BMJ Open

Efficacy of negative pressure wound therapy in the prevention of surgical wound complications in the cesarean section at risk population: a parallel group randomised multicentre trial: the CYGNUS protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035727
Article Type:	Protocol
Date Submitted by the Author:	13-Nov-2019
Complete List of Authors:	Sandy-Hodgetts, Kylie; University of Western Australia, Skin Integrity Clinical Trials Unit, Burn Injury Research Unit, School of Biomedical Sciences Parsons, Richard ; Curtin University Norman, Richard; Curtin University White, Scott; Univ Western Australia Fear, Mark; University of Western Australia, School of Surgery, Burn Injury Research Unit Wood, Fiona; University of Western Australia, School of Surgery, Burn Injury Research Unit; Burns Service of Western Australia, Royal Perth and Princess Margaret Hospitals
Keywords:	WOUND MANAGEMENT, SURGERY, OBSTETRICS, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

BMJ Open Manuscript

Efficacy of negative pressure wound therapy in the prevention of surgical wound complications in the cesarean section at risk population: a parallel group randomised multicentre trial, the **CYGNUS** protocol.

1. Dr Kylie Sandy-Hodgetts, BSc, Hons H1, MBA, Ph.D Director Skin Integrity Clinical Trials Unit, Senior Research Fellow, Burn Injury Research Unit, School of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Western Australia.
2. Dr Richard Parsons, Senior Lecturer in Statistics, School of Occupational Therapy, Social Work and Speech, Curtin University
3. Associate Professor Richard Norman, Health Economist, School of Public Health, Curtin University
4. Dr Scott White, Senior Lecturer, Consultant Obstetrician, Department of Maternal and Fetal Medicine, King Edward Memorial Hospital
5. Dr Mark Fear, Senior Research Fellow, Burns Injury Unit, School of Biomedical Sciences, Faculty of Medicine, University of Western Australia
6. Professor Fiona Wood, Director State Burns Unit, Fiona Stanley Hospital, Perth.

Correspondence to: Dr Kylie Sandy-Hodgetts; kylie.sandy-hodgetts@uwa.edu.au

Abstract word count: 501

Manuscript: 3069 (max 4000 words)

Abstract

Introduction

Caesarean delivery is steadily becoming one of the more common surgical procedures in Australia with over 100, 000 caesarean sections performed each year (1). Over the last 10 years in Australia, the caesarean section rate has increased from 28% in 2003 to 33% in 2013 (1). On the international stage the Australian caesarean delivery rates are higher than the average for the OECD, Australia ranked as 8 out of 33 and is second to the United States (2). Postoperative surgical site infections and wound complications are the most common and costly event following caesarean section (3). Globally, complication rates following caesarean delivery vary from 4.9%-9.8% (4-6). Complications such as infection and wound breakdown affect the postpartum mother's health and wellbeing, and contribute to healthcare costs for clinical management that often spans the acute, community and primary health care settings. Published level one studies utilising advanced wound dressings as prophylactic interventions in a pre-identified at risk population are yet to be forthcoming.

Methods and analysis

A parallel group randomised control trial of 448 patients will be conducted across two hospitals in Perth, Western Australia. We will recruit pregnant women in the last trimester, prior to their admission into the health care facility for delivery of their child. We will use a computer generated block sequence to randomise the 448 participants to either the interventional (negative pressure wound therapy dressing, n=224) or comparator arm (non-negative pressure wound therapy dressing, n=224). The primary outcome measure is the Centres for Disease Control reporting definition of either superficial or deep infection at 30 days and wound dehiscence will be classified as per the World Union of Wound Healing Societies Surgical Wound Dehiscence (SWD) Grading System (Grades I-IV) (7). We will assess recruitment rate and adherence to intervention and follow up. We will assess the potential efficacy of negative pressure wound therapy in the prevention of post-partum

wound complications at three time points during the study; Day 5 post-operative, Day 14 and Day 30 where the participant will be closed out of the trial. We will utilise statistical methods to determine efficacy and risk stratification will be conducted to determine the surgical wound dehiscence risk profile of the participant. Follow up at Day 30 will assess superficial and deep infection and wound dehiscence (Grades I-IV) and the core outcome dataset for wound complications. This study will collect health related quality of life (ED-5D-5L), mortality and late complications such as further surgery with a cost analysis conducted. The primary analysis will be by intention to treat.

Trial registration number: ANZCTR: ACTRN12618002006224p

Protocol version and date: Version 3.0, 6 February 2019.

Strengths and limitations of this study

- This prospective trial will determine the true rate of wound complications according to nationally recognised criteria
- Pragmatically designed and reviewed by consumer groups to allow for integration into routine clinical practice
- Trial available only to women who have proficiency in English language
- This study will recruit from scheduled elective admissions with a probable and coincidental inclusion of urgent or emergency cases

Introduction

Currently in Western Australia the caesarean section delivery rate is reportedly 37% of births compared to the OECD average of 25% (1). Surgical site infection or wound complications such as dehiscence is a common cause of morbidity with reported rates of 4.9%-9.8% in some settings (4-6). The potential risk of surgical wound complications following the caesarean procedure is considerable, and there is still a gap in the literature as to best practice in prevention of wound complications following this type of procedure (4, 5). Several studies in the field have retrospectively investigated the effect of negative pressure wound therapy (NPWT) in the reduction of post-surgical wound complications in the obstetric population (8, 9). However, there is a lack of published level one studies investigating the prophylactic use of NPWT in the prevention of surgical complications in high risk patients with multiple risk factors such as obesity, diabetes and previous caesarean-section (10-12). Whilst a recent study from the Netherlands has identified an effect of the use of NPWT for patients with one risk factor (BMI 30kg/m^2+) (13), there remain considerable gaps in the evidence addressing those patients at risk with multiple risk factors (i.e., diabetes, smoking, previous caesarean section) which may be more generalizable to an average caesarean section population. The utility of risk stratification and the impact of prophylactic NPWT initiated for use in high-risk cohorts for the prevention of wound dehiscence following a caesarean section remains to be determined. Furthermore, and more importantly, is the measure of patient perception of their wound healing after the procedure. An evidence-based approach is important to inform the development of clinical pathways and protocols in patient management, and this study will form the basis of the development of a postoperative wound management pathway for caesarean section surgery patients both at the participating trial sites, and more broadly in both national and international clinical settings.

Study design

CYGNUS is a parallel group randomised control trial (RCT) testing the effectiveness of an intervention (negative pressure wound therapy dressing) to a control (non-negative pressure wound therapy dressing) with respect to wound healing, complications, cost and health-related quality of life.

Study aim and objectives

The aim of the CYGNUS trial is to determine the efficacy of negative pressure wound therapy (intervention) in the prevention of post caesarean section complications in the post-partum mother compared to non-negative pressure wound therapy dressing (control). Our primary objectives are to conduct an RCT to determine the effectiveness of negative pressure wound therapy in prevention of post-operative complications following a caesarean section in low to high risk cohorts and determine the clinical utility of the intervention. Our secondary objectives are to conduct a health-related quality of life (ED-5D-5L) assessment, and to evaluate patient perceptions of wound healing and pain following the surgical procedure in the intervention and control arms. Finally, we aim to determine the cost-effectiveness of the intervention relative to the control utilising a stepped health economic analysis, concluding with a cost-utility analysis reporting a cost per quality-adjusted life year (QALY).

Study setting

The CYGNUS trial will be conducted in two metropolitan Perth maternity hospitals, over a period of 2 years (October 2019-October 2021). All eligible pregnant women at participating sites will be considered for enrolment.

Study participants and eligibility criteria

Pregnant women eligible for recruitment to the CYGNUS trial are those with a singleton, viable pregnancy from 32 weeks and able to provide written informed consent in English and have no known allergies to hydrocolloid, polysiloxanes or silicone resin. Women who are not fluent in English are ineligible to participate.

Recruitment and randomisation

All pregnant women booked for antenatal care will be screened against the eligibility criteria. Eligible participants will receive the CYGNUS Patient Information Sheet (PIS) at least 24 hours prior to their admission booking. This will allow time to consider participation in the trial. The PIS will be accompanied by a letter from the Principal Investigator (PI) informing patients about the trial and inviting them to participate. The PIS will be discussed with eligible women by a member of the research team and potential participants will have the opportunity to discuss the study and ask questions. If a patient wishes to participate they will be provided with a CYGNUS Trial Consent Form where written consent to participate will be sought. The person who interviews the potential study participant and obtains their consent to participate will be blinded to the treatment allocation schedule. Once consent has been obtained, the staff member who is recruiting the patient will contact the senior research fellow in their site to request the next study identifier and treatment allocation. Baseline participant information, demographic and related medical history will be collected. A participant risk profile for surgical wound dehiscence (SWD) will be obtained utilising the Perth Surgical Wound Dehiscence Risk Assessment Tool (PSWDRAT) (14). This will determine the SWD risk profile of the trial participant. The European Quality of Life 5-Dimensions 5-Level Scale (EQ-5D-5L) (15) a validated questionnaire will be administered at baseline and at the end of the trial to allow estimation of QALYs of all participants. The study statistician will generate the allocation sequence for each site before the study commences, using a random number generator on a computer. There will be a separate

sequence for each site, and each sequence will be generated using a permuted random blocks strategy to ensure that recruitment to the two arms of the study occurs at approximately equal rates within each site. The allocation list for each site will be provided to the senior research fellow at each site, and will be kept private from all other personnel at the site. Due the nature of the study device, blinding of participants or study personnel after treatment allocation is not possible. However, the study statistician will be blinded to group allocation.

Post randomisation withdrawals/exclusions

Participants may choose not to participate in the CYGNUS trial or withdraw from the study at any time without prejudice. Choosing either of these options will not affect the standard of care the patient receives.

Study dressings

Participants who elect to have a caesarean section as the chosen method of delivery usually have a scheduled time and day for the procedure. Some patients may be required to undergo an urgent or an emergency caesarean delivery due to a number of uncontrolled factors. Routine antibiotic prophylaxis will be given to patients immediately before surgery and all intraoperative procedures adhere to the WHO (16) surgical site safety checklist and local infection prevention policies in accordance with Australian Commission on Safety and Quality Health Commission National Standard 3: Prevention of Health Care Acquired Complications (17).

Control dressing

The standard dressing for a surgical wound consists of a non-adherent layer applied over the incision and directly onto the incision to cover the incision site. The control dressing does not use negative pressure over the incision site. The standard wear time of the control

dressing is up to and including 7 days. Details of the dressing and wear time will be recorded in the case report forms (CRF's).

Intervention

Negative Pressure Wound Therapy System consists of a non-adherent dressing pad with an adhesive cover that adheres to the surrounding skin near the incision site. The dressing pad is attached to a small silent pump via a soft tube that creates a partial vacuum over the wound. The pump delivers a continual negative pressure of 80mmHg and is a battery-operated device. The negative pressure wound therapy pump can operate for up to 30 days, and the dressing can be worn for 7 days as per the manufacturer's recommendation. In this trial, the dressing will be worn for a standardised period of 7 days (intervention and controls arms). Any further wound dressings after the initial dressing application will be recorded in the CRF's and following the allocated treatment unless otherwise clinically indicated.

Outcome measures

Primary outcome

The primary outcome for this study is surgical wound dehiscence as defined by the WUWHS SWD Grading System (7), and the Centres for Disease Control definitions of SSI (18) will be used as the primary outcome measure for confirmed wound infection. The primary outcome measure definitions include a wound complication that occurs within 30 days of surgery. The treating clinical team will determine the diagnosis of surgical wound dehiscence or infection as per routine clinical wound assessment protocol if there is a confirmed SSI or SWD. Rapid diagnosis and treatment of wound infection is central to patient standard care and the attending clinician will document any changes in the patient medical notes and adhere to local wound management protocols.

Secondary outcomes

Health related quality of life assessment

A qualitative assessment of the participant's perceptions of wound healing will be conducted.

EuroQol EQ-5D-5L

The EuroQol EQ-5D is a validated measure of health related quality of life, comprising a five-dimension health status classification system and a separate Visual Analogue Scale (19). The EQ-5D consists of five dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression), each with either 3 or 5 levels. We will use the five-level version of the instrument, which is likely to be more sensitive to small but important changes in health-related quality of life (15). The responses will be converted into an index score, and total QALYs for each woman will be obtained by estimating the area under the curve defined by their baseline and final EQ-5D-5L responses (20).

Complications

All complications and surgical interventions related to the procedure (i.e. sutures, staples, closure methods) will be recorded in the CRF's.

Economic analysis

All resources utilised in the study will be recorded to help inform the economic analysis. Cost data will be derived from the hospital finance departments and any related community nursing service or primary health care centre where the participant has attended. Cost consequences following discharge including out of pocket expenses (if any) will be recorded in the case report forms at day 30 following the procedure. The incremental cost of the intervention relative to the control will be estimated, and divided by incremental outcomes reported in the study. Each resultant incremental cost-effectiveness ratio (ICER) will be reported separately, with the last step being the cost per QALY. We will conduct univariate and probabilistic sensitivity analyses around the cost per QALY to assess the robustness of

the result, with the threshold for cost-effectiveness determined by recent work by Edney *et al.*(21).

