

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3 BMJ Open Manuscript
4
5
6
7

8 Efficacy of negative pressure wound therapy in the prevention of surgical wound
9 complications in the cesarean section at risk population: a parallel group randomised
10
11
12
13 multicentre trial, the **CYGNUS** protocol.
14
15
16
17

- 18 1. Dr Kylie Sandy-Hodgetts, BSc, Hons H1, MBA, Ph.D Director Skin Integrity Clinical
19 Trials Unit, Senior Research Fellow, Burn Injury Research Unit, School of Biomedical
20 Sciences, Faculty of Health and Medical Sciences, University of Western Australia.
21
22
- 23 2. Dr Richard Parsons, Senior Lecturer in Statistics, School of Occupational Therapy,
24 Social Work and Speech, Curtin University
25
26
- 27 3. Associate Professor Richard Norman, Health Economist, School of Public Health,
28 Curtin University
29
30
- 31 4. Dr Scott White, Senior Lecturer, Consultant Obstetrician, Department of Maternal
32 and Fetal Medicine, King Edward Memorial Hospital
33
34
- 35 5. Dr Mark Fear, Senior Research Fellow, Burns Injury Unit, School of Biomedical
36 Sciences, Faculty of Medicine, University of Western Australia
37
38
- 39 6. Professor Fiona Wood, Director State Burns Unit, Fiona Stanley Hospital, Perth.
40
41
42
43
44
45

46 Correspondence to: Dr Kylie Sandy-Hodgetts; kylie.sandy-hodgetts@uwa.edu.au
47
48

49 Abstract word count: 501
50

51 Manuscript: 3069 (max 4000 words)
52
53
54
55
56
57
58
59
60

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

1
2
3 wound complications at three time points during the study; Day 5 post-operative, Day 14 and
4 Day 30 where the participant will be closed out of the trial. We will utilise statistical methods
5 to determine efficacy and risk stratification will be conducted to determine the surgical wound
6 dehiscence risk profile of the participant. Follow up at Day 30 will assess superficial and
7 deep infection and wound dehiscence (Grades I-IV) and the core outcome dataset for wound
8 complications. This study will collect health related quality of life (ED-5D-5L), mortality and
9 late complications such as further surgery with a cost analysis conducted. The primary
10 analysis will be by intention to treat.
11
12
13
14
15
16
17
18
19

20
21 **Trial registration number:** ANZCTR: ACTRN12618002006224p
22

23 **Protocol version and date:** Version 3.0, 6 February 2019.
24
25

26 **Strengths and limitations of this study**

27
28

- 29 • This prospective trial will determine the true rate of wound complications according to
30 nationally recognised criteria
- 31 • Pragmatically designed and reviewed by consumer groups to allow for integration
32 into routine clinical practice
- 33 • Trial available only to women who have proficiency in English language
- 34 • This study will recruit from scheduled elective admissions with a probable and
35 coincidental inclusion of urgent or emergency cases
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Introduction

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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/m²+) (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

1
2
3 sequence for each site, and each sequence will be generated using a permuted random
4 blocks strategy to ensure that recruitment to the two arms of the study occurs at
5 approximately equal rates within each site. The allocation list for each site will be provided
6 to the senior research fellow at each site, and will be kept private from all other personnel at
7 the site. Due the nature of the study device, blinding of participants or study personnel after
8 treatment allocation is not possible. However, the study statistician will be blinded to group
9 allocation.
10
11
12
13
14
15
16
17
18
19
20

21 **Post randomisation withdrawals/exclusions**

22
23
24 Participants may choose not to participate in the CYGNUS trial or withdraw from the study at
25 any time without prejudice. Choosing either of these options will not affect the standard of
26 care the patient receives.
27
28
29

30 **Study dressings**

31
32
33 Participants who elect to have a caesarean section as the chosen method of delivery usually
34 have a scheduled time and day for the procedure. Some patients may be required to
35 undergo an urgent or an emergency caesarean delivery due to a number of uncontrolled
36 factors. Routine antibiotic prophylaxis will be given to patients immediately before surgery
37 and all intraoperative procedures adhere to the WHO (16) surgical site safety checklist and
38 local infection prevention policies in accordance with Australian Commission on Safety and
39 Quality Health Commission National Standard 3: Prevention of Health Care Acquired
40 Complications (17).
41
42
43
44
45
46
47
48
49

50 **Control dressing**

51
52
53 The standard dressing for a surgical wound consists of a non-adherent layer applied over
54 the incision and directly onto the incision to cover the incision site. The control dressing does
55 not use negative pressure over the incision site. The standard wear time of the control
56
57
58
59
60

1
2
3 dressing is up to and including 7 days. Details of the dressing and wear time will be
4
5 recorded in the case report forms (CRF's).
6
7

8 **Intervention**

9
10 Negative Pressure Wound Therapy System consists of a non-adherent dressing pad with an
11 adhesive cover that adheres to the surrounding skin near the incision site. The dressing pad
12 is attached to a small silent pump via a soft tube that creates a partial vacuum over the
13 wound. The pump delivers a continual negative pressure of 80mmHg and is a battery-
14 operated device. The negative pressure wound therapy pump can operate for up to 30
15 days, and the dressing can be worn for 7 days as per the manufacturer's recommendation.
16
17 In this trial, the dressing will be worn for a standardised period of 7 days (intervention and
18 controls arms). Any further wound dressings after the initial dressing application will be
19 recorded in the CRF's and following the allocated treatment unless otherwise clinically
20 indicated.
21
22
23
24
25
26
27
28
29
30
31

32 **Outcome measures**

33 **Primary outcome**

34
35 The primary outcome for this study is surgical wound dehiscence as defined by the WUWHS
36 SWD Grading System (7), and the Centres for Disease Control definitions of SSI (18) will be
37 used as the primary outcome measure for confirmed wound infection. The primary outcome
38 measure definitions include a wound complication that occurs within 30 days of surgery.
39
40 The treating clinical team will determine the diagnosis of surgical wound dehiscence or
41 infection as per routine clinical wound assessment protocol if there is a confirmed SSI or
42 SWD. Rapid diagnosis and treatment of wound infection is central to patient standard care
43 and the attending clinician will document any changes in the patient medical notes and
44 adhere to local wound management protocols.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 the result, with the threshold for cost-effectiveness determined by recent work by Edney *et*
4
5 *al.*(21).
6
7

8 **Adverse event management**

9

10 Adverse device effect is an adverse event related to the use of an investigational medical
11 device (IMD) (22). Adverse events (AEs) related to an investigational medical device are
12 defined as any untoward medical occurrence, unintended disease or injury, or untoward
13 clinical signs (including abnormal laboratory findings) in participants, users or other persons,
14 whether or not related to in the investigational medical device (22). Definitions of adverse
15 events (AEs), serious adverse device effect (SADE), serious adverse event (SAE)
16 Significant Safety Issue, Unanticipated Serious Adverse Device Effect (USADE) or Urgent
17 Safety Measure (USM) are as per the National Health and Medical Research Council (2016)
18 Guidelines on Safety monitoring and reporting in clinical trials involving therapeutic goods
19 (22).
20
21
22
23
24
25
26
27
28
29
30
31

32 **Follow up**

33

34 Each participant will be followed up during the trial as close as practically possible to the
35 specific time points: Week 1, Week 6 and Week 12 following surgery. The close out time
36 point of the trial participant is Day 30 postoperative. In the event that a participant has an
37 unresolved complication beyond 30 days, follow up will continue to complete wound healing,
38 and participants will have the opportunity to opt out of the extended data collection beyond
39 Day 30. All data recorded during the follow up time points will be recorded on the case report
40 forms and clinical assessment will follow standard postoperative wound care management
41 and clinical procedures.
42
43
44
45
46
47
48
49
50
51

52 **Sample size**

53

54 Participants will be randomised in a 1:1 ratio of trial intervention to control. The sample size
55 calculation is based upon the following estimates: A complication rate of 20% of caesarean
56
57
58
59
60

1
2
3 section patients was observed following a retrospective medical note audit at the major
4 tertiary women's hospital in Perth. If the intervention can reduce this figure to 10% (a
5 reduction of 50% from the current figure) then a sample of size $n=199$ in each arm would be
6 required to detect this difference with power=80% and $\alpha=0.05$. To allow for an attrition rate
7 of 11%, we plan to recruit 224 patients to each arm of the study.
8
9
10
11
12

13 **Data management**

14
15
16
17 The case report forms have been designed by the Senior Research Fellow in consultation
18 with the trial co-investigators. All hard and electronic based patient identifiable information
19 will be stored on a secure password protected database purpose built for the trial. All CRF's
20 will be stored in a locked filing cabinet in a locked office at the participating site. Participants
21 will be identified by a code number only, on the database, but a file linking the code number
22 to the participant name and contact details will be kept separately and securely. This will
23 allow re-identification of the patient for follow-up purposes. Direct access to source data
24 and/or documents may be required for trial related monitoring/audit by the regulatory
25 authorities by written request only. All paper and electronic data will be retained for 5 years
26 after completion of the trial.
27
28
29
30
31
32
33
34
35
36
37
38

39 **Statistical analysis**

40
41 Simple descriptive statistics (means, SDs, medians, IQR for continuous variables and
42 frequencies and percentages for categorical variables) will be used to summarise the profile
43 of the study participants. Comparison of participants in the two groups (control vs
44 intervention) will be performed using the Chi-square tests or t-tests as appropriate. These
45 tests will be used to identify any differences in baseline characteristics between groups.
46
47 Recruitment and retention rates will be reported as per the Consolidated Standards of
48 Reporting Trial (CONSORT) (23) statement. Reasons for ineligibility, protocol deviations or
49 participant withdrawal will be stated and any trends reported.
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Analysis of the trial primary and secondary outcomes will be performed using the Chi-square
4 test or t-tests as appropriate. The Kaplan-Meier method and the LogRank test will be used
5 to analyse any differences in time to wound healing, between the two groups. All statistical
6 analyses will be performed using the SAS version 9.4 software, and, following convention, a
7 p-value < 0.05 will be taken to indicate a significant association in all tests.
8
9
10
11
12
13
14
15
16
17
18
19

20 **Trial oversight**

21
22 A Trial Committee (TC) and Data Safety Monitoring Board (DSMB) will be set up. The DSMB
23 advocates for the ethical and safety interests of the participants while the trial progresses by
24 making nonbinding recommendations to the TC. A data safety monitoring board will be
25 formed to monitor the study at interim periods: first third participants closed out (n=148) and
26 last quarter closed out. The DSMB consists of three independent reviewers; a statistician, a
27 surgeon and a nurse. The DSMB will be bound by the DSMB Terms of Reference and will
28 provide a written report to the TC. The TC consists of the Principal and site investigators, the
29 study biostatistician and health economist. This trial will utilise the Haybittle-Peto (24, 25)
30 boundary as the designated trial statistic for stopping the trial.
31
32
33
34
35
36
37
38
39
40
41

42 **Ethics and dissemination**

43
44
45 Ethics approval was obtained through St John of God Healthcare (HREC1409), Western
46 Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings
47 will be submitted for publication in peer-reviewed journals. We used the SPIRIT checklist
48 when writing our study protocol (26).
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Declarations**
4
5

6 **Funding** This work is funded by an unrestricted educational grant from Convatec Pty Ltd.
7
8 Convatec Pty Ltd., had no input into the design of the study, publications or educational
9
10 matter related to the study.
11
12

13
14 **Contributions** KSH, RP designed the study. KSH wrote the background, methodology and
15
16 developed the research question with input from RP. RP wrote the statistical design section
17
18 and RN wrote the health economic sections of the protocol. All authors reviewed and agreed
19
20 the final manuscript.
21
22

