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ADding negative pRESSure to improve healing in Obese Women undergoing Caesarean Section (the DRESSING trial): Study Protocol

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RUNNING HEADER: Using negative pressure dressings following caesarean section: Trial protocol.
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ADding negative pRESSure to improve healING (the DRESSING trial): A RCT Protocol

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Author's contributions

BG, JW and WC conceived of the study. NC, LT, DE, HS and JAW contributed to the study design and will assist with implementation. All authors are grant holders. LT and NC provided methodological expertise in clinical trial design and LT is leading the primary statistical analysis. JAW provided expertise in the health economic analysis and will lead the economic evaluation. All authors contributed to refinement of the study protocol and approved the final manuscript

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Data Sharing Statement

A summary of the results will be disseminated to the study participants on request. We plan to publish the main trial outcomes in a single paper. Further publications are anticipated after exploring the data in more detail. Findings will be presented at national and international conferences from early 2020.

RUNNING HEADER: Using negative pressure dressings following caesarean section: Trial protocol.
V 2: 12 September 2015

ADding negative pRESSure to improve healing in Obese Women undergoing Caesarean Section (the DRESSING trial): Study Protocol

ABSTRACT

Introduction: Obese women are more likely to develop a surgical site infection (SSI) following caesarean section (CS) than non-obese women. Negative pressure wound therapy (NPWT) is increasingly being used to reduce SSI with limited evidence for its effectiveness.

Objectives: To determine the clinical and cost effectiveness of using NPWT in obese women having elective and semi-urgent CS.

Methods and Analysis: A multisite, superiority parallel pragmatic randomised controlled trial with an economic evaluation. Women with a Body Mass Index (BMI) of ≥ 30, booked for elective and semi-urgent CS at four Australian acute care hospitals will be targeted. A total of 2,090 women will be enrolled. A centralized randomization service will be used with participants block randomised to either NPWT or standard surgical dressings in a 1:1 ratio, stratified by hospital. The primary outcome is SSI; secondary outcomes include: type of SSI, length of stay, readmission, wound complications, and health-related quality of life. Economic outcomes include direct health care costs and cost-effectiveness, which will be evaluated using incremental cost per quality-adjusted life year gained. Data will be collected at baseline, and participants followed up on the second postoperative day and weekly from the day of surgery for four weeks. Outcome assessors will be masked to allocation. The primary statistical analysis will be based on intention-to-treat.

Ethics and Dissemination: Ethics approval has been obtained from the ethics committees of the participating hospitals and universities. The findings of the trial will be disseminated through peer-reviewed journals, national and international conference presentations.

Trial registration Number: Australian New Zealand Clinical Trials Registry, ACTRN12615000286549.

BACKGROUND AND RATIONALE

Between 187 and 281 million surgical procedures are performed around the world each year, or one for every 25 people.[1] Surgical site infections (SSIs) are defined as infections occurring up to 30 days after surgery that affect the incision, deep tissue at the operation site or involve the organs or body spaces.[2] Of concern is that SSIs occur in up to 30% of all surgical procedures, and are the third most commonly reported hospital acquired infection in many countries.[3-5] SSIs have many negative effects including increasing the risk of death, prolonging hospitalisation and increasing costs.[4]

Obesity is an independent predictor of SSI.[6,7] Obese pregnant women are twice as likely to have a caesarean section (CS) than non-obese women.[8.9] Post-operative infection is a potential complication of all surgeries including CS, however overweight and obese women are three times more likely to develop a SSI.[10] SSI extends hospital length of stay by up to six days in women undergoing obstetric and gynaecologic surgery and hospital readmission is more likely, increasing hospital costs by US$14,000 for each SSI.[11]

The use of negative pressure wound therapy in primary wounds

Negative pressure wound therapy (NPWT) is widely used, particularly in the management of wounds healing by secondary intention and for skin grafts.[12-15] However NPWT is increasingly being applied prophylactically to closed surgical wounds in high risk populations to reduce the incidence of SSI. This use of prophylactic NPWT is generally applied to wounds perceived as being at high risk of SSI e.g., CS incisions in obese women.[14,15] A recent

Cochrane review concluded that evidence for the clinical effectiveness of prophylactic NPWT in reducing SSI and wound dehiscence is inconclusive.[16]

Two further randomised controlled trials (RCTs) of NPWT have subsequently been published; both were feasibility studies.[17,18] One of these trials examined the use of NPWT in 70 patients undergoing primary hip replacement.[18] The other pilot study[17] recruited 92 women undergoing elective CS and has demonstrated that a definitive trial is feasible. Neither of these trials was powered to find an effect, so the benefits or harms of NPWT for prophylactic use remain unclear.

Thus a RCT to evaluate the clinical and cost effectiveness of NPWT in obese women undergoing CS is timely and responds to the imperative to provide much-needed evidence to guide practice in a rapidly developing and costly area of health care.

Primary Objective

To compare the effects of prophylactic NPWT and standard surgical dressings on the incidence of SSI in obese women undergoing CS.

Secondary Objectives

To compare: 1) the incidence of superficial, deep, organ/space SSI; 2) the number of dressing changes; 3) the number and type of wound complications (i.e., dehiscence, haematoma, seroma; adverse events); 4) the number of hospital readmissions; 5) hospital length of stay (days); 6) health-related quality of life; and, 7) direct healthcare costs in obese

women undergoing CS who receive prophylactic NPWT with women who receive standard surgical dressings.

Study Design

Multicentre, parallel group, pragmatic, randomised controlled superiority trial.

METHODS

Study Setting and Population

Four acute care public hospitals offering obstetric services in Queensland, Australia have agreed to participate. Across the four sites, the number of births ranges from 2,400 to 10,000 per annum. The study population will consist of 2,090 women with a BMI of ≥ 30, undergoing either elective or semi-urgent CS.

Eligibility Criteria

According to national and international guidelines, CS urgency is based on these four Categories: 1) life-threatening to woman or fetus; 2) maternal or fetal compromise, not life-threatening; 3) needing earlier CS than planned without maternal or fetal compromise; and, 4) a scheduled time acceptable to the woman and CS team.[19,20]

Inclusion criteria:

I. Women booked for elective CS surgery (Category 4);

II. Women whose condition changes to require a semi-urgent CS (Categories 2-3);

III. Recorded pre-pregnancy BMI of ≥ 30 at the first antenatal visit; and,

IV. Able to provide written informed consent.

Exclusion criteria

I. Women who require an urgent CS (Category 1) at any point;

II. Existing infection after admission to hospital in labour / immediately prior to CS;

III. Pre-pregnancy BMI > 50;

IV. Previous participation in this trial; and,

V. Unable to speak or understand English, with no interpreter available.

Interventions

While this will be a pragmatic trial, a checklist based on published current clinical practice guidelines and Queensland Maternity and Neonatal Guidelines will be used to standardize the CS surgical procedure. The participating obstetrician's clinical judgement may produce slight variation in practice in the type of wound closure (i.e., closure of facial layer as well as rectus muscle); selection of suture materials (i.e., staples vs subcuticular absorbable suture for skin); and, standard dressing preference (e.g., semi-permeable vs hydrocolloid). There is no evidence to suggest that the above-mentioned minor variations in clinical practice increase the risk of SSI.

Intervention

At the completion of skin closure, women randomly allocated to the NPWT arm of the trial will receive a PICO™ (Smith & Nephew, Hull, UK) dressing applied by the obstetrician under sterile conditions. The PICO™ product was chosen because it is lightweight and disposable, significantly cheaper than other options, and has performed well in a pilot study.[17] It comprises a small, discrete pump, powered by two AA-lithium batteries with a highly absorbent dressing that holds the wound exudate away from the skin, thus negating the need for a bulky canister. The polyurethane foam dressing will be secured over the incision by the application of an adhesive drape. A tube is embedded into the foam, and continuous negative pressure of 80 mm Hg will be applied to the dressing.

