## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | 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 |
| **AUTHORS** | Sandy-Hodgetts, Kylie; Parsons, Richard; Norman, Richard; Fear, Mark; Wood, Fiona; White, Scott |

## VERSION 1 – REVIEW

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| **REVIEWER** | Brigid Gillespie<br>School of Nursing and Midwifery, Griffith University &<br>Gold Coast University Hospital, Gold Coast Health<br>Australia |
| **REVIEW RETURNED** | 25-Nov-2019 |

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| **GENERAL COMMENTS** | This paper reports a research protocol designed to test the efficacy of NPWT in the prevention of post C-Section wound complications compared with the standard dressing.. This proposed study is one of a growing number of similar studies being undertaken in the use of NPWT in high risk populations (see for example Gilespie et al 2016-protocol; Hydig et al, 2018-completed trial).<br><br>While this type of trial in this high risk population is not new, the results may potentially contribute to the growing body of evidence in this area (Level 1A).<br><br>My comments about methodology are listed below:<br>1. Eligibility criteria-please be more explicit. Will [regnant women be recruited on the basis of their BMI? This is not stated but the use of NPWT is often used in high risk incisions, where a high BMI (>30) is identified as a risk factor. Other risk factors such as C-Section category (1-4), previous C-Section, premature ROM are potential risk factors and should be considered.<br>2. Randomization appears to be planned upon recruitment (or thereafter) but it is unclear when this will be undertaken, and by whom. At what point will theatre personnel be aware of group allocation, and how will this be concealed? Ideally, the surgical team involved in the c-section procedure should not be made aware of group allocation until the conclusion of the procedure, ie., skin suturing.<br>3. Authors please elaborate on how the primary trial outcomes will be ascertained. While blinding of the data collectors and clinicians is not possible, will there be independent outcomes assessors to assess clinical outcomes? Having the statistician blinded is important, however, it is just as important that those assessing the clinical outcomes are also blinded to minimize bias. |

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| | 4. Sample size of 224 per group has been calculated based on a retrospective chart audit, and a 50% reduction in the intervention group. However, other trials in this area (Hydig 2018) used sample sizes that are much larger.<br>5.In terms of the follow up period, please justify why the time points specified will be used. The 30 day time point is self explanatory however, time points for weeks 6 and 12 need to be justified.<br>6. Stopping rules for the trial-this is very controversial. In this case, stopping early for benefit may introduce a bias because of large random fluctuation of the estimated treatment effect. Thus the results of the trial may provide misleading estimates of benefit (see Bassler et al, 2010). Stopping a trial prematurely because of harm is appropriate but stopping a trial of this size for benefit is harder to justify.<br>7. Please include a timeline of trail activities as specified in the SPIRIT Guidelines for reporting.<br>8. Authors, a frank discussion of the strengths but in particular the limitations of the trial. One of the strengths of this trial is the parallel health economic evaluation. need to included to follow the HREC section.<br><br>Summary<br>This trial has the potential to add to the body of work undertaken in the use of NPWT to prevent SSI and other wound complications. However I have some concerns around the clarity of the methods in relation to randomisation, allocation concealment, ascertainment and blinding. Additionally there are very few references to other work undertaken in this area, where a more conservative sample size (larger) may have been drawn and used to inform the sample size in this trial. A real strength of this trial is the parallel economic evaluation. |

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| **REVIEWER** | Steven Jeffery<br>The Queen Elizabeth Hospital, Birmingham, UK |
| **REVIEW RETURNED** | 04-Dec-2019 |

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| **GENERAL COMMENTS** | Hello,<br>given that you will be leaving both dressings on for seven days, I am intrigued by your choice of days 3, 5 and 14 as your wound assessment dates. Please could you elaborate on why you have chosen those days and how the diagnosis of wound complications will be made. Also, will you be photographing the wounds and measuring the degree of dehiscence? |

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| **REVIEWER** | Univ.-Prof. Dr. Prof.h.c .Dr.h.c. Raymund E. Horch<br>Department of Plastic and Hand Surgery<br>and Laboratory for Tissue Engineering and Regenerative Medicine<br>University Hospital Erlangen<br>Friedrich-Alexander University Erlangen-Nuernberg FAU<br>Germany |
| **REVIEW RETURNED** | 13-Jan-2020 |

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| **GENERAL COMMENTS** | All in all this manuscript consists of a checklist for a protocol of a clinical trial that envisions to study the effect of a negative pressure wound therapy in terms of wound complications.<br>It is worthwhile to study the effect of this treatment modality yand the protocol is set uo adequately. |

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| | Nevertheless I have some suggestions or minor revisional points to make as follows:<br><br>Page 4, line nr. 14<br>Please clarify which specific settings!<br><br>Page 2, line 57-59 and page 3 line 3-5<br>Here the authors state that the assessment of the efficacy of negative pressure wound therapy in terms of wound complications will be performed at day 5, 14 and 30 postoperative. I assume this requires the removal of the applied negative pressure wound dressing in order to assess potential wound complications at day 5<br>Page 8, line 23-26<br>“In this trial, the dressing will be worn for a standardised period of 7 days (intervention and controls arms)”<br><br>This seems contradictory. How are you planning to assess the potential efficacy of negative pressure wound therapy in the prevention of post-partum wound complications at day 5 postoperative without removing the negative pressure wound dressing at day 5?<br><br>The wear time of the standard dressing should be more specified. How often will there be a change of standard wound dressing within the first 7 days (eg. on a daily basis?). A wear time of 7 days without change of dressing would be quite long and might result in a possible disadvantage for the control group in terms of proper wound management. Please clarify<br><br>If patients will be discharged within the first 7 days postoperatively it requires the application of a portable negative pressure device in the intervention group before discharge. Please clarify if patients will receive a portable negative pressure device already at day 0 intraoperative or shortly before discharge. |