23 **Competing interests** None declared
24
25

26 **Patient consent** Patient consent will be sought to participate in the study via written
27
28 informed consent
29
30

31
32 **Provenance and peer review** Not commissioned, externally peer reviewed
33
34

35 **Open Access** This is an Open Access article distributed in accordance with the terms of the
36
37 Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix,
38
39 adapt and build upon this work for commercial use, provided the original work is properly
40
41 cited. See: <http://creativecommons.org/licenses/by/4.0/>
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 therapeutic 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, Gøtzsche PC, Krleža-Jerić 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 SPIRIT reporting 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

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	1
2				
3				
4			name of intended registry	
5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	1
7				
8	data set		Registration Data Set	
9				
10				
11	Protocol version	#3	Date and version identifier	1
12				
13				
14				
15	Funding	#4	Sources and types of financial, material, and other	13
16				
17			support	
18				
19				
20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1
21				
22	responsibilities:			
23				
24	contributorship			
25				
26				
27				
28	Roles and	#5b	Name and contact information for the trial sponsor	1
29				
30	responsibilities:			
31				
32	sponsor contact			
33				
34	information			
35				
36				
37				
38	Roles and	#5c	Role of study sponsor and funders, if any, in study	13
39				
40	responsibilities:		design; collection, management, analysis, and	
41				
42	sponsor and funder		interpretation of data; writing of the report; and the	
43				
44			decision to submit the report for publication, including	
45				
46			whether they will have ultimate authority over any of	
47				
48			these activities	
49				
50				
51				
52	Roles and	#5d	Composition, roles, and responsibilities of the	12
53				
54	responsibilities:		coordinating centre, steering committee, endpoint	
55				
56	committees		adjudication committee, data management team, and	
57				
58				
59				
60				

1 other individuals or groups overseeing the trial, if
 2
 3 applicable (see Item 21a for data monitoring committee)
 4
 5

6 Introduction

7
 8
 9 Background and [#6a](#) Description of research question and justification for 2
 10
 11 rationale undertaking the trial, including summary of relevant
 12
 13 studies (published and unpublished) examining benefits
 14

15 and harms for each intervention
 16
 17

18
 19 Background and [#6b](#) Explanation for choice of comparators 7-8
 20
 21 rationale: choice of
 22
 23 comparators
 24

25
 26 Objectives [#7](#) Specific objectives or hypotheses 5
 27
 28

29
 30 Trial design [#8](#) Description of trial design including type of trial (eg, 5
 31
 32 parallel group, crossover, factorial, single group),
 33
 34 allocation ratio, and framework (eg, superiority,
 35
 36 equivalence, non-inferiority, exploratory)
 37
 38

39 Methods:

40
 41 Participants,
 42
 43 interventions, and
 44
 45 outcomes
 46
 47
 48

49
 50 Study setting [#9](#) Description of study settings (eg, community clinic, 5
 51
 52 academic hospital) and list of countries where data will be
 53
 54 collected. Reference to where list of study sites can be
 55
 56 obtained
 57
 58
 59
 60

1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	6
2				
3			applicable, eligibility criteria for study centres and	
4			individuals who will perform the interventions (eg,	
5			surgeons, psychotherapists)	
6				
7				
8				
9				
10				
11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-7
12				
13	description		replication, including how and when they will be	
14			administered	
15				
16				
17				
18				
19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	7
20				
21	modifications		interventions for a given trial participant (eg, drug dose	
22			change in response to harms, participant request, or	
23			improving / worsening disease)	
24				
25				
26				
27				
28				
29	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	7
30				
31	adherence		and any procedures for monitoring adherence (eg, drug	
32			tablet return; laboratory tests)	
33				
34				
35				
36	Interventions:	#11d	Relevant concomitant care and interventions that are	7
37				
38	concomitant care		permitted or prohibited during the trial	
39				
40				
41				
42	Outcomes	#12	Primary, secondary, and other outcomes, including the	8-9
43			specific measurement variable (eg, systolic blood	
44			pressure), analysis metric (eg, change from baseline, final	
45			value, time to event), method of aggregation (eg, median,	
46			proportion), and time point for each outcome. Explanation	
47			of the clinical relevance of chosen efficacy and harm	
48			outcomes is strongly recommended	
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	10
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly recommended	
4			(see Figure)	
5				
6				
7				
8				
9				
10				
11	Sample size	#14	Estimated number of participants needed to achieve	10-11
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any sample	
14			size calculations	
15				
16				
17				
18				
19				
20				
21	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6-7
22			reach target sample size	
23				
24				
25				
26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
31				
32				
33				
34				
35				
36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
43				
44				
45				
46				
47				
48				
49				
50				
51				
52				
53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
54	concealment		central telephone; sequentially numbered, opaque,	
55				
56				
57				
58	mechanism			
59				
60				

sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: [#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): [#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

1	Data collection plan:	#18b	Plans to promote participant retention and complete	11
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
6				
7				
8				
9				
10				
11	Data management	#19	Plans for data entry, coding, security, and storage,	11
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
17				
18	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	11
19			outcomes. Reference to where other details of the	
20			statistical analysis plan can be found, if not in the protocol	
21				
22				
23				
24	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
25	analyses		adjusted analyses)	
26				
27				
28				
29				
30				
31	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
32	population and		adherence (eg, as randomised analysis), and any	
33	missing data		statistical methods to handle missing data (eg, multiple	
34			imputation)	
35				
36				
37				
38				
39				
40				
41				
42				
43				
44				
45				
46	Methods: Monitoring			
47				
48				
49	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	12
50	formal committee		summary of its role and reporting structure; statement of	
51			whether it is independent from the sponsor and	
52			competing interests; and reference to where further	
53				
54				
55				
56				
57				
58				
59				
60				

1 details about its charter can be found, if not in the
 2 protocol. Alternatively, an explanation of why a DMC is
 3 not needed
 4
 5
 6
 7

8	Data monitoring:	#21b	Description of any interim analyses and stopping	12
9	interim analysis		guidelines, including who will have access to these	
10			interim results and make the final decision to terminate	
11			the trial	
12				
13				
14				
15				
16				
17				
18	Harms	#22	Plans for collecting, assessing, reporting, and managing	10
19			solicited and spontaneously reported adverse events and	
20			other unintended effects of trial interventions or trial	
21			conduct	
22				
23				
24				
25				
26				
27				
28	Auditing	#23	Frequency and procedures for auditing trial conduct, if	12
29			any, and whether the process will be independent from	
30			investigators and the sponsor	
31				
32				
33				
34				
35	Ethics and			
36	dissemination			
37				
38				
39				
40				
41	Research ethics	#24	Plans for seeking research ethics committee / institutional	12
42	approval		review board (REC / IRB) approval	
43				
44				
45				
46	Protocol	#25	Plans for communicating important protocol modifications	12
47	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
48			relevant parties (eg, investigators, REC / IRBs, trial	
49			participants, trial registries, journals, regulators)	
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	6,13
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
4				
5				
6				
7				
8				
9	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
12				
13				
14				
15				
16	Confidentiality	#27	How personal information about potential and enrolled	6
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
20				
21				
22				
23				
24				
25				
26	Declaration of	#28	Financial and other competing interests for principal	13
27	interests		investigators for the overall trial and each study site	
28				
29				
30				
31	Data access	#29	Statement of who will have access to the final trial	13
32			dataset, and disclosure of contractual agreements that	
33			limit such access for investigators	
34				
35				
36				
37				
38				
39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	10
40	trial care		compensation to those who suffer harm from trial	
41			participation	
42				
43				
44				
45				
46				
47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	12
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Dissemination policy: #31b	Authorship eligibility guidelines and any intended use of	13
2			
3	authorship	professional writers	
4			
5			
6	Dissemination policy: #31c	Plans, if any, for granting public access to the full	13
7			
8	reproducible	protocol, participant-level dataset, and statistical code	
9			
10	research		
11			
12			
13			
14	Appendices		
15			
16			
17	Informed consent	#32 Model consent form and other related documentation	6
18			
19	materials	given to participants and authorised surrogates	
20			
21			
22			
23	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	NA
24			
25		biological specimens for genetic or molecular analysis in	
26			
27		the current trial and for future use in ancillary studies, if	
28			
29		applicable	
30			
31			

32 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-
 33 BY-ND 3.0. This checklist was completed on 13. November 2019 using <https://www.goodreports.org/>,
 34
 35 a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
 36
 37
 38
 39
 40
 41
 42
 43
 44
 45
 46
 47
 48
 49
 50
 51
 52
 53
 54
 55
 56
 57
 58
 59
 60

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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3 BMJ Open Manuscript
4
5
6
7

8 Effectiveness of negative pressure wound therapy in the prevention of surgical wound
9 complications in the cesarean section at risk population: a parallel group randomised
10
11
12
13 multicentre trial, the **CYGNUS** protocol.
14
15
16

- 17
18 1. Dr Kylie Sandy-Hodgetts, BSc, Hons H1, MBA, Ph.D Director Skin Integrity Clinical
19 Trials Unit, Senior Research Fellow, Burn Injury Research Unit, School of Biomedical
20 Sciences, Faculty of Health and Medical Sciences, University of Western Australia.
21
22 2. Dr Richard Parsons, Senior Lecturer in Statistics, School of Occupational Therapy,
23 Social Work and Speech, Curtin University
24
25 3. Associate Professor Richard Norman, Health Economist, School of Public Health,
26 Curtin University
27
28 4. Dr Scott W White, Senior Lecturer, Consultant Obstetrician, Department of Maternal
29 and Fetal Medicine, King Edward Memorial Hospital
30
31 5. Dr Mark Fear, Senior Research Fellow, Burns Injury Unit, School of Biomedical
32 Sciences, Faculty of Medicine, University of Western Australia
33
34 6. Professor Fiona Wood, Director State Burns Unit, Fiona Stanley Hospital, Perth.
35
36
37
38
39
40
41
42
43
44
45

46 Correspondence to: Dr Kylie Sandy-Hodgetts; kylie.sandy-hodgetts@uwa.edu.au
47
48

49 Abstract word count: 501
50

51 Manuscript: 3069 (max 4000 words)
52
53
54
55
56
57
58
59
60

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

1
2
3 and adherence to intervention and follow up. We will assess the potential effectiveness of
4 negative pressure wound therapy in the prevention of post-partum surgical wound
5 complications at three time points during the study; Day 5 post-operative, Day 14 and Day
6 30 where the participant will be closed out of the trial. We will utilise statistical methods to
7 determine efficacy and risk stratification will be conducted to determine the surgical wound
8 dehiscence risk profile of the participant. Follow up at Day 30 will assess superficial and
9 deep infection and wound dehiscence (Grades I-IV) and the core outcome dataset for wound
10 complications. This study will collect health related quality of life (ED-5D-5L), mortality and
11 late complications such as further surgery with a cost analysis conducted. The primary
12 analysis will be by intention to treat. This clinical trial protocol follows the Standard Protocol
13 Items: Recommendations for Interventional Trials (SPIRIT) guidelines and the Consolidated
14 Standards of Reporting Trials (CONSORT) guidelines. The trial was registered on the
15 Australian and New Zealand Clinical Trials Registry (ACTRN12618002006224) prior to
16 commencement.

