is reported in 10 to 20 percent of the population [1–3], and the incidence appears to be increasing [4]. A gender difference is also seen with neck pain, increasing with age, and being more common in women around the fifth decade [3,5]. For patients with non-traumatic, non-chronic neck pain, weak evidence supports clinicians providing cervical spine non-thrust manipulation [NTM] [6,7], with anterior-to-posterior [AP] seemingly more effective than a transverse/lateral [LAT] technique for pain reduction [8]. Various mechanisms describe the complex, multifaceted effects of NTM [8,9]. Although systematic reviews documenting a sympatho-excitatory response to NTM have been published [10–12], only two cited studies investigated the association of mechanisms with pain reduction. Of these two, Goodsell [13] found no association between stiffness

(biomechanical mechanism) response and hypoalgesia, whereas Vicenzino et al. [14] were able to associate sympatho-excitatory (a neurophysiologic mechanism) skin blood flow response to pain reduction (hypoalgesia) in patients with lateral epicondylalgia. However, a systematic review of using skin blood flow as an indicator of the sympathetic nervous system response is now disputing this practice and its previous interpretation [15]. The current understanding is that sympathetic, and various non-sympathetic mechanisms regulate skin blood flow [15].

Moreover, instead of the anticipated skin blood flow vasoconstriction from a sympatho-excitatory mechanism, a randomized cross-over study [16] found vasodilation (typically related to sympatho-inhibition) during and post spinal NTM. Bialosky et al. [9] presented a comprehensive theoretical model on how manual

**CONTACT** Emmanuel Yung  [yunge@sacredheart.edu](mailto:yunge@sacredheart.edu)  Department of Physical Therapy, Sacred Heart University, 5151 Park Avenue, Fairfield, CT 06825, USA

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therapy works and recommended increased research into mechanisms associated with hypoalgesia following manual therapy; however, it did not include blood pressure-related hypoalgesia as a mechanism. Resting or baseline blood pressure [BP] is known to be associated with pain reduction, a mechanism called BP-related hypoalgesia [17,18], but this mechanism is not well known in manual therapy due to a lack of literature. An autonomic/cardiovascular mechanistic study demonstrated sympatho-excitatory (heart rate increase) effects using AP NTM [19] when dosed at  $3 \times 2$  minutes, but it did not study BP effects. Vicenzino et al. [14] associated sympatho-excitation with immediate hypoalgesia using LAT NTM when dosed at  $3 \times 30$  seconds; however, their study did not investigate any cardiovascular variables. In a separate investigation, Vicenzino et al. [20] utilized LAT NTM to the neck and demonstrated a sympatho-excitatory cardiovascular response in pain-free adults but did not associate these responses with pain since the subjects did not have pain. In our experience, patients who are typically normotensive may at times exhibit a new onset of systolic blood pressure (SBP) increase ( $\geq 30$  mmHg) following acute pain, and a further NTM-related BP increase may be worrisome.

Conversely, AP NTM displayed an SBP and heart rate decrease in pain-free adults when dosed at  $5 \times 10$  seconds [21], but the cardiovascular effects of this dose application remain unknown in those with spinal pain. Therefore, it seems beneficial to investigate if either LAT or AP NTM (when dosed at  $5 \times 10$  seconds) results in sympatho-excitation or sympatho-inhibition, whether one technique is better than the other in reducing neck pain and if this pain reduction correlates with resting BP. It would be useful to understand if this association extends beyond the immediate pain outcome and if there is any co-variance of improvement between associated cardiovascular response and clinical pain outcome [9]. Therefore, this study aimed to: (1) evaluate the association of resting BP with short-term neck pain reduction, and (2) compare the cardiovascular response and pain reduction effects of AP versus LAT NTM.

## Methods

### Study design

This study was a randomized clinical trial. Data were collected in the clinical research laboratories of Sacred Heart University and Azusa Pacific University. Research invitation emails were sent across both universities and respondents who met the inclusion/exclusion criteria for the study participated and attended one data collection session. The Ethics Committee of two institutions approved the study. Before study enrollment, all participants provided their written informed

consent after they were informed of their rights and the purpose and procedure of the study.