Adverse event management

Adverse device effect is an adverse event related to the use of an investigational medical device (IMD) (22). Adverse events (AEs) related to an investigational medical device are defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to in the investigational medical device (22). Definitions of adverse events (AEs), serious adverse device effect (SADE), serious adverse event (SAE) Significant Safety Issue, Unanticipated Serious Adverse Device Effect (USADE) or Urgent Safety Measure (USM) are as per the National Health and Medical Research Council (2016) Guidelines on Safety monitoring and reporting in clinical trials involving therapeutic goods (22).

Follow up

Each participant will be followed up during the trial as close as practically possible to the specific time points: Week 1, Week 6 and Week 12 following surgery. The close out time point of the trial participant is Day 30 postoperative. In the event that a participant has an unresolved complication beyond 30 days, follow up will continue to complete wound healing, and participants will have the opportunity to opt out of the extended data collection beyond Day 30. All data recorded during the follow up time points will be recorded on the case report forms and clinical assessment will follow standard postoperative wound care management and clinical procedures.

Sample size

Participants will be randomised in a 1:1 ratio of trial intervention to control. The sample size calculation is based upon the following estimates: A complication rate of 20% of caesarean

section patients was observed following a retrospective medical note audit at the major tertiary women's hospital in Perth. If the intervention can reduce this figure to 10% (a reduction of 50% from the current figure) then a sample of size n=199 in each arm would be required to detect this difference with power=80% and α=0.05. To allow for an attrition rate of 11%, we plan to recruit 224 patients to each arm of the study.

Data management

The case report forms have been designed by the Senior Research Fellow in consultation with the trial co-investigators. All hard and electronic based patient identifiable information will be stored on a secure password protected database purpose built for the trial. All CRF's will be stored in a locked filing cabinet in a locked office at the participating site. Participants will be identified by a code number only, on the database, but a file linking the code number to the participant name and contact details will be kept separately and securely. This will allow re-identification of the patient for follow-up purposes. Direct access to source data and/or documents may be required for trial related monitoring/audit by the regulatory authorities by written request only. All paper and electronic data will be retained for 5 years after completion of the trial.

Statistical analysis

Simple descriptive statistics (means, SDs, medians, IQR for continuous variables and frequencies and percentages for categorical variables) will be used to summarise the profile of the study participants. Comparison of participants in the two groups (control vs intervention) will be performed using the Chi-square tests or t-tests as appropriate. These tests will be used to identify any differences in baseline characteristics between groups. Recruitment and retention rates will be reported as per the Consolidated Standards of Reporting Trial (CONSORT) (23) statement. Reasons for ineligibility, protocol deviations or participant withdrawal will be stated and any trends reported.

Analysis of the trial primary and secondary outcomes will be performed using the Chi-square test or t-tests as appropriate. The Kaplan-Meier method and the LogRank test will be used to analyse any differences in time to wound healing, between the two groups. All statistical analyses will be performed using the SAS version 9.4 software, and, following convention, a p-value < 0.05 will be taken to indicate a significant association in all tests.

Trial oversight

A Trial Committee (TC) and Data Safety Monitoring Board (DSMB) will be set up. The DSMB advocates for the ethical and safety interests of the participants while the trial progresses by making nonbinding recommendations to the TC. A data safety monitoring board will be formed to monitor the study at interim periods: first third participants closed out (n=148) and last quarter closed out. The DSMB consists of three independent reviewers; a statistician, a surgeon and a nurse. The DSMB will be bound by the DSMB Terms of Reference and will provide a written report to the TC. The TC consists of the Principal and site investigators, the study biostatistician and health economist. This trial will utilise the Haybittle-Peto (24, 25) boundary as the designated trial statistic for stopping the trial.

Ethics and dissemination

Ethics approval was obtained through St John of God Healthcare (HREC1409), Western Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings will be submitted for publication in peer-reviewed journals. We used the SPIRIT checklist when writing our study protocol (26).

Declarations

Funding This work is funded by an unrestricted educational grant from Convatec Pty Ltd. Convatec Pty Ltd., had no input into the design of the study, publications or educational matter related to the study.

Contributions KSH, RP designed the study. KSH wrote the background, methodology and developed the research question with input from RP. RP wrote the statistical design section and RN wrote the health economic sections of the protocol. All authors reviewed and agreed the final manuscript.

Competing interests None declared

Patient consent Patient consent will be sought to participate in the study via written informed consent

Provenance and peer review Not commissioned, externally peer reviewed

References

1. AIHW. Mothers and babies. 'Australia's mothers and babies 2013—in brief. Perinatal statistics series no. 31'. Canberra: AIHW 2017.
2. OECD. Health at a glance 2015: health care activities. Paris: OECD; 2015.
3. Kawakita T, Landy HJ. Surgical site infections after cesarean delivery: epidemiology, prevention and treatment. Maternal health, neonatology and perinatology. 2017;3:12.
4. Wilson J, Wloch C, Saei A, McDougall C, Harrington P, Charlett A, et al. Inter-hospital comparison of rates of surgical site infection following caesarean section delivery: evaluation of a multicentre surveillance study. The Journal of hospital infection. 2013;84(1):44-51.
5. Wloch C, Wilson J, Lamagni T, Harrington P, Charlett A, Sheridan E. Risk factors for surgical site infection following caesarean section in England: results from a multicentre cohort study. BJOG : an international journal of obstetrics and gynaecology. 2012;119(11):1324-33.
6. Ward VP, Charlett A, Fagan J, Crawshaw SC. Enhanced surgical site infection surveillance following caesarean section: experience of a multicentre collaborative post-discharge system. The Journal of hospital infection. 2008;70(2):166-73.
7. Societies WUoWH. Consensus Document. Surgical wound dehiscence: improving prevention and outcomes Wounds International - a division of Omnia-med Ltd; 2018.
8. Orth TA, Gerkovich MM, Heitmann E, Overcash J, Gibbs C, Parrish M. Cesarean Delivery with External Negative Pressure Dressing System: A Retrospective Cohort Study. Surgery journal (New York, NY). 2016;2(3):e59-e65.
9. Smid MC, Dotters-Katz SK, Grace M, Wright ST, Villers MS, Hardy-Fairbanks A, et al. Prophylactic Negative Pressure Wound Therapy for Obese Women After Cesarean Delivery: A Systematic Review and Meta-analysis. Obstetrics and gynecology. 2017;130(5):969-78.
10. Shree R, Park SY, Beigi RH, Dunn SL, Krans EE. Surgical Site Infection following Cesarean Delivery: Patient, Provider, and Procedure-Specific Risk Factors. American journal of perinatology. 2016;33(2):157-64.
11. Schneid-Kofman N, Sheiner, E., Levy, A., Holcberg., G. Risk factors for wound infection following caesarean deliveries. International Journal Gynaecology Obstetrics. 2005;90(1):10-5.
12. Krieger Y, Walfisch A, Sheiner E. Surgical site infection following cesarean deliveries: trends and risk factors. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2017;30(1):8-12.
13. Hyldig N, Vinter CA, Kruse M, Mogensen O, Bille C, Sorensen JA, et al. Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: a pragmatic randomised clinical trial. BJOG : an international journal of obstetrics and gynaecology. 2019;126(5):628-35.
14. Sandy-Hodgetts K, Carville, K., Santamaria, N., Parsons, R., & Leslie, G. The Perth Surgical Wound Dehiscence Risk Assessment Tool (PSWDRAT): development and prospective validation in the clinical setting. Journal of Wound Care. 2019;28(6):1-11.
15. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727-36.

16. WHO. Implementation Manual Surgical Safety Checklist. 1st ed. Geneva, Switzerland: World Health Organisation; 2008.
17. ACSQH. National Safety and Quality Health Service Standards. 2nd ed. . Sydney:ACSQHC2017.
18. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infection control and hospital epidemiology. 1992;13(10):606-8.
19. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of medicine. 2001;33(5):337-43.
20. Norman R, Cronin P, Viney R. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. Applied health economics and health policy. 2013;11(3):287-98.
21. Edney LC, Haji Ali Afzali H, Cheng TC, Karnon J. Estimating the Reference Incremental Cost-Effectiveness Ratio for the Australian Health System. PharmacoEconomics. 2018;36(2):239-52.
22. NHMRC. Guidance: Safety monitoring and reporting in clinical trials involving therapuetic goods. Canberra: National Health and Medical Research Council; 2016.
23. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Annals of internal medicine. 2010;152(11):726-32.
24. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. British Journal of Radiology. 1971;44(526):793-7.
25. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. British journal of cancer. 1976;34(6):585-612.
26. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158(3):200-7.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	12

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
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	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7-8
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	5
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	5

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)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#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)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	8-9

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)	10
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	10-11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
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	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	6

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#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	11

Data collection plan: retention	#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	11
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	11
Statistics: outcomes	#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	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#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)	11
Methods: Monitoring			
Data monitoring: formal committee	#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	12

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	12
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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
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)	12

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6,13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
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	10
Dissemination policy: trial results	#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	12

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6
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	NA

BMJ Open

Effectiveness of negative pressure wound therapy in the prevention of surgical wound complications in the cesarean section at risk population: a parallel group randomised multicentre trial: the CYGNUS protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035727.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Feb-2020
Complete List of Authors:	Sandy-Hodgetts, Kylie; University of Western Australia, Skin Integrity Clinical Trials Unit, Burn Injury Research Unit, School of Biomedical Sciences Parsons, Richard ; Curtin University Norman, Richard; Curtin University White, Scott; Univ Western Australia Fear, Mark; University of Western Australia, School of Surgery, Burn Injury Research Unit Wood, Fiona; University of Western Australia, School of Surgery, Burn Injury Research Unit; Burns Service of Western Australia, Royal Perth and Princess Margaret Hospitals
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Surgery, Evidence based practice
Keywords:	WOUND MANAGEMENT, SURGERY, OBSTETRICS, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

BMJ Open Manuscript

Effectiveness of negative pressure wound therapy in the prevention of surgical wound complications in the cesarean section at risk population: a parallel group randomised multicentre trial, the **CYGNUS** protocol.

1. Dr Kylie Sandy-Hodgetts, BSc, Hons H1, MBA, Ph.D Director Skin Integrity Clinical Trials Unit, Senior Research Fellow, Burn Injury Research Unit, School of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Western Australia.
2. Dr Richard Parsons, Senior Lecturer in Statistics, School of Occupational Therapy, Social Work and Speech, Curtin University
3. Associate Professor Richard Norman, Health Economist, School of Public Health, Curtin University
4. Dr Scott W White, Senior Lecturer, Consultant Obstetrician, Department of Maternal and Fetal Medicine, King Edward Memorial Hospital
5. Dr Mark Fear, Senior Research Fellow, Burns Injury Unit, School of Biomedical Sciences, Faculty of Medicine, University of Western Australia
6. Professor Fiona Wood, Director State Burns Unit, Fiona Stanley Hospital, Perth.

Correspondence to: Dr Kylie Sandy-Hodgetts; kylie.sandy-hodgetts@uwa.edu.au

Abstract word count: 501

Manuscript: 3069 (max 4000 words)

Abstract

Introduction

Caesarean delivery is steadily becoming one of the more common surgical procedures in Australia with over 100, 000 caesarean sections performed each year. Over the last 10 years in Australia, the caesarean section rate has increased from 28% in 2003 to 33% in 2013. On the international stage the Australian caesarean delivery rates are higher than the average for the OECD, Australia ranked as 8 out of 33 and is second to the United States. Postoperative surgical site infections and wound complications are the most common and costly event following caesarean section. Globally, complication rates following caesarean delivery vary from 4.9%-9.8%. Complications such as infection and wound breakdown affect the postpartum mother's health and wellbeing, and contribute to healthcare costs for clinical management that often spans the acute, community and primary health care settings. Published level one studies utilising advanced wound dressings in the identified 'at risk' population prior to surgery, for a prophylactic intervention are yet to be forthcoming.

Methods and analysis

A parallel group randomised control trial of 448 patients will be conducted across two hospitals in Perth, Western Australia. We will recruit pregnant women in the last trimester, prior to their admission into the health care facility for delivery of their child. We will use a computer generated block sequence to randomise the 448 participants to either the interventional (negative pressure wound therapy dressing, n=224) or comparator arm (non-negative pressure wound therapy dressing, n=224). The primary outcome measure is a composite measure of the occurrence of surgical wound dehiscence or surgical site infection or both. The Centres for Disease Control reporting definition of either superficial or deep infection at 30 days will be used as the outcome measure definition. Surgical wound dehiscence will be classified as per the World Union of Wound Healing Societies Surgical Wound Dehiscence (SWD) Grading System (Grades I-IV). We will assess recruitment rate

and adherence to intervention and follow up. We will assess the potential effectiveness of negative pressure wound therapy in the prevention of post-partum surgical wound complications at three time points during the study; Day 5 post-operative, Day 14 and Day 30 where the participant will be closed out of the trial. We will utilise statistical methods to determine efficacy and risk stratification will be conducted to determine the surgical wound dehiscence risk profile of the participant. Follow up at Day 30 will assess superficial and deep infection and wound dehiscence (Grades I-IV) and the core outcome dataset for wound complications. This study will collect health related quality of life (ED-5D-5L), mortality and late complications such as further surgery with a cost analysis conducted. The primary analysis will be by intention to treat. This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The trial was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12618002006224) prior to commencement.