Control

Women in the control arm will have a standard dressing based on the obstetrician's usual preference, applied according to the manufacturer's recommendations after skin closure. In both groups, we anticipate the dressing will remain in situ for four to five days, unless it becomes soiled or dislodged, in which case a new dressing of the same type will be applied. Given the pragmatic nature of this trial, the number of days dressings are left in situ and the number of dressings used will be recorded. To ensure consistency, clinicians providing care to the target population at each of the sites will receive trial-specific education (NPWT and standard). The Research Assistants (RAs) who will also receive trial-specific training will be available to clinical staff during business hours to provide on-going training and support about correct use of the dressings, as well as monitoring dressing changes and completing

documentation daily to assess protocol compliance and outcomes. If our monitoring shows variation from the proposed protocol, this variation will be used as a factor in the analyses.

Outcome Measures

The *primary outcome* is the incidence of an SSI in the CS wound at any time up to 28 days after surgery.

The following *secondary outcomes* will be assessed: depth of SSI, i.e., superficial, deep or organ/body space[3]; number of dressing changes; presence and number of wound complications (i.e., dehiscence, haematoma, seroma, blisters).

Other secondary outcomes: hospital length of stay (HLOS) will be measured in days; number of hospital readmissions will be measured within four weeks from the day of surgery. The secondary outcome, health-related quality of life (QoL) will be assessed using the SF-12v2 (acute one-week recall). The SF-12v2 will be administered at baseline (i.e., recruitment at > 36/40 weeks in women having elective CS, or on the day of CS for women undergoing semi-urgent CS), and via telephone interview weekly for four consecutive weeks after surgery. Direct health care costs will be included as part of an economic evaluation.

Participant Timeline and Trial Duration

Participants will be enrolled in the study for 28 days from the day of surgery (Table 1). The project will take up to five years to complete, with recruitment and data collection expected to occur over 3.5 years. Participants will exit the trial when they: withdraw consent; have

been in the trial for 28 days post randomization; are lost to follow-up; die; or for another reason have to exit based on the clinical judgement of the attending healthcare professional.

Sample Size

The sample size was calculated based on the primary outcome, SSI. Based on other related published studies[21,22], we conservatively estimate the baseline SSI incidence in obese CS women to be 15%. Following discussions with infectious disease experts and obstetricians, we have accepted an absolute difference between groups of 5% to be clinically important. Therefore, to achieve over 90% power to test the superiority of SSI incidence between groups, 950 women per group will be required (Power Analysis & Sample Size system [PASS, Version 12], NCSS). To allow for attrition, a further 10% (n = 95) will be recruited to each group for a total sample of 2,090 (1,045/group). We anticipate recruiting approximately 600 women per year, thus recruitment should be completed in about 3.5 years.

Recruitment of Participants

We will use a staged approach to recruitment, commencing at one site to test procedures, prior to starting at the other sites. All obese women will be given an information brochure informing them of the trial during their routine antenatal visit at 36 weeks. This strategy will facilitate further discussion and assist with consent processes in labour in the event that a semi-urgent CS is required. Women booked for an elective CS will be given the opportunity to provide written consent during their antenatal visit (36/40 weeks). On the day of surgery,

women undergoing elective CS will be screened to ensure they continue to meet the inclusion criteria; those who have yet not provided written consent will be invited to do so. Women undergoing semi urgent CS will be consented on the day of surgery. Figure 1 shows anticipated participant flow through the study.

Implementation of sequence generation and allocation concealment

Women booked for elective CS will not be randomized at recruitment as the long time lag between randomization and receiving the intervention which could lead to poor adherence to allocation and loss to follow-up. All women who continue to meet the eligibility requirements will be randomized using a centralized, independent, web-based randomisation system. The RA will randomize participants in the operating room at the commencement of their CS procedure and advise the operating obstetrician and nursing staff of the allocated treatment as close to the end of the procedure as possible in order to minimise performance bias. The allocation sequence will be used to ensure allocation concealment. To reduce predictability of a random sequence, randomly varying block sizes of four, six and eight will be used.

Blinding

This pragmatic trial tests a clinical intervention that is not amenable to protection against performance bias through the blinding of participants, clinical staff or data collectors.

To minimize the potential for outcome detection bias, an expert clinician, blinded to group allocation, will assess the data to determine the primary outcome. The trial statistician and coordinating PI will also be blinded. It is unlikely that entries to the medical records and hospital databases will be falsified; thus lack of blinding for these outcomes should not affect the data integrity. Subjective outcomes (wound complications, QoL) are reported by patients or observed by RAs, who cannot be blinded because they need to check the dressings and document participants' responses.

Performance bias is a consideration when clinical staff cannot be blinded. To assess the risk of performance bias, a standardised set of questions will be used to document the number of dressing changes and/or protocol violations occurring during the hospital stay, and following discharge. We considered using dressings where tubing was attached to a suction apparatus in both groups; however participants, staff and data collectors would almost certainly be aware if suction was activated and we decided it was most important to measure 'real world' effects and conduct a pragmatic trial.

Data Collection

The RAs will collect SSI related data on day 2 (post surgery) using a structured form. In Queensland Australia, the *Centre for Healthcare Related Infection Surveillance and Prevention* provides guidelines identifying SSI signs and symptoms (i.e., redness, swelling, pain/tenderness, dehiscence, watery or purulent discharge), both during hospitalisation and after hospital discharge. Data which will be collected from a variety of sources including chart audit, direct observation, and patient self-report both during hospitalisation and after

discharge. RAs will record dressings used and antibiotic medication. Data collection will occur on weekdays (Monday-Friday). Clinical outcome data will be collected by the RAs retrospectively though telephone interviews and by accessing participants' medical records.

After hospital discharge, all women will be telephoned weekly (from their day of surgery) and outcomes assessed using a series of questions, which have been used successfully in other research in this area.[17,18,22] Seven-day recall of SSI symptoms and related resource use including health professional visits (e.g. consultations with general practitioners) was demonstrated as being feasible in a recently published pilot trial[17] and will allow accurate SF-12v2 and costing data to be collected.

RAs will collect and directly enter data while in the clinical areas, using portable computers with a purpose-built database and form-based interface (i.e., *Research Electronic Data Capture* [REDCap] database). Clinical characteristics such as age, co-morbidities, and other risk factors for SSI, such as nicotine use and length of operation, will be collected at baseline. Recruitment and data collection will be monitored by the Clinical Trial Coordinator (CTC) weekly and monthly reports will be presented to the study investigators. While there is a potential for loss to follow up, our pilot study has demonstrated retention rates of > 85%.[17] We will also use standard procedures, such as recording alternative phone and email contacts for participants and GPs, in order to assist with tracing women who may have moved house/changed internet providers etc.

Ascertainment of the Primary Outcome

SSI related data will be given to the two blinded expert clinicians, who will compare the data against criteria defined by the *Centres for Disease Control and Prevention Guideline for Prevention of SSI*[3] to decide if a SSI exists. We will use decision rules to ascertain the primary outcome. If the two blinded expert clinicians disagree on whether the patient has sustained a SSI within the 28-day postoperative period, we will use the following combinations with regards to wound infection: yes/no, yes/unsure, no/unsure:

1. If the two assessors say: 'yes/unsure' then we will say the patient has a SSI, using the data provided by the assessor who said 'yes'.
2. If the two assessors say: 'no/unsure' then we will say the patient does not have a SSI.
3. If the two assessors say: 'unsure/unsure' then we will say the patient does not have a SSI.
4. If the two assessors say: 'yes/no' then the third assessor will be consulted and will decide if there is a SSI or not. The third assessor's decision will be final. If s/he is unsure whether the patient has a SSI or not, then the patient will be considered not to have a SSI.

Training, Outcome Assessment and Treatment Fidelity

Adhering to Good Clinical Practice (GCP) recommendations[23], this multisite study will have an experienced CTC coordinating the RA training, and site and data monitoring. Trial-specific RA training to assess the patient's incision/dressing site will be provided by a tissue viability nurse. Additional training in the use of the PICO NPWT dressing product will be provided by a Smith and Nephew clinical nurse educator with specialist knowledge but with

no role in the design, analysis or reporting of the study. Involving a product specialist in the training of the RAs and clinicians who will be using the PICO product ensures that all end-users receive comprehensive and consistent information relative to the appropriate use and management of the study intervention. The RAs will undergo group and individual onsite training to ensure consistency across the four sites. Areas covered will include recruitment and data collection processes, use of the central randomisation service and database.