32 33 **Ethics and dissemination**

34
35
36 Ethics approval was obtained through St John of God Healthcare (HREC1409), Western
37 Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings
38 will be submitted for publication in peer-reviewed journals. We used the SPIRIT checklist
39 when writing our study protocol.
40
41
42
43
44
45
46
47

48 **Trial registration number:** ANZCTR: ACTRN12618002006224p
49

50 **Protocol version and date:** Version 3.0, 6 February 2019.
51
52
53
54
55
56
57
58
59
60

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 cesarean 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/m²+) (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 summarises 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

1
2
3 participant information, demographic and related medical history will be collected. A
4
5 participant risk profile for surgical wound dehiscence (SWD) will be obtained utilising the
6
7 Perth Surgical Wound Dehiscence Risk Assessment Tool (PSWDRAT) (13). This will
8
9 determine the SWD risk profile of the trial participant. The European Quality of Life 5-
10
11 Dimensions 5-Level Scale (EQ-5D-5L) (14) a validated questionnaire will be administered at
12
13 baseline and at the end of the trial to allow estimation of QALYs of all participants. The
14
15 study statistician will generate the allocation sequence for each site before the study
16
17 commences, using a random number generator on a computer. There will be a separate
18
19 sequence for each site, and each sequence will be generated using a permuted random
20
21 blocks strategy to ensure that recruitment to the two arms of the study occurs at
22
23 approximately equal rates within each site. The allocation list for each site will be provided
24
25 to the senior research fellow at each site, and will be kept private from all other personnel at
26
27 the site. Due the nature of the study device, blinding of participants or study personnel after
28
29 treatment allocation is not possible. However, the study statistician will be blinded to group
30
31 allocation.
32
33
34
35
36
37

38 **Patient and public involvement**

39
40
41 No patient involvement in the study design.
42
43
44
45

46 **Post randomisation withdrawals/exclusions**

47
48
49 Participants may choose not to participate in the CYGNUS trial or withdraw from the study at
50
51 any time without prejudice. Choosing either of these options will not affect the standard of
52
53 care the patient receives.
54
55
56
57
58
59
60

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

1
2
3 controls arms). Any further wound dressings after the initial dressing application will be
4 recorded in the CRF's and following the allocated treatment unless otherwise clinically
5 indicated.
6
7
8
9

10 11 12 13 **Outcome measures**

14 15 **Primary outcome**

16
17 The primary outcome for this study is surgical wound dehiscence as defined by the WUWHS
18 SWD Grading System (17), and the Centres for Disease Control definitions of SSI (18) will
19 be used as the primary outcome measure for confirmed wound infection. The primary
20 outcome measure definitions include a wound complication that occurs within 30 days of
21 surgery. The treating clinical team will determine the diagnosis of surgical wound
22 dehiscence or infection as per routine clinical wound assessment protocol if there is a
23 confirmed SSI or SWD. Rapid diagnosis and treatment of wound infection is central to
24 patient standard care and the attending clinician will document any changes in the patient
25 medical notes and adhere to local wound management protocols.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 **Secondary outcomes**

42 *Health related quality of life assessment*

43
44 A qualitative assessment of the participant's perceptions of wound healing will be conducted.
45
46
47
48

49 *EuroQol EQ-5D-5L*

50
51 The EuroQol EQ-5D is a validated measure of health related quality of life, comprising a five-
52 dimension health status classification system and a separate Visual Analogue Scale (19).
53
54 The EQ-5D consists of five dimensions (Mobility, Self-Care, Usual Activities,
55 Pain/Discomfort, and Anxiety/Depression), each with either 3 or 5 levels. We will use the
56
57
58
59
60

1
2
3 five-level version of the instrument, which is likely to be more sensitive to small but important
4 changes in health-related quality of life (14). The responses will be converted into an index
5 score, and total QALYs for each woman will be obtained by estimating the area under the
6 curve defined by their baseline and final EQ-5D-5L responses (20).
7
8
9

10 11 12 *Complications*

13
14 All complications and surgical interventions related to the procedure (i.e. sutures, staples,
15 closure methods) will be recorded in the CRF's.
16
17
18

19 20 *Economic analysis*

21
22 All resources utilised in the study will be recorded to help inform the economic analysis. Cost
23 data will be derived from the hospital finance departments and any related community
24 nursing service or primary health care centre where the participant has attended. Cost
25 consequences following discharge including out of pocket expenses (if any) will be recorded
26 in the case report forms at day 30 following the procedure. The incremental cost of the
27 intervention relative to the control will be estimated, and divided by incremental outcomes
28 reported in the study. Each resultant incremental cost-effectiveness ratio (ICER) will be
29 reported separately, with the last step being the cost per QALY. We will conduct univariate
30 and probabilistic sensitivity analyses around the cost per QALY to assess the robustness of
31 the result, with the threshold for cost-effectiveness determined by recent work by Edney *et*
32 *al.*(21).
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

50 **Adverse event management**

51
52 Adverse device effect is an adverse event related to the use of an investigational medical
53 device (IMD) (22). Adverse events (AEs) related to an investigational medical device are
54 defined as any untoward medical occurrence, unintended disease or injury, or untoward
55 clinical signs (including abnormal laboratory findings) in participants, users or other persons,
56
57
58
59
60

1
2
3 whether or not related to in the investigational medical device (22). Definitions of adverse
4 events (AEs), serious adverse device effect (SADE), serious adverse event (SAE)
5 Significant Safety Issue, Unanticipated Serious Adverse Device Effect (USADE) or Urgent
6 Safety Measure (USM) are as per the National Health and Medical Research Council (2016)
7 Guidelines on Safety monitoring and reporting in clinical trials involving therapeutic goods
8 (22). During the treatment protocol, any USADE will be reported directly to the DSMB and
9 within 7 days to the Australian Government Therapeutics Goods Administration via the
10 electronic Medical Device Incident Reporting System. Reports will also be sent to the local
11 study sites Human Research Ethics Committees. The safety aspects of the study will be
12 closely monitored by the DSMB, which will receive unblinded data for review. In the case of
13 a device related adverse advent the manufacturer will be notified.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

30 **Follow up**

31
32 Each participant will be followed up during the trial as close as practically possible to the
33 specific time points: Day 5, Day 14, and Day 30 following surgery. The close out time point of
34 the trial participant is Day 30 postoperative. In the event that a participant has an unresolved
35 complication beyond 30 days, follow up will continue to complete wound healing, and
36 participants will have the opportunity to opt out of the extended data collection beyond Day
37 30. All data recorded during the follow up time points will be recorded on the case report
38 forms and clinical assessment will follow standard postoperative wound care management
39 and clinical procedures.
40
41
42
43
44
45
46
47
48
49
50
51
52

53 **Sample size**

54
55 Participants will be randomised in a 1:1 ratio of trial intervention to control. The sample size
56 calculation is based upon the following estimates: A complication rate of 20% of caesarean
57
58
59
60

1
2
3 section patients was observed following a retrospective medical note audit at the major
4 tertiary women's hospital in Perth. If the intervention can reduce this figure to 10% (a
5 reduction of 50% from the current figure) then a sample of size $n=199$ in each arm would be
6 required to detect this difference with power=80% and $\alpha=0.05$. To allow for an attrition rate
7 of 11%, we plan to recruit 224 patients to each arm of the study.
8
9
10
11
12
13

14 15 16 17 **Data management**

18
19 The case report forms have been designed by the Senior Research Fellow in consultation
20 with the trial co-investigators. All hard and electronic based patient identifiable information
21 will be stored on a secure password protected database purpose built for the trial. All CRF's
22 will be stored in a locked filing cabinet in a locked office at the participating site. Participants
23 will be identified by a code number only, on the database, but a file linking the code number
24 to the participant name and contact details will be kept separately and securely. This will
25 allow re-identification of the patient for follow-up purposes. Direct access to source data
26 and/or documents may be required for trial related monitoring/audit by the regulatory
27 authorities by written request only. All paper and electronic data will be retained for 5 years
28 after completion of the trial.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44

45 **Statistical analysis**

46
47 Simple descriptive statistics (means, SDs, medians, IQR for continuous variables and
48 frequencies and percentages for categorical variables) will be used to summarise the profile
49 of the study participants. Comparison of participants in the two groups (control vs
50 intervention) will be performed using the Chi-square tests or t-tests as appropriate. These
51 tests will be used to identify any differences in baseline characteristics between groups.
52
53
54
55
56
57 Recruitment and retention rates will be reported as per the Consolidated Standards of
58
59
60

1
2
3 Reporting Trial (CONSORT) (11) statement. Reasons for ineligibility, protocol deviations or
4 participant withdrawal will be stated and any trends reported. A Generalised Estimating
5 Equation (GEE) will be used to analyse each of the primary outcomes over all the time
6 points of the study. This analysis is similar to a Logistic Regression for each of the binary
7 outcome variables, but takes into account the correlation between the repeated
8 measurements made on the same participant. The results of the GEE will be expressed as
9 odds ratios, their 95% confidence intervals and p-values. The GEE model will include a term
10 for the time point, so that changes over time can be assessed, as well as a term for the
11 treatment group allocation (on which the main conclusions of the study will be based). In
12 addition, the GEE model will be extended to include anthropometric measurements (eg:
13 body mass index), presence of health conditions (eg diabetes, hypertension, etc), the
14 recruitment site, and other variables collected at baseline. In this way, variables which are
15 identified as being associated with the outcomes may be used to form a 'risk score' for each
16 outcome. Analysis of the pain scores (which are measured on a continuous scale at each
17 time point through the study), will be performed using a Mixed regression model where the
18 random effect will be the patient identifier, and the time point and treatment allocation group
19 will be fixed effects. The distribution of the pain scores will be assessed for Normality, and
20 transformed to improve Normality (if necessary) prior to analysis.

21
22 All statistical analyses will be performed using the SAS version 9.4 software, and, following
23 convention, a p-value < 0.05 will be taken to indicate a significant association in all tests.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48

49 **Trial oversight**

50
51 A Trial Committee (TC) and Data Safety Monitoring Board (DSMB) will be set up. The DSMB
52 advocates for the ethical and safety interests of the participants while the trial progresses by
53 making nonbinding recommendations to the TC. A data safety monitoring board will be
54 formed to monitor the study at interim periods: first third participants closed out (n=148) and
55
56
57
58
59
60

1
2
3 last quarter closed out. The DSMB consists of three independent reviewers; a statistician, a
4 surgeon and a nurse. The DSMB will be bound by the DSMB Terms of Reference and will
5 provide a written report to the TC. The TC consists of the Principal and site investigators, the
6 study biostatistician and health economist. This trial will utilise the Haybittle-Peto (23, 24)
7 boundary as the designated trial statistic for stopping the trial.
8
9
10
11
12
13
14
15
16

17 **Declarations**

18
19
20 **Funding** This work is funded by an unrestricted educational grant from Convatec Pty Ltd.
21 Convatec Pty Ltd., had no input into the design of the study, publications or educational
22 matter related to the study.
23
24
25
26

27
28 **Contributions** KSH, RP designed the study. KSH wrote the background, methodology and
29 developed the research question with input from RP & SWW. RP wrote the statistical design
30 section and RN wrote the health economic sections of the protocol. Reviews were conducted
31 by MF & FW. All authors reviewed and agreed the final manuscript.
32
33
34
35
36
37
38
39
40

41 **Competing interests** None declared
42
43

44 **Patient consent** Patient consent will be sought to participate in the study via written
45 informed consent
46
47
48

49 **Provenance and peer review** Not commissioned, externally peer reviewed
50
51

52 **Open Access** This is an Open Access article distributed in accordance with the terms of the
53 Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix,
54 adapt and build upon this work for commercial use, provided the original work is properly
55 cited. See: <http://creativecommons.org/licenses/by/4.0/>
56
57
58
59
60

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 therapeutic 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