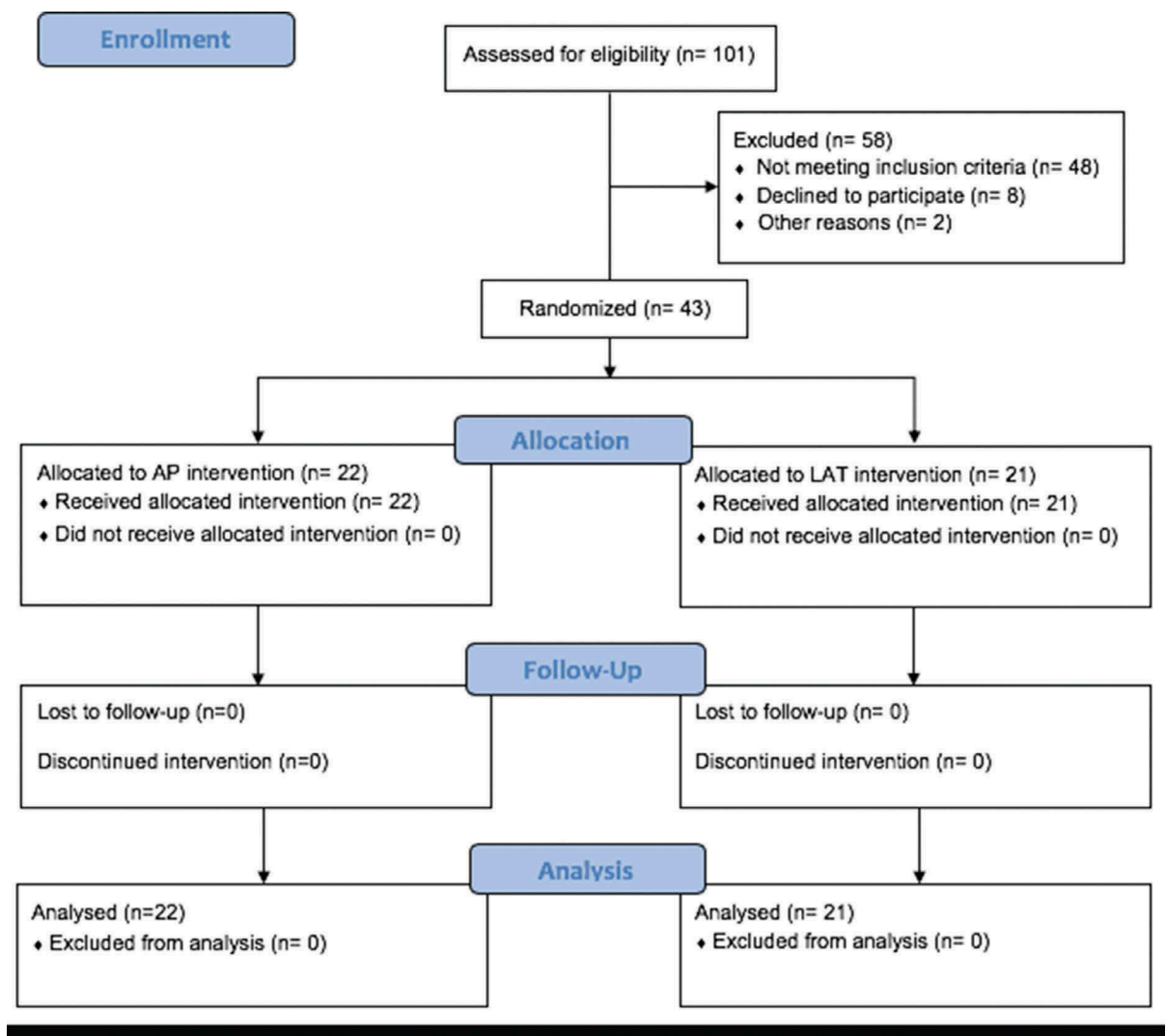
### Participants

Forty-three participants were enrolled by research assistants at both universities and were treated by the primary author between 9/23/2015–6/19/2017. Figure 1 indicates the flow chart of enrollment, allocation, follow-up, and analysis (Appendix 1). The results section reports the participant demographics.

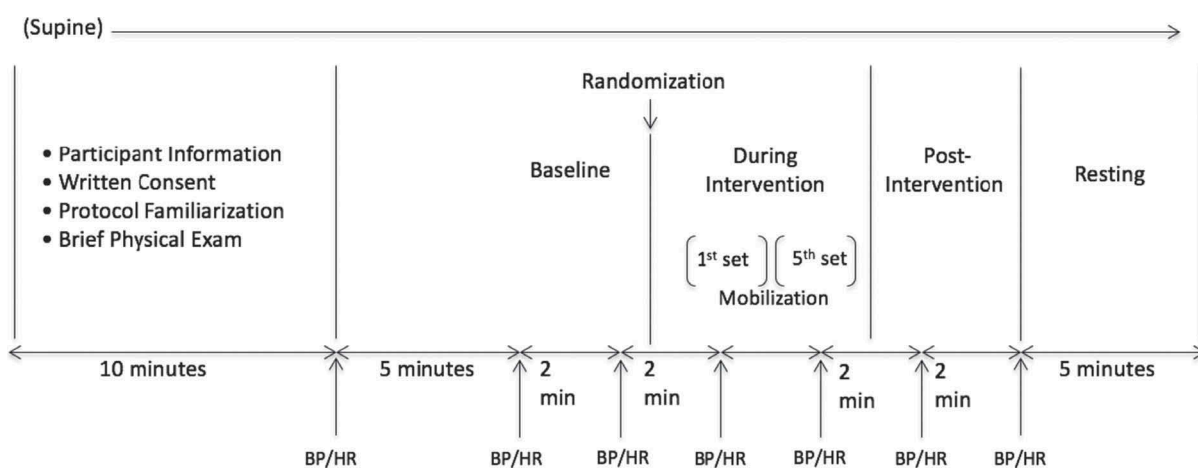
Participants included were: between 21–50 years of age, having unilateral non-traumatic non-chronic neck pain, whose most painful neck movement with its corresponding numeric pain rating scale [NPRS] was determined. The ‘most painful neck movement’ was then retested with the addition of passive scapular elevation, and the NPRS was reassessed with the scapula elevated. Passive scapular elevation was added to ‘the most painful neck movement’ to minimize the contribution of muscle tension/guarding to the patient’s ‘most painful neck movement’ [22]. In doing so, it may indicate whether the underlying pain is related to an impairment in joint mobility, which is what the NTM is hypothesized to be addressing [22]. Furthermore, subjects were required to have resting SBP between 90 and 138 mmHg and resting diastolic blood pressure (DBP) between 60 and 88 mmHg [18], resting heart rate (HR) between 60 and 90 beats per minute and subjects had no prior exposure to AP or LAT NTM. Excluded participants were current smokers and those who had a history of fainting spells or loss of consciousness. Also excluded were those presently on blood thinners or oral contraceptives, or those taking medications for or who had a history of diabetes mellitus. Others excluded had neurologic [23] or cardiovascular disease, had a history of spinal surgery or had neck pain classified or associated with headache, radiating pain [23], or movement coordination impairments [7], or lacked written English proficiency.