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| **REVIEWER** | Nana Hyldig<br>Odense University Hospital<br>Denmark<br>I have previously conducted and published a similar study |
| **REVIEW RETURNED** | 17-Jan-2020 |

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| **GENERAL COMMENTS** | Thank you for the opportunity to review this manuscript. Several studies have been published on NPWT after caesarean section. This study uses a relatively new NPWT dressing that to my knowledges has not yet been evaluated in a clinical trial. Moreover, the focus is on wound dehiscence which often is reported as a secondary outcome. I think this study is relevant and will add knowledge to the current evidence of NPWT after caesarean section.<br>Overall, the manuscript could benefit from being more aligned with the terminology and chronology used in the Consort Statement and SPIRIT guideline.<br>Title<br>The authors should consider changing the title from Efficacy… to Effectiveness… as the study is a pragmatic randomised controlled trial: “Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under 'real-world' conditions” (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3912314/) |

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| | Abstract<br>Please state whether the primary outcome is a composed outcome or two individual outcomes.<br><br>Introduction<br>The introduction does not follow the items from SPIRIT. I am explicit missing the explanation for choice of comparators, which is not explained at page 7-8. One explanation could be that the study investigates the effect of a relatively new NPWT dressing, including any expected benefits from this dressing compared to others, and reasons for using a devise designed for 30 days of use which then only is used for 7 days. Control dressing is probably standard care, but it should be mentioned.<br><br>At page 4, line 31 the authors write that a recent study from the Netherlands has identified an effect of the use of NPWT for patients with high BMI. However the reference is a Danish study. Several other studies have been published so far that focus on NPWT in obese women after caesarean section (meta-analyses: Smid et al 2017, Yu et al 2018, Webster et al 2019). The discrepancy is study results and primary focus on obesity could be used as justification for undertaking this study.<br><br>Study aim and objectives<br>I recommend changing efficacy (page 5 line 23) to effectiveness.<br><br>Randomisation<br>I think randomisation should be a separate section and that it could be more aligned with Consort Statement to improve readability. Though the allocation sequence is computer-generated, allocation lists provided to the senior research fellow could affect the allocation concealment and introduce bias. This should be addressed either in this section or in the final report. How do you ensure that the senior researcher does not have any contact with or knowledges about the participant before randomization?<br><br>Study dressings<br>In the control dressing and intervention sections the description should include the name and manufacturer of the dressings used.<br><br>Primary outcome<br>I am unsure whether you have two primary outcomes: 1) dehiscence, 2) SSI - or it is a composed outcome (dehiscence and SSI). Furthermore, information on how and when the outcomes are assessed is missing. E.g. time points and how outcomes are assessed after discharge. Clinical utility of the intervention is mentioned as a primary objective above, but not as an outcome?<br><br>Secondary outcomes<br>HRQoL is measured using EQ5D-5L. At what time points (“final responses” should be more specific) and how will you collect data? How will you handle missing data when estimating the AUC?<br><br>Please specify each complication, including definition and how and when they are assessed.<br><br>If the economic analysis is part of this protocol, the description should be more detailed. How will you identify, measure, and valuate resources used? I recommend that you conduct a scenario |

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| | analysis to evaluate the prize of the dressing. I am not aware of the prize of the NPWT dressing used in this study, but a dressing designed to operate for up to 30 days is probably more costly than a dressing designed to operate for 7 days.<br><br>Patient perception of wound healing and pain is mentioned as a secondary objective, but not specified as secondary outcomes.<br><br>Follow up<br>The follow up section is confusing. The authors state that outcomes are analysed day 30 after CS, however, participants are followed up after 1 (7 days), 6 (42 days) and 12 weeks (84 days), but not day 30? In the abstract it is stated that wound complications will be assessed day 5, 14 and 30 after CS.<br>How will the participants be followed after discharge; clinical visits, interviews, or questionnaires? Are there any planned actions to avoid lost to follow up and how will lost to follow up be handled in the analysis?<br><br>Sample size<br>The authors have used a retrospective medical note audit as a source to estimate a complication rate of 20%. Does this complication rate only include dehiscence and SSI? Moreover, in the abstract the authors write that “globally, complication rates following CS vary from 4.9-9.8%. Why is the complication rate more than twice as high in Australia?<br>If the primary outcome measure consists of two individual outcomes, a sample size calculation should be conducted for each outcome and the largest of those sample sizes should then be the target sample size.<br><br>An interim analysis is mentioned in the "trial oversight" section. However, interim analysis should be part of the sample size section. What is the argument for performing interim analyses in this study: benefit, harm, futility, ethical, practical etc.? Which outcome will be analysed in the interim analysis? The Haybittle-Peto boundary is used to adjust for multiple analyses. What are the boundaries and how does it affect the overall p value?<br><br>Statistical analysis<br>“The Kaplan-Meier method and LogRank test will be used to analyse any differences in time to wound healing”. Time to wound healing is not mentioned as an outcome in the Outcome measures section.<br>The manuscript does not mention a SAP (statistical analysis plan). Thus, any planned adjustment for stratification factors (study sites) or prognostic factors, sensitivity analysis, or subgroup analysis ought to be mentioned in the statistical analysis section.<br><br>Figures<br>A study flow chart and Participant timeline is strongly recommended. |

