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PC6 Acupoint Stimulation for the Prevention of Post-Cardiac Surgery Nausea and Vomiting: a protocol for a two-group, parallel, superiority randomised clinical trial

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3 **PC6 Acupoint Stimulation for the Prevention of Post-Cardiac Surgery Nausea and**
4 **Vomiting: a protocol for a two-group, parallel, superiority randomised clinical trial.**
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ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) are frequent but unwanted complications for patients following anaesthesia and cardiac surgery, affecting at least a third of patients, despite pharmacologic treatment. The primary aim of the proposed research is to test the efficacy of PC6 acupoint stimulation versus placebo for reducing PONV in cardiac surgery patients. In conjunction with this we aim to develop an understanding of intervention fidelity and factors that support, or impede, the use of PC6 acupoint stimulation, a knowledge translation approach.

Methods and analysis: 712 post-cardiac surgery participants will be recruited to take part in a two-group, parallel, superiority, randomised controlled trial. Participants will be randomised to receive a wrist band on each wrist providing acupressure to PC 6 using acupoint stimulation or a placebo. Randomisation will be computer generated, use randomly varied block sizes, and be concealed prior to the enrolment of each patient. The wristbands will remain in place for 36 hours. PONV will be evaluated by the assessment of both nausea and vomiting, use of rescue anti-emetics, quality of recovery, and cost. Patient satisfaction with PONV care will be measured and clinical staff interviewed about the clinical use, feasibility, acceptability and challenges of using acupressure wristbands for PONV.

Ethics and dissemination: A systematic review of the use of wrist acupressure for PC6 acupoint stimulation reported minor side effects only. Study progress will be reviewed by a Data Safety Monitoring Committee (DSMC) for nausea and vomiting outcomes at $n=350$.

Trial registration number: Australian New Zealand Clinical Trials Registry - ACTRN12614000589684

Article Summary

Article Focus

A protocol for a clinical trial testing PC6 acupoint stimulation as an alternative approach to the prevention of post-operative nausea and vomiting in patients following cardiac surgery.

Key Message

Evidence suggests that PC6 acupoint stimulation can prevent post-operative nausea and vomiting. A large study is required to support this evidence and in particular in relation to those undergoing cardiac surgery.

Strengths and limitations of this study

This protocol outlines the first large study to test the efficacy of PC acupoint stimulation on post-operative nausea and vomiting. A parallel aim of the study is to use an integrated knowledge translation approach to develop a comprehensive understanding of factors that impact on successful implementation of the intervention.

INTRODUCTION

Postoperative nausea and vomiting (PONV) are common unwanted complications for patients following anaesthesia/cardiac surgery, affecting at least 1 in 3 patients, despite pharmacologic prophylaxis and/or treatment. A Cochrane Systematic Review (CSR) specific to medicines for preventing PONV, concluded that PONV affects around 80 of every 100 individuals undergoing surgery, and that if all 100 were given a drug to prevent PONV, only around 28 would benefit¹. The burden of caring for patients post cardiac surgery is immense, with the Australian Institute of Health and Welfare (AIHW)² annual report indicating that in Australia alone nearly 179,000 procedures involving the cardiovascular system were performed between 2011-12. Cardiovascular disease (CVD) remains the most expensive diagnostic group to treat in Australia, costing about \$7.9 billion in 2008–09, with over half of this spent on patients while admitted to hospital³. Similarly, the significant cost of CVD to the United Kingdom health care system in 2009 was reported to be around £8.6 billion with 50% of this attributed to hospital care⁴.

As part of their treatment and recovery, cardiac surgery patients experience varying rates of PONV. Studies in the 1990s found rates of PONV in cardiac surgery patients of 22%⁵, 47%⁶ and 50%⁷. More recent studies reported rates of: 39%-42% in a North American RCT⁸; 26%-27% in a systematic review of 10 RCTs⁹; and 35% in a Canadian study¹⁰. Patients report that they have a strong preference for avoiding PONV¹¹ and, of 10 negative outcomes of surgery, rank vomiting as the most undesirable outcome and nausea as the fourth most undesirable¹². Patient dissatisfaction with anaesthetic care is strongly related to PONV¹³. PONV can delay transfer from the recovery unit by up to 20 minutes¹², and vomiting can place tension on sutures and wounds, produce imbalances in body electrolytes, and cause bleeding¹². Acupressure is a therapeutic intervention endorsed by the World Health Organisation (WHO)¹⁴ and an alternative approach thought to prevent nausea and vomiting through an alteration in endorphins and serotonin levels.

Efficacy of acupressure for PONV

Acupressure as a traditional Chinese medicine has been practised for centuries. The concept is based on life energy (Qi) flowing through channels known as meridians through the body¹⁵. It is argued that acupressure restores equilibrium to disruptions affecting the body's homeostasis by stimulating specific points (acupoints) that connect the meridians to organs¹⁵.

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3 Although the mechanism for the action of acupressure has not been scientifically investigated
4 fully, it is thought that it may prevent nausea and vomiting through an alteration in
5 endorphins and serotonin levels¹⁶. PC6 point stimulation for treating nausea and vomiting
6 was reported in the early 1990s¹⁷. The WHO (Western Pacific Regional Office) reached
7 consensus on acupuncture point locations and published guidelines in 2008¹⁸. The Neiguan
8 PC6 acupoint is the meridian point in the pericardium channel, and is located on the inner
9 forearm between the extensor carpi radialis and palmaris longus tendons, one sixth of the
10 distance from PC7 on the medial wrist crease to PC3 in the cubital fossa¹⁸. Measuring the
11 distance between the palmar wrist crease and inner forearm with a tape measure, and placing
12 the bead on the wristband between the 2 tendons a sixth of the distance measured, is quick,
13 acceptable and feasible in the clinical environment. This method is much more accurate than
14 the previously used procedure of using the three middle fingers on the inside of the patient's
15 wrist to measure distance. Although the PC6 acupoint can be stimulated with a variety of
16 methods (acu-stimulation device, acupressure, acupuncture, capsicum plaster), the important
17 concept is stimulation of the *correct* acupoint¹⁹. A meta-analysis in a recent Cochrane
18 Systematic Review (CSR) by Lee and Fan (2009) of 40 trials¹⁹, totalling 4,858 participants
19 (all surgical patients without age limits), reports a clear positive effect of PC6 acupoint
20 simulation on: nausea (RR 0.71, 95% CI 0.61 - 0.83); vomiting (RR 0.70, 95% CI 0.59 -
21 0.83); and need for rescue antiemetics (RR 0.69, 95% CI 0.57 - 0.83).
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36 Although the Lee and Fan¹⁹ meta-analysis identified a clear positive effect of PC6 acupoint
37 stimulation, the analysed studies were conducted in various clinical settings and with
38 different populations, suggesting that, 'on average', the intervention is known to be effective.
39 It is thought that this intervention is not used in clinical practice despite the positive CSR and
40 the reasons for this are unknown but perhaps related to the following factors. The CSR meta-
41 analysis incorporated only one study undertaken in a cardiac population ($n=152$), and
42 included various methods of PC6 acupoint stimulation versus sham/drug therapy for
43 prevention of PONV. The vast majority of studies had small sample sizes (range 36–250),
44 with only one with a reasonable sample size $n=410$ (sample size calculated on the CSR meta-
45 analysis outlined below indicates a sample of >700 is required); quality of the studies is
46 highly varied, with concerns mostly regarding allocation sequence generation and allocation
47 concealment, which this proposed study addresses. As such, it is argued that a) a large
48 rigorous RCT is needed to provide definitive evidence to inform clinicians, and b) the direct
49 application of this to cardiac population needs further consideration and investigation. There
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3 is also the added significant value in the current planned study of incorporating secondary
4 hypotheses around dose response (dose varied considerably across studies in the CSR) and
5 quality of recovery (rarely addressed in CSR studies) to yield new knowledge and draw
6 conclusions for post-operative management and patient care. The economic evaluation
7 including the side-effects associated with drugs used to treat PONV (e.g. for two common
8 antiemetics: 1. Metoclopramide's side effects include sedation and dystonic reactions and 2.
9 Ondansetron's side effects include headache, dizziness and possible QT interval
10 prolongation) will also provide guidance on the value for money offered by this intervention.
11 Further, despite the CSR, use of acupressure for PONV is not widely practiced, and methods
12 will be used in this study to develop a comprehensive understanding of factors relevant to the
13 successful implementation of acupressure for PONV, a strategy that is recommended when
14 there is a degree of uncertainty about an intervention²⁰. These data will help us to understand
15 factors which might impede implementation, and allow for targeted implementation strategies
16 to be developed, should the study results demonstrate a positive impact²¹.
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28 This two-group, parallel, superiority, blinded, randomised controlled trial (RCT) will test the
29 efficacy of PC6 acupoint stimulation versus placebo for reducing PONV in cardiac surgery
30 patients. Primarily this study aims to investigate whether patients in the PC6 acupoint
31 stimulation group will experience significantly less nausea and vomiting in the first 36 hours
32 following admission to ICU post cardiac surgery, than patients in the sham group. It also
33 aims to investigate whether 1) Patients in the PC6 acupoint stimulation group will
34 experience: a) significantly less severe nausea post-operatively than patients in the sham
35 group in the first 36 hours post-operatively; b) significantly less early- (≤ 16 hours) and late-
36 onset (>16 hours) PONV than patients in the sham group; c) a greater reduction in rescue
37 drug therapy post-operatively than patients in the sham group in the first 36 hours post-
38 operation; and d) a greater quality of recovery at morning of day 4 than patients in the sham
39 group. 2) costs associated with treatment for PONV will be significantly lower in the group
40 using PC6 acupoint stimulation than in the sham group. A parallel aim is to use an integrated
41 knowledge translation approach to develop a comprehensive understanding of factors that
42 impact on successful implementation of the intervention. The focus will be on the delivery of
43 the intervention as intended, processes of implementation and change, and responses of
44 patients and health care professionals to the intervention. Patients' satisfaction with their
45 PONV care will be measured and clinical staff interviewed about the clinical use, feasibility,
46 acceptability and challenges of using acupressure wristbands for PONV in practice. These
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3 data can then be used to assist implementation should the intervention be shown to be
4 effective. If effective, this intervention has the potential to significantly improve the quality
5 of care for hundreds of thousands of patients worldwide, each year through a cost effective
6 and safe intervention for the prevention and management of PONV.
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10 11 **METHODS AND ANALYSIS**