Consistent with GCP recommendations[23], a standardised operating procedure (SOP) manual has been developed to provide more specific detail on the protocol, plans for dealing with intervention fidelity issues, and monitoring the delivery and receipt of the intervention. Assessment of treatment fidelity will focus on type of dressing used, duration of use and number of dressing changes. While this is a pragmatic trial, obtaining information on intervention fidelity may help to explain study results. All members of the research team, including RAs, will be provided with training, a procedure manual and a DVD detailing the NPWT dressing application to ensure protocol consistency. A trial-specific training program and on-going education sessions targeting obstetricians, operating room staff, midwives and nurses will also be implemented at each site.

Withdrawal

If a participant decides to withdraw from the trial after consent is given, any existing data obtained during the trial will be retained and no further follow-up data collected. A withdrawal form will be completed and reasons for withdrawal, noted. Patients who withdraw from randomized treatment prior to randomization will be left in the study and

reported in the flow chart as 'not receiving randomized intervention'. Patients who withdraw *after* they have received the intervention (i.e., after dressing application) will also be included and reported in the flow chart as 'receiving randomized treatment'.

Data Management

All data will be managed using a centralised REDCap (Nashville, US) database repository, hosted on a dedicated secure server within the Clinical Trials Unit at Griffith University. The trial statistician will not have access to the database to ensure he remains blinded to group allocation. This database enables different levels of data access, allowing researcher control over who sees the files and what they can do with them. Data access will therefore be restricted and all data password protected. Each site RA will have a level of access to the database specific to their site and position, and will use a password protected tablet computer for data entry into REDCap.

An electronic case report form (eCRF) will be developed in collaboration with the trial statistician, coordinating PI and CTC. The eCRF will be hosted on the REDCap database within the Griffith University's Clinical Trials Unit. Source data will be entered by the site RAs, who will receive trial-specific training in the use of the eCRF. All entered data will be directly exported into the IBM Statistical Package for the Social Sciences (SPSS v22.0, NY) for analysis.

Identifiable Data

For the purposes of statistical analysis, data will be anonymized and collated by the CTC and uploaded into SPSS. Identifiable data will be entered on the eCRF to enable follow-up. These data will be de-identified when transferred to the statistical database. Participants will be identified on the statistical database using a unique code and hospital site initials.

Statistical Analysis

Primary Analyses

Prior to analysis, a rigorous process of data cleaning to check outlying figures, missing, and implausible data against source data will be undertaken. Baseline characteristics of the patients in each arm of the trial will be calculated using descriptive statistics. We will employ an intention-to-treat approach for the primary analysis with the population defined as all trial participants who completed the baseline assessment and underwent surgery and received the intervention. Adverse events will be analysed and reported on a per protocol analysis. The incidence of SSI per 1000 patients between groups will be compared. Risk ratios (RR), 95% confidence intervals (CI) and P values assuming a 5% significance level will be presented. For the primary outcome, the number needed to treat (NNT) and absolute risk reduction (ARR) will be calculated from the RR. While we do not anticipate differences between groups in terms of known or unknown prognostic factors due to randomization, adjusted analyses using multivariate logistic regression models will be used if any difference in prognostic variables is detected. Despite every effort to minimise missing values it is possible that some may occur. We will evaluate the utility of empirical imputation methods in such cases and only impute them if the explanatory power of the empirical imputation

models is robust. To assess the representativeness of the sample, we will compare the characteristics of the women in our sample with secondary data available at state and national levels.

Secondary Analyses

Secondary endpoints will be compared between groups using statistical methods appropriate to the distribution of measures. A random sample of 5% of the data will be rechecked for accuracy against source data. RRs with 95% CI will be calculated for clinical outcome data. Analysis will be performed by one of the study investigators (blinded to group allocation), trained in biostatistics.

Economic Evaluation

Direct costs to the healthcare system will be obtained from patient records/hospital cost centres (during hospital admission) and self-reported by women (weekly for 4 weeks post surgery). Resources costed during admission will include dressings and related wound management products, medications related to SSI (i.e. use of antibiotics), and resources used to manage any adverse effects of the dressing. Use of dressings, medications and health professional appointments related to wound management will be recorded at weekly intervals for four weeks following surgery. Direct costs will be assigned using standard costing sources (e.g. Medicare Benefits and Pharmaceutical Benefits Schedules; Independent Hospital Pricing Authority). The Australian refined diagnostic-related groups

(AR-DRG) will be used to indicate the costs associated with each hospital admission, adjusted for HLOS.

Cost-Effectiveness Analysis

A within-trial economic evaluation will be undertaken from the health system perspective to compare the costs and effects of NPWT, relative to the standard dressing. Parametric (e.g. ANCOVA) or non-parametric bootstrapping techniques[24] will be employed to compare the mean difference in the total costs between groups. The cost-effectiveness analysis will be undertaken based on the primary outcome measure (SSI). Additionally, a cost-utility analysis will be performed using the quality-adjusted life year (QALY) as the outcome measure. The QALY gain associated with NPWT will be estimated based on SF-12v2 utility weights.[24] Uncertainty around the incremental cost-effectiveness ratios will be tested using one-way sensitivity analysis and non-parametric bootstrapping methods.[24] The cost-effectiveness estimates will inform recommendations on adopting NPWT dressings for CS surgical wounds in clinical practice.

Safety and Data Monitoring

An Adverse Event (AE) is defined as an untoward medical occurrence experienced by the participant, whether or not considered treatment related.[25] In this trial, AE will be classified as non serious (infection, pain, maceration, odour) and serious (dehiscence, return to theatre). Both types of AE would be expected to occur equally in both treatment groups. Patients will be monitored for potential AEs, serious and non serious. All AEs reported will

be assessed to determine whether further diagnostic investigation or treatment is warranted. If an AE occurs, appropriate treatment will be given. Monitoring and reporting of suspected unexpected adverse reactions (SUSARs) will be performed by the site PI and the research team. All SUSARs will be recorded on a dedicated eCRF. Serious AEs associated with the intervention are considered unlikely, although if any are reported the relevant Human Research Ethics Committees will be notified, with appropriate notification of the Therapeutic Goods Administration (TGA) as required.

The results of the trial will be reviewed every six months by an independent Data Safety and Monitoring Committee (DSMC) including an obstetrician, a statistician, and a tissue viability nurse, all of whom will be independent of the study. The DSMC has the ability to terminate the trial prematurely if there is unacceptable harm associated with the treatment.[26] If requested by the DSMC, an interim analysis will be performed by a statistician (independent of the DSMC), blinded for the treatment allocation.

Auditing

Data monitoring of this trial will ensure compliance with GCP.[23] The participating sites will provide access to all trial-related source data/documents and reports for the purposes of monitoring, auditing and inspection by local authorities. The CTC will undertake monitoring in relation to the accuracy of the case report data collected by the site RAs. During the trial, the CTC will use source data to verify the data entered by the RAs into the eCRF.

Ethics and Dissemination

This trial has been approved by the relevant hospital ethics boards and the respective universities where the Principal Investigators are employed. This study will be conducted in accordance with the principles of the Declaration of Helsinki (1996), and the Australian National Health and Medical Research Council (NHMRC) National Statement.[27]

Dissemination strategies will include knowledge translation events involving opinion leaders and stakeholders. Findings will be presented at local hospital and other fora and a press release will be prepared. A succinct non-technical paper discussing the relevance of findings and application to practice, and recommendations for future research, will be prepared and disseminated to the colleges representing the relevant health professional groups. Abstracts will be submitted to major international meetings of infection control, nursing/midwifery and medical groups. We envisage the results will be published in high-impact generalist and specialist journals. We will bring the published study to the attention of the Cochrane Wounds Group and the authors of the relevant Cochrane review to ensure early inclusion in review updates. The results will have international application and we anticipate that they will be rapidly adopted and cited within the GCP literature.

DISCUSSION

Despite a lack of rigorous evidence to support either clinical or cost effectiveness, NPWT is increasingly being used as a prophylaxis against SSI in high-risk surgical groups such as obese women undergoing CS. To the best of our knowledge, this RCT will be the largest of its kind in this area. It has significant potential to inform practice because it assesses the clinical and cost-effectiveness of using NPWT in a patient population at high risk of incurring an SSI. A

RCT design with a sufficiently large sample is time consuming and expensive to undertake but it is nevertheless necessary to determine the efficacy of NPWT in the management of surgical incisions.