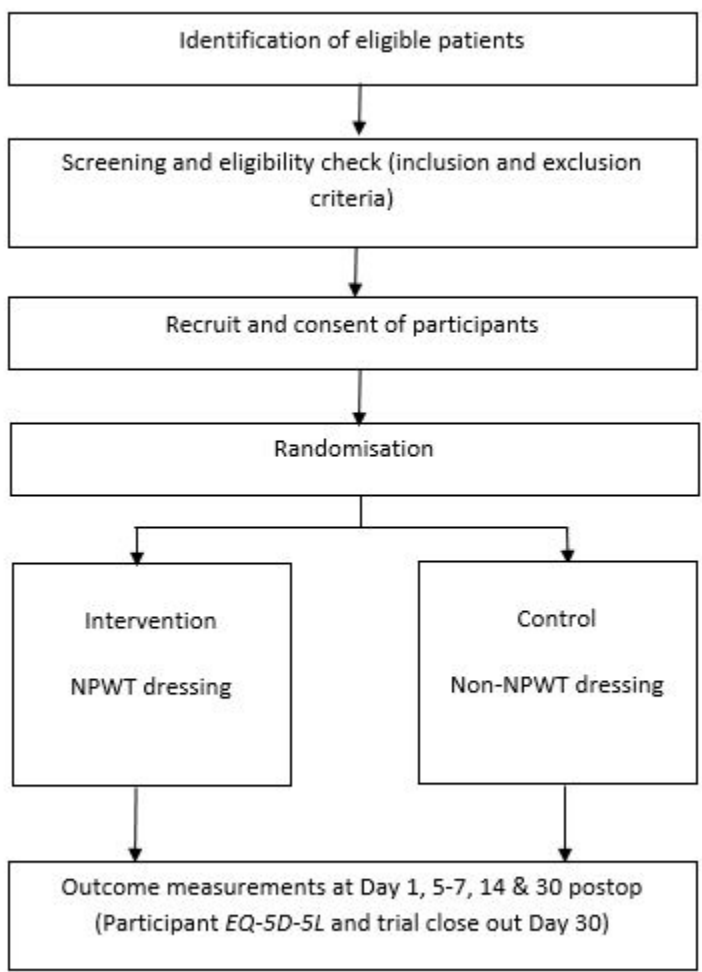


Figure 1. CYGNUS CONSORT Trial Participant

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 SPIRIT reporting 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

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	1
2			name of intended registry	
3				
4				
5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	1
7				
8	data set		Registration Data Set	
9				
10				
11				
12	Protocol version	#3	Date and version identifier	1
13				
14				
15	Funding	#4	Sources and types of financial, material, and other	13
16			support	
17				
18				
19				
20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1
21				
22	responsibilities:			
23				
24	contributorship			
25				
26				
27				
28	Roles and	#5b	Name and contact information for the trial sponsor	1
29				
30	responsibilities:			
31				
32	sponsor contact			
33				
34	information			
35				
36				
37				
38	Roles and	#5c	Role of study sponsor and funders, if any, in study	13
39			design; collection, management, analysis, and	
40	responsibilities:		interpretation of data; writing of the report; and the	
41			decision to submit the report for publication, including	
42	sponsor and funder		whether they will have ultimate authority over any of	
43			these activities	
44				
45				
46				
47				
48				
49				
50				
51				
52	Roles and	#5d	Composition, roles, and responsibilities of the	12
53			coordinating centre, steering committee, endpoint	
54	responsibilities:		adjudication committee, data management team, and	
55				
56	committees			
57				
58				
59				
60				

1 other individuals or groups overseeing the trial, if
 2
 3 applicable (see Item 21a for data monitoring committee)
 4
 5

6 Introduction

7			
8			
9	Background and	#6a	Description of research question and justification for
10			
11	rationale		undertaking the trial, including summary of relevant
12			studies (published and unpublished) examining benefits
13			
14			and harms for each intervention
15			
16			
17			
18			
19	Background and	#6b	Explanation for choice of comparators
20			
21	rationale: choice of		
22			
23	comparators		
24			
25			
26	Objectives	#7	Specific objectives or hypotheses
27			
28			
29	Trial design	#8	Description of trial design including type of trial (eg,
30			parallel group, crossover, factorial, single group),
31			allocation ratio, and framework (eg, superiority,
32			equivalence, non-inferiority, exploratory)
33			
34			
35			
36			
37			
38			
39	Methods:		
40			
41	Participants,		
42			
43	interventions, and		
44			
45	outcomes		
46			
47			
48			
49	Study setting	#9	Description of study settings (eg, community clinic,
50			academic hospital) and list of countries where data will be
51			collected. Reference to where list of study sites can be
52			obtained
53			
54			
55			
56			
57			
58			
59			
60			

1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	6
2				
3			applicable, eligibility criteria for study centres and	
4			individuals who will perform the interventions (eg,	
5			surgeons, psychotherapists)	
6				
7				
8				
9				
10				
11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-7
12				
13	description		replication, including how and when they will be	
14			administered	
15				
16				
17				
18				
19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	7
20				
21	modifications		interventions for a given trial participant (eg, drug dose	
22			change in response to harms, participant request, or	
23			improving / worsening disease)	
24				
25				
26				
27				
28				
29	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	7
30				
31	adherence		and any procedures for monitoring adherence (eg, drug	
32			tablet return; laboratory tests)	
33				
34				
35				
36	Interventions:	#11d	Relevant concomitant care and interventions that are	7
37				
38	concomitant care		permitted or prohibited during the trial	
39				
40				
41				
42	Outcomes	#12	Primary, secondary, and other outcomes, including the	8-9
43			specific measurement variable (eg, systolic blood	
44			pressure), analysis metric (eg, change from baseline, final	
45			value, time to event), method of aggregation (eg, median,	
46			proportion), and time point for each outcome. Explanation	
47			of the clinical relevance of chosen efficacy and harm	
48			outcomes is strongly recommended	
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	10
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly recommended	
4			(see Figure)	
5				
6				
7				
8				
9				
10				
11	Sample size	#14	Estimated number of participants needed to achieve	10-11
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any sample	
14			size calculations	
15				
16				
17				
18				
19				
20				
21	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6-7
22			reach target sample size	
23				
24				
25				
26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
31				
32				
33				
34				
35				
36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
43				
44				
45				
46				
47				
48				
49				
50				
51				
52				
53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
54	concealment		central telephone; sequentially numbered, opaque,	
55				
56				
57				
58	mechanism			
59				
60				

sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: [#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): [#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

1	Data collection plan:	#18b	Plans to promote participant retention and complete	11
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
6				
7				
8				
9				
10				
11	Data management	#19	Plans for data entry, coding, security, and storage,	11
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
17				
18	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	11
19			outcomes. Reference to where other details of the	
20			statistical analysis plan can be found, if not in the protocol	
21				
22				
23	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
24	analyses		adjusted analyses)	
25				
26				
27				
28	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
29	population and		adherence (eg, as randomised analysis), and any	
30	missing data		statistical methods to handle missing data (eg, multiple	
31			imputation)	
32				
33				
34				
35				
36	Methods: Monitoring			
37				
38				
39	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	12
40	formal committee		summary of its role and reporting structure; statement of	
41			whether it is independent from the sponsor and	
42			competing interests; and reference to where further	
43				
44				
45				
46				
47				
48				
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

1 details about its charter can be found, if not in the
 2
 3 protocol. Alternatively, an explanation of why a DMC is
 4
 5 not needed
 6
 7

8	Data monitoring:	#21b	Description of any interim analyses and stopping	12
9				
10	interim analysis		guidelines, including who will have access to these	
11				
12			interim results and make the final decision to terminate	
13				
14			the trial	
15				
16				
17				
18	Harms	#22	Plans for collecting, assessing, reporting, and managing	10
19				
20			solicited and spontaneously reported adverse events and	
21				
22			other unintended effects of trial interventions or trial	
23				
24			conduct	
25				
26				
27				
28	Auditing	#23	Frequency and procedures for auditing trial conduct, if	12
29				
30			any, and whether the process will be independent from	
31				
32			investigators and the sponsor	
33				
34				
35	Ethics and			
36				
37	dissemination			
38				
39				
40				
41	Research ethics	#24	Plans for seeking research ethics committee / institutional	12
42				
43	approval		review board (REC / IRB) approval	
44				
45				
46	Protocol	#25	Plans for communicating important protocol modifications	12
47				
48	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
49				
50			relevant parties (eg, investigators, REC / IRBs, trial	
51				
52			participants, trial registries, journals, regulators)	
53				
54				
55				
56				
57				
58				
59				
60				

1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	6,13
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
4				
5				
6				
7				
8				
9	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
12				
13				
14				
15				
16	Confidentiality	#27	How personal information about potential and enrolled	6
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
20				
21				
22				
23				
24				
25				
26	Declaration of	#28	Financial and other competing interests for principal	13
27	interests		investigators for the overall trial and each study site	
28				
29				
30				
31				
32	Data access	#29	Statement of who will have access to the final trial	13
33			dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
35				
36				
37				
38				
39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	10
40	trial care		compensation to those who suffer harm from trial	
41			participation	
42				
43				
44				
45				
46				
47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	12
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Dissemination policy: #31b	Authorship eligibility guidelines and any intended use of	13
2			
3	authorship	professional writers	
4			
5			
6	Dissemination policy: #31c	Plans, if any, for granting public access to the full	13
7			
8	reproducible	protocol, participant-level dataset, and statistical code	
9			
10	research		
11			
12			
13			
14	Appendices		
15			
16			
17	Informed consent	#32 Model consent form and other related documentation	6
18			
19	materials	given to participants and authorised surrogates	
20			
21			
22	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	NA
23			
24		biological specimens for genetic or molecular analysis in	
25			
26		the current trial and for future use in ancillary studies, if	
27			
28		applicable	
29			
30			
31			

32 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-
 33 BY-ND 3.0. This checklist was completed on 13. November 2019 using <https://www.goodreports.org/>,
 34
 35 a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
 36
 37
 38
 39
 40
 41
 42
 43
 44
 45
 46
 47
 48
 49
 50
 51
 52
 53
 54
 55
 56
 57
 58
 59
 60

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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3 BMJ Open Manuscript
4
5
6
7

8 Effectiveness of negative pressure wound therapy in the prevention of surgical wound
9 complications in the cesarean section at risk population: a parallel group randomised
10
11
12
13 multicentre trial, the **CYGNUS** protocol.
14
15
16
17

- 18 1. Dr Kylie Sandy-Hodgetts, BSc, Hons H1, MBA, Ph.D Director Skin Integrity Research
19 Institute, Senior Research Fellow, Burn Injury Research Unit, School of Biomedical
20 Sciences, Faculty of Health and Medical Sciences, University of Western Australia.
21
22
- 23 2. Dr Richard Parsons, Senior Lecturer in Statistics, School of Occupational Therapy,
24 Social Work and Speech, Curtin University
25
26
- 27 3. Associate Professor Richard Norman, Health Economist, School of Public Health,
28 Curtin University
29
30
- 31 4. Dr Mark Fear, Senior Research Fellow, Burns Injury Unit, School of Biomedical
32 Sciences, Faculty of Medicine, University of Western Australia
33
34
- 35 5. Professor Fiona Wood, Director State Burns Unit, Fiona Stanley Hospital, Perth
36
37
- 38 6. Dr Scott W White, Senior Lecturer, Consultant Obstetrician, Department of Maternal
39 and Fetal Medicine, King Edward Memorial Hospital
40
41
42
43
44
45

46 Correspondence to: Dr Kylie Sandy-Hodgetts; kylie.sandy-hodgetts@uwa.edu.au
47
48

49 Abstract word count: 501
50

51 Manuscript: 3069 (max 4000 words)
52
53
54
55
56
57
58
59
60

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

1
2
3 will assess recruitment rate and adherence to intervention and follow up. We will assess the
4 potential effectiveness of negative pressure wound therapy in the prevention of post-partum
5 surgical wound complications at three time points during the study; Day 5 post-operative,
6 Day 14 and Day 30 where the participant will be closed out of the trial. We will utilise
7 statistical methods to determine efficacy and risk stratification will be conducted to determine
8 the surgical wound dehiscence risk profile of the participant. Follow up at Day 30 will assess
9 superficial and deep infection and wound dehiscence (Grades I-IV) and the core outcome
10 dataset for wound complications. This study will collect health related quality of life (ED-5D-
11 5L), mortality and late complications such as further surgery with a cost analysis conducted.
12 The primary analysis will be by intention to treat. This clinical trial protocol follows the
13 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and
14 the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The trial was
15 registered on the Australian and New Zealand Clinical Trials Registry
16 (ACTRN12618002006224) prior to commencement.