12 13 **Study Design**

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15 The study will use a two-group, parallel, superiority, participant and clinician-masked RCT
16 design. Participants will be post-operative adult cardiac surgery patients. The intervention
17 will be PC6 acupoint stimulation. The main outcome measure will be PONV, with secondary
18 outcome assessment of severe nausea, difference in effect early and late-onset post-
19 operatively, need for rescue antiemetic therapy, and quality of recovery by 4th postoperative
20 day. An economic sub-study will compare costs associated with PC6 stimulation device,
21 costs of antiemetic medication, and hospital length of stay in the two groups. Also
22 incorporated will be a parallel integrated knowledge translation approach, to develop
23 understanding of intervention fidelity and factors that support, or impede, the use of PC6
24 acupoint stimulation. A superiority design has been chosen as this is consistent with the
25 literature to date: the CSR of 40 trials found that all except one trial indicated less nausea in
26 the group receiving PC6 stimulation compared to control. In addition there is no biologically
27 plausible reason that PC6 acupressure would increase post-operative nausea and vomiting.
28 Use of a sham will eliminate the influence of treatment effects other than those caused by the
29 treatment itself (i.e., knowledge of receiving the treatment and expectations of what it might
30 do etc.) by blinding participants, clinicians and also members of the research team, as to who
31 is receiving the acupressure and who is not. The CONSORT guidelines²², with its official
32 extension of Standards for Reporting Interventions in Clinical Trials of Acupuncture²³ have
33 been used to guide study design.
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48 49 **Setting & population**

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51 Trial participants will be sampled from an adult post cardiac surgery population. This
52 population reflects a relatively homogenous group and is, thus, likely to detect an effect if
53 one exists in the population. Two hospital sites will be accessed where on average 22 patients
54 undergo cardiac operative procedures consistent with the inclusion criteria each week. Only
55 patients undergoing primary surgical procedures will be included as patients undergoing
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3 second or subsequent cardiac surgery are more likely to have variable pre-, intra- and post-
4 operative course and care, and the standardized protocol outlined below in concurrent
5 treatment may not be applicable. It is anticipated that recruitment will take eighteen months.
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9 10 **Sample size**

11 The primary outcome of nausea was used to power this study. Only one previous study has
12 specifically examined the effect of acupressure on nausea with a cardiac post-operative
13 group, finding that the proportion of participants with observed nausea in the control group
14 was 35%¹⁰, which is consistent with our unpublished preliminary data. Based on the CSR, to
15 detect a 30% reduction in relative risk of nausea¹⁹ with 90% power, a total of 712 participants
16 ($n=356$ per group) at an alpha of .05 (for a superiority test of 2 independent proportions)²⁴ is
17 needed.
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24 25 **Recruitment**

26 A Registered Research Nurse (RRN) will identify elective patients from operation lists and
27 approach each patient (at pre-admission clinic or on ward) to introduce the study. Those
28 interested will then be formally screened and those eligible will be provided with an
29 information sheet, further explanation of the study and clarification of any questions with the
30 contact details of the study manager provided as a contact for further information. Written
31 informed consent will be obtained. Patients who meet all of the inclusion criteria, and none of
32 the exclusion criteria, will be eligible. The inclusion criteria are: elective or urgent primary
33 cardiac surgery (Coronary Artery Bypass Graft (CABG); valve and double valve
34 replacement; CABG plus single valve replacement); able to understand, speak, read and write
35 English or have a suitable interpreter available; aged 18 years or over, and able to give
36 informed consent. Exclusion Criteria are: impaired renal function – creatinine level >200 or
37 eGFR <40; patients receiving: antiemetic medication within 24-hours prior to surgery, or
38 histamine H2-receptor antagonist within 24-hours prior to surgery; skin damage (e.g. burn
39 scars) over PC6 area; wrist circumference >21cm; and any previous experience of
40 acupressure for nausea and/or vomiting, for example, related to morning sickness,
41 chemotherapy, or travel/motion sickness.
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54 55 **Randomisation & allocation concealment**

56 Computer-generated random assignment will occur at the point of study entry, and each
57 patient will be allocated to a numbered trial group. Randomisation will involve a 1:1 ratio;
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3 stratified assignment by risk of nausea (Apfel Score that can be stratified into low [score 0 or
4 1], moderate [score 2], extremely high [score 3 or 4]²⁵ at study site, with random variation in
5 block sizes of 4-10. RRN will obtain a participant code number corresponding to a study pack
6 to which each participant will be randomly allocated using a web-based independent
7 automated service at the university Clinical Trials Randomisation Service, which is overseen
8 by a biostatistician, and record the study group code in the patient's medical record and on
9 study forms. This process ensures adequate concealment, limiting likelihood of selection
10 bias²⁶.
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18 **Processes to ensure blinding**

19 RRN will obtain the participant code number through the randomisation process outlined
20 below and, thus, is blinded to group allocation and will collect outcome data on day 4 post-
21 operatively and document final nausea scale score at 36 hours. Another RRN (RRN2, trained
22 and assessed to ensure correct PC6 positioning) will apply the intervention/placebo on arrival
23 in the intensive care unit (ICU) following surgery. All clinicians providing care will be
24 blinded to group allocation. ICU and ward registered nurses will collect nausea scores and
25 incidence of vomiting. All patients will be blinded to group allocation, as an occlusive
26 bandage will be applied over the wristband. The acupuncture wristband will be identical in
27 appearance and position for both intervention and placebo groups. All members of the
28 research team involved in participant recruitment, randomisation and data collection, will be
29 blinded to group allocation.
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40 **Intervention**

41 Participants in the acupuncture group will have a Seaband[®] wristband applied on arrival to
42 ICU on both wrists (bilateral application is recommended) by RRN2 ensuring that the bead
43 stimulates the PC6 acupoint and the bands are covered with a light opaque bandage. The
44 wristbands will be removed at 36 hours after admission to ICU just after the final outcome
45 measurement. This same procedure will be applied to participants in the placebo (sham)
46 wristband group, with the point of difference being that they will have a sham (without bead)
47 Seaband[®] wristband applied to their wrists. All members of the research team will receive
48 training and a standardised procedure manual (detailing protocol, plans for dealing with
49 intervention fidelity issues, and monitoring the delivery and receipt of the intervention²⁷), to
50 ensure protocol consistency. All patients will receive identical information and instructions
51 regarding the study, relayed by RRN and also in an information sheet provided at enrolment.
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Concurrent treatment

Patients in both groups will have a standardised anaesthetic protocol for pre-medication, anaesthesia and post-operative pain and nausea management. In cardiac anaesthesia, it is very unusual to give PONV prophylaxis either in the operating theatre or in the ICU. The treatment of PONV in this population is expectant: that is, patients are treated for PONV only when they display signs/symptoms of nausea or vomiting. This is consistent with standards of care, both in Australia and internationally, given that the variable time of waking and ventilator weaning of patients is often unpredictable at the time of surgical case completion in theatre. Premedication will be standardized to Temazepam 10-30mg/Diazepam 5-10mg 1 hour prior to surgery; anaesthesia induced with Midazolam 0.03-0.1mg/kg, Fentanyl 5-15g/kg, Propofol 0.25-1.25mg/kg and Pancuronium 0.1mg/kg/Rocuronium 0.75-1.2mg/kg. Anaesthesia will be maintained with: Propofol infusion 2-5mg/kg/hr, Sevoflurane administered pre-cardiopulmonary bypass for ischemic preconditioning at discretion of attending anaesthetist, air/O₂ mix at discretion of attending anaesthetist. Transfer to ICU, patients will be maintained on propofol infusion and fentanyl infusion at 5-25ug/hr with no prophylactic anti-emetics administered (current usual care). Participants will be sedated with the above mentioned propofol and fentanyl infusions until determined appropriate to extubation of the artificial airway, and then maintained on fentanyl via patient controlled analgesia (background of 0-25ug/hr; bolus of 5-25ug every 5 minutes) for 48 hours or until cardiac drain are removed postoperatively. A standardised rescue anti-emetic protocol involving the use of a grading system will be used (see Table 1). For any patient requiring naso-gastric treatment post-operatively this will be recorded (given this prevents gastric distension and vomiting) and gastric volume recorded for 36 hours.

Table 1 around here

Outcome measures

All data will be collected using structured case report forms by staff blinded to treatment groups. This method of interviewer-led self-report data collection will minimise missing data. Nausea will be assessed at six time points: 6 hours from arrival to the ICU; 12 hours post arrival; then 4 hourly up to 24 hours; and then at 36 hours on a 10-point scale (Table 1) and aggregated into 'all', 'mild', 'moderate-severe' and 'severe' nausea. All episodes of retching

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3 or vomiting in the 36-hour time period will be recorded. Rescue antiemetic will be given and
4 recorded for patients who experience mild-severe nausea or an episode of vomiting within the
5 36-hour study period (Table 1). Time to first rescue treatment will be recorded. Reasons for
6 attrition will be recorded. Participants will self-assess their quality of recovery on the
7 morning of the 4th post-operative day using a 15-item questionnaire – the QOR-15²⁸. Any
8 adverse event (AE) from the wristbands will be assessed and recorded at each assessment
9 time-point. Post-operative AEs will also be recorded. Healthcare resource use related to the
10 management of nausea and vomiting will be assessed and costed. This will include: band use;
11 frequency, dose, route and duration of rescue anti-emetics; length of stay in ICU and length
12 of stay in hospital post ICU; and costs associated with any adverse effects of the PC6
13 stimulation device or the anti-emetics. Demographic information will be collected at pre-
14 operative/baseline. This will include participant's age, gender, and Body Mass Index.
15 Probability of PONV will be predicted based on patient-related factors using the Apfel risk
16 score²⁹. At PC6 stimulation device removal, the RRN will ask the patient (if able) about their
17 satisfaction with their PONV care on a 10-point scale ('0=completely dissatisfied',
18 '10=completely satisfied'). The Study Manager will oversee data quality including
19 undertaking periodic audits and generation of data queries for all missing or improbable
20 values. Clinical staff will be invited to participate in either group or individual semi-
21 structured interviews about the clinical use, feasibility, acceptability, and challenges in using
22 the acupuncture wristbands for PONV in clinical practice, and their trial involvement. The
23 interview schedule will be informed by the Theoretical Domains Framework³⁰, which will
24 enhance the understanding of the perceived risks, benefits and barriers to the use of
25 acupuncture bands so that we can develop strategies to facilitate practice change at the study
26 conclusion.
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45 **Data analysis**

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47 Data from the case report forms will be entered and analysed under the direction of a PhD
48 qualified statistical epidemiologist. Prior to analysis, all missing data and improbable values
49 will be checked against source data. The primary end point will be occurrence of nausea
50 and/or vomiting within 36 hours of the end of surgery. Secondary end points will be nausea
51 and vomiting separately, occurrence of early (≤ 16 hours) and late (>16 hours including
52 repeat events) PONV, QOR score, need for rescue antiemetic therapy and band-related as
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3 well as post-operative AEs. We will use Chi² test (or Fishers Exact test) to compare
4 frequency of nausea and vomiting (all types, nausea, vomiting, early PONV, late PONV,
5 moderate-severe nausea, severe nausea and need for rescue antiemetics) in the two treatment
6 groups. QOR and number of rescue antiemetics will be compared using Wilcoxon two-
7 sample test. Cumulative incidence of rescue antiemetic treatment over time will be plotted
8 using the Kaplan-Meier method and compared across the two treatment groups. We will
9 perform stepwise multiple logistic regression analyses for early and late postoperative nausea
10 and vomiting to identify predictors of these events. The results will be presented as adjusted
11 odds ratios with 95% confidence intervals; we will adjust for all variables that could be
12 independently explanatory at a $P \leq 0.1$ for respective end points. Analyses will be performed
13 according to the intention to treat principle, although a per protocol analysis will be
14 undertaken as a secondary analysis to consider the likely effect on outcome measure of
15 randomised patient attrition prior to and during treatment, missing data, and protocol
16 violations. Patient survey data will be analysed to assess satisfaction with PONV care. The
17 Theoretical Domains Framework³⁰ will inform the analysis of the clinical staff interviews.
18 Economic evaluation will incorporate health-related costs and assess the value for money
19 provided by acupuncture by comparing the incremental costs and effects of the intervention.
20 Bootstrapping will be employed to compare the mean difference in the costs between groups,
21 and to estimate a confidence interval around the mean³¹. A comparative cost-effectiveness
22 analysis will be undertaken based on incidence of nausea or vomiting and the QOR as
23 outcome measures. Uncertainty around incremental cost-effectiveness ratios will be tested
24 using both one-way sensitivity analysis and non-parametric bootstrapping methods³¹.