### Randomization/blinding

Baseline cardiovascular variables (primary outcome measures: SBP, DBP, HR) were measured (during time points #1 and #2- please refer to the next section) before randomization and before the procedure. After which subjects were randomized in blocks either to AP or LAT ( $n = 5$  per block) NTM to equalize the number of participants in each group. One assistant investigator at each university generated a random-allocation sequence from an online randomizer ([www.randomizer.org](http://www.randomizer.org)) and another assistant assigned each participant a sequential number and a random allocation number (1, AP NTM; 2, LAT NTM), that was concealed in an opaque envelope from the



(a)



(b)

**Figure 1.** (1a) Flow chart (above). Abbreviations AP anterior to posterior NTM, LAT lateral glide NTM. (1b) Experimental procedure (below). BP blood pressure, HR heart rate.

physiotherapist and the participants. Accordingly, the participants and the physiotherapist did not know the random allocation number until 30 seconds before the procedure (time point #3). The assistant made

sure that the patient received the correct treatment allocation based on the card indicating either AP or LAT NTM, and the therapist provided 5 sets of 10-seconds of NTM delivered per the previously

determined protocol. Besides being blinded to the cardiovascular variables measured, the physiotherapist was further blinded to all other outcomes [secondary outcome measures: Neck Disability Index (NDI), Numeric Pain Rating Scale (NPRS), Global Rating of Change (GROC)- please see below].

### **Time frame for measurements**

A research assistant collected the NDI, NPRS, and measured the SBP, DBP and, HR with an OMRON HEM-790IT automatic blood pressure monitor [24] (Omron Healthcare, Inc., Bannockburn, IL) that was placed on the left humerus over the brachial artery for each subject. The blood pressure cuff remained intact throughout the entire recording time points. The start button on the automatic blood pressure monitor was pressed at the following time points: (1) 5 minutes, and (2) 7 minutes after lying supine; (3) the start of the 1st set of 10- second glides, (4) the start of the 5th set of 10- second glides, (5) 2 minutes after time point #4, and (6) 4 minutes after time point #4 (Figure 1(b)). Subsequently, the GROC was obtained post-intervention for the most painful neck movement. Two days following the intervention, each of the 43 subjects filled out the NDI and NPRS based on how the patient felt on the second-day post-intervention, and these results were either emailed or texted back to the research assistant (without any identifier). Within these two days, participants were instructed to continue their regular daily routine. Finally, to assess for any subsequent adverse reactions or side effects [8], follow-up phone calls and emails (at two weeks and again at one month) were performed by one of the co-investigators not responsible for implementing the AP or LAT NTM.

### **Participant flow**

The day before the study, phone/email screened participants who met the inclusion criteria were given directions via emails not to do any of the following: ingest caffeinated drinks within four hours of the study, drink alcoholic beverage during the day of the study, or engage in exercise during the day of the study [25].

On the day of the study, participants filled out questionnaires (NDI, NPRS, past medical and current medication history), followed by a brief physical examination (BP, HR, and manual determination of the most symptomatic cervical spine segment for treatment) to confirm meeting the remainder of the inclusion criteria. Participants who met the criteria were then enrolled, and their data were de-identified by assigning a unique number so that their number, not their name, was linked to the test data collected.

### **Treatment groups**

The subject either received (unilateral) AP or LAT (arm in neutral) NTM performed by a licensed physical therapist who was trained and had used these techniques for more than 15 years. This physical therapist is an orthopaedic clinical specialist certified by the American Board of Physical Therapy Specialties and a fellow of the American Academy of Orthopaedic Manual Physical Therapists. Concurrently, another co-investigator monitored the subject with a finger pulse oximeter placed on the right index finger during the treatment to ensure there was no pulselessness occurring greater than 3 seconds. For safety, an a priori decision was made to discontinue or stop the procedure if the blood pressure reading showed a drop of 50 mm Hg or if there were 3 seconds or greater of pulselessness.

For AP NTM, the thumbs were placed over the costal process, anterior to the most symptomatic facet and gentle oscillatory pressure was applied so that there was movement sensed posteriorly by the assessor's second/third fingers or until the participant reported no greater than 2/10 pain on the NPRS [21,26]. For LAT NTM, the primary investigator placed the anterolateral aspect of the 2<sup>nd</sup> metacarpophalangeal joint over the most symptomatic segment and moved the postero-lateral aspect of the segment laterally toward the subject's asymptomatic side [20,26] with oscillatory pressure. Importantly, the therapist performed each technique with a novel dose consisting of five sets of 10 seconds of mobilization, with 10-seconds rest between sets. The therapist applied AP or LAT NTM at a rate of 15 oscillations per 10 seconds (approximately 1.5 Hz) for a total number of 75 oscillations. Following the completion of cardiovascular recording (time point #6), each subject was asked to relax in supine for five more minutes before standing up. Afterward, the subject sat up and rested in the sitting position for at least 5 minutes to determine if there were any immediate adverse reactions or side effects (i.e., nausea, dizziness, lightheadedness, or increased neck pain). A research assistant at each university assessed intervention adherence per the protocol and indicated 100% intervention adherence (Appendix 2- TIDieR checklist).