Our trial has several strengths. First, the RCT design with a robust randomisation process will ensure that any difference in outcomes between the groups is attributable to the intervention. Second, a pragmatic approach allows testing of an intervention that reflects the reality of the clinical environment relative to study population, intervention, comparator, and outcomes.[26] Third, an independent clinician, blinded to group allocation will assess these data to determine SSI status. Fourth, the embedding of an economic evaluation responds to the need to provide health care administrators and decision-makers with meaningful cost-effectiveness data. Finally, this trial is independent of industry funding, and therefore minimises potential for a conflict of interest which may bias the results.

While we envisage that the results of this trial will provide clinicians with definitive answers around the effectiveness of NPWT in this specific patient population, undertaking this 5 year trial is not without its challenges, including meeting our recruitment targets within a 3.5 year timeframe. For each hospital site, yearly recruitment targets will need to range from 120 to 200 women. To maximise both recruitment and generalisability, we will include women who are undergoing both elective and semi-urgent CS. Another major challenge is the potential for missing outcome data due to participant attrition as participants in this study will typically be busy with childcare and other commitments post-operatively. Yet in a recent pilot study, participant attrition was less than 10%[17], which is considered acceptable. Maximising participant retention over a four week follow-up period will be achieved by the

RAs meeting women face-to-face during pregnancy/labour and again post-operatively. These meetings will enable a relationship of trust to be developed and allow the RAs to resolve any queries promptly. It will also provide opportunities for the RAs to reconfirm women's contact details and remind them about the four weekly telephone follow-ups. In the event that an RA is unsuccessful in their first attempt to contact women following discharge, they will try again, perhaps using their alternative contact details. Finally, during the 3.5 year data collection period, there may be clinical innovations introduced that potentially influence the trial outcomes (i.e., 'history'). However we anticipate that both groups to be equally influenced.

Trial status

At the time of manuscript submission, ethics (HREC/15/QRBWH/126) and contract approvals have been given. The investigator team are awaiting final approvals for research governance.

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RUNNING HEADER: Using negative pressure dressings following caesarean section: Trial protocol.
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Table 1: Timeline of Trial Activities

	STUDY PERIOD								
		Allocation (Day 0)							
	Enrolment	Elective CS	Semi-urgent CS	Post-allocation					Closeout
TIMEPOINT				2 days postop	7 days postop	14 days postop	21 day postop	28 days postop	
ENROLMENT				Inpatient	Day of surgery up to 28 days				
Eligibility screen 36/40 week antenatal visit	X	X							
Day of CS	X		X						
Informed consent 36/40 week antenatal visit	X	X							
Day of CS	X		X						
Baseline data 36/40 week antenatal visit	X	X							
Day of CS		X	X						
Randomisation during CS procedure		X	X						
INTERVENTIONS (4-5 days insitu)									
NPWT dressing		**x** **x**	**x**	**x**	**x**				
Standard dressing		**x** **x**	**x**	**x**	**x**				
ASSESSMENTS									
Baseline									
Pre-pregnancy BMI / Height / Weight	X								

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Parity / gravidity	X								
Comorbidities	X								
SF-12 v2	X								
Preoperative data		X							
Surgical data form		X							
Outcome variables									
Dressing change/reason				X					
Allocated dressing				X					
Temp/HR/RR				X					
Wound complications				X					
Patient satisfaction				X					
Prophylactic ABs/type				X					
AB route				X					
AB s 24 hours postop				X					
Inpatient SSI screening				X					
Blood culture				X					
AB therapy				X					
Post-discharge									
Wound complications					X	X	X	X	
SSI symptoms					X	X	X	X	
Resource use associated with CS wound					X	X	X	X	
SF-12 v2					X	X	X	X	
SSI screen (chart audit)								X	X
Closeout hospital site visit									X

Abbreviations: AB=Antibiotic; BMI=Body mass index; CS=Caesarean section; SF12=Short Form.

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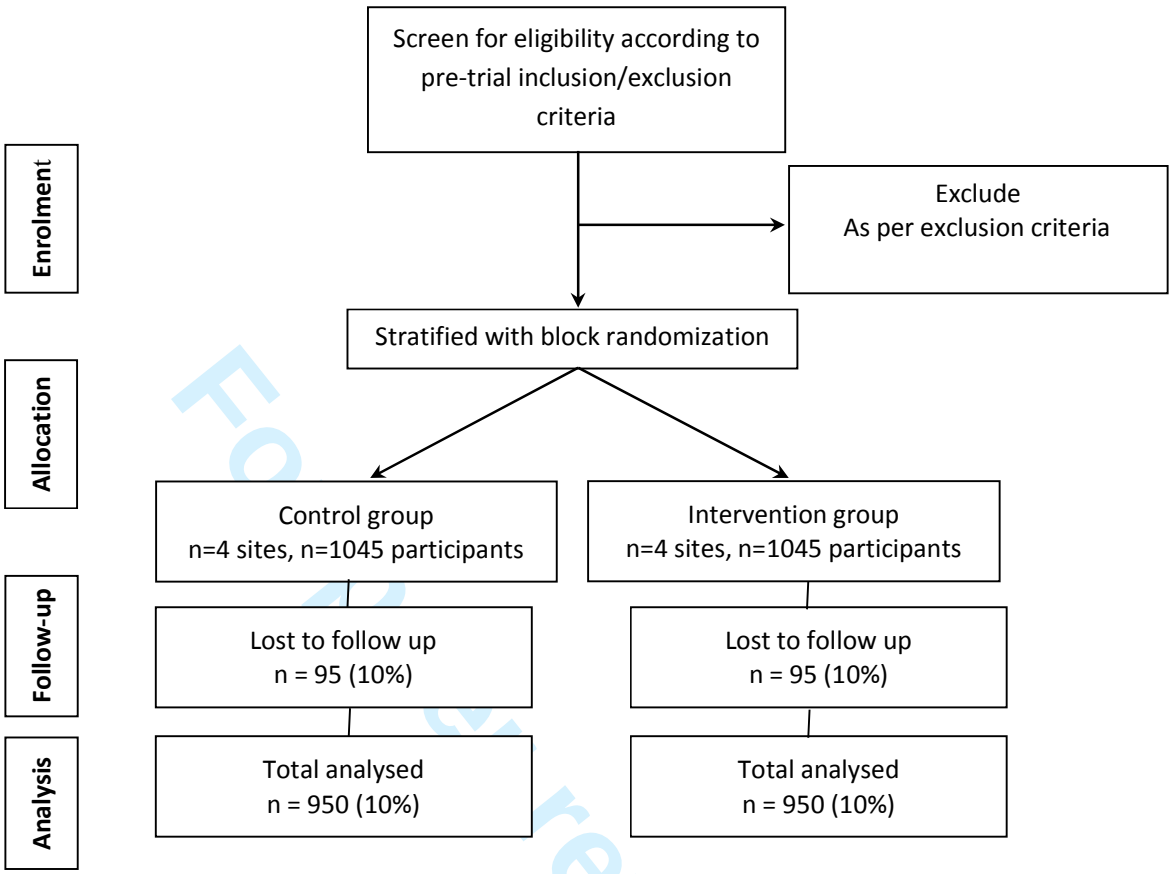

Figure 1: Anticipated participant flow through study

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

ADding negative pRESSure to improve healING (the DRESSING trial): A RCT Protocol

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym pp. 3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry pp. 4
	2b	All items from the World Health Organization Trial Registration Data Set pp. 4
Protocol version	3	Date and version identifier Running header
Funding	4	Sources and types of financial, material, and other support pp.2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors pp.1-2
	5b	Name and contact information for the trial sponsor N/A
	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 pp. 2
	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) pp. 20,21
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 pp. 5-6
	6b	Explanation for choice of comparators pp. 8-10
Objectives	7	Specific objectives or hypotheses pp. 6, 7
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) pp. 7
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 pp. 7
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) pp. 7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered pp. 8,9
	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) pp. 16, 20,21
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) pp. 15,16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial pp. 8-10

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 pp. 10,11
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) pp. 10 + figure
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 pp. 11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size pp. 11, 12
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 pp. 12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned pp. 12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions pp. 12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how pp. 12,13

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial pp. 12,13, 14,15
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol pp. 13,14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols pp. 13,14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol pp. 17,18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol pp. 18-20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) pp. 18-20
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) pp. 18-20
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed pp. 20,21

	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 pp. 20,21
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 pp. 20,21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor pp. 20,21
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval pp. 22
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) pp. 22
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) pp. 11, 13,14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable n/a
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 pp. 17,18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
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 pp. 17
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

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 pp. 22
	31b	Authorship eligibility guidelines and any intended use of professional writers pp. 2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code N/A
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Available on request
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 N/A

*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.