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43 Ethics approval will be sought from appropriate Human Research Ethics Committee/s
44 (HREC) before commencement of study. Participants will be supplied with detailed
45 information regarding the study including data access, storage and confidentiality.
46 Participants will be required to provide informed written consent and have the right of
47 withdrawal from the study at any time. Participation burden is low, and declining to
48 participate will have no negative effect on the patient's continued treatment at the hospitals.
49 There are no anticipated risks to participants. Lee and Fan¹⁹ identified that two trials in their
50 CSR found some participants reported that wristbands were uncomfortable, and produced
51 minor side effects. Any serious AEs will be assessed at all time-points and reported to the
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3 patient's treating doctor to determine whether further diagnostic testing or treatment is
4 warranted. All AEs will be reported in study results. Although serious AEs will be expected
5 given the nature of the surgery, it is highly unlikely that these will be related to the
6 intervention, although these will be reported to the HRECs expeditiously, with appropriate
7 notification of the Therapeutic Goods Administration if required. Serious AEs will be
8 monitored and reported to the HREC. Approvals for any other variations to the protocol will
9 be sought through HREC. The acupuncture bands to be used "Seaband[®]" is a registered
10 medical device with Australian Register of Therapeutic Goods (ARTG 109529)

17 18 **Data and safety monitoring plan**

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20 A DSMC of two biostatisticians and two medically qualified researchers (independent of
21 study) will review nausea and vomiting outcomes after $n=350$. The DSMC will check and
22 advise whether the study needs to be stopped early (for futility) or because the intervention
23 effect is so great that further data collection is unnecessary (with caution given the
24 controversies over stopping early for benefit systematically overestimating treatment effects).
25 Stopping for futility will be considered if the conditional power (the chance of detecting a
26 statistically significant result at the end of the trial given the interim results) is very low
27 ($\leq 15\%$)³². We will utilize a simple predefined statistical stopping rule for benefit, the Peto-
28 Haybittle boundary, which would indicate stopping at a P value for treatment difference
29 (nausea and/or vomiting) at interim analysis of <0.001 .³³ However, we acknowledge that this
30 formal rule is insufficient to prevent bias consequent on stopping early³⁴ and we will
31 additionally require a large number of outcome events and considerations of clinical
32 significance over and above the statistical boundary before early stopping for benefit is
33 contemplated. If a major post-operative complication (e.g. haemorrhage requiring return to
34 theatre, difficulty weaning from artificial ventilation or cerebrovascular event interfering with
35 communication) is experienced, as much data as possible will be recorded to maximise the
36 dataset available for intention to treat analysis³⁵

48 49 50 51 **Reporting & dissemination**

52 It is anticipated that results will be well received by academic, scientific and broader
53 communities. Dissemination will include conference presentations at national and
54 international scientific meetings and publications in peer-reviewed journals with a high
55 readership in anaesthetics and cardiac surgery. Study participants will receive a one-page lay-
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3 summary of results. Use of an integrated knowledge translation approach, purposely
4 including patients and practitioners, will assist with dissemination of study findings and those
5 involved in the study will be encouraged to participate in wider dissemination of study
6 findings.
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For peer review only

Contributorship Statement:

All authors made a significant contribution to the conception and design of the study protocol. The protocol was written by MC and was critically reviewed by CR, IR, SK, AM, TC, SD, AS. All authors gave approval for the publication

Competing Interests

None

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Competing interests statement: There are no competing interests to report.

Table 1: Rescue anti-emetic protocol

Symptoms	Nausea score	Treatment
None	0	No treatment
Mild	1-3	Rescue anti-emetic (Metoclopramide 10-20mg)
Moderate	4 - 6	Rescue anti-emetic (Metoclopramide 10-20mg + Ondansetron 4-8mg)
Severe	7-10	Rescue anti-emetic (Metoclopramide 10-20mg + Ondansetron 4-8mg). If no response in 30 mins: Dexamethasone 8mg, then Droperidol 0.625mg. Change of PCA narcotic if no effect within 30 mins.
Retching/vomiting	N/A	As per protocol for severe nausea



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <i>YES</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <i>YES</i>
	2b	All items from the World Health Organization Trial Registration Data Set <i>N/A</i>
Protocol version	3	Date and version identifier <i>YES</i>
Funding	4	Sources and types of financial, material, and other support <i>YES</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <i>YES</i>
	5b	Name and contact information for the trial sponsor <i>N/A</i>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <i>N/A</i>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) <i>YES</i>
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention <i>YES</i>
	6b	Explanation for choice of comparators <i>YES</i>
Objectives	7	Specific objectives or hypotheses <i>YES</i>
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) <i>YES</i>

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained <i>YES</i>
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) <i>YES</i>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <i>YES</i>
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) <i>N/A</i>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <i>N/A</i>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <i>YES</i>
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended <i>YES</i>
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) <i>YES</i>
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations <i>YES</i>
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size <i>YES</i>

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions <i>YES</i>
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2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned <i>YES</i>
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7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions <i>YES</i>
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10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how <i>YES</i>
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14		17b	If blinded, circumstances under which unblinding is permissible, and
15			procedure for revealing a participant's allocated intervention during
16			the trial <i>YES</i>
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Methods: Data collection, management, and analysis

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21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
22	methods		trial data, including any related processes to promote data quality (eg,
23			duplicate measurements, training of assessors) and a description of
24			study instruments (eg, questionnaires, laboratory tests) along with
25			their reliability and validity, if known. Reference to where data
26			collection forms can be found, if not in the protocol <i>YES</i>
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28		18b	Plans to promote participant retention and complete follow-up,
29			including list of any outcome data to be collected for participants who
30			discontinue or deviate from intervention protocols <i>YES</i>
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33	Data	19	Plans for data entry, coding, security, and storage, including any
34	management		related processes to promote data quality (eg, double data entry;
35			range checks for data values). Reference to where details of data
36			management procedures can be found, if not in the protocol <i>YES</i>
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38	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
39	methods		Reference to where other details of the statistical analysis plan can be
40			found, if not in the protocol <i>YES</i>
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42		20b	Methods for any additional analyses (eg, subgroup and adjusted
43			analyses) <i>YES</i>
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45		20c	Definition of analysis population relating to protocol non-adherence
46			(eg, as randomised analysis), and any statistical methods to handle
47			missing data (eg, multiple imputation) <i>YES</i>
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Methods: Monitoring

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52	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
53			and reporting structure; statement of whether it is independent from
54			the sponsor and competing interests; and reference to where further
55			details about its charter can be found, if not in the protocol.
56			Alternatively, an explanation of why a DMC is not needed
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58			<i>YES</i>
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1		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	YES
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6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	YES
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10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	YES
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Ethics and dissemination

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17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	YES
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20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	YES
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25	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	YES
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28		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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30	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	YES
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35	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	YES
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38	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	YES
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43	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
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46	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	YES
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52		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
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55		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates <i>N/A</i>
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable <i>N/A</i>

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

PC6 Acupoint Stimulation for the Prevention of Post-Cardiac Surgery Nausea and Vomiting: a protocol for a two-group, parallel, superiority randomised clinical trial

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	COMPLEMENTARY MEDICINE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Clinical trials < THERAPEUTICS

SCHOLARONE™
Manuscripts

PC6 Acupoint Stimulation for the Prevention of Post-Cardiac Surgery Nausea and Vomiting: a protocol for a two-group, parallel, superiority randomised clinical trial.

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ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) are frequent but unwanted complications for patients following anaesthesia and cardiac surgery, affecting at least a third of patients, despite pharmacologic treatment. The primary aim of the proposed research is to test the efficacy of PC6 acupoint stimulation versus placebo for reducing PONV in cardiac surgery patients. In conjunction with this we aim to develop an understanding of intervention fidelity and factors that support, or impede, the use of PC6 acupoint stimulation, a knowledge translation approach.

Methods and analysis: 712 post-cardiac surgery participants will be recruited to take part in a two-group, parallel, superiority, randomised controlled trial. Participants will be randomised to receive a wrist band on each wrist providing acupressure to PC 6 using acupoint stimulation or a placebo. Randomisation will be computer generated, use randomly varied block sizes, and be concealed prior to the enrolment of each patient. The wristbands will remain in place for 36 hours. PONV will be evaluated by the assessment of both nausea and vomiting, use of rescue anti-emetics, quality of recovery, and cost. Patient satisfaction with PONV care will be measured and clinical staff interviewed about the clinical use, feasibility, acceptability and challenges of using acupressure wristbands for PONV.

Ethics and dissemination: Ethics approval will be sought from appropriate Human Research Ethics Committee/s before commencement of study. A systematic review of the use of wrist acupressure for PC6 acupoint stimulation reported minor side effects only. Study progress will be reviewed by a Data Safety Monitoring Committee (DSMC) for nausea and vomiting outcomes at $n=350$. Dissemination of results will include conference presentations at national and international scientific meetings and publications in peer-reviewed journals. Study participants will receive a one-page lay-summary of results.

Trial registration number: Australian New Zealand Clinical Trials Registry - ACTRN12614000589684

INTRODUCTION

Postoperative nausea and vomiting (PONV) are common unwanted complications for patients following anaesthesia/cardiac surgery, affecting at least 1 in 3 patients, despite pharmacologic prophylaxis and/or treatment. A Cochrane Systematic Review (CSR) specific to medicines for preventing PONV, concluded that PONV affects around 80 of every 100 individuals undergoing surgery, and that if all 100 were given a drug to prevent PONV, only around 28 would benefit¹. The burden of caring for patients post cardiac surgery is immense, with the Australian Institute of Health and Welfare (AIHW)² annual report indicating that in Australia alone nearly 179,000 procedures involving the cardiovascular system were performed between 2011-12. Cardiovascular disease (CVD) remains the most expensive diagnostic group to treat in Australia, costing about \$7.9 billion in 2008–09, with over half of this spent on patients while admitted to hospital³. Similarly, the significant cost of CVD to the United Kingdom health care system in 2009 was reported to be around £8.6 billion with 50% of this attributed to hospital care⁴.