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| **REVIEWER** | Nelson Echebiri<br>WALDORF WOMEN'S CARE, USA |
| **REVIEW RETURNED** | 26-Jan-2020 |

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| **GENERAL COMMENTS** | 1) Given that with active intervention, most infants born at 26 weeks and above have a high likelihood of survival, why is the |

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| | study limited to pregnancies from 32 weeks? Please justify the rationale for this criteria.<br><br>2) At least 20% of twin gestations are delivered by cesarean delivery. This is large cohort to exclude. At the onset of labor, approximately 80% of first twins are cephalic (42% cephalic/cephalic, 38% cephalic/noncephalic), and 20% are noncephalic (7% noncephalic/cephalic, 13% noncephalic/noncephalic). Consequently, cesarean delivery is preferred for all monoamniotic twins, diamniotic twins with a noncephalic-presenting twin, and for pregnancies with standard obstetric indications for cesarean delivery (eg, placenta previa). Please explain why the protocol is limited to singleton pregnancies.<br><br>3) Prophylactic Use of Negative Pressure Wound Therapy After Cesarean Delivery by Echebiri et al. 2015 may be a helpful review for your economic analysis.<br><br>4) Line 17, Page 3: Please define OECD prior to the abbreviation.<br><br>5) Line 43, Page 7: Given the justification for the study to be generalizable, please provided specific details regarding participant information, demographic and related medical history. This is extremely important given that different socioeconomic variables affect outcomes.<br><br>6) Page 11, Adverse event management. There are no detailed steps in how such events will be managed. Please explain. |

**VERSION 1 – AUTHOR RESPONSE**

| ***Reviewers Comment*** | ***Author Response*** | ***AUTHOR/s to amend*** |
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| ***Editorial Comments:***<br><br>- Please ensure that all acronyms are defined on first mention, including those in the abstract.<br>- Please reformat the abstract so that it follows the structured abstract recommended in the journal's instructions for authors for study protocols. See: https://bmjopen.bmj.com/pages/authors/#protocol<br>- Please revise the Strengths and Limitations section of your manuscript (after the Abstract). This section should contain five short bullet points, no longer than one sentence each, that relate specifically to the methods.<br>- Along with your revised manuscript, please provide an English language examples of the patient consent form as a supplementary file as per item #32 of the SPIRIT checklist. | All acronyms are in full in the first mention.<br><br>Abstract is reformatted as per journal formatting requirements (Introduction, methods and analysis, ethics and dissemination, trial registration).<br><br>Strengths and limitations revised to five short bullet points, one | KSH |

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| | sentence each relating specifically to the methods.<br><br>English language example of patient consent form is attached to be included as a supplementary item as per item #32 of the SPIRIT Checklist.<br><br>Thank you. | |
| ***Reviewer: 1***<br><br>***Reviewer Name: Brigid Gillespie***<br><br>Institution and Country:<br><br>Professor Brigid M. Gillespie<br><br>School of Nursing and Midwifery, Griffith University &<br><br>Gold Coast University Hospital, Gold Coast Health<br><br>Australia<br><br>Please state any competing interests or state 'None declared':No COI declared<br><br>Please leave your comments for the authors below<br><br>This paper reports a research protocol designed to test the efficacy of NPWT in the prevention of post C-Section wound complications compared with the standard dressing.. This proposed study is one of a growing number of similar studies being undertaken in the use of NPWT in high risk populations (see for example Gilespie et al 2016-protocol; Hydig et al, 2018-completed trial). | | |

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| While this type of trial in this high risk population is not new, the results may potentially contribute to the growing body of evidence in this area (Level 1A).<br><br>My comments about methodology are listed below:<br><br>1. Eligibility criteria-please be more explicit. Will [regnant women be recruited on the basis of their BMI? This is not stated but the use of NPWT is often used in high risk incisions, where a high BMI (>30) is identified as a risk factor. Other risk factors such as C-Section category (1-4), previous C-Section, premature ROM are potential risk factors and should be considered.<br><br>2. Randomization appears to be planned upon recruitment (or thereafter) but it is unclear when this will be undertaken, and by whom. At what point will theatre personnel be aware of group allocation, and how will this be concealed? Ideally, the surgical team involved in the c-section procedure should not be made aware of group allocation until the conclusion of the procedure, ie., skin suturing.<br><br>3. Authors please elaborate on how the primary trial outcomes will be ascertained. While blinding of the data collectors and clinicians is not possible, will there be independent outcomes assessors to assess clinical outcomes? Having the statistician blinded is important, however, it is just as important that those assessing the clinical outcomes are also blinded to minimize bias.<br><br>4. Sample size of 224 per group has been calculated based on a retrospective chart audit, and a 50% reduction in the intervention group. However, other trials in this area (Hydig 2018) used sample sizes that are much larger.<br><br>5.In terms of the follow up period, please justify why the time points specified will be used. The 30 day time point is self explanatory however, time points for weeks 6 and 12 need to be justified.<br><br>6. Stopping rules for the trial-this is very controversial. In this case, stopping early for benefit may introduce a bias because of large random fluctuation of the estimated treatment effect. Thus the results of the trial may provide misleading estimates of benefit (see Bassler et al, 2010). Stopping a trial prematurely because of harm is appropriate but stopping a trial of this size for benefit is harder to justify.<br><br>7. Please include a timeline of trail activities as specified in the SPIRIT Guidelines for reporting.<br><br>8. Authors, a frank discussion of the strengths but in particular the limitations of the trial. One of the strengths of this trial is the | Dear Professor Gillespie,<br><br>Thank you for taking the time to review the manuscript and providing detailed feedback. We have taken your recommendations on board and have made the required amendments in the manuscript.<br><br>Methodology<br><br>1. Eligibility criteria as stated. 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. | |