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ADding negative pRESSure to improve healING (the DRESSING trial): A RCT Protocol

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RUNNING HEADER: Using negative pressure dressings following caesarean section: Trial protocol.
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ADding negative pRESSure to improve healING (the DRESSING trial): A RCT Protocol

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RUNNING HEADER: Using negative pressure dressings following caesarean section: Trial protocol.
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ADding negative pRESSure to improve healing in Obese Women undergoing Caesarean Section (the DRESSING trial): Study Protocol

ABSTRACT

Introduction: Obese women are more likely to develop a surgical site infection (SSI) following caesarean section (CS) than non-obese women. Negative pressure wound therapy (NPWT) is increasingly being used to reduce SSI with limited evidence for its effectiveness.

Objectives: To determine the clinical and cost effectiveness of using NPWT in obese women having elective and semi-urgent CS.

Methods and Analysis: A multisite, superiority parallel pragmatic randomised controlled trial with an economic evaluation. Women with a Body Mass Index (BMI) of ≥ 30, booked for elective and semi-urgent CS at four Australian acute care hospitals will be targeted. A total of 2,090 women will be enrolled. A centralized randomization service will be used with participants block randomised to either NPWT or standard surgical dressings in a 1:1 ratio, stratified by hospital. The primary outcome is SSI; secondary outcomes include: type of SSI, length of stay, readmission, wound complications, and health-related quality of life. Economic outcomes include direct health care costs and cost-effectiveness, which will be evaluated using incremental cost per quality-adjusted life year gained. Data will be collected at baseline, and participants followed up on the second postoperative day and weekly from the day of surgery for four weeks. Outcome assessors will be masked to allocation. The primary statistical analysis will be based on intention-to-treat.

Ethics and Dissemination: Ethics approval has been obtained from the ethics committees of the participating hospitals and universities. The findings of the trial will be disseminated through peer-reviewed journals, national and international conference presentations.

Trial registration Number: Australian New Zealand Clinical Trials Registry, ACTRN12615000286549.

BACKGROUND AND RATIONALE

Between 187 and 281 million surgical procedures are performed around the world each year, or one for every 25 people.[1] Surgical site infections (SSIs) are defined as infections occurring up to 30 days after surgery that affect the incision, deep tissue at the operation site or involve the organs or body spaces.[2] Of concern is that SSIs occur in up to 30% of all surgical procedures, and are the third most commonly reported hospital acquired infection in many countries.[3-5] SSIs have many negative effects including increasing the risk of death, prolonging hospitalisation and increasing costs.[4]

Obesity is an independent predictor of SSI.[6,7] Obese pregnant women are twice as likely to have a caesarean section (CS) than non-obese women.[8,9] Post-operative infection is a potential complication of all surgeries including CS, however overweight and obese women are three times more likely to develop a SSI.[10] SSI extends hospital length of stay by up to six days in women undergoing obstetric and gynaecologic surgery and hospital readmission is more likely, increasing hospital costs by US$14,000 for each SSI.[11]

The use of negative pressure wound therapy in primary wounds

Negative pressure wound therapy (NPWT) is widely used, particularly in the management of wounds healing by secondary intention and for skin grafts.[12-15] However NPWT is increasingly being applied prophylactically to closed surgical wounds in high risk populations to reduce the incidence of SSI. This use of prophylactic NPWT is generally applied to wounds perceived as being at high risk of SSI e.g., CS incisions in obese women.[14,15] A recent

Cochrane review concluded that evidence for the clinical effectiveness of prophylactic NPWT in reducing SSI and wound dehiscence is inconclusive.[16]

Two further randomised controlled trials (RCTs) of NPWT have subsequently been published; both were feasibility studies.[17,18] One of these trials examined the use of NPWT in 70 patients undergoing primary hip replacement.[18] The other pilot study[17] recruited 92 women undergoing elective CS and has demonstrated that a definitive trial is feasible. Neither of these trials was powered to find an effect, so the benefits or harms of NPWT for prophylactic use remain unclear.

Thus a RCT to evaluate the clinical and cost effectiveness of NPWT in obese women undergoing CS is timely and responds to the imperative to provide much-needed evidence to guide practice in a rapidly developing and costly area of health care.

Primary Objective

To compare the effects of prophylactic NPWT and standard surgical dressings on the incidence of SSI in obese women undergoing CS.

Secondary Objectives

To compare: 1) the incidence of superficial, deep, organ/space SSI; 2) the number of dressing changes; 3) the number and type of wound complications (i.e., dehiscence, haematoma, seroma; adverse events); 4) the number of hospital readmissions; 5) hospital length of stay (days); 6) health-related quality of life; and, 7) direct healthcare costs in obese

women undergoing CS who receive prophylactic NPWT with women who receive standard surgical dressings.

Study Design

Multicentre, parallel group, pragmatic, randomised controlled superiority trial.

METHODS

Study Setting and Population

Four acute care public hospitals offering obstetric services in Queensland, Australia have agreed to participate. Across the four sites, the number of births ranges from 2,400 to 10,000 per annum. The study population will consist of 2,090 women with a BMI of ≥ 30, undergoing either elective or semi-urgent CS.

Eligibility Criteria

According to national and international guidelines, CS urgency is based on these four Categories: 1) life-threatening to woman or fetus; 2) maternal or fetal compromise, not life-threatening; 3) needing earlier CS than planned without maternal or fetal compromise; and, 4) a scheduled time acceptable to the woman and CS team.[19,20]

Inclusion criteria:

I. Women booked for elective CS surgery (Category 4);

II. Women whose condition changes to require a semi-urgent CS (Categories 2-3);

III. Recorded pre-pregnancy BMI of ≥ 30 at the first antenatal visit; and,

IV. Able to provide written informed consent.

Exclusion criteria

I. Women who require an urgent CS (Category 1) at any point;

II. Existing infection after admission to hospital in labour / immediately prior to CS;

III. Pre-pregnancy BMI > 50;

IV. Previous participation in this trial; and,

V. Unable to speak or understand English, with no interpreter available.

Interventions

While this will be a pragmatic trial, a checklist based on published current clinical practice guidelines and Queensland Maternity and Neonatal Guidelines will be used to standardize the CS surgical procedure. The participating obstetrician's clinical judgement may produce slight variation in practice in the type of wound closure (i.e., closure of facial layer as well as rectus muscle); selection of suture materials (i.e., staples vs subcuticular absorbable suture for skin); and, standard dressing preference (e.g., semi-permeable vs hydrocolloid). There is no evidence to suggest that the above-mentioned minor variations in clinical practice increase the risk of SSI.

Intervention

At the completion of skin closure, women randomly allocated to the NPWT arm of the trial will receive a PICO™ (Smith & Nephew, Hull, UK) dressing applied by the obstetrician under sterile conditions. The PICO™ product was chosen because it is lightweight and disposable, significantly cheaper than other options, and has performed well in a pilot study.[17] It comprises a small, discrete pump, powered by two AA-lithium batteries with a highly absorbent dressing that holds the wound exudate away from the skin, thus negating the need for a bulky canister. The polyurethane foam dressing will be secured over the incision by the application of an adhesive drape. A tube is embedded into the foam, and continuous negative pressure of 80 mm Hg will be applied to the dressing.