As part of their treatment and recovery, cardiac surgery patients experience varying rates of PONV. Studies in the 1990s found rates of PONV in cardiac surgery patients of 22%⁵, 47%⁶ and 50%⁷. More recent studies reported rates of: 39%-42% in a North American RCT⁸; 26%-27% in a systematic review of 10 RCTs⁹; and 35% in a Canadian study¹⁰. Patients report that they have a strong preference for avoiding PONV¹¹ and, of 10 negative outcomes of surgery, rank vomiting as the most undesirable outcome and nausea as the fourth most undesirable¹². Patient dissatisfaction with anaesthetic care is strongly related to PONV¹³. PONV can delay transfer from the recovery unit by up to 20 minutes¹², and vomiting can place tension on sutures and wounds, produce imbalances in body electrolytes, and cause bleeding¹². Acupressure is a therapeutic intervention endorsed by the World Health Organisation (WHO)¹⁴ and an alternative approach thought to prevent nausea and vomiting through an alteration in endorphins and serotonin levels.

Efficacy of acupressure for PONV

Acupressure as a traditional Chinese medicine has been practised for centuries. The concept is based on life energy (Qi) flowing through channels known as meridians through the body¹⁵. It is argued that acupressure restores equilibrium to disruptions affecting the body's homeostasis by stimulating specific points (acupoints) that connect the meridians to organs¹⁵.

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3 Although the mechanism for the action of acupressure has not been scientifically investigated
4 fully, it is thought that it may prevent nausea and vomiting through an alteration in
5 endorphins and serotonin levels¹⁶. PC6 point stimulation for treating nausea and vomiting
6 was reported in the early 1990s¹⁷. The WHO (Western Pacific Regional Office) reached
7 consensus on acupuncture point locations and published guidelines in 2008¹⁸. The PC6
8 acupoint is the meridian point in the pericardium channel, and is located on the inner forearm
9 between the extensor carpi radialis and palmaris longus tendons, one sixth of the distance
10 from PC7 on the medial wrist crease to PC3 in the cubital fossa¹⁸. Measuring the distance
11 between the palmar wrist crease and inner forearm with a tape measure, and placing the bead
12 on the wristband between the 2 tendons a sixth of the distance measured, is quick, acceptable
13 and feasible in the clinical environment. This method is much more accurate than the
14 previously used procedure of using the three middle fingers on the inside of the patient's
15 wrist to measure distance. Although the PC6 acupoint can be stimulated with a variety of
16 methods (acu-stimulation device, acupressure, acupuncture, capsicum plaster), the important
17 concept is stimulation of the *correct* acupoint¹⁹. A meta-analysis in a recent Cochrane
18 Systematic Review (CSR) by Lee and Fan (2009) of 40 trials¹⁹, totalling 4,858 participants
19 (all surgical patients without age limits), reports a clear positive effect of PC6 acupoint
20 stimulation on: nausea (RR 0.71, 95% CI 0.61 - 0.83); vomiting (RR 0.70, 95% CI 0.59 –
21 0.83); and need for rescue antiemetics (RR 0.69, 95% CI 0.57 - 0.83). Given the extensive
22 use of PC 6 acupoint in reported research studies in relation to PONV in the literature and its
23 ease of use in clinical practice, this acupoint has been chosen for this research.
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39 Although the Lee and Fan¹⁹ meta-analysis identified a clear positive effect of PC6 acupoint
40 stimulation, the analysed studies were conducted in various clinical settings and with
41 different populations, suggesting that, 'on average', the intervention is known to be effective.
42 It is thought that this intervention is not used in clinical practice despite the positive CSR and
43 the reasons for this are unknown but perhaps related to the following factors. The CSR meta-
44 analysis incorporated only one study undertaken in a cardiac population ($n=152$), and
45 included various methods of PC6 acupoint stimulation versus sham/drug therapy for
46 prevention of PONV. The vast majority of studies had small sample sizes (range 36–250),
47 with only one with a reasonable sample size $n=410$ (sample size calculated on the CSR meta-
48 analysis outlined below indicates a sample of >700 is required); quality of the studies is
49 highly varied, with concerns mostly regarding allocation sequence generation and allocation
50 concealment, which this proposed study addresses. As such, it is argued that a) a large
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3 rigorous RCT is needed to provide definitive evidence to inform clinicians, and b) the direct
4 application of this to cardiac population needs further consideration and investigation. There
5 is also the added significant value in the current planned study of incorporating secondary
6 hypotheses around dose response (dose varied considerably across studies in the CSR) and
7 quality of recovery (rarely addressed in CSR studies) to yield new knowledge and draw
8 conclusions for post-operative management and patient care. The economic evaluation
9 including the side-effects associated with drugs used to treat PONV (e.g. for two common
10 antiemetics: 1. Metoclopramide's side effects include sedation and dystonic reactions and 2.
11 Ondansetron's side effects include headache, dizziness and possible QT interval
12 prolongation) will also provide guidance on the value for money offered by this intervention.
13 Further, despite the CSR, use of acupressure for PONV is not widely practiced, and methods
14 will be used in this study to develop a comprehensive understanding of factors relevant to the
15 successful implementation of acupressure for PONV, a strategy that is recommended when
16 there is a degree of uncertainty about an intervention²⁰. These data will help us to understand
17 factors which might impede implementation, and allow for targeted implementation strategies
18 to be developed, should the study results demonstrate a positive impact²¹.

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31 This two-group, parallel, superiority, blinded, randomised controlled trial (RCT) will test the
32 efficacy of PC6 acupoint stimulation versus placebo for reducing PONV in cardiac surgery
33 patients. Primarily this study aims to investigate whether patients in the PC6 acupoint
34 stimulation group will experience significantly less nausea and vomiting in the first 36 hours
35 following admission to ICU post cardiac surgery, than patients in the sham group. It also
36 aims to investigate whether 1) Patients in the PC6 acupoint stimulation group will
37 experience: a) significantly less severe nausea post-operatively than patients in the sham
38 group in the first 36 hours post-operatively; b) significantly less early- (≤ 16 hours) and late-
39 onset (>16 hours) PONV than patients in the sham group; c) a greater reduction in rescue
40 drug therapy post-operatively than patients in the sham group in the first 36 hours post-
41 operation; and d) a greater quality of recovery at morning of day 4 than patients in the sham
42 group. 2) costs associated with treatment for PONV will be significantly lower in the group
43 using PC6 acupoint stimulation than in the sham group. Previous PC 6 acupoint stimulation
44 studies for PONV have mostly used durations of 6, 12 and 24 hours. The duration of acupoint
45 stimulation chosen for this study is 36 hours, as this will take account of post-cardiac surgery
46 patients who may be intubated and ventilated for 2-6 hours after surgery. The 36 hours
47 instead of 24 would ensure that we have a full 24-hour period with patient awake/extubated
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3 and mobilising. A parallel aim is to use an integrated knowledge translation approach to
4 develop a comprehensive understanding of factors that impact on successful implementation
5 of the intervention. The focus will be on the delivery of the intervention as intended,
6 processes of implementation and change, and responses of patients and health care
7 professionals to the intervention. Patients' satisfaction with their PONV care will be
8 measured and clinical staff interviewed about the clinical use, feasibility, acceptability and
9 challenges of using acupressure wristbands for PONV in practice. These data can then be
10 used to assist implementation should the intervention be shown to be effective. If effective,
11 this intervention has the potential to significantly improve the quality of care for hundreds of
12 thousands of patients worldwide, each year through a cost effective and safe intervention for
13 the prevention and management of PONV.
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22 **METHODS AND ANALYSIS**

23 **Study Design**

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26 The study will use a two-group, parallel, superiority, participant and clinician-masked RCT
27 design. Participants will be post-operative adult cardiac surgery patients. The intervention
28 will be PC6 acupoint stimulation. The main outcome measure will be PONV, with secondary
29 outcome assessment of severe nausea, difference in effect early and late-onset post-
30 operatively, need for rescue antiemetic therapy, and quality of recovery by 4th postoperative
31 day. An economic sub-study will compare costs associated with PC6 stimulation device,
32 costs of antiemetic medication, and hospital length of stay in the two groups. Also
33 incorporated will be a parallel integrated knowledge translation approach, to develop
34 understanding of intervention fidelity and factors that support, or impede, the use of PC6
35 acupoint stimulation. A superiority design has been chosen as this is consistent with the
36 literature to date: the CSR of 40 trials found that all except one trial indicated less nausea in
37 the group receiving PC6 stimulation compared to control. In addition there is no biologically
38 plausible reason that PC6 acupressure would increase post-operative nausea and vomiting.
39 Use of a sham will eliminate the influence of treatment effects other than those caused by the
40 treatment itself (i.e., knowledge of receiving the treatment and expectations of what it might
41 do etc.) by blinding participants, clinicians and also members of the research team, as to who
42 is receiving the acupressure and who is not. The CONSORT guidelines²², with its official
43 extension of Standards for Reporting Interventions in Clinical Trials of Acupuncture)²³ for
44 reporting trials have been used to guide study design.
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Setting & population

Trial participants will be sampled from an adult post cardiac surgery population. This population reflects a relatively homogenous group and is, thus, likely to detect an effect if one exists in the population. Two hospital sites will be accessed where on average 22 patients undergo cardiac operative procedures consistent with the inclusion criteria each week. Only patients undergoing primary surgical procedures will be included as patients undergoing second or subsequent cardiac surgery are more likely to have variable pre-, intra- and post-operative course and care, and the standardized protocol outlined below in concurrent treatment may not be applicable. It is anticipated that recruitment will take eighteen months.

Sample size

The primary outcome of nausea was used to power this study. Only one previous study has specifically examined the effect of acupressure on nausea with a cardiac post-operative group, finding that the proportion of participants with observed nausea in the control group was 35%¹⁰, which is consistent with our unpublished preliminary data. Based on the CSR, to detect a 30% reduction in relative risk of nausea¹⁹ with 90% power, a total of 712 participants ($n=356$ per group) at an alpha of .05 (for a superiority test of 2 independent proportions)²⁴ is needed.