32 33 **Ethics and dissemination**

34
35
36 Ethics approval was obtained through St John of God Healthcare (HREC1409), Western
37 Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings
38 will be published in peer-reviewed journals and presented at international conferences. We
39 used the SPIRIT checklist when writing our study protocol.
40
41
42
43
44
45
46
47

48 **Trial registration number:** ANZCTR: ACTRN12618002006224p

49
50 **Protocol version and date:** Version 3.0, 6 February 2019.
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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/m²+) (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 summarises 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

1
2
3 schedule. Once consent has been obtained, the staff member who is recruiting the patient
4 will contact the senior research fellow in their site to request the next study identifier and
5 treatment allocation. Baseline participant information, demographic and related medical
6 history will be collected. A participant risk profile for surgical wound dehiscence (SWD) will
7 be obtained utilising the Perth Surgical Wound Dehiscence Risk Assessment Tool
8 (PSWDRAT) (13). This will determine the SWD risk profile of the trial participant. The
9 European Quality of Life 5-Dimensions 5-Level Scale (EQ-5D-5L) (14) a validated
10 questionnaire will be administered at baseline and at the end of the trial to allow estimation
11 of QALYs of all participants. The study statistician will generate the allocation sequence for
12 each site before the study commences, using a random number generator on a computer.
13 There will be a separate sequence for each site, and each sequence will be generated using
14 a permuted random blocks strategy to ensure that recruitment to the two arms of the study
15 occurs at approximately equal rates within each site. The allocation list for each site will be
16 provided to the senior research fellow at each site, and will be kept private from all other
17 personnel at the site. Due the nature of the study device, blinding of participants or study
18 personnel after treatment allocation is not possible. However, the study statistician will be
19 blinded to group allocation.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 **Patient and public involvement**

44
45 No patient involvement in the study design.
46
47
48
49

50 **Post randomisation withdrawals/exclusions**

51
52
53 Participants may choose not to participate in the CYGNUS trial or withdraw from the study at
54 any time without prejudice. Choosing either of these options will not affect the standard of
55 care the patient receives.
56
57
58
59
60

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

1
2
3 intervention group will receive the portable negative pressure device at Day 0. The dressing
4 will be worn for a standardised period of 5 days (intervention and controls arms). Any further
5 wound dressings after the initial dressing application will be recorded in the CRF's and
6 following the allocated treatment unless otherwise clinically indicated.
7
8
9
10

11 12 13 14 15 **Outcome measures**

16 17 18 **Primary outcome**

19
20 The primary outcome for this study is surgical wound dehiscence as defined by the WUWHS
21 SWD Grading System (17), and the Centres for Disease Control definitions of SSI (18) will
22 be used as the primary outcome measure for confirmed wound infection. The primary
23 outcome measure definitions include a wound complication that occurs within 30 days of
24 surgery. The treating clinical team will determine the diagnosis of surgical wound
25 dehiscence or infection as per routine clinical wound assessment protocol if there is a
26 confirmed SSI or SWD. Rapid diagnosis and treatment of wound infection is central to
27 patient standard care and the attending clinician will document any changes in the patient
28 medical notes and adhere to local wound management protocols.
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 44 45 **Secondary outcomes**

46 *Health related quality of life assessment*

47
48 A qualitative assessment of the participant's perceptions of wound healing will be conducted.
49

50 51 *EuroQol EQ-5D-5L*

52
53 The EuroQol EQ-5D is a validated measure of health related quality of life, comprising a five-
54 dimension health status classification system and a separate Visual Analogue Scale (19).
55

56
57 The EQ-5D consists of five dimensions (Mobility, Self-Care, Usual Activities,
58
59
60

1
2
3 Pain/Discomfort, and Anxiety/Depression), each with either 3 or 5 levels. We will use the
4 five-level version of the instrument, which is likely to be more sensitive to small but important
5 changes in health-related quality of life (14). The responses will be converted into an index
6 score, and total QALYs for each woman will be obtained by estimating the area under the
7 curve defined by their baseline and final EQ-5D-5L responses (20).
8
9
10
11
12
13
14
15
16

17 *Economic analysis*

18
19 All resources utilised in the study will be recorded to help inform the economic analysis. Cost
20 data will be derived from the hospital finance departments and any related community
21 nursing service or primary health care centre where the participant has attended. Cost
22 consequences following discharge including out of pocket expenses (if any) will be recorded
23 in the case report forms at day 30 following the procedure. The incremental cost of the
24 intervention relative to the control will be estimated, and divided by incremental outcomes
25 reported in the study. Each resultant incremental cost-effectiveness ratio (ICER) will be
26 reported separately, with the last step being the cost per QALY. We will conduct univariate
27 and probabilistic sensitivity analyses around the cost per QALY to assess the robustness of
28 the result, with the threshold for cost-effectiveness determined by recent work by Edney *et*
29 *al.*(21).
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

47 **Adverse event management**

48
49 Adverse device effect is an adverse event related to the use of an investigational medical
50 device (IMD) (22). Adverse events (AEs) related to an investigational medical device are
51 defined as any untoward medical occurrence, unintended disease or injury, or untoward
52 clinical signs (including abnormal laboratory findings) in participants, users or other persons,
53 whether or not related to in the investigational medical device (22). Definitions of adverse
54
55
56
57
58
59
60

1
2
3 events (AEs), serious adverse device effect (SADE), serious adverse event (SAE)
4
5 Significant Safety Issue, Unanticipated Serious Adverse Device Effect (USADE) or Urgent
6
7 Safety Measure (USM) are as per the National Health and Medical Research Council (2016)
8
9 Guidelines on Safety monitoring and reporting in clinical trials involving therapeutic goods
10
11 (22). During the treatment protocol, any USADE will be reported directly to the DSMB and
12
13 within 7 days to the Australian Government Therapeutics Goods Administration via the
14
15 electronic Medical Device Incident Reporting System. Reports will also be sent to the local
16
17 study sites Human Research Ethics Committees. The safety aspects of the study will be
18
19 closely monitored by the DSMB, which will receive unblinded data for review. In the case of
20
21 a device related adverse advent the manufacturer will be notified.
22
23
24
25
26
27

28 **Follow up**

29
30 Each participant will be followed up during the trial as close as practically possible to the
31
32 specific time points: Day 5, Day 14, and Day 30 following surgery. The close out time point of
33
34 the trial participant is Day 30 postoperative. In the event that a participant has an unresolved
35
36 complication beyond 30 days, follow up will continue to complete wound healing, and
37
38 participants will have the opportunity to opt out of the extended data collection beyond Day
39
40 30. All participants will be followed up by the Visiting Midwifery Service (VMS) and a scripted
41
42 phone call at the trial close out time point. Various forms of communication will be used in
43
44 engaging the participation, email, phone call and face-to-face consultation to reduce loss to
45
46 follow up. All data recorded during the follow up time points will be recorded on the case
47
48 report forms and clinical assessment will follow standard postoperative wound care
49
50 management and clinical procedures.
51
52
53
54
55
56
57
58
59
60

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 $\alpha=0.05$. 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.

1
2
3 All statistical analyses will be performed using the SAS version 9.4 software, and, following
4 convention, a p-value < 0.05 will be taken to indicate a significant association in all tests.
5
6
7
8
9

10 **Trial oversight**

11
12
13 A Trial Committee (TC) and Data Safety Monitoring Board (DSMB) will be set up. The DSMB
14 advocates for the ethical and safety interests of the participants while the trial progresses by
15 making nonbinding recommendations to the TC. A data safety monitoring board will be
16 formed to monitor the study at interim periods: first third participants closed out (n=148) and
17 last quarter closed out. The DSMB consists of three independent reviewers; a statistician, a
18 surgeon and a nurse. The DSMB will be bound by the DSMB Terms of Reference and will
19 provide a written report to the TC. The TC consists of the Principal and site investigators, the
20 study biostatistician and health economist. This trial will utilise the Haybittle-Peto (23, 24)
21 boundary as the designated trial statistic for stopping the trial.
22
23
24
25
26
27
28
29
30
31
32
33
34
35

36 **Ethics and dissemination**

37
38
39 Ethics approval was obtained through St John of God Healthcare (HREC1409), Western
40 Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings
41 will be published in peer-reviewed journals and presented at local and international
42 conferences. We used the SPIRIT checklist when writing our study protocol.
43
44
45
46
47
48
49

50 **Discussion on strengths and limitations of the CYGNUS trial**

51
52
53 The CYGNUS trial is a designed as a multicenter randomized control trial that is powered to
54 determine treatment effectiveness. This robust study design has been engaged to ensure
55 that any differences between the two arms of the study are attributable to the intervention.
56
57
58
59
60

1
2
3 Hyldig et al (2019) have yielded positive findings in the application of negative pressure
4 wound therapy, for potential reduction in the occurrence of surgical wound complications in
5 postpartum mothers who have a BMI 35+ (10). The CYGNUS trial will contribute further
6 research to this particular issue, and is the first to use a prescreening risk assessment tool
7 designed to identify those patients at risk with multiple risk factors. Another strength to this
8 study is a within trial health economic evaluation comparing the negative pressure wound
9 therapy to standard care from multiple health care perspectives. This will include the acute,
10 community and primary health care setting. In light of the increased use of negative pressure
11 wound therapy in patients with high BMI 35+, there remains a considerable gap in the
12 evidence base for clinical or cost effectiveness.
13
14
15
16
17
18
19
20
21
22
23
24

- 25 • This study will challenge the current rationale for initiating negative pressure wound
26 therapy based on a single risk factor (BMI 35+), by utilizing a validated risk
27 assessment tool with multiple predictors, which is more reflective of a real world
28 setting.
29
30
31
32
- 33 • Due to the nature of the intervention, blinding of participants and providers is not
34 possible. However, statistical analysis will be blinded.
35
36
37
- 38 • The exclusion of emergency cases may result in sample bias and exclude an already
39 'at risk' cohort.
40
41
- 42 • Participants will be followed up via face-to-face meetings or telephone call to ensure
43 participant wellbeing and data capture. This may potentially halt any loss to follow up.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17 **Declarations**

18
19
20 **Funding** This work is funded by an unrestricted educational grant from Convatec Pty Ltd.
21 Grant ID UWA52001100. Convatec Pty Ltd., had no input into the design of the study,
22 publications or educational matter related to the study.
23
24
25

26
27 **Contributions** KSH, RP designed the study. KSH wrote the background, methodology and
28 developed the research question with input from RP & SWW. RP wrote the statistical design
29 section and RN wrote the health economic sections of the protocol. Reviews were conducted
30 by MF & FW. All authors reviewed and agreed the final manuscript.
31
32
33
34
35
36
37
38
39

40 **Competing interests** None declared
41
42

43
44 **Patient consent** Patient consent will be sought to participate in the study via written
45 informed consent
46
47

48
49 **Provenance and peer review** Not commissioned, externally peer reviewed
50

51
52 **Open Access** This is an Open Access article distributed in accordance with the terms of the
53 Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix,
54 adapt and build upon this work for commercial use, provided the original work is properly
55 cited. See: <http://creativecommons.org/licenses/by/4.0/>
56
57
58
59
60

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 therapeutic 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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1. CYGNUS CONSORT Trial Participant