### **Sample size calculation**

Published sympatho-excitatory responses using LAT [20] NTM versus sympatho-inhibitory responses using AP [21] NTM, assuming common baseline values of the latter study provided cardiovascular data for sample size calculation. Thus, the estimated pre-/post-intervention changes of between-group differences in mean HR was  $-5.46 \pm 11.65$  beats per minute, mean SBP was  $-13.0 \pm 14$  mmHg, and mean DBP was

$-7.94 \pm 5.4$  mmHg. Using an unpaired t-test, if powered at 80% for a Type I error = 0.05 [27], the number of pairs of subjects needed in a paired design study were 18, 10, and 5 per group, respectively. Consequently, 18 participants were chosen per group with an additional three subjects to account for possible loss to follow-up, thereby resulting in 42 as the total number of participants.

### Statistical analysis

The demographic and clinical characteristics of subjects were first summarized using descriptive statistics and reported as the mean  $\pm$  standard deviation for continuous variables or percentage (counts) for categorical variables. All continuous outcome variables were checked for normality and homogeneity of variance before the statistical analyses. We evaluated the changes of clinical characteristics between baseline and post-treatment on all subjects using a paired T-test or Wilcoxon nonparametric test, and the changes of HR, SBP, and DBP across baseline, during, and post-treatment using an analysis of variance test. A linear regression model was used to evaluate the association between independent variables and pain score reduction in a univariate manner. Subsequently, multivariate regression models were also fitted to the data to identify independent predictors of outcomes while controlling for confounders. All variables with  $p < 0.1$  on the univariate analysis were considered for initial inclusion in the multivariate model, but the final model retained only those which remained significant at  $p < 0.05$ .

All baseline demographic and clinical characteristics were also compared between AP and LAT NTM groups using unpaired T-tests for continuous data and chi-squared tests for categorical data. Mean differences between AP and LAT NTM groups on HR, SBP and DBP were compared using multi-level mixed-effect modeling for repeated measures across three-time points, adjusting for baseline

characteristics by entering treatment, time, and baseline values [age, gender, and body mass index as covariates]. Separate analyses were performed with HR, SBP, and DBP as the dependent variables. All statistical analysis was conducted in the R-statistical package ([www.r-project.org](http://www.r-project.org)). The fits of the mixed model were done using function `lme` of the `nlme` package for the R environment of version 3.0.3. Statistical significance of  $p < 0.05$  was considered to be relevant. Bonferroni correction was applied to account for multiple comparisons.

### Results

A total of 43 participants started and completed the study providing a baseline to post-treatment differences in BP and HR, changes in neck pain, and NDI scores. The mean age (SD) of all participants was 29.00 (9.09) years, and 53.5% ( $n = 23$ ) were female. Changes of HR, SBP, and DBP values across the baseline to follow-up times for all subjects were first assessed (Table 1). Cardiovascular parameters and 'neck pain at best' were not statistically significant, whereas all other changes in outcome measures from baseline to post-treatment were statistically significant but not clinically meaningful [9]. Also, the overall comparison of 'neck pain at worst' over time for all patients demonstrated statistical significance ( $p < 0.001$ ), almost reaching a clinically significant reduction of 2/10 on the NPRS (Table 1). The ANOVA test did not reveal significant differences across follow-up times in HR and BP (Table 1).

SBP and average pain scores at baseline were significantly associated with the averaged pain reduction under the univariate ( $p = 0.036$  and  $0.002$ ) and multivariate ( $p = 0.032$  and  $0.002$ ) models, respectively (Table 2).

Table 3 indicates that the p-values for all comparisons between AP and LAT NTM groups were not significant, except '(neck pain at) worst' experienced '2-days post-intervention' using AP NTM (mean  $2.95 \pm$  SD  $1.86$ ) which was significantly lower ( $p = 0.027$ )

**Table 1.** Descriptive summary over time on all subjects ( $n = 43$ ).

Variable	Baseline	Post-treatment	P value <sup>1</sup>	
Neck pain at best (0–10)	1.09 $\pm$ 1.25	0.79 $\pm$ 1.28	0.090	
Neck pain at worst (0–10)	5.69 $\pm$ 1.92	3.74 $\pm$ 2.39	<0.001	
Neck pain at present (0–10)	2.12 $\pm$ 1.58	1.21 $\pm$ 1.19	0.0002	
Neck pain average (at best, at worst, & at present)	2.92 $\pm$ 1.25	1.90 $\pm$ 1.26	<0.001	
Neck Disability Index	7.74 $\pm$ 3.41	4.95 $\pm$ 4.04	<0.001	
	Baseline	During	Post	P value <sup>2</sup>
Heart rate	61.34 $\pm$ 8.70	61.24 $\pm$ 8.88	61.62 $\pm$ 9.39	0.98
SBP	114.16 $\pm$ 13.84	112.22 $\pm$ 12.80	113.79 $\pm$ 13.99	0.78
DBP	71.23 $\pm$ 6.95	70.41 $\pm$ 7.75	70.90 $\pm$ 7.84	0.88

Abbreviation: SBP = Systolic blood pressure. DBP = Diastolic blood pressure.

Values are expressed as mean  $\pm$  standard deviation.

**P value<sup>1</sup>** using a paired T-test or Wilcoxon nonparametric test.

**P value<sup>2</sup>** using ANOVA.

Pain levels at rest.

**Table 2.** Potential predictive variables for averaged pain reduction using linear regression.

Variable	Univariate	Multivariate
	Coefficient (SD)/p-value	
Technique LAT NTM	-0.063 (0.385)/0.870	NA
BMI	-0.042 (0.034)/ 0.226	NA
Gender Male	0.168 (0.385)/ 0.665	NA
Age	-0.024 (0.021)/ 0.249	NA
SBP at baseline*	-0.29 (0.13)/ 0.036	-0.26 (0.12)/ 0.032
Average Pain at baseline	0.453 (0.136)/ 0.002	0.435 (0.130) /0.002

Pain reduction = baseline-post-intervention (higher + indicates a greater reduction, whereas - indicates increase).