Recruitment

A Registered Research Nurse (RRN) will identify elective patients from operation lists and approach each patient (at pre-admission clinic or on ward) to introduce the study. Those interested will then be formally screened and those eligible will be provided with an information sheet, further explanation of the study and clarification of any questions with the contact details of the study manager provided as a contact for further information. Written informed consent will be obtained. Patients, who meet all of the inclusion criteria, and none of the exclusion criteria, will be eligible. The inclusion criteria are: elective or urgent primary cardiac surgery (Coronary Artery Bypass Graft (CABG); valve and double valve replacement; CABG plus single valve replacement); able to understand, speak, read and write English or have a suitable interpreter available; aged 18 years or over, and able to give informed consent. Exclusion Criteria are: impaired renal function – creatinine level >200 or eGFR <40; patients receiving: antiemetic medication within 24-hours prior to surgery, or histamine H2-receptor antagonist within 24-hours prior to surgery; skin damage (e.g. burn

scars) over PC6 area; wrist circumference >21cm; and any previous experience of acupressure for nausea and/or vomiting, for example, related to morning sickness, chemotherapy, or travel/motion sickness.

Randomisation & allocation concealment

Computer-generated random assignment will occur at the point of study entry, and each patient will be allocated to a numbered trial group. Randomisation will involve a 1:1 ratio; stratified assignment by risk of nausea (Apfel Score that can be stratified into low [score 0 or 1], moderate [score 2], extremely high [score 3 or 4]²⁵ at study site, with random variation in block sizes of 4-10. RRN will obtain a participant code number corresponding to a study pack to which each participant will be randomly allocated using a web-based independent automated service at the university Clinical Trials Randomisation Service, which is overseen by a biostatistician, and record the study group code in the patient's medical record and on study forms. This process ensures adequate concealment, limiting likelihood of selection bias²⁶.

Processes to ensure blinding

RRN will obtain the participant code number through the randomisation process outlined below and, thus, is blinded to group allocation and will collect outcome data on day 4 post-operatively and document final nausea scale score at 36 hours. Another RRN (RRN2, trained and assessed to ensure correct PC6 positioning) will apply the intervention/placebo on arrival in the intensive care unit (ICU) following surgery. All clinicians providing care will be blinded to group allocation. ICU and ward registered nurses will collect nausea scores and incidence of vomiting. All patients will be blinded to group allocation, as an occlusive bandage will be applied over the wristband. The acupressure wristband will be identical in appearance and position for both intervention and placebo groups. All members of the research team involved in participant recruitment, randomisation and data collection, will be blinded to group allocation.

Intervention

Participants in the acupressure group will have a Seaband[®] wristband applied on arrival to ICU on both wrists (bilateral application is recommended) by RRN2 ensuring that the bead stimulates the PC6 acupoint and the bands are covered with a light opaque bandage. The wristbands will be removed at 36 hours after admission to ICU just after the final outcome

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3 measurement. This same procedure will be applied to participants in the placebo (sham)
4 wristband group, with the point of difference being that they will have a sham (without bead)
5 Seaband® wristband applied to their wrists. All members of the research team will receive
6 training and a standardised procedure manual (detailing protocol, plans for dealing with
7 intervention fidelity issues, and monitoring the delivery and receipt of the intervention²⁷), to
8 ensure protocol consistency. All patients will receive identical information and instructions
9 regarding the study, relayed by RRN and also in an information sheet provided at enrolment.
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15 16 **Concurrent treatment**

17 Patients in both groups will have a standardised anaesthetic protocol for pre-medication,
18 anaesthesia and post-operative pain and nausea management. In cardiac anaesthesia, it is very
19 unusual to give PONV prophylaxis either in the operating theatre or in the ICU. The
20 treatment of PONV in this population is expectant: that is, patients are treated for PONV only
21 when they display signs/symptoms of nausea or vomiting. This is consistent with standards of
22 care, both in Australia and internationally, given that the variable time of waking and
23 ventilator weaning of patients is often unpredictable at the time of surgical case completion in
24 theatre. Premedication will be standardized to Temazepam 10-30mg/Diazepam 5-10mg 1
25 hour prior to surgery; anaesthesia induced with Midazolam 0.03-0.1mg/kg, Fentanyl 5-
26 15g/kg, Propofol 0.25-1.25mg/kg and Pancuronium 0.1mg/kg/Rocuronium 0.75-1.2mg/kg.
27 Anaesthesia will be maintained with: Propofol infusion 2-5mg/kg/hr, Sevoflurane
28 administered pre-cardiopulmonary bypass for ischemic preconditioning at discretion of
29 attending anaesthetist, air/O₂ mix at discretion of attending anaesthetist. Transfer to ICU,
30 patients will be maintained on propofol infusion and fentanyl infusion at 5-25ug/hr with no
31 prophylactic anti-emetics administered (current usual care). Participants will be sedated with
32 the above mentioned propofol and fentanyl infusions until determined appropriate to
33 extubation of the artificial airway, and then maintained on fentanyl via patient controlled
34 analgesia (background of 0-25ug/hr; bolus of 5-25ug every 5 minutes) for 48 hours or until
35 cardiac drain are removed postoperatively. A standardised rescue anti-emetic protocol
36 involving the use of a grading system will be used (see Table 1). For any patient requiring
37 naso-gastric treatment post-operatively this will be recorded (given this prevents gastric
38 distension and vomiting) and gastric volume recorded for 36 hours.
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Outcome measures

All data will be collected using structured case report forms by staff blinded to treatment groups. This method of interviewer-led self-report data collection will minimise missing data. Nausea will be assessed at six time points: 6 hours from arrival to the ICU; 12 hours post arrival; then 4 hourly up to 24 hours; and then at 36 hours on a 10-point scale (Table 1) and aggregated into 'all', 'mild', 'moderate-severe' and 'severe' nausea. All episodes of retching or vomiting in the 36-hour time period will be recorded. Rescue antiemetic will be given and recorded for patients who experience mild-severe nausea or an episode of vomiting within the 36-hour study period (Table 1). Reasons for non-adherence to intervention protocol will be recorded. Time to first rescue treatment will be recorded. Reasons for attrition will be recorded. Participants will self-assess their quality of recovery on the morning of the 4th post-operative day using a 15-item questionnaire – the QOR-15²⁸. Any adverse event (AE) from the wristbands will be assessed and recorded at each assessment time-point. Post-operative AEs will also be recorded. Healthcare resource use related to the management of nausea and vomiting will be assessed and costed. This will include: band use; frequency, dose, route and duration of rescue anti-emetics; length of stay in ICU and length of stay in hospital post ICU; and costs associated with any adverse effects of the PC6 stimulation device or the anti-emetics. Demographic information will be collected at pre-operative/baseline. This will include participant's age, gender, and Body Mass Index. Probability of PONV will be predicted based on patient-related factors using the Apfel risk score²⁹. At PC6 stimulation device removal, the RRN will ask the patient (if able) about their satisfaction with their PONV care on a 10-point scale ('0=completely dissatisfied', '10=completely satisfied'). The Study Manager will oversee data quality including undertaking periodic audits and generation of data queries for all missing or improbable values. Clinical staff will be invited to participate in either group or individual semi-structured interviews about the clinical use, feasibility, acceptability, and challenges in using the acupressure wristbands for PONV in clinical practice, and their trial involvement. The interview schedule will be informed by the Theoretical Domains Framework³⁰, which will enhance the understanding of any intervention fidelity issues identified, the perceived risks, benefits and barriers to the use of acupressure bands so that we can develop strategies to facilitate practice change at the study conclusion.

Data analysis

Data from the case report forms will be entered and analysed under the direction of a PhD qualified statistical epidemiologist blinded to allocation. Prior to analysis, all missing data and improbable values will be checked against source data. The primary end point will be occurrence of nausea and/or vomiting within 36 hours of the end of surgery. Secondary end points will be nausea and vomiting separately, occurrence of early (≤ 16 hours) and late (>16 hours including repeat events) PONV, QOR score, need for rescue antiemetic therapy and band-related as well as post-operative AEs. We will use Chi^2 test (or Fishers Exact test) to compare frequency of nausea and vomiting (all types, nausea, vomiting, early PONV, late PONV, moderate-severe nausea, severe nausea and need for rescue antiemetics) in the two treatment groups. QOR and number of rescue antiemetics will be compared using Wilcoxon two-sample test. Cumulative incidence of rescue antiemetic treatment over time will be plotted using the Kaplan-Meier method and compared across the two treatment groups. We will perform stepwise multiple logistic regression analyses for early and late postoperative nausea and vomiting to identify predictors of these events. The results will be presented as adjusted odds ratios with 95% confidence intervals; we will adjust for all variables that could be independently explanatory at a $P \leq 0.1$ for respective end points. Analyses will be performed according to the intention to treat principle, although a per protocol analysis will be undertaken as a secondary analysis to consider the likely effect on outcome measure of randomised patient attrition prior to and during treatment, missing data, and protocol violations. Patient survey data will be analysed to assess satisfaction with PONV care. The Theoretical Domains Framework³⁰ will inform the analysis of the clinical staff interviews. Economic evaluation will incorporate health-related costs and assess the value for money provided by acupuncture by comparing the incremental costs and effects of the intervention. Bootstrapping will be employed to compare the mean difference in the costs between groups, and to estimate a confidence interval around the mean³¹. A comparative cost-effectiveness analysis will be undertaken based on incidence of nausea or vomiting and the QOR as outcome measures. Uncertainty around incremental cost-effectiveness ratios will be tested using both one-way sensitivity analysis and non-parametric bootstrapping methods³¹.

ETHICS AND DISSEMINATION

Ethics approval will be sought from appropriate Human Research Ethics Committee/s (HREC) before commencement of study. Participants will be supplied with detailed

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3 information regarding the study including data access, storage and confidentiality.
4 Participants will be required to provide informed written consent and have the right of
5 withdrawal from the study at any time. Participation burden is low, and declining to
6 participate will have no negative effect on the patient's continued treatment at the hospitals.
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8 There are no anticipated risks to participants. Lee and Fan¹⁹ identified that two trials in their
9 CSR found some participants reported that wristbands were uncomfortable, and produced
10 minor side effects. Any serious AEs will be assessed at all time-points and reported to the
11 patient's treating doctor to determine whether further diagnostic testing or treatment is
12 warranted. All AEs will be reported in study results. Although serious AEs will be expected
13 given the nature of the surgery, it is highly unlikely that these will be related to the
14 intervention, although these will be reported to the HRECs expeditiously, with appropriate
15 notification of the Therapeutic Goods Administration if required. Serious AEs will be
16 monitored and reported to the HREC. Approvals for any other variations to the protocol will
17 be sought through HREC. The acupressure bands to be used "Seaband[®]" is a registered
18 medical device with Australian Register of Therapeutic Goods (ARTG 109529
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29 **Data and safety monitoring plan**