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| parallel health economic evaluation. need to included to follow the HREC section.<br><br>Summary<br><br>This trial has the potential to add to the body of work undertaken in the use of NPWT to prevent SSI and other wound complications. However I have some concerns around the clarity of the methods in relation to randomisation, allocation concealment, ascertainment and blinding. Additionally there are very few references to other work undertaken in this area, where a more conservative sample size (larger) may have been drawn and used to inform the sample size in this trial. A real strength of this trial is the parallel economic evaluation. | 2. Randomisation will be undertaken during the initial consult in antenatal clinic by the research officer. Theatre staff will not be made aware of the allocation until the procedure is complete.<br>3. Primary outcomes (surgical wound dehiscence and surgical site infection) will be ascertained via complete wound assessment by a wound clinical nurse on the allocated times points of the study.<br>4. This is a statement. Do you have specific question in regards to the sample size calculation?<br>5. Post discharge surveillance during these time points is essential to determining the patient's progress and early identification of a complication. Assessing the wound only at Day 30 creates a gap in the post discharge surveillance period and the opportunity to identify any complications and treat accordingly.<br>6. While trial-stopping rules are a topic of much discourse, this study will adhere to standard trial conduct stopping rule recommendations. We are mindful this is a Phase IV trial and the aim is to determine efficacy compared to standard practice as safety has been established in this type of therapy.<br>7. Trial timeline complete as per SPIRIT Guidelines and incorporated into the manuscript. | |

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| ***Reviewer: 2***<br><br>***Reviewer Name: Steven Jeffery***<br><br>Institution and Country: The Queen Elizabeth Hospital, Birmingham, UK<br><br>Please state any competing interests or state 'None declared': None declared<br><br>Please leave your comments for the authors below<br><br>Hello,<br><br>given that you will be leaving both dressings on for seven days, I am intrigued by your choice of days 3, 5 and 14 as your wound assessment dates. Please could you elaborate on why you have chosen those days and how the diagnosis of wound complications will be made. Also, will you be photographing the wounds and measuring the degree of dehiscence? | Dear Professor Jeffery,<br><br>Thank you for taking the time to review the manuscript and providing feedback. Professor Jeffery, the time points selected for wound assessment are time critical points for early detection of a wound complication, especially in the first 3 weeks following surgery, according to the literature. We thought it prudent to have several time points for wound assessment to detect very early, whether any complications have occurred. Post discharge surveillance is key in this study.<br><br>Wound assessment and diagnosis of any potential complications will be conducted by a wound clinician and with a standard assessment framework for surgical wound management. Participants will have the opportunity to opt out of having medical photographs taken of their wound.<br><br>The degree of dehiscence will be categorised as per the World Union of Wound Healing Societies Sandy Surgical Wound Dehiscence Grading System (WUWHS SWD Grading System) as in the Appendices of the manuscript. The dehiscence will also be categorised as per the standard reporting definition for SSI; CDC definition for deep/organ space surgical site infection. | |

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| ***Reviewer: 3***<br><br>***Reviewer Name: Univ.-Prof. Dr. Prof.h.c .Dr.h.c. Raymund E. Horch***<br><br>Institution and Country:<br><br>Department of Plastic and Hand Surgery<br><br>and Laboratory for Tissue Engineering and Regenerative Medicine<br><br>University Hospital Erlangen<br><br>Friedrich-Alexander University Erlangen-Nuernberg FAU<br><br>Germany<br><br>Please state any competing interests or state 'None declared': None declared with this paper, but Reviewer has received thrd Party Funding for Research on negative pressure wound therapy and has served as a member of a scientific advisory board for KCI-Acelity in the past<br><br>Please leave your comments for the authors below<br><br>All in all this manuscript consists of a checklist for a protocol of a clinical trial that envisions to study the effect of a negative pressure wound therapy in terms of wound complications.<br><br>It is worthwhile to study the effect of this treatment modality yand the protocol is set uo adequately.<br><br>Nevertheless I have some suggestions or minor revisional points to make as follows:<br><br>Page 4, line nr. 14<br><br>Please clarify which specific settings! | Dear Professor Dr Horch,<br><br>Thank you for your review and feedback on the manuscript. We have taken your feedback on board and have revised the manuscript accordingly.<br><br>Page 4 line nr.14<br><br>Setting clarified: Odense University Hospital, Denmark | |