For peer review only

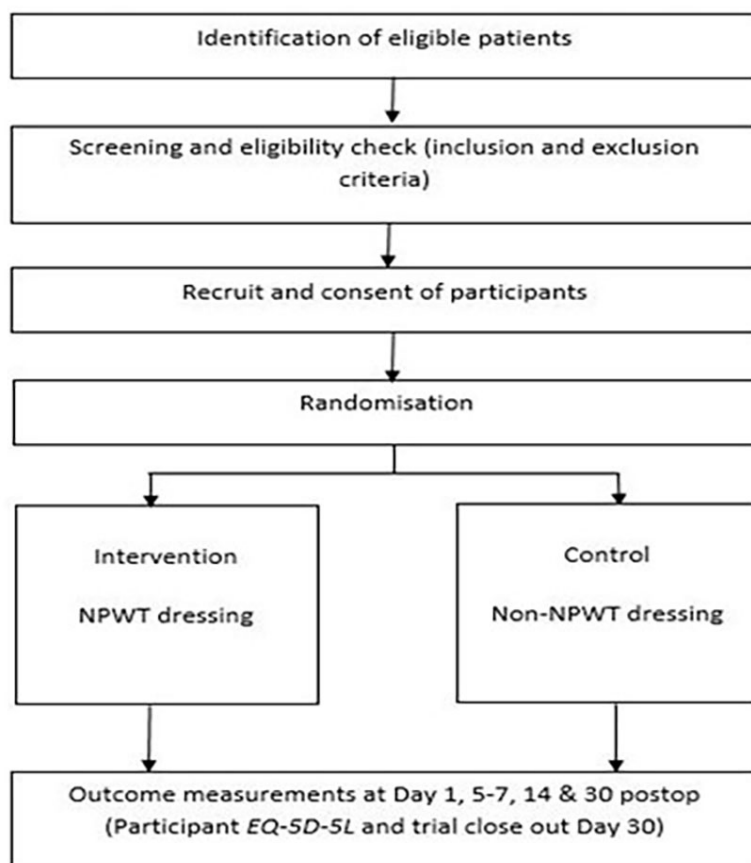


Figure 1. CYGNUS Trial CONSORT

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 SPIRIT reporting 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

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	1
2				
3				
4			name of intended registry	
5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	1
7				
8	data set		Registration Data Set	
9				
10				
11	Protocol version	#3	Date and version identifier	1
12				
13				
14				
15	Funding	#4	Sources and types of financial, material, and other	13
16				
17			support	
18				
19				
20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1
21				
22	responsibilities:			
23				
24	contributorship			
25				
26				
27				
28	Roles and	#5b	Name and contact information for the trial sponsor	1
29				
30	responsibilities:			
31				
32	sponsor contact			
33				
34	information			
35				
36				
37				
38	Roles and	#5c	Role of study sponsor and funders, if any, in study	13
39				
40	responsibilities:		design; collection, management, analysis, and	
41				
42	sponsor and funder		interpretation of data; writing of the report; and the	
43				
44			decision to submit the report for publication, including	
45				
46			whether they will have ultimate authority over any of	
47				
48			these activities	
49				
50				
51				
52	Roles and	#5d	Composition, roles, and responsibilities of the	12
53				
54	responsibilities:		coordinating centre, steering committee, endpoint	
55				
56	committees		adjudication committee, data management team, and	
57				
58				
59				
60				

1 other individuals or groups overseeing the trial, if
 2
 3 applicable (see Item 21a for data monitoring committee)
 4
 5

6 Introduction

7
 8
 9 Background and [#6a](#) Description of research question and justification for 2
 10
 11 rationale undertaking the trial, including summary of relevant
 12
 13 studies (published and unpublished) examining benefits
 14
 15
 16 and harms for each intervention
 17

18
 19 Background and [#6b](#) Explanation for choice of comparators 7-8
 20
 21 rationale: choice of
 22
 23 comparators
 24
 25

26 Objectives [#7](#) Specific objectives or hypotheses 5
 27
 28

29 Trial design [#8](#) Description of trial design including type of trial (eg, 5
 30
 31 parallel group, crossover, factorial, single group),
 32
 33 allocation ratio, and framework (eg, superiority,
 34
 35 equivalence, non-inferiority, exploratory)
 36
 37
 38

39 Methods:

40
 41 Participants,
 42
 43 interventions, and
 44
 45 outcomes
 46
 47
 48

49 Study setting [#9](#) Description of study settings (eg, community clinic, 5
 50
 51 academic hospital) and list of countries where data will be
 52
 53 collected. Reference to where list of study sites can be
 54
 55 obtained
 56
 57
 58
 59
 60

1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	6
2				
3			applicable, eligibility criteria for study centres and	
4			individuals who will perform the interventions (eg,	
5			surgeons, psychotherapists)	
6				
7				
8				
9				
10				
11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-7
12				
13	description		replication, including how and when they will be	
14			administered	
15				
16				
17				
18				
19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	7
20				
21	modifications		interventions for a given trial participant (eg, drug dose	
22			change in response to harms, participant request, or	
23			improving / worsening disease)	
24				
25				
26				
27				
28				
29	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	7
30				
31	adherence		and any procedures for monitoring adherence (eg, drug	
32			tablet return; laboratory tests)	
33				
34				
35				
36	Interventions:	#11d	Relevant concomitant care and interventions that are	7
37				
38	concomitant care		permitted or prohibited during the trial	
39				
40				
41				
42	Outcomes	#12	Primary, secondary, and other outcomes, including the	8-9
43			specific measurement variable (eg, systolic blood	
44			pressure), analysis metric (eg, change from baseline, final	
45			value, time to event), method of aggregation (eg, median,	
46			proportion), and time point for each outcome. Explanation	
47			of the clinical relevance of chosen efficacy and harm	
48			outcomes is strongly recommended	
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	10
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly recommended	
4			(see Figure)	
5				
6	Sample size	#14	Estimated number of participants needed to achieve	10-11
7			study objectives and how it was determined, including	
8			clinical and statistical assumptions supporting any sample	
9			size calculations	
10				
11	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6-7
12			reach target sample size	
13				
14				
15				
16	Methods:			
17	Assignment of			
18	interventions (for			
19	controlled trials)			
20				
21	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
22	generation		computer-generated random numbers), and list of any	
23			factors for stratification. To reduce predictability of a	
24			random sequence, details of any planned restriction (eg,	
25			blocking) should be provided in a separate document that	
26			is unavailable to those who enrol participants or assign	
27			interventions	
28				
29	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
30	concealment		central telephone; sequentially numbered, opaque,	
31	mechanism			

sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Allocation: [#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): [#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

1	Data collection plan:	#18b	Plans to promote participant retention and complete	11
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
6				
7				
8				
9				
10				
11	Data management	#19	Plans for data entry, coding, security, and storage,	11
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
17				
18				
19				
20				
21				
22				
23	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	11
24			outcomes. Reference to where other details of the	
25			statistical analysis plan can be found, if not in the protocol	
26				
27				
28				
29				
30				
31	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
32			adjusted analyses)	
33	analyses			
34				
35				
36	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
37			adherence (eg, as randomised analysis), and any	
38	population and		statistical methods to handle missing data (eg, multiple	
39			imputation)	
40	missing data			
41				
42				
43				
44				
45				
46	Methods: Monitoring			
47				
48				
49	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	12
50			summary of its role and reporting structure; statement of	
51	formal committee		whether it is independent from the sponsor and	
52			competing interests; and reference to where further	
53				
54				
55				
56				
57				
58				
59				
60				

1 details about its charter can be found, if not in the
 2 protocol. Alternatively, an explanation of why a DMC is
 3 not needed
 4
 5
 6
 7

8	Data monitoring:	#21b	Description of any interim analyses and stopping	12
9	interim analysis		guidelines, including who will have access to these	
10			interim results and make the final decision to terminate	
11			the trial	
12				
13				
14				
15				
16				
17				
18	Harms	#22	Plans for collecting, assessing, reporting, and managing	10
19			solicited and spontaneously reported adverse events and	
20			other unintended effects of trial interventions or trial	
21			conduct	
22				
23				
24				
25				
26				
27				
28	Auditing	#23	Frequency and procedures for auditing trial conduct, if	12
29			any, and whether the process will be independent from	
30			investigators and the sponsor	
31				
32				
33				
34				
35	Ethics and			
36	dissemination			
37				
38				
39				
40				
41	Research ethics	#24	Plans for seeking research ethics committee / institutional	12
42	approval		review board (REC / IRB) approval	
43				
44				
45				
46	Protocol	#25	Plans for communicating important protocol modifications	12
47	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
48			relevant parties (eg, investigators, REC / IRBs, trial	
49			participants, trial registries, journals, regulators)	
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	6,13
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
4				
5				
6				
7				
8				
9	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
12				
13				
14				
15				
16	Confidentiality	#27	How personal information about potential and enrolled	6
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
20				
21				
22				
23				
24				
25				
26	Declaration of	#28	Financial and other competing interests for principal	13
27	interests		investigators for the overall trial and each study site	
28				
29				
30				
31				
32	Data access	#29	Statement of who will have access to the final trial	13
33			dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
35				
36				
37				
38				
39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	10
40	trial care		compensation to those who suffer harm from trial	
41			participation	
42				
43				
44				
45				
46				
47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	12
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Dissemination policy: #31b	Authorship eligibility guidelines and any intended use of	13
2			
3	authorship	professional writers	
4			
5			
6	Dissemination policy: #31c	Plans, if any, for granting public access to the full	13
7			
8	reproducible	protocol, participant-level dataset, and statistical code	
9			
10	research		
11			
12			
13			
14	Appendices		
15			
16			
17	Informed consent	#32 Model consent form and other related documentation	6
18			
19	materials	given to participants and authorised surrogates	
20			
21			
22			
23	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	NA
24			
25		biological specimens for genetic or molecular analysis in	
26			
27		the current trial and for future use in ancillary studies, if	
28			
29		applicable	
30			
31			

32 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-
 33 BY-ND 3.0. This checklist was completed on 13. November 2019 using <https://www.goodreports.org/>,
 34
 35 a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
 36
 37
 38
 39
 40
 41
 42
 43
 44
 45
 46
 47
 48
 49
 50
 51
 52
 53
 54
 55
 56
 57
 58
 59
 60

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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3 BMJ Open Manuscript
4
5
6
7

8 Effectiveness of negative pressure wound therapy in the prevention of surgical wound
9 complications in the cesarean section at risk population: a parallel group randomised
10
11
12
13 multicentre trial, the **CYGNUS** protocol.
14
15
16
17

- 18 1. Dr Kylie Sandy-Hodgetts, BSc, Hons H1, MBA, Ph.D Director Skin Integrity Research
19 Institute, Senior Research Fellow, Burn Injury Research Unit, School of Biomedical
20 Sciences, Faculty of Health and Medical Sciences, University of Western Australia.
21
22
- 23 2. Dr Richard Parsons, Senior Lecturer in Statistics, School of Occupational Therapy,
24 Social Work and Speech, Curtin University
25
26
- 27 3. Associate Professor Richard Norman, Health Economist, School of Public Health,
28 Curtin University
29
30
- 31 4. Dr Mark Fear, Senior Research Fellow, Burns Injury Unit, School of Biomedical
32 Sciences, Faculty of Medicine, University of Western Australia
33
34
- 35 5. Professor Fiona Wood, Director State Burns Unit, Fiona Stanley Hospital, Perth
36
37
- 38 6. Dr Scott W White, Senior Lecturer, Consultant Obstetrician, Department of Maternal
39 and Fetal Medicine, King Edward Memorial Hospital
40
41
42
43
44
45

46 Correspondence to: Dr Kylie Sandy-Hodgetts; kylie.sandy-hodgetts@uwa.edu.au
47
48

49 Abstract word count: 501
50

51 Manuscript: 3069 (max 4000 words)
52
53
54
55
56
57
58
59
60

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

1
2
3 will assess recruitment rate and adherence to intervention and follow up. We will assess the
4 potential effectiveness of negative pressure wound therapy in the prevention of post-partum
5 surgical wound complications at three time points during the study; Day 5 post-operative,
6 Day 14 and Day 30 where the participant will be closed out of the trial. We will utilise
7 statistical methods to determine efficacy and risk stratification will be conducted to determine
8 the surgical wound dehiscence risk profile of the participant. Follow up at Day 30 will assess
9 superficial and deep infection and wound dehiscence (Grades I-IV) and the core outcome
10 dataset for wound complications. This study will collect health related quality of life (ED-5D-
11 5L), mortality and late complications such as further surgery with a cost analysis conducted.
12 The primary analysis will be by intention to treat. This clinical trial protocol follows the
13 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and
14 the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The trial was
15 registered on the Australian and New Zealand Clinical Trials Registry
16 (ACTRN12618002006224) prior to commencement.