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32 A DSMC of two biostatisticians and two medically qualified researchers (independent of
33 study) will review nausea and vomiting outcomes after $n=350$. The DSMC will check and
34 advise whether the study needs to be stopped early (for futility) or because the intervention
35 effect is so great that further data collection is unnecessary (with caution given the
36 controversies over stopping early for benefit systematically overestimating treatment effects).
37 Stopping for futility will be considered if the conditional power (the chance of detecting a
38 statistically significant result at the end of the trial given the interim results) is very low
39 ($\leq 15\%$)³². We will utilize a simple predefined statistical stopping rule for benefit, the Peto-
40 Haybittle boundary, which would indicate stopping at a P value for treatment difference
41 (nausea and/or vomiting) at interim analysis of <0.001 .³³ However, we acknowledge that this
42 formal rule is insufficient to prevent bias consequent on stopping early³⁴ and we will
43 additionally require a large number of outcome events and considerations of clinical
44 significance over and above the statistical boundary before early stopping for benefit is
45 contemplated. If a major post-operative complication (e.g. haemorrhage requiring return to
46 theatre, difficulty weaning from artificial ventilation or cerebrovascular event interfering with
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3 communication) is experienced, as much data as possible will be recorded to maximise the
4 dataset available for intention to treat analysis³⁵
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8 **Reporting & dissemination**

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10 It is anticipated that results will be well received by academic, scientific and broader
11 communities. Dissemination will include conference presentations at national and
12 international scientific meetings and publications in peer-reviewed journals with a high
13 readership in anaesthetics and cardiac surgery. Study participants will receive a one-page lay-
14 summary of results. Use of an integrated knowledge translation approach, purposely
15 including patients and practitioners, will assist with dissemination of study findings and those
16 involved in the study will be encouraged to participate in wider dissemination of study
17 findings.
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3 **Authors' contributions:** All authors made a significant contribution to the conception and
4 design of the study protocol. The protocol was written by MC and was critically reviewed by
5 CR, IR, SK, AM, TC, SD, AS. All authors gave approval for the publication.
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10 public, commercial or not-for-profit sectors.
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13 **Competing interests statement:** There are no competing interests to report.
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49 **Table 1: Rescue anti-emetic protocol**

Symptoms	Nausea score	Treatment
None	0	No treatment
Mild	1-3	Rescue anti-emetic (Metoclopramide 10-20mg)
Moderate	4 - 6	Rescue anti-emetic (Metoclopramide 10-20mg + Ondansetron 4-8mg)

Severe	7-10	Rescue anti-emetic (Metoclopramide 10-20mg + Ondansetron 4-8mg). If no response in 30 mins: Dexamethasone 8mg, then Droperidol 0.625mg. Change of PCA narcotic if no effect within 30 mins.
Retching/vomiting	N/A	As per protocol for severe nausea

For peer review only

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7 **PC6 Acupoint Stimulation for the Prevention of Post-Cardiac Surgery Nausea and**
8 **Vomiting: a protocol for a two-group, parallel, superiority randomised clinical trial.**
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Comment [s1]: Affiliation has changed since submission

ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) are frequent but unwanted complications for patients following anaesthesia and cardiac surgery, affecting at least a third of patients, despite pharmacologic treatment. The primary aim of the proposed research is to test the efficacy of PC6 acupoint stimulation versus placebo for reducing PONV in cardiac surgery patients. In conjunction with this we aim to develop an understanding of intervention fidelity and factors that support, or impede, the use of PC6 acupoint stimulation, a knowledge translation approach.

Methods and analysis: 712 post-cardiac surgery participants will be recruited to take part in a two-group, parallel, superiority, randomised controlled trial. Participants will be randomised to receive a wrist band on each wrist providing acupressure to PC 6 using acupoint stimulation or a placebo. Randomisation will be computer generated, use randomly varied block sizes, and be concealed prior to the enrolment of each patient. The wristbands will remain in place for 36 hours. PONV will be evaluated by the assessment of both nausea and vomiting, use of rescue anti-emetics, quality of recovery, and cost. Patient satisfaction with PONV care will be measured and clinical staff interviewed about the clinical use, feasibility, acceptability and challenges of using acupressure wristbands for PONV.

Ethics and dissemination: Ethics approval will be sought from appropriate Human Research Ethics Committee/s before commencement of study. A systematic review of the use of wrist acupressure for PC6 acupoint stimulation reported minor side effects only. Study progress will be reviewed by a Data Safety Monitoring Committee (DSMC) for nausea and vomiting outcomes at $n=350$. Dissemination of results will include conference presentations at national and international scientific meetings and publications in peer-reviewed journals. Study participants will receive a one-page lay-summary of results.

Trial registration number: Australian New Zealand Clinical Trials Registry - ACTRN12614000589684

Article Summary**Article Focus**

A protocol for a clinical trial testing PC6 acupoint stimulation as an alternative approach to the prevention of post-operative nausea and vomiting in patients following cardiac surgery.

Key Message

Evidence suggests that PC6 acupoint stimulation can prevent post-operative nausea and vomiting. A large study is required to support this evidence and in particular in relation to those undergoing cardiac surgery.

Strengths and limitations of this study

This protocol outlines the first large study to test the efficacy of PC acupoint stimulation on post-operative nausea and vomiting. A parallel aim of the study is to use an integrated knowledge translation approach to develop a comprehensive understanding of factors that impact on successful implementation of the intervention.

INTRODUCTION

Postoperative nausea and vomiting (PONV) are common unwanted complications for patients following anaesthesia/cardiac surgery, affecting at least 1 in 3 patients, despite pharmacologic prophylaxis and/or treatment. A Cochrane Systematic Review (CSR) specific to medicines for preventing PONV, concluded that PONV affects around 80 of every 100 individuals undergoing surgery, and that if all 100 were given a drug to prevent PONV, only around 28 would benefit¹. The burden of caring for patients post cardiac surgery is immense, with the Australian Institute of Health and Welfare (AIHW)² annual report indicating that in Australia alone nearly 179,000 procedures involving the cardiovascular system were performed between 2011-12. Cardiovascular disease (CVD) remains the most expensive diagnostic group to treat in Australia, costing about \$7.9 billion in 2008–09, with over half of this spent on patients while admitted to hospital³. Similarly, the significant cost of CVD to the United Kingdom health care system in 2009 was reported to be around £8.6 billion with 50% of this attributed to hospital care⁴.

As part of their treatment and recovery, cardiac surgery patients experience varying rates of PONV. Studies in the 1990s found rates of PONV in cardiac surgery patients of 22%⁵, 47%⁶ and 50%⁷. More recent studies reported rates of: 39%-42% in a North American RCT⁸; 26%-27% in a systematic review of 10 RCTs⁹; and 35% in a Canadian study¹⁰. Patients report that they have a strong preference for avoiding PONV¹¹ and, of 10 negative outcomes of surgery, rank vomiting as the most undesirable outcome and nausea as the fourth most undesirable¹². Patient dissatisfaction with anaesthetic care is strongly related to PONV¹³. PONV can delay transfer from the recovery unit by up to 20 minutes¹², and vomiting can place tension on sutures and wounds, produce imbalances in body electrolytes, and cause bleeding¹². Acupressure is a therapeutic intervention endorsed by the World Health Organisation (WHO)¹⁴ and an alternative approach thought to prevent nausea and vomiting through an alteration in endorphins and serotonin levels.

Efficacy of acupressure for PONV

Acupressure as a traditional Chinese medicine has been practised for centuries. The concept is based on life energy (Qi) flowing through channels known as meridians through the body¹⁵. It is argued that acupressure restores equilibrium to disruptions affecting the body's homeostasis by stimulating specific points (acupoints) that connect the meridians to organs¹⁵.

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7 Although the mechanism for the action of acupressure has not been scientifically investigated
8 fully, it is thought that it may prevent nausea and vomiting through an alteration in
9 endorphins and serotonin levels¹⁶. PC6 point stimulation for treating nausea and vomiting
10 was reported in the early 1990s¹⁷. The WHO (Western Pacific Regional Office) reached
11 consensus on acupuncture point locations and published guidelines in 2008¹⁸. The PC6
12 acupoint is the meridian point in the pericardium channel, and is located on the inner forearm
13 between the extensor carpi radialis and palmaris longus tendons, one sixth of the distance
14 from PC7 on the medial wrist crease to PC3 in the cubital fossa¹⁸. Measuring the distance
15 between the palmar wrist crease and inner forearm with a tape measure, and placing the bead
16 on the wristband between the 2 tendons a sixth of the distance measured, is quick, acceptable
17 and feasible in the clinical environment. This method is much more accurate than the
18 previously used procedure of using the three middle fingers on the inside of the patient's
19 wrist to measure distance. Although the PC6 acupoint can be stimulated with a variety of
20 methods (acu-stimulation device, acupressure, acupuncture, capsicum plaster), the important
21 concept is stimulation of the *correct* acupoint¹⁹. A meta-analysis in a recent Cochrane
22 Systematic Review (CSR) by Lee and Fan (2009) of 40 trials¹⁹, totalling 4,858 participants
23 (all surgical patients without age limits), reports a clear positive effect of PC6 acupoint
24 stimulation on: nausea (RR 0.71, 95% CI 0.61 - 0.83); vomiting (RR 0.70, 95% CI 0.59 -
25 0.83); and need for rescue antiemetics (RR 0.69, 95% CI 0.57 - 0.83). [Given the extensive
26 use of PC 6 acupoint in reported research studies in relation to PONV in the literature and its
27 ease of use in clinical practice, this acupoint has been chosen for this research.](#)
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38 Although the Lee and Fan¹⁹ meta-analysis identified a clear positive effect of PC6 acupoint
39 stimulation, the analysed studies were conducted in various clinical settings and with
40 different populations, suggesting that, 'on average', the intervention is known to be effective.
41 It is thought that this intervention is not used in clinical practice despite the positive CSR and
42 the reasons for this are unknown but perhaps related to the following factors. The CSR meta-
43 analysis incorporated only one study undertaken in a cardiac population ($n=152$), and
44 included various methods of PC6 acupoint stimulation versus sham/drug therapy for
45 prevention of PONV. The vast majority of studies had small sample sizes (range 36–250),
46 with only one with a reasonable sample size $n=410$ (sample size calculated on the CSR meta-
47 analysis outlined below indicates a sample of >700 is required); quality of the studies is
48 highly varied, with concerns mostly regarding allocation sequence generation and allocation
49 concealment, which this proposed study addresses. As such, it is argued that a) a large
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7 rigorous RCT is needed to provide definitive evidence to inform clinicians, and b) the direct
8 application of this to cardiac population needs further consideration and investigation. There
9 is also the added significant value in the current planned study of incorporating secondary
10 hypotheses around dose response (dose varied considerably across studies in the CSR) and
11 quality of recovery (rarely addressed in CSR studies) to yield new knowledge and draw
12 conclusions for post-operative management and patient care. The economic evaluation
13 including the side-effects associated with drugs used to treat PONV (e.g. for two common
14 antiemetics: 1. Metoclopramide's side effects include sedation and dystonic reactions and 2.
15 Ondansetron's side effects include headache, dizziness and possible QT interval
16 prolongation) will also provide guidance on the value for money offered by this intervention.
17 Further, despite the CSR, use of acupressure for PONV is not widely practiced, and methods
18 will be used in this study to develop a comprehensive understanding of factors relevant to the
19 successful implementation of acupressure for PONV, a strategy that is recommended when
20 there is a degree of uncertainty about an intervention²⁰. These data will help us to understand
21 factors which might impede implementation, and allow for targeted implementation strategies
22 to be developed, should the study results demonstrate a positive impact²¹.
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31 This two-group, parallel, superiority, blinded, randomised controlled trial (RCT) will test the
32 efficacy of PC6 acupoint stimulation versus placebo for reducing PONV in cardiac surgery
33 patients. Primarily this study aims to investigate whether patients in the PC6 acupoint
34 stimulation group will experience significantly less nausea and vomiting in the first 36 hours
35 following admission to ICU post cardiac surgery, than patients in the sham group. It also
36 aims to investigate whether 1) Patients in the PC6 acupoint stimulation group will
37 experience: a) significantly less severe nausea post-operatively than patients in the sham
38 group in the first 36 hours post-operatively; b) significantly less early- (≤ 16 hours) and late-
39 onset (>16 hours) PONV than patients in the sham group; c) a greater reduction in rescue
40 drug therapy post-operatively than patients in the sham group in the first 36 hours post-
41 operation; and d) a greater quality of recovery at morning of day 4 than patients in the sham
42 group. 2) costs associated with treatment for PONV will be significantly lower in the group
43 using PC6 acupoint stimulation than in the sham group. [Previous PC 6 acupoint stimulation
44 studies for PONV have mostly used durations of 6, 12 and 24 hours. The duration of acupoint
45 stimulation chosen for this study is 36 hours, as this will take account of post-cardiac surgery
46 patients who may be intubated and ventilated for 2-6 hours after surgery. The 36 hours
47 instead of 24 would ensure that we have a full 24-hour period with patient awake/extubated](#)
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7 | [and mobilising](#). A parallel aim is to use an integrated knowledge translation approach to
8 develop a comprehensive understanding of factors that impact on successful implementation
9 of the intervention. The focus will be on the delivery of the intervention as intended,
10 processes of implementation and change, and responses of patients and health care
11 professionals to the intervention. Patients' satisfaction with their PONV care will be
12 measured and clinical staff interviewed about the clinical use, feasibility, acceptability and
13 challenges of using acupressure wristbands for PONV in practice. These data can then be
14 used to assist implementation should the intervention be shown to be effective. If effective,
15 this intervention has the potential to significantly improve the quality of care for hundreds of
16 thousands of patients worldwide, each year through a cost effective and safe intervention for
17 the prevention and management of PONV.
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24 **METHODS AND ANALYSIS**