Control

Women in the control arm will have a standard dressing based on the obstetrician's usual preference, applied according to the manufacturer's recommendations after skin closure. In both groups, we anticipate the dressing will remain in situ for four to five days, unless it becomes soiled or dislodged, in which case a new dressing of the same type will be applied. Given the pragmatic nature of this trial, the number of days dressings are left in situ and the number of dressings used will be recorded. To ensure consistency, clinicians providing care to the target population at each of the sites will receive trial-specific education (NPWT and standard). The Research Assistants (RAs) who will also receive trial-specific training will be available to clinical staff during business hours to provide on-going training and support about correct use of the dressings, as well as monitoring dressing changes and completing

documentation daily to assess protocol compliance and outcomes. If our monitoring shows variation from the proposed protocol, this variation will be used as a factor in the analyses.

Outcome Measures

The *primary outcome* is the incidence of an SSI in the CS wound at any time up to 28 days after surgery.

The following *secondary outcomes* will be assessed: depth of SSI, i.e., superficial, deep or organ/body space[3]; number of dressing changes; presence and number of wound complications (i.e., dehiscence, haematoma, seroma, blisters).

Other secondary outcomes: hospital length of stay (HLOS) will be measured in days; number of hospital readmissions will be measured within four weeks from the day of surgery. The secondary outcome, health-related quality of life (QoL) will be assessed using the SF-12v2 (acute one-week recall). The SF-12v2 will be administered at baseline (i.e., recruitment at > 36/40 weeks in women having elective CS, or on the day of CS for women undergoing semi-urgent CS), and via telephone interview weekly for four consecutive weeks after surgery. Direct health care costs will be included as part of an economic evaluation.

Participant Timeline and Trial Duration

Participants will be enrolled in the study for 28 days from the day of surgery (Table 1). The project will take up to five years to complete, with recruitment and data collection expected to occur over 3.5 years. Participants will exit the trial when they: withdraw consent; have

been in the trial for 28 days post randomization; are lost to follow-up; die; or for another reason have to exit based on the clinical judgement of the attending healthcare professional.

Sample Size

The sample size was calculated based on the primary outcome, SSI. Based on other related published studies[21,22], we conservatively estimate the baseline SSI incidence in obese CS women to be 15%. Following discussions with infectious disease experts and obstetricians, we have accepted an absolute difference between groups of 5% to be clinically important. Therefore, to achieve over 90% power to test the superiority of SSI incidence between groups, 950 women per group will be required (Power Analysis & Sample Size system [PASS, Version 12], NCSS). To allow for attrition, a further 10% (n = 95) will be recruited to each group for a total sample of 2,090 (1,045/group). We anticipate recruiting approximately 600 women per year, thus recruitment should be completed in about 3.5 years.

Recruitment of Participants

We will use a staged approach to recruitment, commencing at one site to test procedures, prior to starting at the other sites. All obese women will be given an information brochure informing them of the trial during their routine antenatal visit at 36 weeks. This strategy will facilitate further discussion and assist with consent processes in labour in the event that a semi-urgent CS is required. Women booked for an elective CS will be given the opportunity to provide written consent during their antenatal visit (36/40 weeks). On the day of surgery,

women undergoing elective CS will be screened to ensure they continue to meet the inclusion criteria; those who have not yet provided written consent will be invited to do so. Women undergoing semi urgent CS will be consented on the day of surgery. Figure 1 shows anticipated participant flow through the study.

Implementation of sequence generation and allocation concealment

Women booked for elective CS will not be randomized at recruitment as the long time lag between randomization and receiving the intervention which could lead to poor adherence to allocation and loss to follow-up. All women who continue to meet the eligibility requirements will be randomized using a centralized, independent, web-based randomisation system. The RA will randomize participants in the operating room at the commencement of their CS procedure and advise the operating obstetrician and nursing staff of the allocated treatment as close to the end of the procedure as possible in order to minimise performance bias. The allocation sequence will be used to ensure allocation concealment. To reduce predictability of a random sequence, randomly varying block sizes of four, six and eight will be used.

Blinding

This pragmatic trial tests a clinical intervention that is not amenable to protection against performance bias through the blinding of participants, clinical staff or data collectors.

To minimize the potential for outcome detection bias, an expert clinician, blinded to group allocation, will assess the data to determine the primary outcome. The trial statistician and coordinating PI will also be blinded. It is unlikely that entries to the medical records and hospital databases will be falsified; thus lack of blinding for these outcomes should not affect the data integrity. Subjective outcomes (wound complications, QoL) are reported by patients or observed by RAs, who cannot be blinded because they need to check the dressings and document participants' responses.

Performance bias is a consideration when clinical staff cannot be blinded. To assess the risk of performance bias, a standardised set of questions will be used to document the number of dressing changes and/or protocol violations occurring during the hospital stay, and following discharge. We considered using dressings where tubing was attached to a suction apparatus in both groups; however participants, staff and data collectors would almost certainly be aware if suction was activated and we decided it was most important to measure 'real world' effects and conduct a pragmatic trial.

Data Collection

The RAs will collect SSI related data on day 2 (post surgery) using a structured form. In Queensland Australia, the *Centre for Healthcare Related Infection Surveillance and Prevention* provides guidelines identifying SSI signs and symptoms (i.e., redness, swelling, pain/tenderness, dehiscence, watery or purulent discharge), both during hospitalisation and after hospital discharge. Data which will be collected from a variety of sources including chart audit, direct observation, and patient self-report both during hospitalisation and after

discharge. RAs will record dressings used and antibiotic medication. Data collection will occur on weekdays (Monday-Friday). Clinical outcome data will be collected by the RAs retrospectively though telephone interviews and by accessing participants' medical records.

After hospital discharge, all women will be telephoned weekly (from their day of surgery) and outcomes assessed using a series of questions, which have been used successfully in other research in this area.[17,18,22] Seven-day recall of SSI symptoms and related resource use including health professional visits (e.g. consultations with general practitioners) was demonstrated as being feasible in a recently published pilot trial[17] and will allow accurate SF-12v2 and costing data to be collected.

RAs will collect and directly enter data while in the clinical areas, using portable computers with a purpose-built database and form-based interface (i.e., *Research Electronic Data Capture* [REDCap] database). Clinical characteristics such as age, co-morbidities, and other risk factors for SSI, such as nicotine use and length of operation, will be collected at baseline. Recruitment and data collection will be monitored by the Clinical Trial Coordinator (CTC) weekly and monthly reports will be presented to the study investigators. While there is a potential for loss to follow up, our pilot study has demonstrated retention rates of > 85%.[17] We will also use standard procedures, such as recording alternative phone and email contacts for participants and GPs, in order to assist with tracing women who may have moved house/changed internet providers etc.

Ascertainment of the Primary Outcome

SSI related data will be given to the two blinded expert clinicians, who will compare the data against criteria defined by the *Centres for Disease Control and Prevention Guideline for Prevention of SSI*[3] to decide if a SSI exists. We will use decision rules to ascertain the primary outcome. If the two blinded expert clinicians disagree on whether the patient has sustained a SSI within the 28-day postoperative period, we will use the following combinations with regards to wound infection: yes/no, yes/unsure, no/unsure:

1. If the two assessors say: 'yes/unsure' then we will say the patient has a SSI, using the data provided by the assessor who said 'yes'.
2. If the two assessors say: 'no/unsure' then we will say the patient does not have a SSI.
3. If the two assessors say: 'unsure/unsure' then we will say the patient does not have a SSI.
4. If the two assessors say: 'yes/no' then the third assessor will be consulted and will decide if there is a SSI or not. The third assessor's decision will be final. If s/he is unsure whether the patient has a SSI or not, then the patient will be considered not to have a SSI.

Training, Outcome Assessment and Treatment Fidelity

Adhering to Good Clinical Practice (GCP) recommendations[23], this multisite study will have an experienced CTC coordinating the RA training, and site and data monitoring. Trial-specific RA training to assess the patient's incision/dressing site will be provided by a tissue viability nurse. Additional training in the use of the PICO NPWT dressing product will be provided by a Smith and Nephew clinical nurse educator with specialist knowledge but with

no role in the design, analysis or reporting of the study. Involving a product specialist in the training of the RAs and clinicians who will be using the PICO product ensures that all end-users receive comprehensive and consistent information relative to the appropriate use and management of the study intervention. The RAs will undergo group and individual onsite training to ensure consistency across the four sites. Areas covered will include recruitment and data collection processes, use of the central randomisation service and database.