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| Page 2, line 57-59 and page 3 line 3-5<br><br>Here the authors state that the assessment of the efficacy of negative pressure wound therapy in terms of wound complications will be performed at day 5, 14 and 30 postoperative. I assume this requires the removal of the applied negative pressure wound dressing in order to assess potential wound complications at day 5<br><br>Page 8, line 23-26<br><br>"In this trial, the dressing will be worn for a standardised period of 7 days (intervention and controls arms)"<br><br>This seems contradictory. How are you planning to assess the potential efficacy of negative pressure wound therapy in the prevention of post-partum wound complications at day 5 postoperative without removing the negative pressure wound dressing at day 5?<br><br>The wear time of the standard dressing should be more specified. How often will there be a change of standard wound dressing within the first 7 days (eg. on a daily basis?). A wear time of 7 days without change of dressing would be quite long and might result in a possible disadvantage for the control group in terms of proper wound management. Please clarify<br><br>If patients will be discharged within the first 7 days postoperatively it requires the application of a portable negative pressure device in the intervention group before discharge. Please clarify if patients will receive a portable negative pressure device already at day 0 intraoperative or shortly before discharge. | Page 2, line 57-59 page 3 line 3-5<br><br>*"I assume this requires the removal of the applied negative pressure wound dressing in order to assess potential wound complications at day 5"*<br><br>Prof Dr Horch, yes that is correct. One dressing change will be required to remove suture material, assess and reapply the dressing in both the interventional and control arms. This is standard hospital practice prior to patient discharge. A maximum time of one hour is allocated to conduct the removal, assessment and dressing reapplication as per the study protocol and in adherence to aseptic technique.<br><br>*Please clarify if patients will receive a portable negative pressure device already at day 0 intraoperative or shortly before discharge.*<br><br>Trial participants will receive the portable negative pressure device at day 0 intraoperative. This will be clarified in the revised manuscript. Thank you Prof Dr Horch. | |

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| ***Reviewer: 4***<br><br>***Reviewer Name: Nana Hyldig***<br><br>Institution and Country:<br><br>Odense University Hospital<br><br>Denmark<br><br>Please state any competing interests or state 'None declared': I have previously conducted and published a similar study<br><br>Please leave your comments for the authors below<br><br>Thank you for the opportunity to review this manuscript. Several studies have been published on NPWT after caesarean section. This study uses a relatively new NPWT dressing that to my knowledges has not yet been evaluated in a clinical trial. Moreover, the focus is on wound dehiscence which often is reported as a secondary outcome. I think this study is relevant and will add knowledge to the current evidence of NPWT after caesarean section.<br><br>Overall, the manuscript could benefit from being more aligned with the terminology and chronology used in the Consort Statement and SPIRIT guideline.<br><br>Title<br><br>The authors should consider changing the title from Efficacy… to Effectiveness… as the study is a pragmatic randomised controlled trial: "Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under 'real-world' conditions" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3912314/)<br><br>Abstract<br><br>Please state whether the primary outcome is a composed outcome or two individual outcomes. | Dear Dr Hyldig,<br><br>Thank you for your review and feedback on the manuscript. Please see responses to your comments below.<br><br>Title<br><br>*Title change from 'Efficacy' to Effectiveness.* Manuscript to be amended to reflect contemporary methodologists thought on the definition of the terms. Thank you Dr Hyldig for highlighting this point.<br><br>Abstract<br><br>The primary outcome is composed of two individual outcomes and reporting definitions. Manuscript will be amended to reflect this. | |

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| Introduction<br><br>The introduction does not follow the items from SPIRIT. I am explicit missing the explanation for choice of comparators, which is not explained at page 7-8. One explanation could be that the study investigates the effect of a relatively new NPWT dressing, including any expected benefits from this dressing compared to others, and reasons for using a devise designed for 30 days of use which then only is used for 7 days. Control dressing is probably standard care, but it should be mentioned.<br><br>At page 4, line 31 the authors write that a recent study from the Netherlands has identified an effect of the use of NPWT for patients with high BMI. However the reference is a Danish study. Several other studies have been published so far that focus on NPWT in obese women after caesarean section (meta-analyses: Smid et al 2017, Yu et al 2018, Webster et al 2019). The discrepancy is study results and primary focus on obesity could be used as justification for undertaking this study.<br><br>Study aim and objectives<br><br>I recommend changing efficacy (page 5 line 23) to effectiveness.<br><br>Randomisation<br><br>I think randomisation should be a separate section and that it could be more aligned with Consort Statement to improve readability. Though the allocation sequence is computer-generated, allocation lists provided to the senior research fellow could affect the allocation concealment and introduce bias. This should be addressed either in this section or in the final report. How do you ensure that the senior researcher does not have any contact with or knowledges about the participant before randomization?<br><br>Study dressings<br><br>In the control dressing and intervention sections the description should include the name and manufacturer of the dressings used. | Introduction<br><br>The introduction has adhered to the SPIRIT Checklist, explanation of dressing choice is specified as an item that is required in the TidIER checklist (Item 3), a supplemental to Item 11 SPIRIT Consort; Hoffmann T, Glasziou P, Boutron I, Milne R, Perera R, Moher D, Altman D, Barbour V, Macdonald H, Johnston M, Lamb S, Dixon-Woods M, McCulloch P, Wyatt J, Chan A, Michie S. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687).<br><br>As such and in the interests of enhancing transparency and replicability of the study the following amendments have been made to the manuscript to provide more detail in regards to the intervention and control dressings engaged in the study. The amendments are on page 8 of the manuscript:<br><br>The comparator dressing for all study sites is a non negative pressure film dressing (Tegaderm™ film dressing, 3M). | |

