The 'NeoHyp TRIAL'

PERIOPERATIVE ACTIVE WARMING VERSUS NO ACTIVE WARMING DURING CAESAREAN SECTION FOR PREVENTING NEONATAL HYPOTHERMIA IN WOMEN PERFORMING SKIN-TO-SKIN CONTACT: A RANDOMIZED CONTROLLED TRIAL.

A thesis presented to the University of Dublin, Trinity College Dublin, for the Degree of Doctor in Philosophy.

Aliona Vilinsky-Redmond

6-11-2020

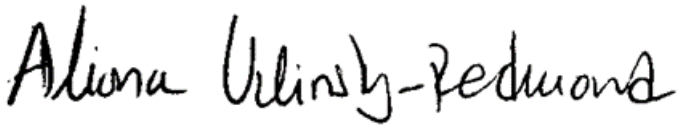
DECLERATION

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

I agree to deposit this thesis in the University's open access institutional repository or allow the library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

Date: 4/11/2019

Signature: Aliona Vilinsky-Redmond



SUMMARY

Background

The initiation of at birth skin-to-skin contact (SSC) and early breastfeeding is a well-established practice after vaginal birth, not only in Ireland but in many developed countries. It offers many health benefits for both newborns and their mothers. Over recent years this practice is also increasingly implemented during Caesarean Section (CS). Due to the increased frequency of maternal and neonatal hypothermia during CS, this patient population are at an increased risk of health complications associated with hypothermia. They also have a higher chance of maternal/newborn separation due to the need to manage postoperative hypothermia. Preventing perioperative neonatal and maternal hypothermia is key not only in supporting the mother/newborn dyad but also in promoting early and longer duration of SSC and breastfeeding during and after CS. The use of perioperative warm IV fluids is a well-established practice used in the prevention of inadvertent perioperative hypothermia (IPH) in the general population undergoing an operation, however it is not widely researched on pregnant women undergoing CS while performing at birth SSC. A Systematic Review (SR) was undertaken as part of this thesis to identify evidence regarding the effectiveness and safety of maternal active warming during CS as a method to prevent maternal and neonatal hypothermia during CS on newborns who perform at birth SSC. The critical analysis of the existing randomized controlled trial (RCT) evidence found only three RCTs that directly compared maternal active warming versus no active warming while SSC was performed. However, these three studies were of low quality and used different methods of active warming, different equipment and different body sites for measuring maternal and neonatal temperatures. This suggests that the findings of the SR need to be interpreted with caution and that a new, robust RCT with sufficient sample size needed to be undertaken. The aim of this study was to compare the effectiveness of perioperative active warming by administering warmed IV fluids to women undergoing elective CS and performing SSC, at term, versus the administration of room temperature IV fluids, on neonatal and maternal outcomes.

Study Design

This thesis reports and details the design, implementation and outcomes of a single centre parallel RCT. The allocation sequence was generated by the hospital statistician with the use of computer randomisation software and participants were assigned to either the intervention or control group using sequenced opaque sealed numbered envelopes, which ensured allocation concealment. The primary outcome was the occurrence of neonatal hypothermia. The trial population was pregnant women (over the age of 18) and their newborns (at term gestation) who were booked for elective CS and

willing to part take in SSC. In total 150 of the 159 eligible patients signed the informed consent to participate in this trial (94.3% response rate and 5.6% refusal rate), with 75 women randomly assigned to the intervention group (who received warm IV fluids heated to 39°C) and 75 to the control group (who received room temperature fluids at approximately 25°C). Findings are based on an 'intention-to-treat' analysis.

Findings

The trial proved that perioperative administration of warm IV fluids was more effective in reducing the occurrence of neonatal hypothermia at the end of SSC in operative theatre compared to the current hospital practice of the administration of room temperature IV fluids (RR 0.28, 95% CI 0.09 to 0.82; p=0.02). Maternal hypothermia during SSC in OT occurred significantly less in women receiving warmed IV fluids compared to women receiving room temperature IV fluids (RR 0.15, 95% CI 0.03 to 0.65; p=.0027). Similar significant differences between the two groups were recorded for the proportion of women with maternal hypothermia on PACU admission (RR 0.38, 95% CI 0.2 to 0.74, p= .0022). Before PACU discharge to the postnatal ward, although clinically more participants receiving usual care experienced hypothermia than participants in the intervention group, there was no statistical difference between the two groups; *n*=5/75 (6.6%) and *n*=0/75 (0%; RR 0.09, 95% CI 0.005 to 1.61, p=.10), respectively. Furthermore, the occurrence of maternal shivering was significantly reduced (RR 0.1, 95% CI 0.03 to 0.31; p= .0001), while there was no difference on the thermal comfort of mothers during their stay in PACU between the two groups (RR 1.03, 95% CI 0.72 to 1.47; p= 0.86). It was also evident that additional warming methods of mothers and newborns was statistically less indicated in the participants of the intervention group than that of the control group, RR 0.31 (95% CI 0.18 to 0.52; p=.0001) and RR 0.29 (95% CI 0.14 to 0.6; p= .0009), respectively. There was also a statistically significant difference in the occurrence of interruption of SSC (RR 0.29, 95% CI 0.14 to 0.6; p= .0009) and breastfeeding (RR 0.27, 95% CI 0.10 to 0.71; p=.0076) between the two groups, with mothers and newborns of the control group having higher SSC and early feeding cessation due to hypothermic mothers and newborns having to be warmed separately prior to their transfer to the postnatal wards.