Consistent with GCP recommendations[23], a standardised operating procedure (SOP) manual has been developed to provide more specific detail on the protocol, plans for dealing with intervention fidelity issues, and monitoring the delivery and receipt of the intervention. Assessment of treatment fidelity will focus on type of dressing used, duration of use and number of dressing changes. While this is a pragmatic trial, obtaining information on intervention fidelity may help to explain study results. All members of the research team, including RAs, will be provided with training, a procedure manual and a DVD detailing the NPWT dressing application to ensure protocol consistency. A trial-specific training program and on-going education sessions targeting obstetricians, operating room staff, midwives and nurses will also be implemented at each site.

Withdrawal

If a participant decides to withdraw from the trial after consent is given, any existing data obtained during the trial will be retained and no further follow-up data collected. A withdrawal form will be completed and reasons for withdrawal, noted. Patients who withdraw from randomized treatment prior to randomization will be left in the study and

reported in the flow chart as 'not receiving randomized intervention'. Patients who withdraw *after* they have received the intervention (i.e., after dressing application) will also be included and reported in the flow chart as 'receiving randomized treatment'.

Data Management

All data will be managed using a centralised REDCap (Nashville, US) database repository, hosted on a dedicated secure server within the Clinical Trials Unit at Griffith University. The trial statistician will not have access to the database to ensure he remains blinded to group allocation. This database enables different levels of data access, allowing researcher control over who sees the files and what they can do with them. Data access will therefore be restricted and all data password protected. Each site RA will have a level of access to the database specific to their site and position, and will use a password protected tablet computer for data entry into REDCap.

An electronic case report form (eCRF) will be developed in collaboration with the trial statistician, coordinating PI and CTC. The eCRF will be hosted on the REDCap database within the Griffith University's Clinical Trials Unit. Source data will be entered by the site RAs, who will receive trial-specific training in the use of the eCRF. All entered data will be directly exported into the IBM Statistical Package for the Social Sciences (SPSS v22.0, NY) for analysis.

Identifiable Data

For the purposes of statistical analysis, data will be anonymized and collated by the CTC and uploaded into SPSS. Identifiable data will be entered on the eCRF to enable follow-up. These data will be de-identified when transferred to the statistical database. Participants will be identified on the statistical database using a unique code and hospital site initials.

Statistical Analysis

Primary Analyses

Prior to analysis, a rigorous process of data cleaning to check outlying figures, missing, and implausible data against source data will be undertaken. Baseline characteristics of the patients in each arm of the trial will be calculated using descriptive statistics. We will employ an intention-to-treat approach for the primary analysis with the population defined as all trial participants who completed the baseline assessment and underwent surgery and received the intervention. Adverse events will be analysed and reported on a per protocol analysis. The incidence of SSI per 1000 patients between groups will be compared. Risk ratios (RR), 95% confidence intervals (CI) and P values assuming a 5% significance level will be presented. For the primary outcome, the number needed to treat (NNT) and absolute risk reduction (ARR) will be calculated from the RR. While we do not anticipate differences between groups in terms of known or unknown prognostic factors due to randomization, adjusted analyses using multivariate logistic regression models will be used if any difference in prognostic variables is detected. Despite every effort to minimise missing values it is possible that some may occur. We will evaluate the utility of empirical imputation methods in such cases and only impute them if the explanatory power of the empirical imputation

models is robust. To assess the representativeness of the sample, we will compare the characteristics of the women in our sample with secondary data available at state and national levels.

Secondary Analyses

Secondary endpoints will be compared between groups using statistical methods appropriate to the distribution of measures. A random sample of 5% of the data will be rechecked for accuracy against source data. RRs with 95% CI will be calculated for clinical outcome data. Analysis will be performed by one of the study investigators (blinded to group allocation), trained in biostatistics.

Economic Evaluation

Direct costs to the healthcare system will be obtained from patient records/hospital cost centres (during hospital admission) and self-reported by women (weekly for 4 weeks post surgery). Resources costed during admission will include dressings and related wound management products, medications related to SSI (i.e. use of antibiotics), and resources used to manage any adverse effects of the dressing. Use of dressings, medications and health professional appointments related to wound management will be recorded at weekly intervals for four weeks following surgery. Direct costs will be assigned using standard costing sources (e.g. Medicare Benefits and Pharmaceutical Benefits Schedules; Independent Hospital Pricing Authority). The Australian refined diagnostic-related groups

(AR-DRG) will be used to indicate the costs associated with each hospital admission, adjusted for HLOS.

Cost-Effectiveness Analysis

A within-trial economic evaluation will be undertaken from the health system perspective to compare the costs and effects of NPWT, relative to the standard dressing. Parametric (e.g. ANCOVA) or non-parametric bootstrapping techniques[24] will be employed to compare the mean difference in the total costs between groups. The cost-effectiveness analysis will be undertaken based on the primary outcome measure (SSI). Additionally, a cost-utility analysis will be performed using the quality-adjusted life year (QALY) as the outcome measure. The QALY gain associated with NPWT will be estimated based on SF-12v2 utility weights.[24] Uncertainty around the incremental cost-effectiveness ratios will be tested using one-way sensitivity analysis and non-parametric bootstrapping methods.[24] The cost-effectiveness estimates will inform recommendations on adopting NPWT dressings for CS surgical wounds in clinical practice.

Safety and Data Monitoring

An Adverse Event (AE) is defined as an untoward medical occurrence experienced by the participant, whether or not considered treatment related.[25] In this trial, AE will be classified as non serious (infection, pain, maceration, odour) and serious (dehiscence, return to theatre). Both types of AE would be expected to occur equally in both treatment groups. Patients will be monitored for potential AEs, serious and non serious. All AEs reported will

be assessed to determine whether further diagnostic investigation or treatment is warranted. If an AE occurs, appropriate treatment will be given. Monitoring and reporting of suspected unexpected adverse reactions (SUSARs) will be performed by the site PI and the research team. All SUSARs will be recorded on a dedicated eCRF. Serious AEs associated with the intervention are considered unlikely, although if any are reported the relevant Human Research Ethics Committees will be notified, with appropriate notification of the Therapeutic Goods Administration (TGA) as required.

The results of the trial will be reviewed every six months by an independent Data Safety and Monitoring Committee (DSMC) including an obstetrician, a statistician, and a tissue viability nurse, all of whom will be independent of the study. The DSMC has the ability to terminate the trial prematurely if there is unacceptable harm associated with the treatment.[26] If requested by the DSMC, an interim analysis will be performed by a statistician (independent of the DSMC), blinded for the treatment allocation.

Auditing

Data monitoring of this trial will ensure compliance with GCP.[23] The participating sites will provide access to all trial-related source data/documents and reports for the purposes of monitoring, auditing and inspection by local authorities. The CTC will undertake monitoring in relation to the accuracy of the case report data collected by the site RAs. During the trial, the CTC will use source data to verify the data entered by the RAs into the eCRF.

Ethics and Dissemination

This trial has been approved by the relevant hospital ethics boards and the respective universities where the Principal Investigators are employed. This study will be conducted in accordance with the principles of the Declaration of Helsinki (1996), and the Australian National Health and Medical Research Council (NHMRC) National Statement.[27]

Dissemination strategies will include knowledge translation events involving opinion leaders and stakeholders. Findings will be presented at local hospital and other fora and a press release will be prepared. A succinct non-technical paper discussing the relevance of findings and application to practice, and recommendations for future research, will be prepared and disseminated to the colleges representing the relevant health professional groups. Abstracts will be submitted to major international meetings of infection control, nursing/midwifery and medical groups. We envisage the results will be published in high-impact generalist and specialist journals. We will bring the published study to the attention of the Cochrane Wounds Group and the authors of the relevant Cochrane review to ensure early inclusion in review updates. The results will have international application and we anticipate that they will be rapidly adopted and cited within the GCP literature.

DISCUSSION

Despite a lack of rigorous evidence to support either clinical or cost effectiveness, NPWT is increasingly being used as a prophylaxis against SSI in high-risk surgical groups such as obese women undergoing CS. To the best of our knowledge, this RCT will be the largest of its kind in this area. It has significant potential to inform practice because it assesses the clinical and cost-effectiveness of using NPWT in a patient population at high risk of incurring an SSI. A

RCT design with a sufficiently large sample is time consuming and expensive to undertake but it is nevertheless necessary to determine the efficacy of NPWT in the management of surgical incisions.