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| Primary outcome<br><br>I am unsure whether you have two primary outcomes: 1) dehiscence, 2) SSI - or it is a composed outcome (dehiscence and SSI). Furthermore, information on how and when the outcomes are assessed is missing. E.g. time points and how outcomes are assessed after discharge. Clinical utility of the intervention is mentioned as a primary objective above, but not as an outcome?<br><br>Secondary outcomes<br><br>HRQoL is measured using EQ5D-5L. At what time points ("final responses" should be more specific) and how will you collect data? How will you handle missing data when estimating the AUC?<br><br>Please specify each complication, including definition and how and when they are assessed.<br><br>If the economic analysis is part of this protocol, the description should be more detailed. How will you identify, measure, and valuate resources used? I recommend that you conduct a scenario analysis to evaluate the prize of the dressing. I am not aware of the prize of the NPWT dressing used in this study, but a dressing designed to operate for up to 30 days is probably more costly than a dressing designed to operate for 7 days.<br><br>Patient perception of wound healing and pain is mentioned as a secondary objective, but not specified as secondary outcomes.<br><br>Follow up<br><br>The follow up section is confusing. The authors state that outcomes are analysed day 30 after CS, however, participants are followed up after 1 (7 days), 6 (42 days) and 12 weeks (84 days), but not day 30? In the abstract it is stated that wound complications will be assessed day 5, 14 and 30 after CS.<br><br>How will the participants be followed after discharge; clinical visits, interviews, or questionnaires? Are there any planned actions to avoid lost to follow up and how will lost to follow up be handled in the analysis? | Primary outcome is clearly described on page 8 of the manuscript:<br><br>"The primary outcome for this study is surgical wound dehiscence as defined by the WUWHS SWD Grading System (7), and the Centres for Disease Control definitions of SSI (18) will be used as the primary outcome measure for confirmed wound infection. The primary outcome measure definitions include a wound complication that occurs within 30 days of surgery".<br><br>Secondary outcomes<br><br>The ED5D-5L will be administered on Day 30 postoperatively. As it inherent in studies, missing data will be reported accordingly and discussed in the study limitations.<br><br>*Please specify each complication, including definition and how and when they are assessed.*<br><br>As stated on page 8:<br><br>"The primary outcome for this study is surgical wound dehiscence as defined by the WUWHS SWD Grading System (7), and the Centres for Disease Control definitions of SSI (18) will be used as the primary outcome measure for confirmed wound infection. The primary outcome measure definitions include a | |

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| Sample size<br><br>The authors have used a retrospective medical note audit as a source to estimate a complication rate of 20%. Does this complication rate only include dehiscence and SSI? Moreover, in the abstract the authors write that “globally, complication rates following CS vary from 4.9-9.8%. Why is the complication rate more than twice as high in Australia?<br><br>If the primary outcome measure consists of two individual outcomes, a sample size calculation should be conducted for each outcome and the largest of those sample sizes should then be the target sample size.<br><br>An interim analysis is mentioned in the "trial oversight" section. However, interim analysis should be part of the sample size section. What is the argument for performing interim analyses in this study: benefit, harm, futility, ethical, practical etc.? Which outcome will be analysed in the interim analysis? The Haybittle-Peto boundary is used to adjust for multiple analyses. What are the boundaries and how does it affect the overall p value?<br><br>Statistical analysis<br><br>“The Kaplan-Meier method and LogRank test will be used to analyse any differences in time to wound healing”. Time to wound healing is not mentioned as an outcome in the Outcome measures section.<br><br>The manuscript does not mention a SAP (statistical analysis plan). Thus, any planned adjustment for stratification factors (study sites) or prognostic factors, sensitivity analysis, or subgroup analysis ought to be mentioned in the statistical analysis section.<br><br>Figures<br><br>A study flow chart and Participant timeline is strongly recommended. | wound complication that occurs within 30 days of surgery”.<br><br>In response to the price point of the interventional dressing, there is a price parity for other known NPWT devices and the interventional dressing.<br><br>Follow up:<br><br>The section will be clarified as such:<br><br>Follow up time points; Day 5, Day 14 and Day 30 as is stated on page 3 & amended on page 10 of the manuscript. Participants will be followed up via outpatient clinic visits, visiting midwifery service and via a scripted phone call. With regards to loss to follow up, all attempts will be made in line with the ethics approved protocol to follow up the participant at each specific time point. Various forms of communication will be used in engaging the participation, email, phone call and face-to-face consultation.<br><br>Statistical analysis<br><br>The second paragraph of the statistical analysis section has been expanded to give more detail, as requested.<br><br>The sentence raised concerning the Log-rank test and Kaplan-Meier curves has been deleted, since these are not appropriate for the outcomes named in the trial.<br><br>The second paragraph now reads: | |

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| | *"A Generalised Estimating Equation (GEE) will be used to analyse each of the primary outcomes over all the time points of the study. This analysis is similar to a Logistic Regression for each of the binary outcome variables, but takes into account the correlation between the repeated measurements made on the same participant. The results of the GEE will be expressed as odds ratios, their 95% confidence intervals and p-values. The GEE model will include a term for the time point, so that changes over time can be assessed, as well as a term for the treatment group allocation (on which the main conclusions of the study will be based). In addition, the GEE model will be extended to include anthropometric measurements (eg: body mass index), presence of health conditions (eg diabetes, hypertension, etc), the recruitment site, and other variables collected at baseline. In this way, variables which are identified as being associated with the outcomes may be used to form a 'risk score' for each outcome. Analysis of the pain scores (which are measured on a continuous scale at each time point through the study), will be performed using a Mixed regression model where the random effect will be the patient identifier, and the time point and treatment allocation group will be fixed effects. The distribution of the pain scores will be assessed for Normality, and transformed to improve Normality (if necessary) prior to analysis. All statistical analyses will be performed using the SAS version 9.4 software, and, following convention, a p-value < 0.05 will be taken to* | RICHARD PARSONS |