SD: Standard deviation. LAT: Lateral glide non-thrust manipulation (NTM). BMI: Body mass index. NA: not applicable, not selected from the univariate analysis.

\*Each 10 mmHg higher baseline SBP was associated with a 0.29 unit decrease in average pain at follow-up, holding baseline pain constant.

than post LAT NTM (mean  $4.60 \pm SD 2.64$ ). However, the change in 'worst' pain (' $\Delta = \text{Baseline} - \text{Post}$ ' accounting for the change in pain from the baseline) was not significantly different between the AP and LAT NTM groups ( $p = 0.191$ ). Therefore, there was no difference between AP and LAT NTM in their ability to reduce pain in this study.

Within the AP NTM group, the change in the worst pain ( $\Delta = \text{Baseline} - \text{Post} = -2.43 \pm 2.66$ ) exceeded 2/10 on the NPRS, making it clinically significant.

Finally, linear mixed-effects models were fitted to examine the longitudinal relationship between techniques and heart rate, systolic and diastolic blood pressure, while adjusting for patient baseline characteristics such as age, gender, and BMI. As shown in Table 4, there was no evidence of a significant between-treatment difference in HR, SBP, and DBP. Conversely, the SBP was significantly reduced from baseline to during ( $p = 0.007$  Figure 2). Male patients had a significantly lower HR (estimate  $-5.62$ , SD 2.62,  $p = 0.03$ ) and higher SBP (estimate 14.54, SD 3.39,  $p < 0.001$ ) than female patients (Table 4).

As a post-hoc analysis, we further evaluated the SBP reduction in each gender group separately. Although the SBP was significantly reduced between baseline and during the intervention among male patients ( $p$ -value estimate  $-2.87$ , SD 1.23,  $p = 0.026$ , Figure 3), it did not achieve statistical significance after Bonferroni correction for multiple comparisons ( $p < 0.025$ ).

**Adverse effects**

All participants denied any adverse and side effects during the intervention and the post-treatment follow-up period of 2 days, two weeks, and four weeks.

**Discussion**

To our knowledge, this is the first spinal NTM study that used blood pressure as a primary outcome measure in

**Table 3.** Comparison between AP and LAT NTM for baseline to post-intervention outcomes in GROC, NPRS, and NDI.

Variable	AP (n = 22)	LAT (n = 21)	P Value*	
Gender (n female)	12 (54.5%)	11 (52.4%)	1*	
Age, years	$29.00 \pm 9.09$	$30.38 \pm 9.59$	0.631	
BMI	$24.56 \pm 3.34$	$26.86 \pm 6.98$	0.181	
Heart rate	Baseline	$61.23 \pm 8.78$	$61.45 \pm 8.84$	0.933
	During	$60.45 \pm 9.13$	$62.07 \pm 8.76$	0.556
	Post	$61.32 \pm 9.20$	$61.93 \pm 9.81$	0.834
SBP	Baseline	$113.89 \pm 13.15$	$114.45 \pm 14.84$	0.895
	During	$112.25 \pm 12.42$	$112.19 \pm 13.50$	0.988
	Post	$114.36 \pm 13.07$	$113.19 \pm 15.20$	0.787
DBP	Baseline	$71.50 \pm 6.62$	$70.95 \pm 7.44$	0.800
	During	$70.25 \pm 7.49$	$70.57 \pm 8.21$	0.894
	Post	$71.09 \pm 8.03$	$70.69 \pm 7.83$	0.869
<b>GROC</b>				
Post-intervention	$1.73 \pm 1.88$	$1.71 \pm 1.76$	0.892	
<b>PAIN</b>				
Best				
Baseline	$1.05 \pm 1.29$	$1.14 \pm 1.24$	0.801	
2 Days post-intervention	$0.91 \pm 1.60$	$0.67 \pm 0.86$	0.537	
$\Delta = \text{Baseline} - \text{Post}$	$-0.14 \pm 1.25$	$-0.48 \pm 1.03$	0.334	
Worst				
Baseline	$5.33 \pm 1.96$	$6.05 \pm 1.86$	0.232	
2 Days post-intervention	$2.95 \pm 1.86$	$4.60 \pm 2.64$	0.027	
$\Delta = \text{Baseline} - \text{Post}$	$-2.43 \pm 2.66$	$-1.50 \pm 1.73$	0.191	
Present				
Baseline	$2.18 \pm 1.71$	$2.05 \pm 1.47$	0.783	
2 Days post-intervention	$1.32 \pm 1.32$	$1.10 \pm 1.04$	0.542	
$\Delta = \text{Baseline} - \text{Post}$	$-0.86 \pm 1.58$	$-0.95 \pm 1.02$	0.827	
Average				
Baseline	$2.76 \pm 1.39$	$3.08 \pm 1.11$	0.417	
2 Days post-intervention	$1.73 \pm 1.31$	$2.1 \pm 1.22$	0.345	
$\Delta = \text{Baseline} - \text{Post}$	$1.06 \pm 1.44$	$1 \pm 0.97$	0.869	
<b>NDI</b>				
Baseline	$7.73 \pm 3.48$	$7.76 \pm 3.42$	0.973	
2 days post-intervention	$5.14 \pm 4.54$	$4.76 \pm 3.55$	0.764	
$\Delta = \text{Baseline} - \text{Post}$	$-2.59 \pm 2.24$	$-3.00 \pm 2.53$	0.578	

Abbreviation: AP = anterior to posterior non-thrust manipulation (NTM). LAT = lateral glide NTM. BMI = Body mass index. GROC = Global rating of change. NDI = Neck Disability Index. NPRS = Numeric pain rating scale. SD = standard deviation.