25 **Study Design**

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27 The study will use a two-group, parallel, superiority, participant and clinician-masked RCT
28 design. Participants will be post-operative adult cardiac surgery patients. The intervention
29 will be PC6 acupoint stimulation. The main outcome measure will be PONV, with secondary
30 outcome assessment of severe nausea, difference in effect early and late-onset post-
31 operatively, need for rescue antiemetic therapy, and quality of recovery by 4th postoperative
32 day. An economic sub-study will compare costs associated with PC6 stimulation device,
33 costs of antiemetic medication, and hospital length of stay in the two groups. Also
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35 | [incorporated](#) will be a parallel integrated knowledge translation approach, to develop
36 understanding of intervention fidelity and factors that support, or impede, the use of PC6
37 acupoint stimulation. A superiority design has been chosen as this is consistent with the
38 literature to date: the CSR of 40 trials found that all except one trial indicated less nausea in
39 the group receiving PC6 stimulation compared to control. In addition there is no biologically
40 plausible reason that PC6 acupressure would increase post-operative nausea and vomiting.
41 Use of a sham will eliminate the influence of treatment effects other than those caused by the
42 treatment itself (i.e., knowledge of receiving the treatment and expectations of what it might
43 do etc.) by blinding participants, clinicians and also members of the research team, as to who
44 is receiving the acupressure and who is not. The CONSORT guidelines²², with its official
45 extension of Standards for Reporting Interventions in Clinical Trials of Acupuncture)²³ [for](#)
46 [reporting trials](#) have been used to guide study design.
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Setting & population

Trial participants will be sampled from an adult post cardiac surgery population. This population reflects a relatively homogenous group and is, thus, likely to detect an effect if one exists in the population. Two hospital sites will be accessed where on average 22 patients undergo cardiac operative procedures consistent with the inclusion criteria each week. Only patients undergoing primary surgical procedures will be included as patients undergoing second or subsequent cardiac surgery are more likely to have variable pre-, intra- and post-operative course and care, and the standardized protocol outlined below in concurrent treatment may not be applicable. It is anticipated that recruitment will take eighteen months.

Sample size

The primary outcome of nausea was used to power this study. Only one previous study has specifically examined the effect of acupressure on nausea with a cardiac post-operative group, finding that the proportion of participants with observed nausea in the control group was 35%¹⁰, which is consistent with our unpublished preliminary data. Based on the CSR, to detect a 30% reduction in relative risk of nausea¹⁹ with 90% power, a total of 712 participants ($n=356$ per group) at an alpha of .05 (for a superiority test of 2 independent proportions)²⁴ is needed.

Recruitment

A Registered Research Nurse (RRN) will identify elective patients from operation lists and approach each patient (at pre-admission clinic or on ward) to introduce the study. Those interested will then be formally screened and those eligible will be provided with an information sheet, further explanation of the study and clarification of any questions with the contact details of the study manager provided as a contact for further information. Written informed consent will be obtained. Patients who meet all of the inclusion criteria, and none of the exclusion criteria, will be eligible. The inclusion criteria are: elective or urgent primary cardiac surgery (Coronary Artery Bypass Graft (CABG); valve and double valve replacement; CABG plus single valve replacement); able to understand, speak, read and write English or have a suitable interpreter available; aged 18 years or over, and able to give informed consent. Exclusion Criteria are: impaired renal function – creatinine level >200 or eGFR <40; patients receiving: antiemetic medication within 24-hours prior to surgery, or histamine H2-receptor antagonist within 24-hours prior to surgery; skin damage (e.g. burn

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7 scars) over PC6 area; wrist circumference >21cm; and any previous experience of
8 acupressure for nausea and/or vomiting, for example, related to morning sickness,
9 chemotherapy, or travel/motion sickness.
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11 12 **Randomisation & allocation concealment**

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14 Computer-generated random assignment will occur at the point of study entry, and each
15 patient will be allocated to a numbered trial group. Randomisation will involve a 1:1 ratio;
16 stratified assignment by risk of nausea (Apfel Score that can be stratified into low [score 0 or
17 1], moderate [score 2], extremely high [score 3 or 4]²⁵ at study site, with random variation in
18 block sizes of 4-10. RRN will obtain a participant code number corresponding to a study pack
19 to which each participant will be randomly allocated using a web-based independent
20 automated service at the university Clinical Trials Randomisation Service, which is overseen
21 by a biostatistician, and record the study group code in the patient's medical record and on
22 study forms. This process ensures adequate concealment, limiting likelihood of selection
23 bias²⁶.
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30 **Processes to ensure blinding**

31 RRN will obtain the participant code number through the randomisation process outlined
32 below and, thus, is blinded to group allocation and will collect outcome data on day 4 post-
33 operatively and document final nausea scale score at 36 hours. Another RRN (RRN2, trained
34 and assessed to ensure correct PC6 positioning) will apply the intervention/placebo on arrival
35 in the intensive care unit (ICU) following surgery. All clinicians providing care will be
36 blinded to group allocation. ICU and ward registered nurses will collect nausea scores and
37 incidence of vomiting. All patients will be blinded to group allocation, as an occlusive
38 bandage will be applied over the wristband. The acupressure wristband will be identical in
39 appearance and position for both intervention and placebo groups. All members of the
40 research team involved in participant recruitment, randomisation and data collection, will be
41 blinded to group allocation.
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48 **Intervention**

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50 Participants in the acupressure group will have a Seaband[®] wristband applied on arrival to
51 ICU on both wrists (bilateral application is recommended) by RRN2 ensuring that the bead
52 stimulates the PC6 acupoint and the bands are covered with a light opaque bandage. The
53 wristbands will be removed at 36 hours after admission to ICU just after the final outcome
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7 measurement. This same procedure will be applied to participants in the placebo (sham)
8 wristband group, with the point of difference being that they will have a sham (without bead)
9 Seaband[®] wristband applied to their wrists. All members of the research team will receive
10 training and a standardised procedure manual (detailing protocol, plans for dealing with
11 intervention fidelity issues, and monitoring the delivery and receipt of the intervention²⁷), to
12 ensure protocol consistency. All patients will receive identical information and instructions
13 regarding the study, relayed by RRN and also in an information sheet provided at enrolment.
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17 18 **Concurrent treatment**

19 Patients in both groups will have a standardised anaesthetic protocol for pre-medication,
20 anaesthesia and post-operative pain and nausea management. In cardiac anaesthesia, it is very
21 unusual to give PONV prophylaxis either in the operating theatre or in the ICU. The
22 treatment of PONV in this population is expectant: that is, patients are treated for PONV only
23 when they display signs/symptoms of nausea or vomiting. This is consistent with standards of
24 care, both in Australia and internationally, given that the variable time of waking and
25 ventilator weaning of patients is often unpredictable at the time of surgical case completion in
26 theatre. Premedication will be standardized to Temazepam 10-30mg/Diazepam 5-10mg 1
27 hour prior to surgery; anaesthesia induced with Midazolam 0.03-0.1mg/kg, Fentanyl 5-
28 15g/kg, Propofol 0.25-1.25mg/kg and Pancuronium 0.1mg/kg/Rocuronium 0.75-1.2mg/kg.
29 Anaesthesia will be maintained with: Propofol infusion 2-5mg/kg/hr, Sevoflurane
30 administered pre-cardiopulmonary bypass for ischemic preconditioning at discretion of
31 attending anaesthetist, air/O₂ mix at discretion of attending anaesthetist. Transfer to ICU,
32 patients will be maintained on propofol infusion and fentanyl infusion at 5-25ug/hr with no
33 prophylactic anti-emetics administered (current usual care). Participants will be sedated with
34 the above mentioned propofol and fentanyl infusions until determined appropriate to
35 extubation of the artificial airway, and then maintained on fentanyl via patient controlled
36 analgesia (background of 0-25ug/hr; bolus of 5-25ug every 5 minutes) for 48 hours or until
37 cardiac drain are removed postoperatively. A standardised rescue anti-emetic protocol
38 involving the use of a grading system will be used (see Table 1). For any patient requiring
39 naso-gastric treatment post-operatively this will be recorded (given this prevents gastric
40 distension and vomiting) and gastric volume recorded for 36 hours.
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Outcome measures