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| | *indicate a significant association in all tests."*<br><br>Figures: Please see addition of CYGNUS Trial CONSORT page 9. | |
| ***Reviewer: 5***<br><br>***Reviewer Name: Nelson Echebiri***<br><br>Institution and Country: WALDORF WOMEN'S CARE, USA<br><br>Please state any competing interests or state 'None declared': None<br><br>Please leave your comments for the authors below<br><br>1) Given that with active intervention, most infants born at 26 weeks and above have a high likelihood of survival, why is the study limited to pregnancies from 32 weeks? Please justify the rationale for this criteria.<br><br>2) At least 20% of twin gestations are delivered by cesarean delivery. This is large cohort to exclude. At the onset of labor, approximately 80% of first twins are cephalic (42% cephalic/cephalic, 38% cephalic/noncephalic), and 20% are noncephalic (7% noncephalic/cephalic, 13% noncephalic/noncephalic). Consequently, cesarean delivery is preferred for all monoamniotic twins, diamniotic twins with a noncephalic-presenting twin, and for pregnancies with standard obstetric indications for cesarean delivery (eg, placenta previa).<br><br>Please explain why the protocol is limited to singleton pregnancies.<br><br>3) Prophylactic Use of Negative Pressure Wound Therapy After Cesarean Delivery by Echebiri et al. 2015 may be a helpful review for your economic analysis.<br><br>4) Line 17, Page 3: Please define OECD prior to the abbreviation. | 1. This is an arbitrary allocation. Text deleted (page 6).<br><br>*2.* Thank you for drawing our attention to this. It would be remiss of us to not include this cohort as part of the sample. Please see amended text; *Pregnant women eligible for recruitment to the CYGNUS trial are those with a viable pregnancy and are able to provide written consent. (page 6).*<br><br>3. Thank you for the reference.<br><br>4. OECD acronym corrected, thankyou. | |

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| 5) Line 43, Page 7: Given the justification for the study to be generalizable, please provided specific details regarding participant information, demographic and related medical history. This is extremely important given that different socioeconomic variables affect outcomes.<br><br>6) Page 11, Adverse event management. There are no detailed steps in how such events will be managed. Please explain. | 5. Thank you for your observation, and yes, agreed, that often socioeconomic variables, related medical history and demographic influence outcome, particularly as seen currently in low-middle income resource settings. For the CYGNUS trial, we do not have this information about the participants to this level at this time, and any statement's beyond a '*tertiary teaching hospital in metropolitan Perth'* about the sample may be misleading. We do not wish to be presumptive about the sample characteristics. To address your concerns, the best description of the sample setting has been listed as a tertiary teaching hospital in metropolitan Perth. The subsequent results paper will have specific data in relation to demographic and medical history and socioeconomic status in the baseline statistics.<br><br>6) Page 11: Thank you for drawing our attention to this. The following text has been added;<br><br>*"During the treatment protocol, any USADE will be reported directly to the DSMB and within 7 days to the Australian Government Therapeutics Goods Administration via the electronic Medical Device Incident Reporting System. Reports will also be sent to the local study sites Human Research Ethics Committees. The safety aspects of the study will be closely monitored by the DSMB, which will receive unblinded data for review. In the case of a device* | |

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| | *related adverse advent the manufacturer will be notified"*. (page 10) | |

**VERSION 2 – REVIEW**

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| **REVIEWER** | Nana Hyldig<br>Odense University Hospital, Denmark |
| **REVIEW RETURNED** | 11-Mar-2020 |

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| **GENERAL COMMENTS** | I think it is a shame that the authors do not relate to all the comments given by my co-reviewers and me. I believe it would increase the transparency and the quality of the study.<br><br>First of all, I think the study is underpowered to demonstrate a statistically significant effect of iNPWT for SSI and/or wound dehiscence. I am concerned about the power calculation that uses a baseline risk twice as high as other studies have reported. I am missing a statement clarifying whether the complication rate from a retrospective medical note audit only include SSI and wound dehiscence or also include other types of complications and why the complication rate is so high. Furthermore, the study protocol does not address the stopping rules, which typically will adjust the p-value to take the interim analyses into account. One simple stopping rule is for the data monitoring committee to recommend stopping the trial only if an extreme level of significance is reached, e.g. p = 0.002 [Peto Haybittle rule] and the results seen are likely to change clinical practice (Khan and Hills 2006). Thus, interim analyses does often increase the overall sample size. Moreover, I agree with Dr. Gillespie that stopping for benefit may introduce bias and has a risk of overestimating the treatment effect due to the small sample size and relatively few numbers of events.<br><br>I can only recommend that the authors state in the text, that the primary outcome is a composed outcome. The text is currently still confusing as to whether it is two individual outcomes or a composed outcome.<br><br>The authors have a subsection in the section "secondary outcomes" named "complications". I am still missing a clear |

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| | definition of each of these other complications. If it is not outcomes but data collected during the trial, it should be removed from the outcome section.<br><br>Dr Raymund E. Horch as commend on the planned outcome assessment at day 5. I see no reason for changing the dressing at day five only to remove it again after two days. It is simple not cost-effective. I can only recommend that the authors either leave the dressing on for seven days or remove it after five days. Alternatively leave the second dressing on for additional seven days. In our study the dressing was removed after five days in order to remove staples at day five as standard practise. The reason was, that our study was one of the first studies using iNPWT and there was no evidence for leaving the suture material for a longer period. Now, based on our experience, the dressing is left on for seven days to maximize the effect and suture material are removed at the same time without any problems / concern. |

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| **REVIEWER** | Nelson Echebiri<br>Waldorf Women's Care, USA |
| **REVIEW RETURNED** | 01-Mar-2020 |

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| **GENERAL COMMENTS** | Excellent work |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer(s)' Comments to Author:

Reviewer: 5

Reviewer Name: Nelson Echebiri

Institution and Country: Waldorf Women's Care, USA

Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below

Excellent work

Reviewer: 4

Reviewer Name: Nana Hyldig

Institution and Country: Odense University Hospital, Denmark

Please state any competing interests or state ‘None declared’: statet earlier

Please leave your comments for the authors below

I think it is a shame that the authors do not relate to all the comments given by my co-reviewers and me. I believe it would increase the transparency and the quality of the study.