Ethics and dissemination

Ethics approval was obtained through St John of God Healthcare (HREC1409), Western Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings will be submitted for publication in peer-reviewed journals. We used the SPIRIT checklist when writing our study protocol.

Trial registration number: ANZCTR: ACTRN12618002006224p

Protocol version and date: Version 3.0, 6 February 2019.

Strengths and limitations of this study

- The CYGNUS trial is a large multicentre trial that will provide important evidence on the effectiveness of a therapy for prevention of a wound complication after cesearean section
- This study will address an important gap in the current evidence for early identification of those at risk prior to surgery
- Pragmatically designed and reviewed by clinicians, and consumer groups to allow for integration into routine clinical practice
- Due to the nature of the intervention, blinding of participants and providers is not possible
- Trial available only to women who have proficiency in English language

This study will recruit from scheduled elective admissions with a probable and coincidental inclusion of urgent or emergency cases

Introduction

Currently in Western Australia the caesarean section delivery rate is reportedly 37% of births compared to the Organisation of Economic and Cooperative Development (OECD) average of 25% (1). Surgical site infection or wound complications such as dehiscence is a common cause of morbidity with reported rates of 4.9%-9.8% in some settings (2-4). The potential risk of surgical wound complications following the caesarean procedure is considerable, and there is still a gap in the literature as to best practice in prevention of wound complications following this type of procedure (2, 3). Several studies in the field have retrospectively investigated the effect of negative pressure wound therapy (NPWT) in the reduction of post-surgical wound complications in the obstetric population (5, 6). However, there is a lack of published level one studies investigating the prophylactic use of NPWT in the prevention of surgical complications in high risk patients with multiple risk factors such as obesity, diabetes and previous caesarean-section (7-9). Whilst a recent study from Denmark has identified an effect of the use of NPWT for patients with one risk factor (BMI 30kg/m^2+) (10), there remain considerable gaps in the evidence addressing those patients at risk with multiple risk factors (i.e., diabetes, smoking, previous caesarean section) which may be more generalizable to an average caesarean section population. The utility of risk stratification and the impact of prophylactic NPWT initiated for use in high-risk cohorts for the prevention of wound dehiscence following a caesarean section remains to be determined. Furthermore, and more importantly, is the measure of patient perception of their wound healing after the procedure. An evidence-based approach is important to inform the development of clinical pathways and protocols in patient management, and this study will form the basis of the development of a postoperative wound management pathway for caesarean section surgery patients both at the participating trial sites, and more broadly in both national and international clinical settings.

Study design

CYGNUS is a parallel group randomised control trial (RCT) testing the effectiveness of an intervention (negative pressure wound therapy dressing) to a control (non-negative pressure wound therapy dressing) with respect to wound healing, complications, cost and health-related quality of life. Figure 1 summaries the design of the trial and each of the trial aspects described below as per Consolidated Standards of Reporting Trials (CONSORT) (11). This study was designed using the SPIRIT checklist (12).

Study aim and objectives

The aim of the CYGNUS trial is to determine the effectiveness of negative pressure wound therapy (intervention) in the prevention of post caesarean section complications in the post-partum mother compared to non-negative pressure wound therapy dressing (control). Our primary objectives are to conduct an RCT to determine the effectiveness of negative pressure wound therapy in prevention of post-operative complications such as surgical wound dehiscence and surgical site infection following a caesarean section in low to high risk cohorts and determine the clinical utility of the intervention. Our secondary objectives are to conduct a health-related quality of life (ED-5D-5L) assessment, and to evaluate patient perceptions of wound healing and pain following the surgical procedure in the intervention and control arms. Finally, we aim to determine the cost-effectiveness of the intervention relative to the control utilising a stepped health economic analysis, concluding with a cost-utility analysis reporting a cost per quality-adjusted life year (QALY).

Study setting

The CYGNUS trial will be conducted in two metropolitan Perth maternity hospitals, over a period of 2 years (October 2019-October 2021). All eligible pregnant women at participating sites will be considered for enrolment.

Study participants and eligibility criteria

Pregnant women eligible for recruitment to the CYGNUS trial are those with a, viable pregnancy and able to provide written informed consent in English and have no known allergies to hydrocolloid, polysiloxanes or silicone resin. Women who are not fluent in English are ineligible to participate.

Recruitment and randomisation

All pregnant women booked for antenatal care will be screened against the eligibility criteria. Eligible participants will receive the CYGNUS Patient Information Sheet (PIS) at least 24 hours prior to their admission booking. This will allow time to consider participation in the trial. The PIS will be accompanied by a letter from the Principal Investigator (PI) informing patients about the trial and inviting them to participate. The PIS will be discussed with eligible women by a member of the research team and potential participants will have the opportunity to discuss the study and ask questions. If a patient wishes to participate they will be provided with a CYGNUS Trial Consent Form where written consent to participate will be sought. The person who interviews the potential study participant and obtains their consent to participate will be blinded to the treatment allocation schedule. Once consent has been obtained, the staff member who is recruiting the patient will contact the senior research fellow in their site to request the next study identifier and treatment allocation. Baseline

participant information, demographic and related medical history will be collected. A participant risk profile for surgical wound dehiscence (SWD) will be obtained utilising the Perth Surgical Wound Dehiscence Risk Assessment Tool (PSWDRAT) (13). This will determine the SWD risk profile of the trial participant. The European Quality of Life 5-Dimensions 5-Level Scale (EQ-5D-5L) (14) a validated questionnaire will be administered at baseline and at the end of the trial to allow estimation of QALYs of all participants. The study statistician will generate the allocation sequence for each site before the study commences, using a random number generator on a computer. There will be a separate sequence for each site, and each sequence will be generated using a permuted random blocks strategy to ensure that recruitment to the two arms of the study occurs at approximately equal rates within each site. The allocation list for each site will be provided to the senior research fellow at each site, and will be kept private from all other personnel at the site. Due the nature of the study device, blinding of participants or study personnel after treatment allocation is not possible. However, the study statistician will be blinded to group allocation.

Patient and public involvement

No patient involvement in the study design.

Post randomisation withdrawals/exclusions

Participants may choose not to participate in the CYGNUS trial or withdraw from the study at any time without prejudice. Choosing either of these options will not affect the standard of care the patient receives.

Study dressings

Participants who elect to have a caesarean section as the chosen method of delivery usually have a scheduled time and day for the procedure. Some patients may be required to undergo an urgent or an emergency caesarean delivery due to a number of uncontrolled factors. Routine antibiotic prophylaxis will be given to patients immediately before surgery and all intraoperative procedures adhere to the WHO (15) surgical site safety checklist and local infection prevention policies in accordance with Australian Commission on Safety and Quality Health Commission National Standard 3: Prevention of Health Care Acquired Complications (16).

Control dressing

The standard dressing for a surgical wound consists of a non-adherent layer applied over the incision and directly onto the incision to cover the incision site. The control dressing does not use negative pressure over the incision site. The standard wear time of the control dressing is up to and including 7 days. Details of the dressing and wear time will be recorded in the case report forms (CRF's).

Intervention

Negative Pressure Wound Therapy System consists of a non-adherent dressing pad with an adhesive cover that adheres to the surrounding skin near the incision site. The dressing pad is attached to a small silent pump via a soft tube that creates a partial vacuum over the wound. The pump delivers a continual negative pressure of 80mmHg and is a battery-operated device. The negative pressure wound therapy pump can operate for up to 30 days, and the dressing can be worn for 7 days as per the manufacturer's recommendation. In this trial, the dressing will be worn for a standardised period of 7 days (intervention and

controls arms). Any further wound dressings after the initial dressing application will be recorded in the CRF's and following the allocated treatment unless otherwise clinically indicated.

Outcome measures

Primary outcome

The primary outcome for this study is surgical wound dehiscence as defined by the WUWHS SWD Grading System (17), and the Centres for Disease Control definitions of SSI (18) will be used as the primary outcome measure for confirmed wound infection. The primary outcome measure definitions include a wound complication that occurs within 30 days of surgery. The treating clinical team will determine the diagnosis of surgical wound dehiscence or infection as per routine clinical wound assessment protocol if there is a confirmed SSI or SWD. Rapid diagnosis and treatment of wound infection is central to patient standard care and the attending clinician will document any changes in the patient medical notes and adhere to local wound management protocols.

Secondary outcomes

Health related quality of life assessment

A qualitative assessment of the participant's perceptions of wound healing will be conducted.

EuroQol EQ-5D-5L

The EuroQol EQ-5D is a validated measure of health related quality of life, comprising a five-dimension health status classification system and a separate Visual Analogue Scale (19). The EQ-5D consists of five dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression), each with either 3 or 5 levels. We will use the

five-level version of the instrument, which is likely to be more sensitive to small but important changes in health-related quality of life (14). The responses will be converted into an index score, and total QALYs for each woman will be obtained by estimating the area under the curve defined by their baseline and final EQ-5D-5L responses (20).

Complications

All complications and surgical interventions related to the procedure (i.e. sutures, staples, closure methods) will be recorded in the CRF's.

Economic analysis

All resources utilised in the study will be recorded to help inform the economic analysis. Cost data will be derived from the hospital finance departments and any related community nursing service or primary health care centre where the participant has attended. Cost consequences following discharge including out of pocket expenses (if any) will be recorded in the case report forms at day 30 following the procedure. The incremental cost of the intervention relative to the control will be estimated, and divided by incremental outcomes reported in the study. Each resultant incremental cost-effectiveness ratio (ICER) will be reported separately, with the last step being the cost per QALY. We will conduct univariate and probabilistic sensitivity analyses around the cost per QALY to assess the robustness of the result, with the threshold for cost-effectiveness determined by recent work by Edney *et al.*(21).

Adverse event management

Adverse device effect is an adverse event related to the use of an investigational medical device (IMD) (22). Adverse events (AEs) related to an investigational medical device are defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons,

whether or not related to in the investigational medical device (22). Definitions of adverse events (AEs), serious adverse device effect (SADE), serious adverse event (SAE) Significant Safety Issue, Unanticipated Serious Adverse Device Effect (USADE) or Urgent Safety Measure (USM) are as per the National Health and Medical Research Council (2016) Guidelines on Safety monitoring and reporting in clinical trials involving therapeutic goods (22). During the treatment protocol, any USADE will be reported directly to the DSMB and within 7 days to the Australian Government Therapeutics Goods Administration via the electronic Medical Device Incident Reporting System. Reports will also be sent to the local study sites Human Research Ethics Committees. The safety aspects of the study will be closely monitored by the DSMB, which will receive unblinded data for review. In the case of a device related adverse advent the manufacturer will be notified.

Follow up

Each participant will be followed up during the trial as close as practically possible to the specific time points: Day 5, Day 14,and Day 30 following surgery. The close out time point of the trial participant is Day 30 postoperative. In the event that a participant has an unresolved complication beyond 30 days, follow up will continue to complete wound healing, and participants will have the opportunity to opt out of the extended data collection beyond Day 30. All data recorded during the follow up time points will be recorded on the case report forms and clinical assessment will follow standard postoperative wound care management and clinical procedures.

Sample size

Participants will be randomised in a 1:1 ratio of trial intervention to control. The sample size calculation is based upon the following estimates: A complication rate of 20% of caesarean

section patients was observed following a retrospective medical note audit at the major tertiary women's hospital in Perth. If the intervention can reduce this figure to 10% (a reduction of 50% from the current figure) then a sample of size n=199 in each arm would be required to detect this difference with power=80% and α=0.05. To allow for an attrition rate of 11%, we plan to recruit 224 patients to each arm of the study.

Data management

The case report forms have been designed by the Senior Research Fellow in consultation with the trial co-investigators. All hard and electronic based patient identifiable information will be stored on a secure password protected database purpose built for the trial. All CRF's will be stored in a locked filing cabinet in a locked office at the participating site. Participants will be identified by a code number only, on the database, but a file linking the code number to the participant name and contact details will be kept separately and securely. This will allow re-identification of the patient for follow-up purposes. Direct access to source data and/or documents may be required for trial related monitoring/audit by the regulatory authorities by written request only. All paper and electronic data will be retained for 5 years after completion of the trial.

Statistical analysis

Simple descriptive statistics (means, SDs, medians, IQR for continuous variables and frequencies and percentages for categorical variables) will be used to summarise the profile of the study participants. Comparison of participants in the two groups (control vs intervention) will be performed using the Chi-square tests or t-tests as appropriate. These tests will be used to identify any differences in baseline characteristics between groups. Recruitment and retention rates will be reported as per the Consolidated Standards of

Reporting Trial (CONSORT) (11) statement. Reasons for ineligibility, protocol deviations or participant withdrawal will be stated and any trends reported. A Generalised Estimating Equation (GEE) will be used to analyse each of the primary outcomes over all the time points of the study. This analysis is similar to a Logistic Regression for each of the binary outcome variables, but takes into account the correlation between the repeated measurements made on the same participant. The results of the GEE will be expressed as odds ratios, their 95% confidence intervals and p-values. The GEE model will include a term for the time point, so that changes over time can be assessed, as well as a term for the treatment group allocation (on which the main conclusions of the study will be based). In addition, the GEE model will be extended to include anthropometric measurements (eg: body mass index), presence of health conditions (eg diabetes, hypertension, etc), the recruitment site, and other variables collected at baseline. In this way, variables which are identified as being associated with the outcomes may be used to form a 'risk score' for each outcome. Analysis of the pain scores (which are measured on a continuous scale at each time point through the study), will be performed using a Mixed regression model where the random effect will be the patient identifier, and the time point and treatment allocation group will be fixed effects. The distribution of the pain scores will be assessed for Normality, and transformed to improve Normality (if necessary) prior to analysis.