Our trial has several strengths. First, the RCT design with a robust randomisation process will ensure that any difference in outcomes between the groups is attributable to the intervention. Second, a pragmatic approach allows testing of an intervention that reflects the reality of the clinical environment relative to study population, intervention, comparator, and outcomes.[26] Third, an independent clinician, blinded to group allocation will assess these data to determine SSI status. Fourth, the embedding of an economic evaluation responds to the need to provide health care administrators and decision-makers with meaningful cost-effectiveness data. Finally, this trial is independent of industry funding, and therefore minimises potential for a conflict of interest which may bias the results.

While we envisage that the results of this trial will provide clinicians with definitive answers around the effectiveness of NPWT in this specific patient population, undertaking this 5 year trial is not without its challenges, including meeting our recruitment targets within a 3.5 year timeframe. For each hospital site, yearly recruitment targets will need to range from 120 to 200 women. To maximise both recruitment and generalisability, we will include women who are undergoing both elective and semi-urgent CS. Another major challenge is the potential for missing outcome data due to participant attrition as participants in this study will typically be busy with childcare and other commitments post-operatively. Yet in a recent pilot study, participant attrition was less than 10%[17], which is considered acceptable. Maximising participant retention over a four week follow-up period will be achieved by the

RAs meeting women face-to-face during pregnancy/labour and again post-operatively. These meetings will enable a relationship of trust to be developed and allow the RAs to resolve any queries promptly. It will also provide opportunities for the RAs to reconfirm women's contact details and remind them about the four weekly telephone follow-ups. In the event that an RA is unsuccessful in their first attempt to contact women following discharge, they will try again, perhaps using their alternative contact details. Finally, during the 3.5 year data collection period, there may be clinical innovations introduced that potentially influence the trial outcomes (i.e., 'history'). However we anticipate that both groups to be equally influenced.

Trial status

At the time of manuscript submission, ethics (HREC/15/QRBWH/126) and contract approvals have been given. The investigator team are awaiting final approvals for research governance.

Author's contributions

BG, JW and WC conceived of the study. NC, LT, DE, HS, JAW and KM contributed to the study design and will assist with implementation. All authors are grant holders. LT and NC provided methodological expertise in clinical trial design and LT is leading the primary statistical analysis. JAW provided expertise in the health economic analysis and will lead the economic evaluation. All authors contributed to refinement of the study protocol and approved the final manuscript.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

This trial is funded through an Australian National Health & Medical Research Project Grant (APP1081026). This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Data Sharing Statement

A summary of the results will be disseminated to the study participants on request. We plan to publish the main trial outcomes in a single paper. Further publications are anticipated after exploring the data in more detail. Findings will be presented at national and international conferences from early 2020.

RUNNING HEADER: Using negative pressure dressings following caesarean section: Trial protocol.
Revised version: 17 November 2015

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Table 1: Timeline of Trial Activities

	STUDY PERIOD								
		Allocation (Day 0)							
	Enrolment	Elective CS	Semi-urgent CS	Post-allocation					Closeout
TIMEPOINT				2 days postop	7 days postop	14 days postop	21 day postop	28 days postop	
ENROLMENT				Inpatient	Day of surgery up to 28 days				
Eligibility screen 36/40 week antenatal visit	X	X							
Day of CS	X		X						
Informed consent 36/40 week antenatal visit	X	X							
Day of CS	X		X						
Baseline data 36/40 week antenatal visit	X	X							
Day of CS		X	X						
Randomisation during CS procedure		X	X						
INTERVENTIONS (4-5 days insitu)									
NPWT dressing		**x** **x**	**x**	**x**	**x**				
Standard dressing		**x** **x**	**x**	**x**	**x**				
ASSESSMENTS									
Baseline									
Pre-pregnancy BMI / Height / Weight	X								

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Parity / gravidity	X								
Comorbidities	X								
SF-12 v2	X								
Preoperative data		X							
Surgical data form		X							
Outcome variables									
Dressing change/reason				X					
Allocated dressing				X					
Temp/HR/RR				X					
Wound complications				X					
Patient satisfaction				X					
Prophylactic ABs/type				X					
AB route				X					
AB s 24 hours postop				X					
Inpatient SSI screening				X					
Blood culture				X					
AB therapy				X					
Post-discharge									
Wound complications					X	X	X	X	
SSI symptoms					X	X	X	X	
Resource use associated with CS wound					X	X	X	X	
SF-12 v2					X	X	X	X	
SSI screen (chart audit)								X	X
Closeout hospital site visit									X

Abbreviations: AB=Antibiotic; BMI=Body mass index; CS=Caesarean section; SF12=Short Form.

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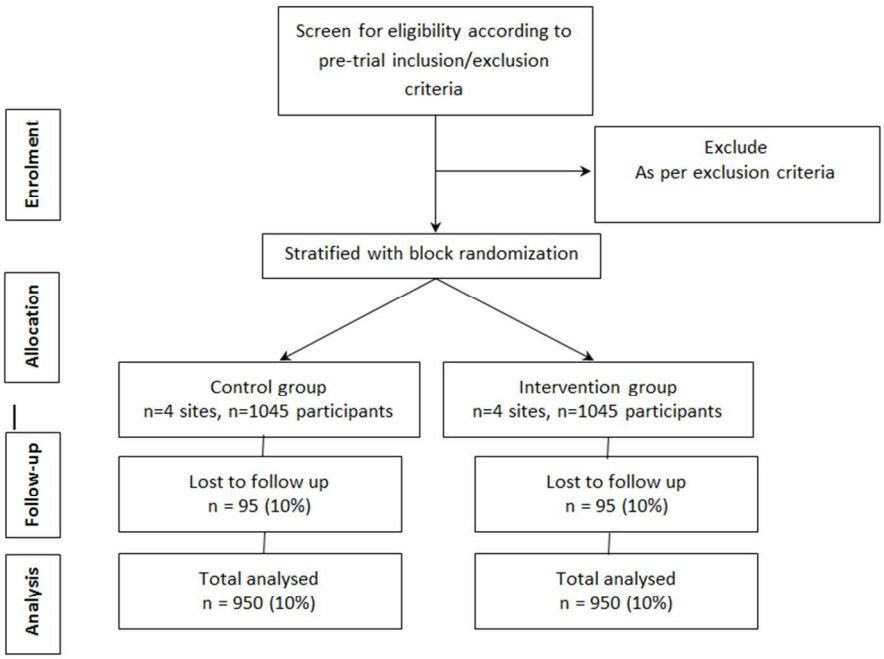

Figure 1: Anticipated participant flow through study

Figure 1: Anticipated participant flow through study

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

ADding negative pRESSure to improve healING (the DRESSING trial): A RCT Protocol

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym pp. 3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry pp. 4
	2b	All items from the World Health Organization Trial Registration Data Set pp. 4
Protocol version	3	Date and version identifier Running header
Funding	4	Sources and types of financial, material, and other support pp.2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors pp.1-2
	5b	Name and contact information for the trial sponsor N/A
	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 pp. 2
	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) pp. 20,21
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 pp. 5-6
	6b	Explanation for choice of comparators pp. 8-10
Objectives	7	Specific objectives or hypotheses pp. 6, 7
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) pp. 7
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 pp. 7
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) pp. 7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered pp. 8,9
	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) pp. 16, 20,21
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) pp. 15,16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial pp. 8-10

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 pp. 10,11
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) pp. 10 + figure
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 pp. 11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size pp. 11, 12
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 pp. 12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned pp. 12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions pp. 12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how pp. 12,13

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial pp. 12,13, 14,15
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol pp. 13,14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols pp. 13,14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol pp. 17,18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol pp. 18-20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) pp. 18-20
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) pp. 18-20
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed pp. 20,21

	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 pp. 20,21
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 pp. 20,21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor pp. 20,21
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval pp. 22
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) pp. 22
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) pp. 11, 13,14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable n/a
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 pp. 17,18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
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 pp. 17
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

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 pp. 22
	31b	Authorship eligibility guidelines and any intended use of professional writers pp. 2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code N/A
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Available on request
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 N/A

*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.