- Dr Hyldig, thank you for your initial review and subsequent review of the revised manuscript. We appreciate your time and comments. Dr Hyldig, we believe we have adequately addressed all five reviewers comments and adjusted the manuscript accordingly. May I request if you could please specify exactly which comments you are referring to by paragraph and line number as this statement is generic without adequate detail to allow the author group to respond accordingly. Thank you.

First of all, I think the study is underpowered to demonstrate a statistically significant effect of iNPWT for SSI and/or wound dehiscence. I am concerned about the power calculation that uses a baseline risk twice as high as other studies have reported. I am missing a statement clarifying whether the complication rate from a retrospective medical note audit only include SSI and wound dehiscence or also include other types of complications and why the complication rate is so high. Furthermore, the study protocol does not address the stopping rules, which typically will adjust the p-value to take the interim analyses into account. One simple stopping rule is for the data monitoring committee to recommend stopping the trial only if an extreme level of significance is reached, e.g. p = 0.002 [Peto Haybittle rule] and the results seen are likely to change clinical practice (Khan and Hills 2006). Thus, interim analyses does often increase the overall sample size. Moreover, I agree with Dr. Gillespie that stopping for benefit may introduce bias and has a risk of overestimating the treatment effect due to the small sample size and relatively few numbers of events.

- Thank you for your observation Dr Hyldig. We believe that this study is sufficiently powered to detect an effect size within the hypothetical parameters. There has been a number of power calculations conducted by the study biostatistician to ensure we have accurately determined the sample size for the study.

- Thank you for your observation Dr Hyldig. We believe that this study is sufficiently powered to detect an effect size within the hypothetical parameters. There has been a number of power calculations conducted by the study biostatistician to ensure we have accurately determined the sample size for the study.

Whilst some studies around the world have reported high and low incidence rates, it is fairly clear from the literature there is considerable variation in incidence rates. We are basing our study on data obtained from the trial site.

- Dr Hyldig, we have clearly stated our trial stopping rule on page 15 of the manuscript.

I can only recommend that the authors state in the text, that the primary outcome is a composed outcome. The text is currently still confusing as to whether it is two individual outcomes or a composed outcome.

- Dr Hyldig, contemporary discourse regarding wound complications discerns between SSI and SWD. There are two internationally agreed definitions for SSI and SWD. They are two separate wound types and are to be identified and classified accordingly for accurate representation of frequency and incidence.

The authors have a subsection in the section "secondary outcomes" named "complications". I am still missing a clear definition of each of these other complications. If it is not outcomes but data collected during the trial, it should be removed from the outcome section.

- Dr Hyldig, contemporary discourse regarding wound complications discerns between SSI and SWD. There are two internationally agreed definitions for SSI and SWD. They are two separate wound types and are to be identified and classified accordingly for accurate representation of frequency and incidence.

Dr Raymund E. Horch as commend on the planned outcome assessment at day 5. I see no reason for changing the dressing at day five only to remove it again after two days. It is simple not cost-effective. I can only recommend that the authors either leave the dressing on for seven days or remove it after five days. Alternatively leave the second dressing on for additional seven days. In our study the dressing was removed after five days in order to remove staples at day five as standard practise. The reason was, that our study was one of the first studies using iNPWT and there was no evidence for leaving the suture material for a longer period. Now, based on our experience, the dressing is left on for seven days to maximize the effect and suture material are removed at the same time without any problems / concern.

- Dr Hyldig, the study is adhering to local infection control policy at the site. Whilst we know from a handful of studies that imply dressing removal at Day 5 for improved outcomes, the hospital policy must be adhered to until sufficient evidence is yielded to warrant policy and subsequent guideline changes at the site.

**VERSION 3 – REVIEW**

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| **REVIEWER** | Nana Hyldig<br>Odense University Hospital<br>Denmark |
| **REVIEW RETURNED** | 10-Aug-2020 |

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| **GENERAL COMMENTS** | I have no further comments. I wish the study group good luck with the completion of the project. |

**VERSION 3 – AUTHOR RESPONSE**

Thank you for taking the time to review the manuscript. The required revisions are attached in the updated version. The revisions are as follows;

1. In accordance to a previous comment from reviewer 1 from the first round of reviews, please justify your sample size calculation based on a retrospective chart audit and discuss whether your study will be sufficiently powered.
". Sample size of 224 per group has been calculated based on a retrospective chart audit, and a 50% reduction in the intervention group. However, other trials in this area (Hydig 2018) used sample sizes that are much larger."

The inclusion of the following statement "However, other trials in this area (Hydig 2018) used sample sizes that are much larger", as suggested by Hyldig and the editor will not be included in the statistics section as it is not relevant to the section. The statement requires further substantiation and critique and will detract from the descriptive nature of the statistics section. The Hyldig 2018 paper has been discussed elsewhere in the manuscript. Thank you.

2. Strengths and limitations have been restricted to 5 bullet points with sentences.

Thank you