All statistical analyses will be performed using the SAS version 9.4 software, and, following convention, a p-value < 0.05 will be taken to indicate a significant association in all tests.

Trial oversight

A Trial Committee (TC) and Data Safety Monitoring Board (DSMB) will be set up. The DSMB advocates for the ethical and safety interests of the participants while the trial progresses by making nonbinding recommendations to the TC. A data safety monitoring board will be formed to monitor the study at interim periods: first third participants closed out (n=148) and

last quarter closed out. The DSMB consists of three independent reviewers; a statistician, a surgeon and a nurse. The DSMB will be bound by the DSMB Terms of Reference and will provide a written report to the TC. The TC consists of the Principal and site investigators, the study biostatistician and health economist. This trial will utilise the Haybittle-Peto (23, 24) boundary as the designated trial statistic for stopping the trial.

Declarations

Funding This work is funded by an unrestricted educational grant from Convatec Pty Ltd. Convatec Pty Ltd., had no input into the design of the study, publications or educational matter related to the study.

Contributions KSH, RP designed the study. KSH wrote the background, methodology and developed the research question with input from RP & SWW. RP wrote the statistical design section and RN wrote the health economic sections of the protocol. Reviews were conducted by MF & FW. All authors reviewed and agreed the final manuscript.

Competing interests None declared

Patient consent Patient consent will be sought to participate in the study via written informed consent

Provenance and peer review Not commissioned, externally peer reviewed

References

1. AIHW. Mothers and babies. 'Australia's mothers and babies 2013—in brief. Perinatal statistics series no. 31'. Canberra: AIHW 2017.
2. Wilson J, Wloch C, Saei A, McDougall C, Harrington P, Charlett A, et al. Inter-hospital comparison of rates of surgical site infection following caesarean section delivery: evaluation of a multicentre surveillance study. The Journal of hospital infection. 2013;84(1):44-51.
3. Wloch C, Wilson J, Lamagni T, Harrington P, Charlett A, Sheridan E. Risk factors for surgical site infection following caesarean section in England: results from a multicentre cohort study. BJOG : an international journal of obstetrics and gynaecology. 2012;119(11):1324-33.
4. Ward VP, Charlett A, Fagan J, Crawshaw SC. Enhanced surgical site infection surveillance following caesarean section: experience of a multicentre collaborative post-discharge system. The Journal of hospital infection. 2008;70(2):166-73.
5. Orth TA, Gerkovich MM, Heitmann E, Overcash J, Gibbs C, Parrish M. Cesarean Delivery with External Negative Pressure Dressing System: A Retrospective Cohort Study. Surgery journal (New York, NY). 2016;2(3):e59-e65.
6. Smid MC, Dotters-Katz SK, Grace M, Wright ST, Villers MS, Hardy-Fairbanks A, et al. Prophylactic Negative Pressure Wound Therapy for Obese Women After Cesarean Delivery: A Systematic Review and Meta-analysis. Obstetrics and gynecology. 2017;130(5):969-78.
7. Shree R, Park SY, Beigi RH, Dunn SL, Krans EE. Surgical Site Infection following Cesarean Delivery: Patient, Provider, and Procedure-Specific Risk Factors. American journal of perinatology. 2016;33(2):157-64.
8. Schneid-Kofman N, Sheiner, E., Levy, A., Holcberg., G. Risk factors for wound infection following caesarean deliveries. International Journal Gynaecology Obstetrics. 2005;90(1):10-5.
9. Krieger Y, Walfisch A, Sheiner E. Surgical site infection following cesarean deliveries: trends and risk factors. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2017;30(1):8-12.
10. Hyldig N, Vinter CA, Kruse M, Mogensen O, Bille C, Sorensen JA, et al. Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: a pragmatic randomised clinical trial. BJOG : an international journal of obstetrics and gynaecology. 2019;126(5):628-35.
11. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Annals of internal medicine. 2010;152(11):726-32.
12. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158(3):200-7.
13. Sandy-Hodgetts K, Carville, K., Santamaria, N., Parsons, R., & Leslie, G. The Perth Surgical Wound Dehiscence Risk Assessment Tool (PSWDRAT): development and prospective validation in the clinical setting. Journal of Wound Care. 2019;28(6):1-11.
14. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727-36.
15. WHO. Implementation Manual Surgical Safety Checklist. 1st ed. Geneva, Switzerland: World Health Organisation; 2008.
16. ACSQH. National Safety and Quality Health Service Standards. 2nd ed. . Sydney:ACSQHC2017.

17. WUWHS Consensus Document. Surgical wound dehiscence: improving prevention and outcomes Wounds International - a division of Omnia-med Ltd; 2018.
18. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infection control and hospital epidemiology. 1992;13(10):606-8.
19. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of medicine. 2001;33(5):337-43.
20. Norman R, Cronin P, Viney R. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. Applied health economics and health policy. 2013;11(3):287-98.
21. Edney LC, Haji Ali Afzali H, Cheng TC, Karnon J. Estimating the Reference Incremental Cost-Effectiveness Ratio for the Australian Health System. PharmacoEconomics. 2018;36(2):239-52.
22. NHMRC. Guidance: Safety monitoring and reporting in clinical trials involving therapuetic goods. Canberra: National Health and Medical Research Council; 2016.
23. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. British Journal of Radiology. 1971;44(526):793-7.
24. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. British journal of cancer. 1976;34(6):585-612.

Figure 1. CYGNUS CONSORT Trial Participant

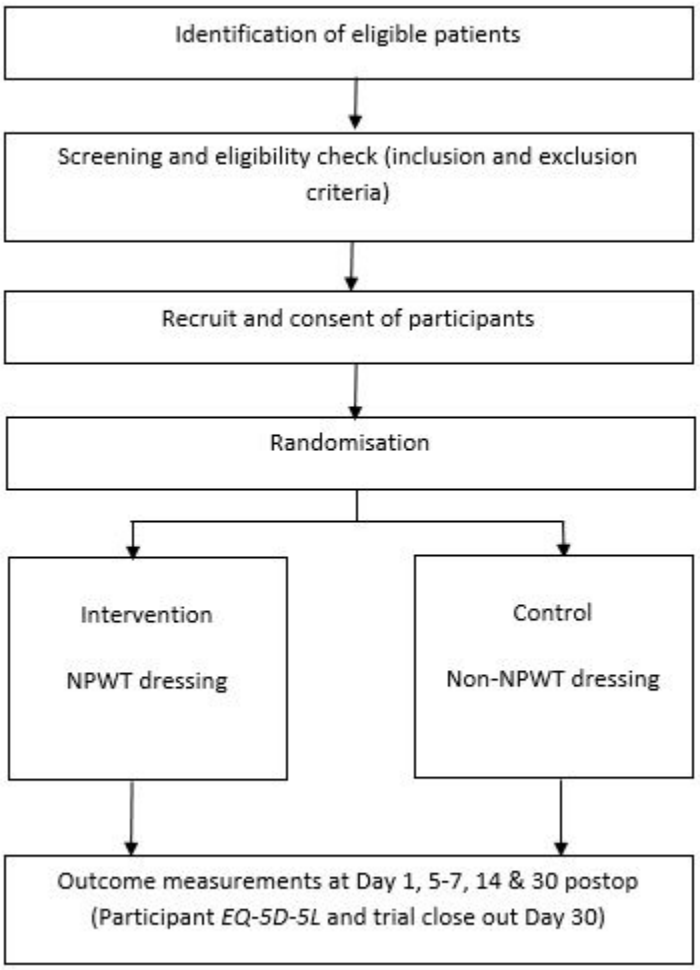

Figure 1. CYGNUS CONSORT Trial Participant

81x98mm (144 x 144 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	12

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
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	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7-8
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	5
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	5

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)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#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)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	8-9

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)	10
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	10-11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
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	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	6

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#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	11

Data collection plan: retention	#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	11
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	11
Statistics: outcomes	#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	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#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)	11
Methods: Monitoring			
Data monitoring: formal committee	#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	12

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	12
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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
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)	12

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6,13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
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	10
Dissemination policy: trial results	#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	12

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6
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	NA

BMJ Open

Effectiveness of negative pressure wound therapy in the prevention of surgical wound complications in the cesarean section at risk population, a parallel group randomised multicentre trial: the CYGNUS protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035727.R2
Article Type:	Protocol
Date Submitted by the Author:	01-Jul-2020
Complete List of Authors:	Sandy-Hodgetts, Kylie; University of Western Australia, Skin Integrity Research Institute, School of Biomedical Sciences Parsons, Richard ; Curtin University Faculty of Health Sciences, School of Occupational Therapy, Social work and Speech Pathology Norman, Richard; Curtin University Faculty of Health Sciences, School of Public Health White, Scott; The University of Western Australia Faculty of Health and Medical Sciences; King Edward Memorial Hospital, Maternal Fetal Medicine Service Fear, Mark; University of Western Australia, Burn Injury Research Unit, School of Biomedical Sciences Wood, Fiona; University of Western Australia, Burn Injury Research Unit, School of Biomedical Sciences; Burns Service of Western Australia, Fiona Stanley and Princess Margaret Hospitals
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Surgery, Evidence based practice
Keywords:	WOUND MANAGEMENT, SURGERY, OBSTETRICS, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

BMJ Open Manuscript

Effectiveness of negative pressure wound therapy in the prevention of surgical wound complications in the cesarean section at risk population: a parallel group randomised multicentre trial, the **CYGNUS** protocol.

1. Dr Kylie Sandy-Hodgetts, BSc, Hons H1, MBA, Ph.D Director Skin Integrity Research Institute, Senior Research Fellow, Burn Injury Research Unit, School of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Western Australia.
2. Dr Richard Parsons, Senior Lecturer in Statistics, School of Occupational Therapy, Social Work and Speech, Curtin University
3. Associate Professor Richard Norman, Health Economist, School of Public Health, Curtin University
4. Dr Mark Fear, Senior Research Fellow, Burns Injury Unit, School of Biomedical Sciences, Faculty of Medicine, University of Western Australia
5. Professor Fiona Wood, Director State Burns Unit, Fiona Stanley Hospital, Perth
6. Dr Scott W White, Senior Lecturer, Consultant Obstetrician, Department of Maternal and Fetal Medicine, King Edward Memorial Hospital

Correspondence to: Dr Kylie Sandy-Hodgetts; kylie.sandy-hodgetts@uwa.edu.au

Abstract word count: 501

Manuscript: 3069 (max 4000 words)

Abstract

Introduction

Caesarean delivery is steadily becoming one of the more common surgical procedures in Australia with over 100, 000 caesarean sections performed each year. Over the last 10 years in Australia, the caesarean section rate has increased from 28% in 2003 to 33% in 2013. On the international stage the Australian caesarean delivery rates are higher than the average for the OECD, Australia ranked as 8 out of 33 and is second to the United States. Postoperative surgical site infections and wound complications are the most common and costly event following caesarean section. Globally, complication rates following caesarean delivery vary from 4.9%-9.8%. Complications such as infection and wound breakdown affect the postpartum mother's health and wellbeing, and contribute to healthcare costs for clinical management that often spans the acute, community and primary health care settings. Published level one studies utilising advanced wound dressings in the identified 'at risk' population prior to surgery, for a prophylactic intervention are yet to be forthcoming.

Methods and analysis

A parallel group randomised control trial of 448 patients will be conducted across two metropolitan hospitals in Perth, Western Australia, which provide obstetric and midwifery services. We will recruit pregnant women in the last trimester, prior to their admission into the health care facility for delivery of their child. We will use a computer generated block sequence to randomise the 448 participants to either the interventional (negative pressure wound therapy dressing, n=224) or comparator arm (non-negative pressure wound therapy dressing, n=224). The primary outcome measure is the occurrence of surgical wound dehiscence or surgical site infection. The Centres for Disease Control reporting definition of either superficial or deep infection at 30 days will be used as the outcome measure definition. Surgical wound dehiscence will be classified as per the World Union of Wound Healing Societies Surgical Wound Dehiscence (SWD) Grading System (Grades I-IV). We

will assess recruitment rate and adherence to intervention and follow up. We will assess the potential effectiveness of negative pressure wound therapy in the prevention of post-partum surgical wound complications at three time points during the study; Day 5 post-operative, Day 14 and Day 30 where the participant will be closed out of the trial. We will utilise statistical methods to determine efficacy and risk stratification will be conducted to determine the surgical wound dehiscence risk profile of the participant. Follow up at Day 30 will assess superficial and deep infection and wound dehiscence (Grades I-IV) and the core outcome dataset for wound complications. This study will collect health related quality of life (ED-5D-5L), mortality and late complications such as further surgery with a cost analysis conducted. The primary analysis will be by intention to treat. This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The trial was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12618002006224) prior to commencement.