Values expressed as mean  $\pm$  SD or count (%), except where otherwise indicated. \*p-value by T-tests for normal data/Wilcoxon test non-normal data.

a clinical population [10–12]. Cardiovascular response to AP and LAT NTM in the cervical spine was investigated as a possible mechanism for pain relief. The results from the current study indicated there was no difference in the change in cardiovascular parameters between the AP and LAT NTM groups. This study identified a significant reduction in SBP from baseline to during-intervention for both AP and LAT NTM, suggesting sympatho-inhibitory SBP. In healthy individuals, the literature presents conflicting findings regarding the SBP response during cervical NTM with both sympatho-excitatory [20,25] and sympatho-inhibitory [21,28] SBP effects reported.

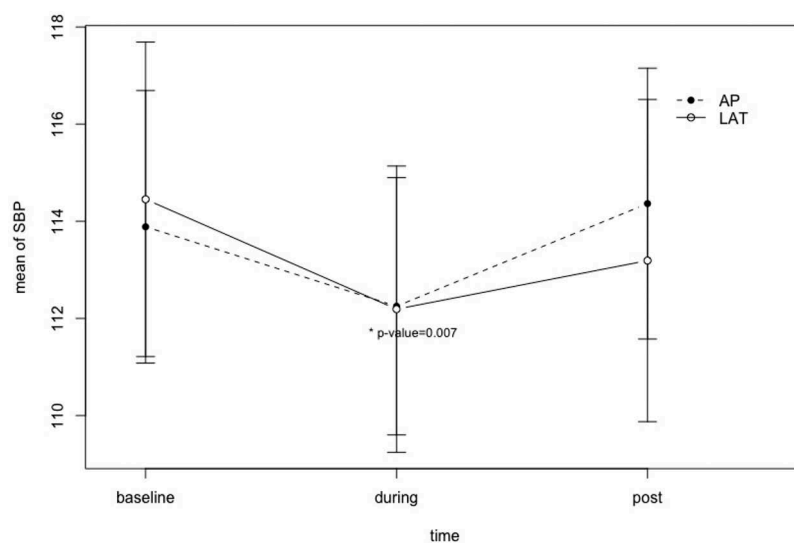
The novel dosage used in this study has demonstrated sympatho-inhibitory cardiovascular effects previously in pain-free subjects [21,28] and has now shown sympatho-inhibitory effects in subjects with neck pain. Research has not fully explored the impact of various dosage

**Table 4.** Estimated effects of technique, time and demographics on heart rate, systolic blood pressure and diastolic blood pressure .

Variable	Heart rate		SBP		DBP	
	Estimate (SD)	p-value*	Estimate (SD)	p-value*	Estimate (SD)	p-value*
<b>Treatment</b>						
AP NTM	Ref		Ref		Ref	
LAT NTM	0.03 (2.49)	0.74	-1.84 (3.22)	0.94	-1.08 (2.21)	0.92
<b>Time</b>						
Baseline	Ref		Ref		Ref	
During	-0.09 (0.69)	0.89	-1.94 (0.70)	0.007	-0.82 (0.51)	0.11
Post	0.27 (0.69)	0.68	-0.37 (0.70)	0.59	-0.33 (0.51)	0.51
<b>Gender</b>						
Female	Ref		Ref		Ref	
Male	-5.62 (2.62)	0.03	14.54 (3.39)	<0.001	1.08 (2.32)	0.51
<b>Age</b>	0.07 (0.14)	0.33	-0.06 (0.18)	0.78	0.04 (0.12)	0.42
<b>BMI</b>	0.35 (0.24)	0.16	0.60 (0.31)	0.06	0.35 (0.21)	0.11

(Abbreviation: AP = anterior to posterior non-thrust manipulation (NTM). LAT = lateral glide NTM. Ref = Reference category. SBP = Systolic blood pressure. DBP = Diastolic blood pressure. SD = standard deviation. BMI = Body mass index.)

\*p-value by mixed-effect model for repeated measures analysis adjusted for age, gender and BMI.



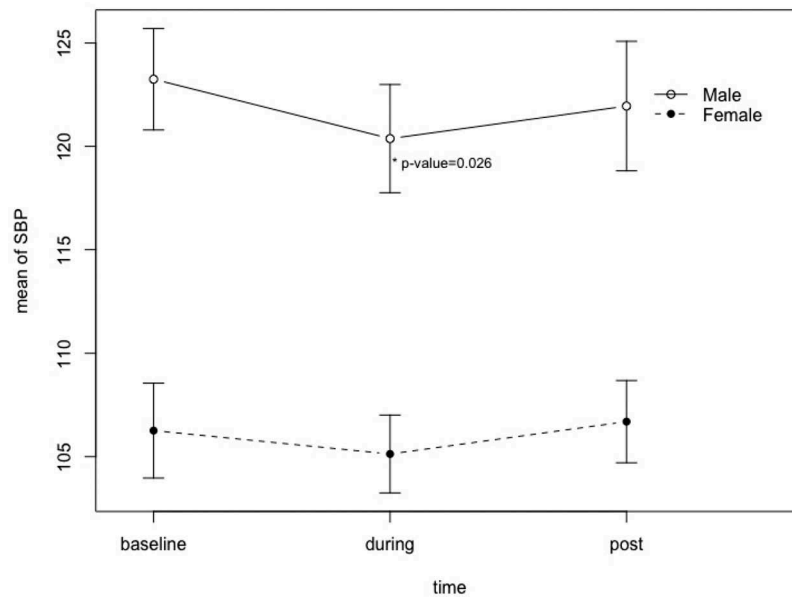
**Figure 2.** Mean changes in systolic blood pressure (SBP) across the follow-up time. Values expressed as means and standard errors. Error bars represent the standard error of measurement (SEM). The significant reduction is seen from baseline to during intervention ( $p = 0.007$ ). (Abbreviation: AP = anterior to posterior non-thrust manipulation (NTM). LAT = lateral glide) NTM.

parameters for NTM, and our results suggest that this dosage may provide an alternative for clinicians seeking to use cervical NTM to reduce pain without causing an increase in BP.