32 33 **Ethics and dissemination**

34
35
36 Ethics approval was obtained through St John of God Healthcare (HREC1409), Western
37 Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings
38 will be published in peer-reviewed journals and presented at international conferences. We
39 used the SPIRIT checklist when writing our study protocol.
40
41
42
43
44
45
46
47

48 **Trial registration number:** ANZCTR: ACTRN12618002006224p

49
50 **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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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/m²+) (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 summarises 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

1
2
3 schedule. Once consent has been obtained, the staff member who is recruiting the patient
4 will contact the senior research fellow in their site to request the next study identifier and
5 treatment allocation. Baseline participant information, demographic and related medical
6 history will be collected. A participant risk profile for surgical wound dehiscence (SWD) will
7 be obtained utilising the Perth Surgical Wound Dehiscence Risk Assessment Tool
8 (PSWDRAT) (13). This will determine the SWD risk profile of the trial participant. The
9 European Quality of Life 5-Dimensions 5-Level Scale (EQ-5D-5L) (14) a validated
10 questionnaire will be administered at baseline and at the end of the trial to allow estimation
11 of QALYs of all participants. The study statistician will generate the allocation sequence for
12 each site before the study commences, using a random number generator on a computer.
13 There will be a separate sequence for each site, and each sequence will be generated using
14 a permuted random blocks strategy to ensure that recruitment to the two arms of the study
15 occurs at approximately equal rates within each site. The allocation list for each site will be
16 provided to the senior research fellow at each site, and will be kept private from all other
17 personnel at the site. Due the nature of the study device, blinding of participants or study
18 personnel after treatment allocation is not possible. However, the study statistician will be
19 blinded to group allocation.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 **Patient and public involvement**

44
45 No patient involvement in the study design.
46
47
48
49

50 **Post randomisation withdrawals/exclusions**

51
52
53 Participants may choose not to participate in the CYGNUS trial or withdraw from the study at
54 any time without prejudice. Choosing either of these options will not affect the standard of
55 care the patient receives.
56
57
58
59
60

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

1
2
3 intervention group will receive the portable negative pressure device at Day 0. The dressing
4 will be worn for a standardised period of 5 days (intervention and controls arms). Any further
5 wound dressings after the initial dressing application will be recorded in the CRF's and
6 following the allocated treatment unless otherwise clinically indicated.
7
8
9
10

11 12 13 14 15 **Outcome measures**

16 17 **Primary outcome**

18
19
20 The primary outcome for this study is surgical wound dehiscence as defined by the WUWHS
21 SWD Grading System (17), and the Centres for Disease Control definitions of SSI (18) will
22 be used as the primary outcome measure for confirmed wound infection. The primary
23 outcome measure definitions include a wound complication that occurs within 30 days of
24 surgery. The treating clinical team will determine the diagnosis of surgical wound
25 dehiscence or infection as per routine clinical wound assessment protocol if there is a
26 confirmed SSI or SWD. Rapid diagnosis and treatment of wound infection is central to
27 patient standard care and the attending clinician will document any changes in the patient
28 medical notes and adhere to local wound management protocols.
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 **Secondary outcomes**

44 *Health related quality of life assessment*

45
46 A qualitative assessment of the participant's perceptions of wound healing will be conducted.
47
48

49 *EuroQol EQ-5D-5L*

50
51 The EuroQol EQ-5D is a validated measure of health related quality of life, comprising a five-
52 dimension health status classification system and a separate Visual Analogue Scale (19).
53
54

55 The EQ-5D consists of five dimensions (Mobility, Self-Care, Usual Activities,
56
57
58
59
60

1
2
3 Pain/Discomfort, and Anxiety/Depression), each with either 3 or 5 levels. We will use the
4 five-level version of the instrument, which is likely to be more sensitive to small but important
5 changes in health-related quality of life (14). The responses will be converted into an index
6 score, and total QALYs for each woman will be obtained by estimating the area under the
7 curve defined by their baseline and final EQ-5D-5L responses (20).
8
9
10
11
12
13
14
15
16

17 *Economic analysis*

18
19 All resources utilised in the study will be recorded to help inform the economic analysis. Cost
20 data will be derived from the hospital finance departments and any related community
21 nursing service or primary health care centre where the participant has attended. Cost
22 consequences following discharge including out of pocket expenses (if any) will be recorded
23 in the case report forms at day 30 following the procedure. The incremental cost of the
24 intervention relative to the control will be estimated, and divided by incremental outcomes
25 reported in the study. Each resultant incremental cost-effectiveness ratio (ICER) will be
26 reported separately, with the last step being the cost per QALY. We will conduct univariate
27 and probabilistic sensitivity analyses around the cost per QALY to assess the robustness of
28 the result, with the threshold for cost-effectiveness determined by recent work by Edney *et*
29 *al.*(21).
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

47 **Adverse event management**

48
49 Adverse device effect is an adverse event related to the use of an investigational medical
50 device (IMD) (22). Adverse events (AEs) related to an investigational medical device are
51 defined as any untoward medical occurrence, unintended disease or injury, or untoward
52 clinical signs (including abnormal laboratory findings) in participants, users or other persons,
53 whether or not related to in the investigational medical device (22). Definitions of adverse
54
55
56
57
58
59
60

1
2
3 events (AEs), serious adverse device effect (SADE), serious adverse event (SAE)
4
5 Significant Safety Issue, Unanticipated Serious Adverse Device Effect (USADE) or Urgent
6
7 Safety Measure (USM) are as per the National Health and Medical Research Council (2016)
8
9 Guidelines on Safety monitoring and reporting in clinical trials involving therapeutic goods
10
11 (22). During the treatment protocol, any USADE will be reported directly to the DSMB and
12
13 within 7 days to the Australian Government Therapeutics Goods Administration via the
14
15 electronic Medical Device Incident Reporting System. Reports will also be sent to the local
16
17 study sites Human Research Ethics Committees. The safety aspects of the study will be
18
19 closely monitored by the DSMB, which will receive unblinded data for review. In the case of
20
21 a device related adverse advent the manufacturer will be notified.
22
23
24
25
26
27

28 **Follow up**

29
30 Each participant will be followed up during the trial as close as practically possible to the
31
32 specific time points: Day 5, Day 14, and Day 30 following surgery. The close out time point of
33
34 the trial participant is Day 30 postoperative. In the event that a participant has an unresolved
35
36 complication beyond 30 days, follow up will continue to complete wound healing, and
37
38 participants will have the opportunity to opt out of the extended data collection beyond Day
39
40 30. All participants will be followed up by the Visiting Midwifery Service (VMS) and a scripted
41
42 phone call at the trial close out time point. Various forms of communication will be used in
43
44 engaging the participation, email, phone call and face-to-face consultation to reduce loss to
45
46 follow up. All data recorded during the follow up time points will be recorded on the case
47
48 report forms and clinical assessment will follow standard postoperative wound care
49
50 management and clinical procedures.
51
52
53
54
55
56
57
58
59
60

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 $\alpha=0.05$. 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.

1
2
3 All statistical analyses will be performed using the SAS version 9.4 software, and, following
4 convention, a p-value < 0.05 will be taken to indicate a significant association in all tests.
5
6
7
8
9

10 **Trial oversight**

11
12
13 A Trial Committee (TC) and Data Safety Monitoring Board (DSMB) will be set up. The DSMB
14 advocates for the ethical and safety interests of the participants while the trial progresses by
15 making nonbinding recommendations to the TC. A data safety monitoring board will be
16 formed to monitor the study at interim periods: first third participants closed out (n=148) and
17 last quarter closed out. The DSMB consists of three independent reviewers; a statistician, a
18 surgeon and a nurse. The DSMB will be bound by the DSMB Terms of Reference and will
19 provide a written report to the TC. The TC consists of the Principal and site investigators, the
20 study biostatistician and health economist. This trial will utilise the Haybittle-Peto (23, 24)
21 boundary as the designated trial statistic for stopping the trial.
22
23
24
25
26
27
28
29
30
31
32
33
34
35

36 **Ethics and dissemination**

37
38
39 Ethics approval was obtained through St John of God Healthcare (HREC1409), Western
40 Australia Department of Health King Edward Memorial Hospital (HREC3111). Study findings
41 will be published in peer-reviewed journals and presented at local and international
42 conferences. We used the SPIRIT checklist when writing our study protocol.
43
44
45
46
47
48
49

50 **Discussion on strengths and limitations of the CYGNUS trial**

51
52
53 The CYGNUS trial is a designed as a multicenter randomized control trial that is powered to
54 determine treatment effectiveness. This robust study design has been engaged to ensure
55 that any differences between the two arms of the study are attributable to the intervention.
56
57
58
59
60

1
2
3 Hyldig et al (2019) have yielded positive findings in the application of negative pressure
4 wound therapy, for potential reduction in the occurrence of surgical wound complications in
5 postpartum mothers who have a BMI 35+ (10). The CYGNUS trial will contribute further
6 research to this particular issue, and is the first to use a prescreening risk assessment tool
7 designed to identify those patients at risk with multiple risk factors. Another strength to this
8 study is a within trial health economic evaluation comparing the negative pressure wound
9 therapy to standard care from multiple health care perspectives. This will include the acute,
10 community and primary health care setting. In light of the increased use of negative pressure
11 wound therapy in patients with high BMI 35+, there remains a considerable gap in the
12 evidence base for clinical or cost effectiveness.
13
14
15
16
17
18
19
20
21
22
23
24

- 25 • This study will challenge the current rationale for initiating negative pressure wound
26 therapy based on a single risk factor (BMI 35+), by utilizing a validated risk
27 assessment tool with multiple predictors, which is more reflective of a real world
28 setting.
29
30
31
32
- 33 • Due to the nature of the intervention, blinding of participants and providers is not
34 possible. However, statistical analysis will be blinded.
35
36
- 37 • The exclusion of emergency cases may result in sample bias and exclude an already
38 'at risk' cohort.
39
40
- 41 • Participants will be followed up via face-to-face meetings or telephone call to ensure
42 participant wellbeing and data capture. This may potentially halt any loss to follow up.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17 **Declarations**
18
19

20 **Funding** This work is funded by an unrestricted educational grant from Convatec Pty Ltd.
21 Grant ID UWA52001100. Convatec Pty Ltd., had no input into the design of the study,
22 publications or educational matter related to the study.
23
24
25
26

27 **Contributions** KSH, RP designed the study. KSH wrote the background, methodology and
28 developed the research question with input from RP & SWW. RP wrote the statistical design
29 section and RN wrote the health economic sections of the protocol. Reviews were conducted
30 by MF & FW. All authors reviewed and agreed the final manuscript.
31
32
33
34
35
36
37
38
39

40 **Competing interests** None declared
41
42

43 **Patient consent** Patient consent will be sought to participate in the study via written
44 informed consent
45
46
47
48