Ethics and dissemination

Ethics approval was obtained through St John of God Healthcare (HREC1409), Western Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings will be published in peer-reviewed journals and presented at international conferences. We used the SPIRIT checklist when writing our study protocol.

Trial registration number: ANZCTR: ACTRN12618002006224p

Protocol version and date: Version 3.0, 6 February 2019.

Strengths and limitations of this study

- The CYGNUS trial is a large multicentre trial that will provide important evidence on the effectiveness of a therapy for prevention of a wound complication after caesarean section
- This study will address an important gap in the current evidence for early identification of those at risk prior to surgery
- Pragmatically designed and reviewed by clinicians, and consumer groups to allow for integration into routine clinical practice
- Due to the nature of the intervention, blinding of participants and providers is not possible
- Trial available only to women who have proficiency in English language

This study will recruit from scheduled elective admissions at a tertiary women's hospital with a probable and coincidental inclusion of urgent or emergency cases.

Introduction

Currently in Western Australia the caesarean section delivery rate is reportedly 37% of births compared to the Organisation of Economic and Cooperative Development (OECD) average of 25% (1). Surgical site infection or wound complications such as dehiscence is a common cause of morbidity with reported rates of 4.9%-9.8% in some acute care settings (2-4). The potential risk of surgical wound complications following the caesarean procedure is considerable, and there is still a gap in the literature as to best practice in prevention of wound complications following this type of procedure (2, 3). Several studies in the field have retrospectively investigated the effect of negative pressure wound therapy (NPWT) in the reduction of post-surgical wound complications in the obstetric population (5, 6). However, there is a lack of published level one studies investigating the prophylactic use of NPWT in the prevention of surgical complications in high risk patients with multiple risk factors such as obesity, diabetes and previous caesarean-section (7-9). Whilst a recent study from Odense University Hospital, Denmark has identified an effect of the use of NPWT for patients with one risk factor (BMI 30kg/m^2+) (10), there remain considerable gaps in the evidence addressing those patients at risk with multiple risk factors (i.e., diabetes, smoking, previous caesarean section) which may be more generalizable to an average caesarean section population. The utility of risk stratification and the impact of prophylactic NPWT initiated for use in high-risk cohorts for the prevention of wound dehiscence following a caesarean section remains to be determined. Furthermore, and more importantly, is the measure of patient perception of their wound healing after the procedure. An evidence-based approach is important to inform the development of clinical pathways and protocols in patient management, and this study will form the basis of the development of a postoperative wound management pathway for caesarean section surgery patients both at the participating trial sites, and more broadly in both national and international clinical settings.

Study design

CYGNUS is a parallel group randomised control trial (RCT) testing the effectiveness of an intervention (negative pressure wound therapy dressing) to a control (non-negative pressure wound therapy dressing) with respect to wound healing, complications, cost and health-related quality of life. Figure 1 summaries the design of the trial and each of the trial aspects described below as per Consolidated Standards of Reporting Trials (CONSORT) (11). This study was designed using the SPIRIT checklist (12).

Study aim and objectives

The aim of the CYGNUS trial is to determine the effectiveness of negative pressure wound therapy (intervention) in the prevention of post caesarean section complications in the post-partum mother compared to non-negative pressure wound therapy dressing (control). Our primary objectives are to conduct an RCT to determine the effectiveness of negative pressure wound therapy in prevention of post-operative complications such as surgical wound dehiscence and surgical site infection following a caesarean section in low to high risk cohorts and determine the clinical utility of the intervention. Our secondary objectives are to conduct a health-related quality of life (ED-5D-5L) assessment, and to evaluate patient perceptions of wound healing and pain following the surgical procedure in the intervention and control arms. Finally, we aim to determine the cost-effectiveness of the intervention relative to the control utilising a stepped health economic analysis, concluding with a cost-utility analysis reporting a cost per quality-adjusted life year (QALY).

Study setting

The CYGNUS trial will be conducted in two metropolitan Perth maternity hospitals, over a period of 2 years (October 2019-October 2021). All eligible pregnant women at participating sites will be considered for enrolment.

Study participants and eligibility criteria

Pregnant women eligible for recruitment to the CYGNUS trial are those with a, viable pregnancy and able to provide written informed consent in English and have no known allergies to hydrocolloid, polysiloxanes or silicone resin. Women who are not fluent in English are ineligible to participate.

Recruitment and randomisation

All pregnant women booked for antenatal care will be screened against the eligibility criteria. Participants will be screened according to their risk level using the validated PSWDRAT, which has a number of risk factors embedded into the tool. Any participant who has a score above 2 will be deemed at risk. Eligible participants will receive the CYGNUS Patient Information Sheet (PIS) at least 24 hours prior to their admission booking. This will allow time to consider participation in the trial. The PIS will be accompanied by a letter from the Principal Investigator (PI) informing patients about the trial and inviting them to participate. The PIS will be discussed with eligible women by a member of the research team and potential participants will have the opportunity to discuss the study and ask questions. If a patient wishes to participate they will be provided with a CYGNUS Trial Consent Form where written consent to participate will be sought. The person who interviews the potential study participant and obtains their consent to participate will be blinded to the treatment allocation

schedule. Once consent has been obtained, the staff member who is recruiting the patient will contact the senior research fellow in their site to request the next study identifier and treatment allocation. Baseline participant information, demographic and related medical history will be collected. A participant risk profile for surgical wound dehiscence (SWD) will be obtained utilising the Perth Surgical Wound Dehiscence Risk Assessment Tool (PSWDRAT) (13). This will determine the SWD risk profile of the trial participant. The European Quality of Life 5-Dimensions 5-Level Scale (EQ-5D-5L) (14) a validated questionnaire will be administered at baseline and at the end of the trial to allow estimation of QALYs of all participants. The study statistician will generate the allocation sequence for each site before the study commences, using a random number generator on a computer. There will be a separate sequence for each site, and each sequence will be generated using a permuted random blocks strategy to ensure that recruitment to the two arms of the study occurs at approximately equal rates within each site. The allocation list for each site will be provided to the senior research fellow at each site, and will be kept private from all other personnel at the site. Due the nature of the study device, blinding of participants or study personnel after treatment allocation is not possible. However, the study statistician will be blinded to group allocation.

Patient and public involvement

No patient involvement in the study design.

Post randomisation withdrawals/exclusions

Participants may choose not to participate in the CYGNUS trial or withdraw from the study at any time without prejudice. Choosing either of these options will not affect the standard of care the patient receives.

Study dressings

Participants who elect to have a caesarean section as the chosen method of delivery usually have a scheduled time and day for the procedure. Some patients may be required to undergo an urgent or an emergency caesarean delivery due to a number of uncontrolled factors. Routine antibiotic prophylaxis will be given to patients immediately before surgery and all intraoperative procedures adhere to the WHO (15) surgical site safety checklist and local infection prevention policies in accordance with Australian Commission on Safety and Quality Health Commission National Standard 3: Prevention of Health Care Acquired Complications (16).

Control dressing

The standard dressing for a surgical wound consists of a non-adherent film dressing applied over the incision and directly onto the incision to cover the incision site (Tegaderm™ film dressing, 3M). The control dressing does not use negative pressure over the incision site. The standard wear time of the control dressing is up to and including 7 days. Details of the dressing and wear time will be recorded in the case report forms (CRF's).

Intervention

The Negative Pressure Wound Therapy System (Avelle™ Convatec Pty Ltd), consists of a non-adherent dressing pad with an adhesive cover that adheres to the surrounding skin near the incision site. The dressing pad is attached to a small silent pump via a soft tube that creates a partial vacuum over the wound. The pump delivers a continual negative pressure of 80mmHg and is a battery-operated device. The negative pressure wound therapy pump can operate for up to 30 days, and the dressing can be worn for 7 days as per the manufacturer's recommendation. In this trial, those participants randomised to the

intervention group will receive the portable negative pressure device at Day 0. The dressing will be worn for a standardised period of 5 days (intervention and controls arms). Any further wound dressings after the initial dressing application will be recorded in the CRF's and following the allocated treatment unless otherwise clinically indicated.

Outcome measures

Primary outcome

The primary outcome for this study is surgical wound dehiscence as defined by the WUWHS SWD Grading System (17), and the Centres for Disease Control definitions of SSI (18) will be used as the primary outcome measure for confirmed wound infection. The primary outcome measure definitions include a wound complication that occurs within 30 days of surgery. The treating clinical team will determine the diagnosis of surgical wound dehiscence or infection as per routine clinical wound assessment protocol if there is a confirmed SSI or SWD. Rapid diagnosis and treatment of wound infection is central to patient standard care and the attending clinician will document any changes in the patient medical notes and adhere to local wound management protocols.

Secondary outcomes

Health related quality of life assessment

A qualitative assessment of the participant's perceptions of wound healing will be conducted.

EuroQol EQ-5D-5L

The EuroQol EQ-5D is a validated measure of health related quality of life, comprising a five-dimension health status classification system and a separate Visual Analogue Scale (19). The EQ-5D consists of five dimensions (Mobility, Self-Care, Usual Activities,

Pain/Discomfort, and Anxiety/Depression), each with either 3 or 5 levels. We will use the five-level version of the instrument, which is likely to be more sensitive to small but important changes in health-related quality of life (14). The responses will be converted into an index score, and total QALYs for each woman will be obtained by estimating the area under the curve defined by their baseline and final EQ-5D-5L responses (20).

Economic analysis

All resources utilised in the study will be recorded to help inform the economic analysis. Cost data will be derived from the hospital finance departments and any related community nursing service or primary health care centre where the participant has attended. Cost consequences following discharge including out of pocket expenses (if any) will be recorded in the case report forms at day 30 following the procedure. The incremental cost of the intervention relative to the control will be estimated, and divided by incremental outcomes reported in the study. Each resultant incremental cost-effectiveness ratio (ICER) will be reported separately, with the last step being the cost per QALY. We will conduct univariate and probabilistic sensitivity analyses around the cost per QALY to assess the robustness of the result, with the threshold for cost-effectiveness determined by recent work by Edney *et al.*(21).

Adverse event management

Adverse device effect is an adverse event related to the use of an investigational medical device (IMD) (22). Adverse events (AEs) related to an investigational medical device are defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to in the investigational medical device (22). Definitions of adverse

events (AEs), serious adverse device effect (SADE), serious adverse event (SAE) Significant Safety Issue, Unanticipated Serious Adverse Device Effect (USADE) or Urgent Safety Measure (USM) are as per the National Health and Medical Research Council (2016) Guidelines on Safety monitoring and reporting in clinical trials involving therapeutic goods (22). During the treatment protocol, any USADE will be reported directly to the DSMB and within 7 days to the Australian Government Therapeutics Goods Administration via the electronic Medical Device Incident Reporting System. Reports will also be sent to the local study sites Human Research Ethics Committees. The safety aspects of the study will be closely monitored by the DSMB, which will receive unblinded data for review. In the case of a device related adverse advent the manufacturer will be notified.

Follow up

Each participant will be followed up during the trial as close as practically possible to the specific time points: Day 5, Day 14,and Day 30 following surgery. The close out time point of the trial participant is Day 30 postoperative. In the event that a participant has an unresolved complication beyond 30 days, follow up will continue to complete wound healing, and participants will have the opportunity to opt out of the extended data collection beyond Day 30. All participants will be followed up by the Visiting Midwifery Service (VMS) and a scripted phone call at the trial close out time point. Various forms of communication will be used in engaging the participation, email, phone call and face-to-face consultation to reduce loss to follow up. All data recorded during the follow up time points will be recorded on the case report forms and clinical assessment will follow standard postoperative wound care management and clinical procedures.

Sample size

Participants will be randomised in a 1:1 ratio of trial intervention to control. The sample size calculation is based upon the following estimates: A complication rate of 20% of caesarean section patients was observed following a retrospective medical note audit at the major tertiary women's hospital in Perth. If the intervention can reduce this figure to 10% (a reduction of 50% from the current figure) then a sample of size n=199 in each arm would be required to detect this difference with power=80% and α=0.05. To allow for an attrition rate of 11%, we plan to recruit 224 patients to each arm of the study. The total sample size for the study is 448 participants. Loss to follow up and non-adherence will be reviewed as the trial progresses and numbers will be revised as required.

Data management

The case report forms have been designed by the Senior Research Fellow in consultation with the trial co-investigators. All hard and electronic based patient identifiable information will be stored on a secure password protected database purpose built for the trial. All CRF's will be stored in a locked filing cabinet in a locked office at the participating site. Participants will be identified by a code number only, on the database, but a file linking the code number to the participant name and contact details will be kept separately and securely. This will allow re-identification of the patient for follow-up purposes. Direct access to source data and/or documents may be required for trial related monitoring/audit by the regulatory authorities by written request only. All paper and electronic data will be retained for 5 years after completion of the trial.