Historically, sympatho-excitatory cardiovascular effects were believed to result from cervical NTM. La Touche and colleagues [19] reported sympatho-excitatory heart rate effects resulting from an AP NTM in subjects with cervico-craniofacial pain delivered for three bouts of 2 minutes each with 30-seconds rest in between bouts. Vicenzino and colleagues [20] also found sympatho-excitatory cardiovascular effects following LAT NTM in healthy individuals, provided for three sets of 30 seconds each with a 60-second rest period between sets. McGuinness and colleagues [25] demonstrated sympatho-excitatory cardiovascular effects in healthy volunteers following central posterior-to-anterior NTM, dispensed for three bouts of 60 seconds, with a 60-second rest between each bout. The contradicting response reported from the current study

may be explained, in part, by the dosage of the NTM technique. This study is the first to demonstrate that short-term neck pain reduction with a decrease in SBP (during-intervention signifying sympatho-inhibition) is possible using a novel dosage of two cervical NTM techniques which have previously been shown to be sympatho-excitatory when delivered under traditional dosage parameters.

This spinal NTM study is the first to evaluate the association of resting SBP with short-term pain reduction [10–12]. Biomechanical, neurophysiological, and placebo effects are proposed mechanisms for improvements in pain and function following NTM [8]. Neurophysiological effects were examined in the current study through a cardiovascular response to explore that as a mechanism linked to pain relief. The results indicated that resting SBP was significantly associated with average pain reduction two days later, consistent with a mechanism referred to as BP-related hypoalgesia [17,18,29–31].



**Figure 3.** Mean changes in systolic blood pressure (SBP) by gender and the follow-up time. Values expressed as means and standard errors. The significant reduction is seen from baseline to during intervention among males ( $p = 0.026$ ). Male patients also had significantly higher SBP than female patients.

Table 2 shows that each 10 mmHg higher resting SBP was associated with a 0.29-unit decrease in average pain at follow-up, holding baseline pain constant. When considering a clinical scenario where a difference of 40 mmHg exists in resting SBP between two patients with an average baseline pain of 3/10 (as was seen in our cohort), the patient with the higher resting SBP may experience a reduction in pain by 1.16 ( $-0.029 \times 40$ ), resulting in a clinically insignificant pain rating of 1.84/10. The current study adds new knowledge and clinical value by offering an alternative for some patients who have a resting borderline BP (e.g., 138/90 mmHg).

On the one hand, their resting borderline hypertensive BP may be associated with better hypoalgesia (than those with lower BP, based on the above calculation derived from our study). Performing either AP or LAT NTM with the novel dose used in this study would likely *not* increase the BP toward the hypertensive range, which may add an important safety value to the clinical reasoning process. This study did not use a placebo as previous work has demonstrated a difference between placebo and cervical NTM [20,21,23,28].

The results also provide additional evidence supporting the pain-relieving effects of cervical spine NTM. The application of either AP or LAT NTM in subjects with non-chronic unilateral neck pain resulted in a significant decrease in the self-reported level of average pain. On average, the GROC and NDI did not reveal any meaningful improvements in the 'most painful neck movement' and self-reported function in this study, respectively. However, 36.4% [or 8/22] of the AP NTM group versus 28.6% [or 6/21] of the LAT NTM group achieved a clinically meaningful GROC of 3 or greater perceived improvement [32], with no significant

difference between both proportions. These findings agree with previous literature that has failed to identify a significant benefit from cervical NTM in individuals with neck pain for improving function and quality of life in the immediate and intermediate timeframe [8].

The present study has limitations. First, the sample consisted of a younger population of individuals with lower levels of self-reported pain and dysfunction and may not be representative of those individuals who commonly present to physical therapy for the treatment of neck pain. Lower levels of pain and dysfunction at baseline may have also limited the ability to achieve significant reductions in pain and dysfunction with treatment. Additionally, this sample consisted specifically of individuals with unilateral non-chronic neck pain and thus limited the generalizability of the findings. Having a single, highly trained, and experienced physiotherapist delivers the intervention further limits the generalizability of these findings.

Additional research should be conducted to determine the differences in pain modulation between females and males as well as continue to explore dosage parameters of cervical NTM. Further investigation could assist in revealing the complex and multifactorial mechanisms underlying NTM techniques and aid in determining the appropriate dosage or procedure based on the possible mechanism that is mediating, moderating [9] and causing relief in a patient's pain.

## Conclusion

Both AP and LAT NTM reduced pain and SBP in subjects with non-chronic unilateral neck pain. SBP reduction was noted from baseline to during-intervention,



suggesting sympathoinhibition. SBP at baseline was associated with the averaged pain reduction two days later, indicating SBP-associated hypoalgesia. Using a distinct dose of either AP or LAT NTM, physiotherapists could reduce neck pain 2-days later and produce a possible sympatho-inhibitory decrease in BP during-intervention. This effect may be ideal for cases where a sympatho-excitatory BP increase during treatment is worrisome.