All data will be collected using structured case report forms by staff blinded to treatment groups. This method of interviewer-led self-report data collection will minimise missing data. Nausea will be assessed at six time points: 6 hours from arrival to the ICU; 12 hours post arrival; then 4 hourly up to 24 hours; and then at 36 hours on a 10-point scale (Table 1) and aggregated into 'all', 'mild', 'moderate-severe' and 'severe' nausea. All episodes of retching or vomiting in the 36-hour time period will be recorded. Rescue antiemetic will be given and recorded for patients who experience mild-severe nausea or an episode of vomiting within the 36-hour study period (Table 1). [Reasons for non-adherence to intervention protocol will be recorded.](#) Time to first rescue treatment will be recorded. Reasons for attrition will be recorded. Participants will self-assess their quality of recovery on the morning of the 4th post-operative day using a 15-item questionnaire – the QOR-15²⁸. Any adverse event (AE) from the wristbands will be assessed and recorded at each assessment time-point. Post-operative AEs will also be recorded. Healthcare resource use related to the management of nausea and vomiting will be assessed and costed. This will include: band use; frequency, dose, route and duration of rescue anti-emetics; length of stay in ICU and length of stay in hospital post ICU; and costs associated with any adverse effects of the PC6 stimulation device or the anti-emetics. Demographic information will be collected at pre-operative/baseline. This will include participant's age, gender, and Body Mass Index. Probability of PONV will be predicted based on patient-related factors using the Apfel risk score²⁹. At PC6 stimulation device removal, the RRN will ask the patient (if able) about their satisfaction with their PONV care on a 10-point scale ('0=completely dissatisfied', '10=completely satisfied'). The Study Manager will oversee data quality including undertaking periodic audits and generation of data queries for all missing or improbable values. Clinical staff will be invited to participate in either group or individual semi-structured interviews about the clinical use, feasibility, acceptability, and challenges in using the acupressure wristbands for PONV in clinical practice, and their trial involvement. The interview schedule will be informed by the Theoretical Domains Framework³⁰, which will enhance the understanding of [any intervention fidelity issues identified](#), the perceived risks, benefits and barriers to the use of acupressure bands so that we can develop strategies to facilitate practice change at the study conclusion.

Data analysis

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7 Data from the case report forms will be entered and analysed under the direction of a PhD
8 qualified statistical epidemiologist [blinded to allocation](#). Prior to analysis, all missing data
9 and improbable values will be checked against source data. The primary end point will be
10 occurrence of nausea and/or vomiting within 36 hours of the end of surgery. Secondary end
11 points will be nausea and vomiting separately, occurrence of early (≤ 16 hours) and late (>16
12 hours including repeat events) PONV, QOR score, need for rescue antiemetic therapy and
13 band-related as well as post-operative AEs. We will use Chi^2 test (or Fishers Exact test) to
14 compare frequency of nausea and vomiting (all types, nausea, vomiting, early PONV, late
15 PONV, moderate-severe nausea, severe nausea and need for rescue antiemetics) in the two
16 treatment groups. QOR and number of rescue antiemetics will be compared using Wilcoxon
17 two-sample test. Cumulative incidence of rescue antiemetic treatment over time will be
18 plotted using the Kaplan-Meier method and compared across the two treatment groups. We
19 will perform stepwise multiple logistic regression analyses for early and late postoperative
20 nausea and vomiting to identify predictors of these events. The results will be presented as
21 adjusted odds ratios with 95% confidence intervals; we will adjust for all variables that could
22 be independently explanatory at a $P \leq 0.1$ for respective end points. Analyses will be
23 performed according to the intention to treat principle, although a per protocol analysis will
24 be undertaken as a secondary analysis to consider the likely effect on outcome measure of
25 randomised patient attrition prior to and during treatment, missing data, and protocol
26 violations. Patient survey data will be analysed to assess satisfaction with PONV care. The
27 Theoretical Domains Framework³⁰ will inform the analysis of the clinical staff interviews.
28 Economic evaluation will incorporate health-related costs and assess the value for money
29 provided by acupuncture by comparing the incremental costs and effects of the intervention.
30 Bootstrapping will be employed to compare the mean difference in the costs between groups,
31 and to estimate a confidence interval around the mean³¹. A comparative cost-effectiveness
32 analysis will be undertaken based on incidence of nausea or vomiting and the QOR as
33 outcome measures. Uncertainty around incremental cost-effectiveness ratios will be tested
34 using both one-way sensitivity analysis and non-parametric bootstrapping methods³¹.

47 48 ETHICS AND DISSEMINATION

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50 Ethics approval will be sought from appropriate Human Research Ethics Committee/s
51 (HREC) before commencement of study. Participants will be supplied with detailed
52 information regarding the study including data access, storage and confidentiality.
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7 Participants will be required to provide informed written consent and have the right of
8 withdrawal from the study at any time. Participation burden is low, and declining to
9 participate will have no negative effect on the patient's continued treatment at the hospitals.
10 There are no anticipated risks to participants. Lee and Fan¹⁹ identified that two trials in their
11 CSR found some participants reported that wristbands were uncomfortable, and produced
12 minor side effects. Any serious AEs will be assessed at all time-points and reported to the
13 patient's treating doctor to determine whether further diagnostic testing or treatment is
14 warranted. All AEs will be reported in study results. Although serious AEs will be expected
15 given the nature of the surgery, it is highly unlikely that these will be related to the
16 intervention, although these will be reported to the HRECs expeditiously, with appropriate
17 notification of the Therapeutic Goods Administration if required. Serious AEs will be
18 monitored and reported to the HREC. Approvals for any other variations to the protocol will
19 be sought through HREC. The acupressure bands to be used "Seaband[®]" is a registered
20 medical device with Australian Register of Therapeutic Goods (ARTG 109529)

27 28 **Data and safety monitoring plan**

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30 A DSMC of two biostatisticians and two medically qualified researchers (independent of
31 study) will review nausea and vomiting outcomes after $n=350$. The DSMC will check and
32 advise whether the study needs to be stopped early (for futility) or because the intervention
33 effect is so great that further data collection is unnecessary (with caution given the
34 controversies over stopping early for benefit systematically overestimating treatment effects).
35 Stopping for futility will be considered if the conditional power (the chance of detecting a
36 statistically significant result at the end of the trial given the interim results) is very low
37 ($\leq 15\%$)³². We will utilize a simple predefined statistical stopping rule for benefit, the Peto-
38 Haybittle boundary, which would indicate stopping at a P value for treatment difference
39 (nausea and/or vomiting) at interim analysis of < 0.001 .³³ However, we acknowledge that this
40 formal rule is insufficient to prevent bias consequent on stopping early³⁴ and we will
41 additionally require a large number of outcome events and considerations of clinical
42 significance over and above the statistical boundary before early stopping for benefit is
43 contemplated. If a major post-operative complication (e.g. haemorrhage requiring return to
44 theatre, difficulty weaning from artificial ventilation or cerebrovascular event interfering with
45 communication) is experienced, as much data as possible will be recorded to maximise the
46 dataset available for intention to treat analysis³⁵

Reporting & dissemination

It is anticipated that results will be well received by academic, scientific and broader communities. Dissemination will include conference presentations at national and international scientific meetings and publications in peer-reviewed journals with a high readership in anaesthetics and cardiac surgery. Study participants will receive a one-page lay-summary of results. Use of an integrated knowledge translation approach, purposely including patients and practitioners, will assist with dissemination of study findings and those involved in the study will be encouraged to participate in wider dissemination of study findings.

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Table 1: Rescue anti-emetic protocol

Symptoms	Nausea score	Treatment
None	0	No treatment
Mild	1-3	Rescue anti-emetic (Metoclopramide 10-20mg)
Moderate	4 - 6	Rescue anti-emetic (Metoclopramide 10-20mg + Ondansetron 4-8mg)
Severe	7-10	Rescue anti-emetic (Metoclopramide 10-20mg + Ondansetron 4-8mg). If no response in 30 mins: Dexamethasone 8mg, then Droperidol 0.625mg. Change of PCA narcotic if no effect within 30 mins.
Retching/vomiting	N/A	As per protocol for severe nausea



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <i>YES</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <i>YES</i>
	2b	All items from the World Health Organization Trial Registration Data Set <i>N/A</i>
Protocol version	3	Date and version identifier <i>YES</i>
Funding	4	Sources and types of financial, material, and other support <i>YES</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <i>YES</i>
	5b	Name and contact information for the trial sponsor <i>N/A</i>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <i>N/A</i>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) <i>YES</i>
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention <i>YES</i>
	6b	Explanation for choice of comparators <i>YES</i>
Objectives	7	Specific objectives or hypotheses <i>YES</i>
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) <i>YES</i>

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained <i>YES</i>
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) <i>YES</i>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <i>YES</i>
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) <i>N/A</i>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <i>N/A</i>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <i>YES</i>
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended <i>YES</i>
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) <i>YES</i>
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations <i>YES</i>
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size <i>YES</i>

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions <i>YES</i>
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1			
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned <i>YES</i>
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions <i>YES</i>
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how <i>YES</i>
13			
14		17b	If blinded, circumstances under which unblinding is permissible, and
15			procedure for revealing a participant's allocated intervention during
16			the trial <i>YES</i>
17			
18			

19 Methods: Data collection, management, and analysis

20			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
22	methods		trial data, including any related processes to promote data quality (eg,
23			duplicate measurements, training of assessors) and a description of
24			study instruments (eg, questionnaires, laboratory tests) along with
25			their reliability and validity, if known. Reference to where data
26			collection forms can be found, if not in the protocol <i>YES</i>
27			
28		18b	Plans to promote participant retention and complete follow-up,
29			including list of any outcome data to be collected for participants who
30			discontinue or deviate from intervention protocols <i>YES</i>
31			
32			
33	Data	19	Plans for data entry, coding, security, and storage, including any
34	management		related processes to promote data quality (eg, double data entry;
35			range checks for data values). Reference to where details of data
36			management procedures can be found, if not in the protocol <i>YES</i>
37			
38	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
39	methods		Reference to where other details of the statistical analysis plan can be
40			found, if not in the protocol <i>YES</i>
41			
42		20b	Methods for any additional analyses (eg, subgroup and adjusted
43			analyses) <i>YES</i>
44			
45		20c	Definition of analysis population relating to protocol non-adherence
46			(eg, as randomised analysis), and any statistical methods to handle
47			missing data (eg, multiple imputation) <i>YES</i>
48			
49			

50 Methods: Monitoring

51			
52	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
53			and reporting structure; statement of whether it is independent from
54			the sponsor and competing interests; and reference to where further
55			details about its charter can be found, if not in the protocol.
56			Alternatively, an explanation of why a DMC is not needed
57			
58			<i>YES</i>
59			
60			

1		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	YES
2				
3				
4				
5				
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	YES
7				
8				
9				
10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	YES
11				
12				
13				
14				

Ethics and dissemination

15				
16				
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	YES
18				
19				
20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	YES
21				
22				
23				
24				
25	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	YES
26				
27				
28		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
29				
30	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	YES
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36	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	YES
37				
38				
39	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	YES
40				
41				
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43	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
44				
45				
46	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	YES
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52		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
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54				
55		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
56				
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60				

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates <i>N/A</i>
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable <i>N/A</i>

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.