49 **Provenance and peer review** Not commissioned, externally peer reviewed
50

51 **Open Access** This is an Open Access article distributed in accordance with the terms of the
52 Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix,
53 adapt and build upon this work for commercial use, provided the original work is properly
54 cited. See: <http://creativecommons.org/licenses/by/4.0/>
55
56
57
58
59
60

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 therapeutic 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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1. CYGNUS CONSORT Trial Participant

For peer review only

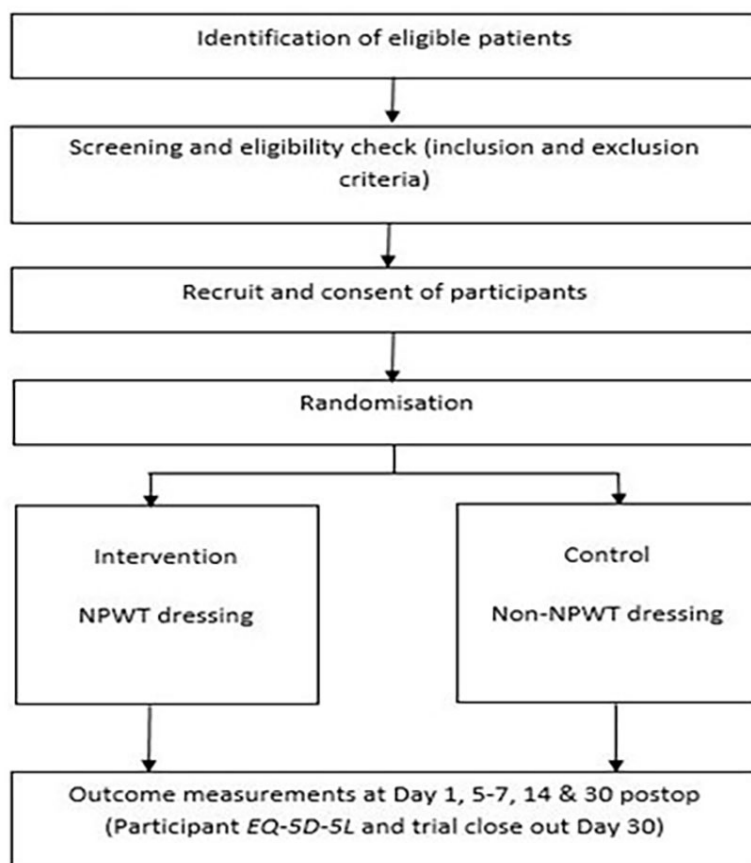


Figure 1. CYGNUS Trial CONSORT

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 SPIRIT reporting 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

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

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	1
2			name of intended registry	
3				
4				
5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	1
7				
8	data set		Registration Data Set	
9				
10				
11				
12	Protocol version	#3	Date and version identifier	1
13				
14				
15	Funding	#4	Sources and types of financial, material, and other	13
16			support	
17				
18				
19				
20	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1
21				
22	responsibilities:			
23				
24	contributorship			
25				
26				
27				
28	Roles and	#5b	Name and contact information for the trial sponsor	1
29				
30	responsibilities:			
31				
32	sponsor contact			
33				
34	information			
35				
36				
37				
38	Roles and	#5c	Role of study sponsor and funders, if any, in study	13
39			design; collection, management, analysis, and	
40	responsibilities:		interpretation of data; writing of the report; and the	
41			decision to submit the report for publication, including	
42	sponsor and funder		whether they will have ultimate authority over any of	
43			these activities	
44				
45				
46				
47				
48				
49				
50				
51				
52	Roles and	#5d	Composition, roles, and responsibilities of the	12
53			coordinating centre, steering committee, endpoint	
54	responsibilities:		adjudication committee, data management team, and	
55				
56	committees			
57				
58				
59				
60				

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

1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	6
2				
3			applicable, eligibility criteria for study centres and	
4			individuals who will perform the interventions (eg,	
5			surgeons, psychotherapists)	
6				
7				
8				
9				
10				
11	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-7
12				
13	description		replication, including how and when they will be	
14			administered	
15				
16				
17				
18				
19	Interventions:	#11b	Criteria for discontinuing or modifying allocated	7
20				
21	modifications		interventions for a given trial participant (eg, drug dose	
22			change in response to harms, participant request, or	
23			improving / worsening disease)	
24				
25				
26				
27				
28				
29	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	7
30				
31	adherence		and any procedures for monitoring adherence (eg, drug	
32			tablet return; laboratory tests)	
33				
34				
35				
36	Interventions:	#11d	Relevant concomitant care and interventions that are	7
37				
38	concomitant care		permitted or prohibited during the trial	
39				
40				
41				
42	Outcomes	#12	Primary, secondary, and other outcomes, including the	8-9
43			specific measurement variable (eg, systolic blood	
44			pressure), analysis metric (eg, change from baseline, final	
45			value, time to event), method of aggregation (eg, median,	
46			proportion), and time point for each outcome. Explanation	
47			of the clinical relevance of chosen efficacy and harm	
48			outcomes is strongly recommended	
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Participant timeline	#13	Time schedule of enrolment, interventions (including any	10
2			run-ins and washouts), assessments, and visits for	
3			participants. A schematic diagram is highly recommended	
4			(see Figure)	
5				
6				
7				
8				
9				
10				
11	Sample size	#14	Estimated number of participants needed to achieve	10-11
12			study objectives and how it was determined, including	
13			clinical and statistical assumptions supporting any sample	
14			size calculations	
15				
16				
17				
18				
19				
20				
21	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6-7
22			reach target sample size	
23				
24				
25				
26	Methods:			
27				
28	Assignment of			
29	interventions (for			
30	controlled trials)			
31				
32				
33				
34				
35				
36	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
37	generation		computer-generated random numbers), and list of any	
38			factors for stratification. To reduce predictability of a	
39			random sequence, details of any planned restriction (eg,	
40			blocking) should be provided in a separate document that	
41			is unavailable to those who enrol participants or assign	
42			interventions	
43				
44				
45				
46				
47				
48				
49				
50				
51				
52				
53	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
54	concealment		central telephone; sequentially numbered, opaque,	
55				
56				
57				
58	mechanism			
59				
60				

sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

1			
2			
3			
4			
5			
6	Allocation:	#16c	Who will generate the allocation sequence, who will enrol
7			
8	implementation		participants, and who will assign participants to
9			
10			interventions
11			
12			
13	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,
14			
15			trial participants, care providers, outcome assessors, data
16			
17			analysts), and how
18			
19			
20			
21	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is
22			
23	emergency		permissible, and procedure for revealing a participant's
24			
25	unblinding		allocated intervention during the trial
26			
27			
28			
29	Methods: Data		
30			
31	collection,		
32			
33	management, and		
34			
35	analysis		
36			
37			
38			
39	Data collection plan	#18a	Plans for assessment and collection of outcome,
40			
41			baseline, and other trial data, including any related
42			
43			processes to promote data quality (eg, duplicate
44			
45			measurements, training of assessors) and a description
46			
47			of study instruments (eg, questionnaires, laboratory tests)
48			
49			along with their reliability and validity, if known. Reference
50			
51			to where data collection forms can be found, if not in the
52			
53			protocol
54			
55			
56			
57			
58			
59			
60			

1	Data collection plan:	#18b	Plans to promote participant retention and complete	11
2				
3	retention		follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate from	
5			intervention protocols	
6				
7				
8				
9				
10				
11	Data management	#19	Plans for data entry, coding, security, and storage,	11
12			including any related processes to promote data quality	
13			(eg, double data entry; range checks for data values).	
14			Reference to where details of data management	
15			procedures can be found, if not in the protocol	
16				
17				
18	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	11
19			outcomes. Reference to where other details of the	
20			statistical analysis plan can be found, if not in the protocol	
21				
22				
23				
24	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	11
25	analyses		adjusted analyses)	
26				
27				
28				
29				
30				
31	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	11
32	population and		adherence (eg, as randomised analysis), and any	
33	missing data		statistical methods to handle missing data (eg, multiple	
34			imputation)	
35				
36				
37				
38				
39				
40				
41				
42				
43				
44				
45				
46	Methods: Monitoring			
47				
48				
49	Data monitoring:	#21a	Composition of data monitoring committee (DMC);	12
50	formal committee		summary of its role and reporting structure; statement of	
51			whether it is independent from the sponsor and	
52			competing interests; and reference to where further	
53				
54				
55				
56				
57				
58				
59				
60				

1 details about its charter can be found, if not in the
 2 protocol. Alternatively, an explanation of why a DMC is
 3 not needed
 4
 5
 6
 7

8	Data monitoring:	#21b	Description of any interim analyses and stopping	12
9	interim analysis		guidelines, including who will have access to these	
10			interim results and make the final decision to terminate	
11			the trial	
12				
13				
14				
15				
16				
17				
18	Harms	#22	Plans for collecting, assessing, reporting, and managing	10
19			solicited and spontaneously reported adverse events and	
20			other unintended effects of trial interventions or trial	
21			conduct	
22				
23				
24				
25				
26				
27				
28	Auditing	#23	Frequency and procedures for auditing trial conduct, if	12
29			any, and whether the process will be independent from	
30			investigators and the sponsor	
31				
32				
33				
34				
35	Ethics and			
36	dissemination			
37				
38				
39				
40				
41	Research ethics	#24	Plans for seeking research ethics committee / institutional	12
42	approval		review board (REC / IRB) approval	
43				
44				
45				
46	Protocol	#25	Plans for communicating important protocol modifications	12
47	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
48			relevant parties (eg, investigators, REC / IRBs, trial	
49			participants, trial registries, journals, regulators)	
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Consent or assent	#26a	Who will obtain informed consent or assent from potential	6,13
2			trial participants or authorised surrogates, and how (see	
3			Item 32)	
4				
5				
6				
7				
8				
9	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
10	ancillary studies		participant data and biological specimens in ancillary	
11			studies, if applicable	
12				
13				
14				
15				
16	Confidentiality	#27	How personal information about potential and enrolled	6
17			participants will be collected, shared, and maintained in	
18			order to protect confidentiality before, during, and after	
19			the trial	
20				
21				
22				
23				
24				
25				
26	Declaration of	#28	Financial and other competing interests for principal	13
27	interests		investigators for the overall trial and each study site	
28				
29				
30				
31				
32	Data access	#29	Statement of who will have access to the final trial	13
33			dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
35				
36				
37				
38				
39	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	10
40	trial care		compensation to those who suffer harm from trial	
41			participation	
42				
43				
44				
45				
46				
47	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	12
48	trial results		results to participants, healthcare professionals, the	
49			public, and other relevant groups (eg, via publication,	
50			reporting in results databases, or other data sharing	
51			arrangements), including any publication restrictions	
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Dissemination policy: #31b	Authorship eligibility guidelines and any intended use of	13
2			
3	authorship	professional writers	
4			
5			
6	Dissemination policy: #31c	Plans, if any, for granting public access to the full	13
7			
8	reproducible	protocol, participant-level dataset, and statistical code	
9			
10	research		
11			
12			
13			
14	Appendices		
15			
16			
17	Informed consent	#32 Model consent form and other related documentation	6
18			
19	materials	given to participants and authorised surrogates	
20			
21			
22	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	NA
23			
24		biological specimens for genetic or molecular analysis in	
25			
26		the current trial and for future use in ancillary studies, if	
27			
28		applicable	
29			
30			
31			

32 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-
 33 BY-ND 3.0. This checklist was completed on 13. November 2019 using <https://www.goodreports.org/>,
 34
 35 a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
 36
 37
 38
 39
 40
 41
 42
 43
 44
 45
 46
 47
 48
 49
 50
 51
 52
 53
 54
 55
 56
 57
 58
 59
 60