Statistical analysis

Simple descriptive statistics (means, SDs, medians, IQR for continuous variables and frequencies and percentages for categorical variables) will be used to summarise the profile of the study participants. Comparison of participants in the two groups (control vs intervention) will be performed using the Chi-square tests or t-tests as appropriate. These tests will be used to identify any differences in baseline characteristics between groups. Recruitment and retention rates will be reported as per the Consolidated Standards of Reporting Trial (CONSORT) (11) statement. Reasons for ineligibility, protocol deviations or participant withdrawal will be stated and any trends reported. A Generalised Estimating Equation (GEE) will be used to analyse each of the primary outcomes over all the time points of the study. This analysis is similar to a Logistic Regression for each of the binary outcome variables, but takes into account the correlation between the repeated measurements made on the same participant. The results of the GEE will be expressed as odds ratios, their 95% confidence intervals and p-values. The GEE model will include a term for the time point, so that changes over time can be assessed, as well as a term for the treatment group allocation (on which the main conclusions of the study will be based). In addition, the GEE model will be extended to include anthropometric measurements (eg: body mass index), presence of health conditions (eg diabetes, hypertension, etc), the recruitment site, and other variables collected at baseline. In this way, variables which are identified as being associated with the outcomes may be used to form a 'risk score' for each outcome. Analysis of the pain scores (which are measured on a continuous scale at each time point through the study), will be performed using a Mixed regression model where the random effect will be the patient identifier, and the time point and treatment allocation group will be fixed effects. The distribution of the pain scores will be assessed for Normality, and transformed to improve Normality (if necessary) prior to analysis.

All statistical analyses will be performed using the SAS version 9.4 software, and, following convention, a p-value < 0.05 will be taken to indicate a significant association in all tests.

Trial oversight

A Trial Committee (TC) and Data Safety Monitoring Board (DSMB) will be set up. The DSMB advocates for the ethical and safety interests of the participants while the trial progresses by making nonbinding recommendations to the TC. A data safety monitoring board will be formed to monitor the study at interim periods: first third participants closed out (n=148) and last quarter closed out. The DSMB consists of three independent reviewers; a statistician, a surgeon and a nurse. The DSMB will be bound by the DSMB Terms of Reference and will provide a written report to the TC. The TC consists of the Principal and site investigators, the study biostatistician and health economist. This trial will utilise the Haybittle-Peto (23, 24) boundary as the designated trial statistic for stopping the trial.

Ethics and dissemination

Ethics approval was obtained through St John of God Healthcare (HREC1409), Western Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings will be published in peer-reviewed journals and presented at local and international conferences. We used the SPIRIT checklist when writing our study protocol.

Discussion on strengths and limitations of the CYGNUS trial

The CYGNUS trial is a designed as a multicenter randomized control trial that is powered to determine treatment effectiveness. This robust study design has been engaged to ensure that any differences between the two arms of the study are attributable to the intervention.

Hyldig et al (2019) have yielded positive findings in the application of negative pressure wound therapy, for potential reduction in the occurrence of surgical wound complications in postpartum mothers who have a BMI 35+ (10). The CYGNUS trial will contribute further research to this particular issue, and is the first to use a prescreening risk assessment tool designed to identify those patients at risk with multiple risk factors. Another strength to this study is a within trial health economic evaluation comparing the negative pressure wound therapy to standard care from multiple health care perspectives. This will include the acute, community and primary health care setting. In light of the increased use of negative pressure wound therapy in patients with high BMI 35+, there remains a considerable gap in the evidence base for clinical or cost effectiveness.

- This study will challenge the current rationale for initiating negative pressure wound therapy based on a single risk factor (BMI 35+), by utilizing a validated risk assessment tool with multiple predictors, which is more reflective of a real world setting.
- Due to the nature of the intervention, blinding of participants and providers is not possible. However, statistical analysis will be blinded.
- The exclusion of emergency cases may result in sample bias and exclude an already 'at risk' cohort.
- Participants will be followed up via face-to-face meetings or telephone call to ensure participant wellbeing and data capture. This may potentially halt any loss to follow up.

Declarations

Funding This work is funded by an unrestricted educational grant from Convatec Pty Ltd. Grant ID UWA52001100. Convatec Pty Ltd., had no input into the design of the study, publications or educational matter related to the study.

Contributions KSH, RP designed the study. KSH wrote the background, methodology and developed the research question with input from RP & SWW. RP wrote the statistical design section and RN wrote the health economic sections of the protocol. Reviews were conducted by MF & FW. All authors reviewed and agreed the final manuscript.

Competing interests None declared

Patient consent Patient consent will be sought to participate in the study via written informed consent

Provenance and peer review Not commissioned, externally peer reviewed

References

1. AIHW. Mothers and babies. 'Australia's mothers and babies 2013—in brief. Perinatal statistics series no. 31'. Canberra: AIHW 2017.
2. Wilson J, Wloch C, Saei A, McDougall C, Harrington P, Charlett A, et al. Inter-hospital comparison of rates of surgical site infection following caesarean section delivery: evaluation of a multicentre surveillance study. The Journal of hospital infection. 2013;84(1):44-51.
3. Wloch C, Wilson J, Lamagni T, Harrington P, Charlett A, Sheridan E. Risk factors for surgical site infection following caesarean section in England: results from a multicentre cohort study. BJOG : an international journal of obstetrics and gynaecology. 2012;119(11):1324-33.
4. Ward VP, Charlett A, Fagan J, Crawshaw SC. Enhanced surgical site infection surveillance following caesarean section: experience of a multicentre collaborative post-discharge system. The Journal of hospital infection. 2008;70(2):166-73.
5. Orth TA, Gerkovich MM, Heitmann E, Overcash J, Gibbs C, Parrish M. Cesarean Delivery with External Negative Pressure Dressing System: A Retrospective Cohort Study. Surgery journal (New York, NY). 2016;2(3):e59-e65.
6. Smid MC, Dotters-Katz SK, Grace M, Wright ST, Villers MS, Hardy-Fairbanks A, et al. Prophylactic Negative Pressure Wound Therapy for Obese Women After Cesarean Delivery: A Systematic Review and Meta-analysis. Obstetrics and gynecology. 2017;130(5):969-78.
7. Shree R, Park SY, Beigi RH, Dunn SL, Krans EE. Surgical Site Infection following Cesarean Delivery: Patient, Provider, and Procedure-Specific Risk Factors. American journal of perinatology. 2016;33(2):157-64.
8. Schneid-Kofman N, Sheiner, E., Levy, A., Holcberg., G. Risk factors for wound infection following caesarean deliveries. International Journal Gynaecology Obstetrics. 2005;90(1):10-5.
9. Krieger Y, Walfisch A, Sheiner E. Surgical site infection following cesarean deliveries: trends and risk factors. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2017;30(1):8-12.
10. Hyldig N, Vinter CA, Kruse M, Mogensen O, Bille C, Sorensen JA, et al. Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: a pragmatic randomised clinical trial. BJOG : an international journal of obstetrics and gynaecology. 2019;126(5):628-35.
11. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Annals of internal medicine. 2010;152(11):726-32.
12. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158(3):200-7.

13. Sandy-Hodgetts K, Carville, K., Santamaria, N., Parsons, R., & Leslie, G. The Perth Surgical Wound Dehiscence Risk Assessment Tool (PSWDRAT): development and prospective validation in the clinical setting. Journal of Wound Care. 2019;28(6):1-11.
14. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727-36.
15. WHO. Implementation Manual Surgical Safety Checklist. 1st ed. Geneva, Switzerland: World Health Organisation; 2008.
16. ACSQH. National Safety and Quality Health Service Standards. 2nd ed. . Sydney:ACSQHC2017.
17. Societies WUoWH. Consensus Document. Surgical wound dehiscence: improving prevention and outcomes Wounds International - a division of Omnia-med Ltd; 2018.
18. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infection control and hospital epidemiology. 1992;13(10):606-8.
19. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of medicine. 2001;33(5):337-43.
20. Norman R, Cronin P, Viney R. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. Applied health economics and health policy. 2013;11(3):287-98.
21. Edney LC, Haji Ali Afzali H, Cheng TC, Karnon J. Estimating the Reference Incremental Cost-Effectiveness Ratio for the Australian Health System. PharmacoEconomics. 2018;36(2):239-52.
22. NHMRC. Guidance: Safety monitoring and reporting in clinical trials involving therapuetic goods. Canberra: National Health and Medical Research Council; 2016.
23. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. British Journal of Radiology. 1971;44(526):793-7.
24. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. British journal of cancer. 1976;34(6):585-612.

Figure 1. CYGNUS CONSORT Trial Participant

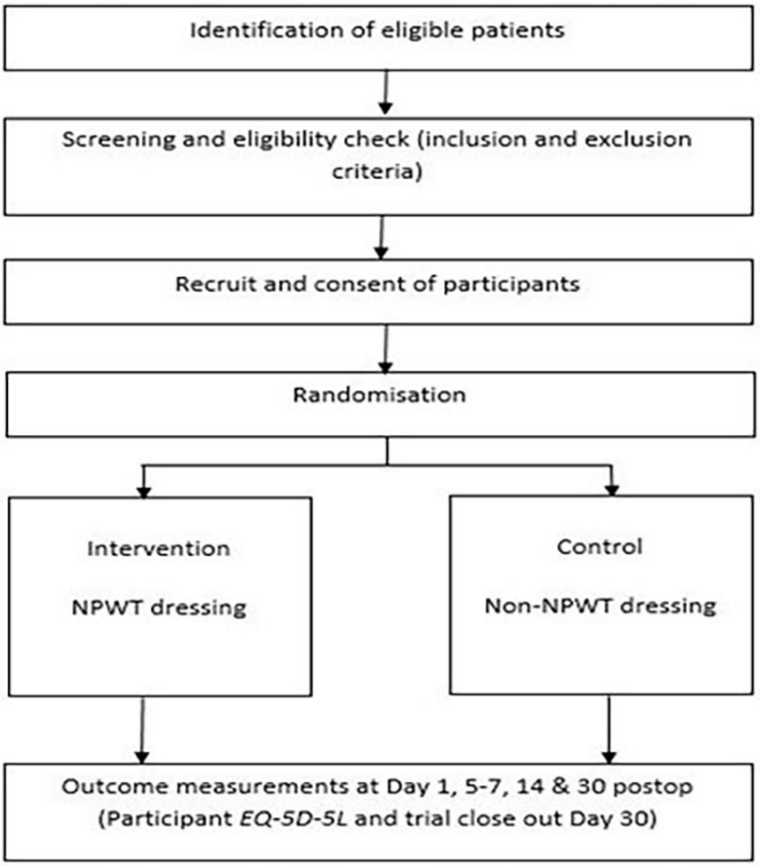

Figure 1. CYGNUS Trial CONSORT

89x90mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	12

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
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	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7-8
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	5
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	5

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)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#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)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	8-9

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)	10
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	10-11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
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	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	6

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#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	11

Data collection plan: retention	#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	11
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	11
Statistics: outcomes	#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	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#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)	11
Methods: Monitoring			
Data monitoring: formal committee	#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	12

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	12
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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
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)	12

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6,13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
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	10
Dissemination policy: trial results	#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	12

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6
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	NA

BMJ Open

Effectiveness of negative pressure wound therapy in the prevention of surgical wound complications in the cesarean section at risk population: a parallel group randomised multicentre trial, the CYGNUS protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035727.R3
Article Type:	Protocol
Date Submitted by the Author:	15-Sep-2020
Complete List of Authors:	Sandy-Hodgetts, Kylie; University of Western Australia, Skin Integrity Research Institute, School of Biomedical Sciences Parsons, Richard ; Curtin University Faculty of Health Sciences, School of Occupational Therapy, Social work and Speech Pathology Norman, Richard; Curtin University Faculty of Health Sciences, School of Public Health Fear, Mark; University of Western Australia, Burn Injury Research Unit, School of Biomedical Sciences Wood, Fiona; University of Western Australia, Burn Injury Research Unit, School of Biomedical Sciences; Burns Service of Western Australia, Fiona Stanley and Princess Margaret Hospitals White, Scott; The University of Western Australia Faculty of Health and Medical Sciences; King Edward Memorial Hospital, Maternal Fetal Medicine Service
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Surgery, Evidence based practice
Keywords:	WOUND MANAGEMENT, SURGERY, OBSTETRICS, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

BMJ Open Manuscript

Effectiveness of negative pressure wound therapy in the prevention of surgical wound complications in the cesarean section at risk population: a parallel group randomised multicentre trial, the **CYGNUS** protocol.