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No potential conflict of interest was reported by the authors.

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## Notes on contributors

**Emmanuel Yung**, DPT, OCS, FAAOMPT is a Clinical Assistant Professor of Physical Therapy at Sacred Heart University in Fairfield, Connecticut. Manny is a Board-Certified Orthopaedic Clinical Specialist since 1998 and is a Fellow in the American Academy of Orthopaedic Manual Physical Therapists having completed his Manual Therapy Fellowship training at Southern California Kaiser Permanente program since 2003. He graduated from the University of Southern California with a Doctor of Physical Therapy and is a PhD student at New York University.

**Cheongeun Oh**, PhD did her postdoc training in Biostatistics at Yale University, after receiving her PhD from the State University of New York at Stony Brook. She holds a tenure track assistant professorship from Biostatistics Division at Department of Population Health, New York University School of Medicine. Dr. Oh has over 70 peer-reviewed publications and teaches numerous statistical courses in NYU School of Medicine. Over the past five years, she has collaborated and has supported the Department of Orthopaedic Surgery. She has served as a senior advisory member of collaborative research groups in funded collaborations.

**Michael Wong**, DPT, OCS, FAAOMPT holds a full-time appointment as an Associate Professor at Azusa Pacific University, teaching in the specialty areas of Orthopedic Physical Therapy. He is a residency and fellowship trained orthopaedic clinical specialist. Dr. Wong currently lectures for the Southern California Kaiser Permanente Orthopaedic

Fellowship and Sports Rehabilitation Program and the University of Southern California Spine Fellowship. He also currently serves as Chair of the Institutional Review Board at Azusa Pacific University.

**Jason K. Grimes** PT, DPT, PhD is a Clinical Associate Professor in the Doctor of Physical Therapy Program at Sacred Heart University where he also serves the Sacred Heart University Orthopaedic Physical Therapy Residency Program Director. He graduated with his Master's degree in Physical Therapy from Quinnipiac University and DPT and PhD from Nova Southeastern University. He has been Board-Certified as an Orthopaedic Clinical Specialist since 2007 and has over 15 years of clinical experience working with orthopaedic and sports populations.

**Erica Mae Barton**, DPT, OCS graduated with a Doctorate of Physical Therapy from Azusa Pacific University, Azusa, California. Dr. Barton is a Board-Certified Orthopaedic Clinical Specialist who is currently the Physical Therapist at Kaiser Permanente Regional Spine Center in Panorama City, California. She completed both her Orthopaedic Residency and Spine Rehabilitation Fellowship at Southern California Kaiser Permanente in Los Angeles, California.

**Muhammad I. Ali**, DPT is a physical therapist with the United States Air Force currently stationed in the United Kingdom. He graduated from Sacred Heart University with a Doctor of Physical Therapy and completed his orthopaedic residency program with Evidence In Motion Prior to serving in the Air Force, Dr. Ali also served in the United States Army Reserve for eight years as a Medical Laboratory Noncommissioned Officer and has been a Platoon Sergeant for three years, overseeing 40 officers.

**Allison Breakey**, DPT graduated from Sacred Heart University Doctor of Physical Therapy Program. She is a physical therapist for Hartford Healthcare at Backus Outpatient Care Center in Norwich, Connecticut. Previously, she was a member of the APTA Student Assembly Board of Directors and represented the student assembly as a student physical therapist delegate. Allison is also engaged in patient advocacy and was awarded the Victor Vaughan Legislative Service award by Sacred Heart University for her dedication to advocacy efforts.

## ORCID

Michael Wong  <http://orcid.org/0000-0001-5381-8664>

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## Appendix 1. CONSORT statement.



## CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable (N/A)
Participants	4a	Eligibility criteria for participants	5-7
	4b	Settings and locations where the data were collected	1, 5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	10-11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	9-10
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	6-8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7-8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7-8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7-8
<b>Blinding</b>			
	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7-8
	11b	If relevant, description of the similarity of interventions	7-10
<b>Statistical methods</b>			
	12a	Statistical methods used to compare groups for primary and secondary outcomes	11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11-12
<b>Results</b>			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	14, (Figure 1)
	13b	For each group, losses and exclusions after randomisation, together with reasons	(Figure 1)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12-15, Table 3
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12-15, Figure 1 and Table 3
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-15, Table 3-4, Figure 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	15-17, Table 4, Figure 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	17
<b>Discussion</b>			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17-21
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18-21
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	18-21
<b>Other information</b>			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

**Appendix 2: TIDieR checklist.**



**The TIDieR (Template for Intervention Description and Replication) Checklist\*:**

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	<b>BRIEF NAME</b>	1) 1	
1.	Provide the name or a phrase that describes the intervention.	_____	_____
	<b>WHY</b>	2) 1-4	
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	_____	_____
	<b>WHAT</b>	3) 9-10	
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	_____	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	4) 9-10	_____
	<b>WHO PROVIDED</b>	5) 9-10	
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	_____	_____
	<b>HOW</b>	6) 9-10	
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	_____	_____
	<b>WHERE</b>	7) 1, 5	
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	_____	_____

TIDieR checklist

	<b>WHEN and HOW MUCH</b>	8) 6,9-10	
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	_____	_____
	<b>TAILORING</b>	N/A	
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	_____	_____
	<b>MODIFICATIONS</b>	N/A	
10.*	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	_____	_____
	<b>HOW WELL</b>	11) 8-10	
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	_____	_____
12.*	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	12) 8-10	_____