1. Dr Kylie Sandy-Hodgetts, BSc, Hons H1, MBA, Ph.D Director Skin Integrity Research Institute, Senior Research Fellow, Burn Injury Research Unit, School of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Western Australia.
2. Dr Richard Parsons, Senior Lecturer in Statistics, School of Occupational Therapy, Social Work and Speech, Curtin University
3. Associate Professor Richard Norman, Health Economist, School of Public Health, Curtin University
4. Dr Mark Fear, Senior Research Fellow, Burns Injury Unit, School of Biomedical Sciences, Faculty of Medicine, University of Western Australia
5. Professor Fiona Wood, Director State Burns Unit, Fiona Stanley Hospital, Perth
6. Dr Scott W White, Senior Lecturer, Consultant Obstetrician, Department of Maternal and Fetal Medicine, King Edward Memorial Hospital

Correspondence to: Dr Kylie Sandy-Hodgetts; kylie.sandy-hodgetts@uwa.edu.au

Abstract word count: 501

Manuscript: 3069 (max 4000 words)

Abstract

Introduction

Caesarean delivery is steadily becoming one of the more common surgical procedures in Australia with over 100, 000 caesarean sections performed each year. Over the last 10 years in Australia, the caesarean section rate has increased from 28% in 2003 to 33% in 2013. On the international stage the Australian caesarean delivery rates are higher than the average for the OECD, Australia ranked as 8 out of 33 and is second to the United States. Postoperative surgical site infections and wound complications are the most common and costly event following caesarean section. Globally, complication rates following caesarean delivery vary from 4.9%-9.8%. Complications such as infection and wound breakdown affect the postpartum mother's health and wellbeing, and contribute to healthcare costs for clinical management that often spans the acute, community and primary health care settings. Published level one studies utilising advanced wound dressings in the identified 'at risk' population prior to surgery, for a prophylactic intervention are yet to be forthcoming.

Methods and analysis

A parallel group randomised control trial of 448 patients will be conducted across two metropolitan hospitals in Perth, Western Australia, which provide obstetric and midwifery services. We will recruit pregnant women in the last trimester, prior to their admission into the health care facility for delivery of their child. We will use a computer generated block sequence to randomise the 448 participants to either the interventional (negative pressure wound therapy dressing, n=224) or comparator arm (non-negative pressure wound therapy dressing, n=224). The primary outcome measure is the occurrence of surgical wound dehiscence or surgical site infection. The Centres for Disease Control reporting definition of either superficial or deep infection at 30 days will be used as the outcome measure definition. Surgical wound dehiscence will be classified as per the World Union of Wound Healing Societies Surgical Wound Dehiscence (SWD) Grading System (Grades I-IV). We

will assess recruitment rate and adherence to intervention and follow up. We will assess the potential effectiveness of negative pressure wound therapy in the prevention of post-partum surgical wound complications at three time points during the study; Day 5 post-operative, Day 14 and Day 30 where the participant will be closed out of the trial. We will utilise statistical methods to determine efficacy and risk stratification will be conducted to determine the surgical wound dehiscence risk profile of the participant. Follow up at Day 30 will assess superficial and deep infection and wound dehiscence (Grades I-IV) and the core outcome dataset for wound complications. This study will collect health related quality of life (ED-5D-5L), mortality and late complications such as further surgery with a cost analysis conducted. The primary analysis will be by intention to treat. This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The trial was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12618002006224) prior to commencement.

Ethics and dissemination

Ethics approval was obtained through St John of God Healthcare (HREC1409), Western Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings will be published in peer-reviewed journals and presented at international conferences. We used the SPIRIT checklist when writing our study protocol.

Trial registration number: ANZCTR: ACTRN12618002006224p

Protocol version and date: Version 3.0, 6 February 2019.

Strengths and limitations of this study

- The CYGNUS trial is a large multicentre trial that will provide important evidence on the effectiveness of a therapy for prevention of a wound complication after caesarean section
- This study will address an important gap in the current evidence for early identification of those at risk prior to surgery
- Pragmatically designed and reviewed by clinicians, and consumer groups to allow for integration into routine clinical practice
- Due to the nature of the intervention, blinding of participants and providers is not possible
- Trial available only to women who have proficiency in English language

This study will recruit from scheduled elective admissions at a tertiary women's hospital with a probable and coincidental inclusion of urgent or emergency cases.

Introduction

Currently in Western Australia the caesarean section delivery rate is reportedly 37% of births compared to the Organisation of Economic and Cooperative Development (OECD) average of 25% (1). Surgical site infection or wound complications such as dehiscence is a common cause of morbidity with reported rates of 4.9%-9.8% in some acute care settings (2-4). The potential risk of surgical wound complications following the caesarean procedure is considerable, and there is still a gap in the literature as to best practice in prevention of wound complications following this type of procedure (2, 3). Several studies in the field have retrospectively investigated the effect of negative pressure wound therapy (NPWT) in the reduction of post-surgical wound complications in the obstetric population (5, 6). However, there is a lack of published level one studies investigating the prophylactic use of NPWT in the prevention of surgical complications in high risk patients with multiple risk factors such as obesity, diabetes and previous caesarean-section (7-9). Whilst a recent study from Odense University Hospital, Denmark has identified an effect of the use of NPWT for patients with one risk factor (BMI 30kg/m^2+) (10), there remain considerable gaps in the evidence addressing those patients at risk with multiple risk factors (i.e., diabetes, smoking, previous caesarean section) which may be more generalizable to an average caesarean section population. The utility of risk stratification and the impact of prophylactic NPWT initiated for use in high-risk cohorts for the prevention of wound dehiscence following a caesarean section remains to be determined. Furthermore, and more importantly, is the measure of patient perception of their wound healing after the procedure. An evidence-based approach is important to inform the development of clinical pathways and protocols in patient management, and this study will form the basis of the development of a postoperative wound management pathway for caesarean section surgery patients both at the participating trial sites, and more broadly in both national and international clinical settings.

Study design

CYGNUS is a parallel group randomised control trial (RCT) testing the effectiveness of an intervention (negative pressure wound therapy dressing) to a control (non-negative pressure wound therapy dressing) with respect to wound healing, complications, cost and health-related quality of life. Figure 1 summaries the design of the trial and each of the trial aspects described below as per Consolidated Standards of Reporting Trials (CONSORT) (11). This study was designed using the SPIRIT checklist (12).

Study aim and objectives

The aim of the CYGNUS trial is to determine the effectiveness of negative pressure wound therapy (intervention) in the prevention of post caesarean section complications in the post-partum mother compared to non-negative pressure wound therapy dressing (control). Our primary objectives are to conduct an RCT to determine the effectiveness of negative pressure wound therapy in prevention of post-operative complications such as surgical wound dehiscence and surgical site infection following a caesarean section in low to high risk cohorts and determine the clinical utility of the intervention. Our secondary objectives are to conduct a health-related quality of life (ED-5D-5L) assessment, and to evaluate patient perceptions of wound healing and pain following the surgical procedure in the intervention and control arms. Finally, we aim to determine the cost-effectiveness of the intervention relative to the control utilising a stepped health economic analysis, concluding with a cost-utility analysis reporting a cost per quality-adjusted life year (QALY).

Study setting

The CYGNUS trial will be conducted in two metropolitan Perth maternity hospitals, over a period of 2 years (October 2019-October 2021). All eligible pregnant women at participating sites will be considered for enrolment.

Study participants and eligibility criteria

Pregnant women eligible for recruitment to the CYGNUS trial are those with a, viable pregnancy and able to provide written informed consent in English and have no known allergies to hydrocolloid, polysiloxanes or silicone resin. Women who are not fluent in English are ineligible to participate.

Recruitment and randomisation

All pregnant women booked for antenatal care will be screened against the eligibility criteria. Participants will be screened according to their risk level using the validated PSWDRAT, which has a number of risk factors embedded into the tool. Any participant who has a score above 2 will be deemed at risk. Eligible participants will receive the CYGNUS Patient Information Sheet (PIS) at least 24 hours prior to their admission booking. This will allow time to consider participation in the trial. The PIS will be accompanied by a letter from the Principal Investigator (PI) informing patients about the trial and inviting them to participate. The PIS will be discussed with eligible women by a member of the research team and potential participants will have the opportunity to discuss the study and ask questions. If a patient wishes to participate they will be provided with a CYGNUS Trial Consent Form where written consent to participate will be sought. The person who interviews the potential study participant and obtains their consent to participate will be blinded to the treatment allocation

schedule. Once consent has been obtained, the staff member who is recruiting the patient will contact the senior research fellow in their site to request the next study identifier and treatment allocation. Baseline participant information, demographic and related medical history will be collected. A participant risk profile for surgical wound dehiscence (SWD) will be obtained utilising the Perth Surgical Wound Dehiscence Risk Assessment Tool (PSWDRAT) (13). This will determine the SWD risk profile of the trial participant. The European Quality of Life 5-Dimensions 5-Level Scale (EQ-5D-5L) (14) a validated questionnaire will be administered at baseline and at the end of the trial to allow estimation of QALYs of all participants. The study statistician will generate the allocation sequence for each site before the study commences, using a random number generator on a computer. There will be a separate sequence for each site, and each sequence will be generated using a permuted random blocks strategy to ensure that recruitment to the two arms of the study occurs at approximately equal rates within each site. The allocation list for each site will be provided to the senior research fellow at each site, and will be kept private from all other personnel at the site. Due the nature of the study device, blinding of participants or study personnel after treatment allocation is not possible. However, the study statistician will be blinded to group allocation.

Patient and public involvement

No patient involvement in the study design.

Post randomisation withdrawals/exclusions

Participants may choose not to participate in the CYGNUS trial or withdraw from the study at any time without prejudice. Choosing either of these options will not affect the standard of care the patient receives.

Study dressings

Participants who elect to have a caesarean section as the chosen method of delivery usually have a scheduled time and day for the procedure. Some patients may be required to undergo an urgent or an emergency caesarean delivery due to a number of uncontrolled factors. Routine antibiotic prophylaxis will be given to patients immediately before surgery and all intraoperative procedures adhere to the WHO (15) surgical site safety checklist and local infection prevention policies in accordance with Australian Commission on Safety and Quality Health Commission National Standard 3: Prevention of Health Care Acquired Complications (16).

Control dressing

The standard dressing for a surgical wound consists of a non-adherent film dressing applied over the incision and directly onto the incision to cover the incision site (Tegaderm™ film dressing, 3M). The control dressing does not use negative pressure over the incision site. The standard wear time of the control dressing is up to and including 7 days. Details of the dressing and wear time will be recorded in the case report forms (CRF's).

Intervention

The Negative Pressure Wound Therapy System (Avelle™ Convatec Pty Ltd), consists of a non-adherent dressing pad with an adhesive cover that adheres to the surrounding skin near the incision site. The dressing pad is attached to a small silent pump via a soft tube that creates a partial vacuum over the wound. The pump delivers a continual negative pressure of 80mmHg and is a battery-operated device. The negative pressure wound therapy pump can operate for up to 30 days, and the dressing can be worn for 7 days as per the manufacturer's recommendation. In this trial, those participants randomised to the

intervention group will receive the portable negative pressure device at Day 0. The dressing will be worn for a standardised period of 5 days (intervention and controls arms). Any further wound dressings after the initial dressing application will be recorded in the CRF's and following the allocated treatment unless otherwise clinically indicated.

Outcome measures

Primary outcome

The primary outcome for this study is surgical wound dehiscence as defined by the WUWHS SWD Grading System (17), and the Centres for Disease Control definitions of SSI (18) will be used as the primary outcome measure for confirmed wound infection. The primary outcome measure definitions include a wound complication that occurs within 30 days of surgery. The treating clinical team will determine the diagnosis of surgical wound dehiscence or infection as per routine clinical wound assessment protocol if there is a confirmed SSI or SWD. Rapid diagnosis and treatment of wound infection is central to patient standard care and the attending clinician will document any changes in the patient medical notes and adhere to local wound management protocols.

Secondary outcomes

Health related quality of life assessment

A qualitative assessment of the participant's perceptions of wound healing will be conducted.

EuroQol EQ-5D-5L

The EuroQol EQ-5D is a validated measure of health related quality of life, comprising a five-dimension health status classification system and a separate Visual Analogue Scale (19). The EQ-5D consists of five dimensions (Mobility, Self-Care, Usual Activities,

Pain/Discomfort, and Anxiety/Depression), each with either 3 or 5 levels. We will use the five-level version of the instrument, which is likely to be more sensitive to small but important changes in health-related quality of life (14). The responses will be converted into an index score, and total QALYs for each woman will be obtained by estimating the area under the curve defined by their baseline and final EQ-5D-5L responses (20).

Economic analysis

All resources utilised in the study will be recorded to help inform the economic analysis. Cost data will be derived from the hospital finance departments and any related community nursing service or primary health care centre where the participant has attended. Cost consequences following discharge including out of pocket expenses (if any) will be recorded in the case report forms at day 30 following the procedure. The incremental cost of the intervention relative to the control will be estimated, and divided by incremental outcomes reported in the study. Each resultant incremental cost-effectiveness ratio (ICER) will be reported separately, with the last step being the cost per QALY. We will conduct univariate and probabilistic sensitivity analyses around the cost per QALY to assess the robustness of the result, with the threshold for cost-effectiveness determined by recent work by Edney *et al.*(21).

Adverse event management

Adverse device effect is an adverse event related to the use of an investigational medical device (IMD) (22). Adverse events (AEs) related to an investigational medical device are defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to in the investigational medical device (22). Definitions of adverse

events (AEs), serious adverse device effect (SADE), serious adverse event (SAE) Significant Safety Issue, Unanticipated Serious Adverse Device Effect (USADE) or Urgent Safety Measure (USM) are as per the National Health and Medical Research Council (2016) Guidelines on Safety monitoring and reporting in clinical trials involving therapeutic goods (22). During the treatment protocol, any USADE will be reported directly to the DSMB and within 7 days to the Australian Government Therapeutics Goods Administration via the electronic Medical Device Incident Reporting System. Reports will also be sent to the local study sites Human Research Ethics Committees. The safety aspects of the study will be closely monitored by the DSMB, which will receive unblinded data for review. In the case of a device related adverse advent the manufacturer will be notified.

Follow up

Each participant will be followed up during the trial as close as practically possible to the specific time points: Day 5, Day 14,and Day 30 following surgery. The close out time point of the trial participant is Day 30 postoperative. In the event that a participant has an unresolved complication beyond 30 days, follow up will continue to complete wound healing, and participants will have the opportunity to opt out of the extended data collection beyond Day 30. All participants will be followed up by the Visiting Midwifery Service (VMS) and a scripted phone call at the trial close out time point. Various forms of communication will be used in engaging the participation, email, phone call and face-to-face consultation to reduce loss to follow up. All data recorded during the follow up time points will be recorded on the case report forms and clinical assessment will follow standard postoperative wound care management and clinical procedures.

Sample size

Participants will be randomised in a 1:1 ratio of trial intervention to control. The sample size calculation is based upon the following estimates: A complication rate of 20% of caesarean section patients was observed following a retrospective medical note audit at the major tertiary women's hospital in Perth. If the intervention can reduce this figure to 10% (a reduction of 50% from the current figure) then a sample of size n=199 in each arm would be required to detect this difference with power=80% and α=0.05. To allow for an attrition rate of 11%, we plan to recruit 224 patients to each arm of the study. The total sample size for the study is 448 participants. Loss to follow up and non-adherence will be reviewed as the trial progresses and numbers will be revised as required.

Data management

The case report forms have been designed by the Senior Research Fellow in consultation with the trial co-investigators. All hard and electronic based patient identifiable information will be stored on a secure password protected database purpose built for the trial. All CRF's will be stored in a locked filing cabinet in a locked office at the participating site. Participants will be identified by a code number only, on the database, but a file linking the code number to the participant name and contact details will be kept separately and securely. This will allow re-identification of the patient for follow-up purposes. Direct access to source data and/or documents may be required for trial related monitoring/audit by the regulatory authorities by written request only. All paper and electronic data will be retained for 5 years after completion of the trial.

Statistical analysis

Simple descriptive statistics (means, SDs, medians, IQR for continuous variables and frequencies and percentages for categorical variables) will be used to summarise the profile of the study participants. Comparison of participants in the two groups (control vs intervention) will be performed using the Chi-square tests or t-tests as appropriate. These tests will be used to identify any differences in baseline characteristics between groups. Recruitment and retention rates will be reported as per the Consolidated Standards of Reporting Trial (CONSORT) (11) statement. Reasons for ineligibility, protocol deviations or participant withdrawal will be stated and any trends reported. A Generalised Estimating Equation (GEE) will be used to analyse each of the primary outcomes over all the time points of the study. This analysis is similar to a Logistic Regression for each of the binary outcome variables, but takes into account the correlation between the repeated measurements made on the same participant. The results of the GEE will be expressed as odds ratios, their 95% confidence intervals and p-values. The GEE model will include a term for the time point, so that changes over time can be assessed, as well as a term for the treatment group allocation (on which the main conclusions of the study will be based). In addition, the GEE model will be extended to include anthropometric measurements (eg: body mass index), presence of health conditions (eg diabetes, hypertension, etc), the recruitment site, and other variables collected at baseline. In this way, variables which are identified as being associated with the outcomes may be used to form a 'risk score' for each outcome. Analysis of the pain scores (which are measured on a continuous scale at each time point through the study), will be performed using a Mixed regression model where the random effect will be the patient identifier, and the time point and treatment allocation group will be fixed effects. The distribution of the pain scores will be assessed for Normality, and transformed to improve Normality (if necessary) prior to analysis.

All statistical analyses will be performed using the SAS version 9.4 software, and, following convention, a p-value < 0.05 will be taken to indicate a significant association in all tests.

Trial oversight

A Trial Committee (TC) and Data Safety Monitoring Board (DSMB) will be set up. The DSMB advocates for the ethical and safety interests of the participants while the trial progresses by making nonbinding recommendations to the TC. A data safety monitoring board will be formed to monitor the study at interim periods: first third participants closed out (n=148) and last quarter closed out. The DSMB consists of three independent reviewers; a statistician, a surgeon and a nurse. The DSMB will be bound by the DSMB Terms of Reference and will provide a written report to the TC. The TC consists of the Principal and site investigators, the study biostatistician and health economist. This trial will utilise the Haybittle-Peto (23, 24) boundary as the designated trial statistic for stopping the trial.

Ethics and dissemination

Ethics approval was obtained through St John of God Healthcare (HREC1409), Western Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings will be published in peer-reviewed journals and presented at local and international conferences. We used the SPIRIT checklist when writing our study protocol.

Discussion on strengths and limitations of the CYGNUS trial

The CYGNUS trial is a designed as a multicenter randomized control trial that is powered to determine treatment effectiveness. This robust study design has been engaged to ensure that any differences between the two arms of the study are attributable to the intervention.

Hyldig et al (2019) have yielded positive findings in the application of negative pressure wound therapy, for potential reduction in the occurrence of surgical wound complications in postpartum mothers who have a BMI 35+ (10). The CYGNUS trial will contribute further research to this particular issue, and is the first to use a prescreening risk assessment tool designed to identify those patients at risk with multiple risk factors. Another strength to this study is a within trial health economic evaluation comparing the negative pressure wound therapy to standard care from multiple health care perspectives. This will include the acute, community and primary health care setting. In light of the increased use of negative pressure wound therapy in patients with high BMI 35+, there remains a considerable gap in the evidence base for clinical or cost effectiveness.

- This study will challenge the current rationale for initiating negative pressure wound therapy based on a single risk factor (BMI 35+), by utilizing a validated risk assessment tool with multiple predictors, which is more reflective of a real world setting.
- Due to the nature of the intervention, blinding of participants and providers is not possible. However, statistical analysis will be blinded.
- The exclusion of emergency cases may result in sample bias and exclude an already 'at risk' cohort.
- Participants will be followed up via face-to-face meetings or telephone call to ensure participant wellbeing and data capture. This may potentially halt any loss to follow up.

Declarations

Funding This work is funded by an unrestricted educational grant from Convatec Pty Ltd. Grant ID UWA52001100. Convatec Pty Ltd., had no input into the design of the study, publications or educational matter related to the study.

Contributions KSH, RP designed the study. KSH wrote the background, methodology and developed the research question with input from RP & SWW. RP wrote the statistical design section and RN wrote the health economic sections of the protocol. Reviews were conducted by MF & FW. All authors reviewed and agreed the final manuscript.

Competing interests None declared

Patient consent Patient consent will be sought to participate in the study via written informed consent

Provenance and peer review Not commissioned, externally peer reviewed

References

1. AIHW. Mothers and babies. 'Australia's mothers and babies 2013—in brief. Perinatal statistics series no. 31'. Canberra: AIHW 2017.
2. Wilson J, Wloch C, Saei A, McDougall C, Harrington P, Charlett A, et al. Inter-hospital comparison of rates of surgical site infection following caesarean section delivery: evaluation of a multicentre surveillance study. The Journal of hospital infection. 2013;84(1):44-51.
3. Wloch C, Wilson J, Lamagni T, Harrington P, Charlett A, Sheridan E. Risk factors for surgical site infection following caesarean section in England: results from a multicentre cohort study. BJOG : an international journal of obstetrics and gynaecology. 2012;119(11):1324-33.
4. Ward VP, Charlett A, Fagan J, Crawshaw SC. Enhanced surgical site infection surveillance following caesarean section: experience of a multicentre collaborative post-discharge system. The Journal of hospital infection. 2008;70(2):166-73.
5. Orth TA, Gerkovich MM, Heitmann E, Overcash J, Gibbs C, Parrish M. Cesarean Delivery with External Negative Pressure Dressing System: A Retrospective Cohort Study. Surgery journal (New York, NY). 2016;2(3):e59-e65.
6. Smid MC, Dotters-Katz SK, Grace M, Wright ST, Villers MS, Hardy-Fairbanks A, et al. Prophylactic Negative Pressure Wound Therapy for Obese Women After Cesarean Delivery: A Systematic Review and Meta-analysis. Obstetrics and gynecology. 2017;130(5):969-78.
7. Shree R, Park SY, Beigi RH, Dunn SL, Krans EE. Surgical Site Infection following Cesarean Delivery: Patient, Provider, and Procedure-Specific Risk Factors. American journal of perinatology. 2016;33(2):157-64.
8. Schneid-Kofman N, Sheiner, E., Levy, A., Holcberg., G. Risk factors for wound infection following caesarean deliveries. International Journal Gynaecology Obstetrics. 2005;90(1):10-5.
9. Krieger Y, Walfisch A, Sheiner E. Surgical site infection following cesarean deliveries: trends and risk factors. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2017;30(1):8-12.
10. Hyldig N, Vinter CA, Kruse M, Mogensen O, Bille C, Sorensen JA, et al. Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: a pragmatic randomised clinical trial. BJOG : an international journal of obstetrics and gynaecology. 2019;126(5):628-35.
11. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Annals of internal medicine. 2010;152(11):726-32.
12. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158(3):200-7.

13. Sandy-Hodgetts K, Carville, K., Santamaria, N., Parsons, R., & Leslie, G. The Perth Surgical Wound Dehiscence Risk Assessment Tool (PSWDRAT): development and prospective validation in the clinical setting. Journal of Wound Care. 2019;28(6):1-11.
14. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727-36.
15. WHO. Implementation Manual Surgical Safety Checklist. 1st ed. Geneva, Switzerland: World Health Organisation; 2008.
16. ACSQH. National Safety and Quality Health Service Standards. 2nd ed. . Sydney:ACSQHC2017.
17. Societies WUoWH. Consensus Document. Surgical wound dehiscence: improving prevention and outcomes Wounds International - a division of Omnia-med Ltd; 2018.
18. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infection control and hospital epidemiology. 1992;13(10):606-8.
19. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of medicine. 2001;33(5):337-43.
20. Norman R, Cronin P, Viney R. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. Applied health economics and health policy. 2013;11(3):287-98.
21. Edney LC, Haji Ali Afzali H, Cheng TC, Karnon J. Estimating the Reference Incremental Cost-Effectiveness Ratio for the Australian Health System. PharmacoEconomics. 2018;36(2):239-52.
22. NHMRC. Guidance: Safety monitoring and reporting in clinical trials involving therapuetic goods. Canberra: National Health and Medical Research Council; 2016.
23. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. British Journal of Radiology. 1971;44(526):793-7.
24. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. British journal of cancer. 1976;34(6):585-612.

Figure 1. CYGNUS CONSORT Trial Participant

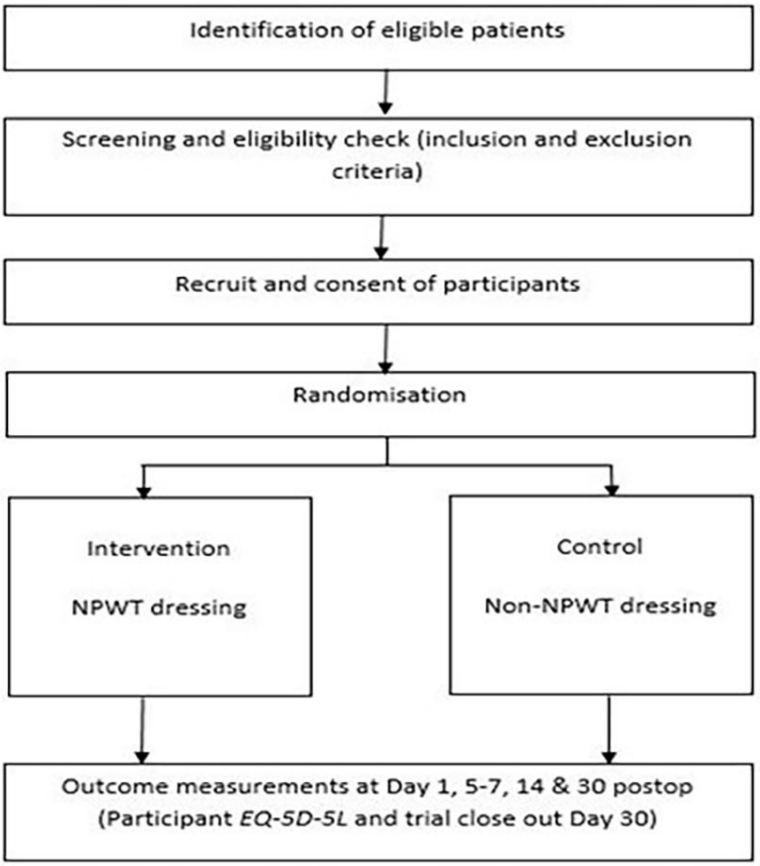

Figure 1. CYGNUS Trial CONSORT

89x90mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	12

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
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	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7-8
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	5
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	5

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)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#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)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	8-9

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)	10
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	10-11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
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	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	6

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#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	11

Data collection plan: retention	#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	11
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	11
Statistics: outcomes	#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	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#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)	11
Methods: Monitoring			
Data monitoring: formal committee	#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	12

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#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	12
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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
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)	12

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6,13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
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	10
Dissemination policy: trial results	#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	12

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6
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	NA