Adverse events in the trial were observed in three women in the intervention group, while no adverse events were experienced in the women in the control group. There was not a statistical difference in the occurrence of adverse events between the two groups (RR 3, 95% CI 0.12 to 72.48; p=.499). Normothermia was restored shortly after the discontinuation of the intervention in all three women who experienced adverse events. Trial findings suggest that administration of warm IV fluids to pregnant women

undergoing CS is a safe practice with multiple health benefits for both mothers and their newborns. The trial was registered prior to participant recruitment on the 'clinicaltrials.gov' website with registration number: NCT03316716. Trial interventions (HotLine© giving sets) were provided free of charge by Smiths-Medical. This company had no involvement in the planning or conduct of the trial.

ACKNOWLEDGEMENTS

My thesis would not have been completed without the help and support of a number of people. Specifically, I would like to thank:

The pregnant women and their newborns that participated in this trial, it was a privilege meeting them during my daily visits to the theatre department.

Both my supervisors for their advice and guidance through the PhD journey, I am forever grateful for all their hard work associated with supervising this thesis:

• Dr Margaret McCann for becoming not only my supervisor but also my mentor in the most difficult phase of my PhD. Her reassurance, guidance, kindness and support helped me to overcome every problem;

• Professor Maria Brenner for her expertise, patience, encouragement and clinical input, which will be for ever appreciated;

Professor Conan McCaul for agreeing to act as trial Principal Investigator, without him this trial would not have been possible. His guidance, expertise and support on clinical issues during the planning, implementation and completion of this trial and thesis were invaluable.

The theatre department nurse managers, whose support and input made this trial possible: Jane Hickey and Derval Dickson.

The admission midwives for recruiting the study participants notwithstanding their extremely busy daily schedule: Marina Cullen and Giulia Milia.

The theatre nursing, midwifery and medical staff for actively supporting this trial and for all their hard work implementing the trial protocol. Their input ensured the success of the trial.

Mr Colin Kirkham, Rotunda Hospital for his expertise and advice on randomization and statistical analysis.

The Master of the Rotunda hospital, the Director of Midwifery and the hospital Consultants for their support of the trial.

Smiths-Medical for providing free of charge the HotLine© giving sets used in the trial. Special thanks to Sylvain Dumarchat and David Tierney from Smiths-Medical the provision and delivery of these products.

Dr Mark Hehir, Professor McCaul and Ms Christine McDermott for their work on the Trial Monitoring Committee.

Finally, my deepest gratitude to my husband Niall Redmond, my mother Eleni Trikka and my mother in law Jacinta Redmond for being by my side during my darkest moments for all their support, encouragement and protection over each hurdle I encountered. I am eternally grateful for being by myside during every step of my PhD journey.

Table of Contents

List of Tables

List of Figures

GLOSSARY OF TERMS

Active warming: A method of transferring heat to a patient

Adverse event: Unintended injury or complication caused by medical management, as opposed to an underlying medical condition.

Hypothermia: The condition of having an abnormally low body temperature.

Homeotherm: A living organism that maintains its body temperature at a constant level, usually above that of the environment, by its metabolic activity.

Inadvertent perioperative hypothermia: Is a common but preventable complication of perioperative procedures, which is associated with poor outcomes for patients.

Normothermia: A condition of normal body temperature.

Skin-to-skin contact or kangaroo care: The practice where a newborn is dried and laid directly on their mother's bare chest after birth, both of them covered in a warm blanket and left for at least an hour or until after the first feed.

Systematic review: An attempt to identify, appraise and synthesize research based on literature that meets pre-specified eligibility criteria to answer a given research question.

Thermogenesis: The production of heat in the body.

Thermoregulation: A process that allows the body to maintain its core internal temperature.

ABBREVIATIONS

AERF	Adverse Event Recording Form
ANOVA	Analysis of Variance
ASA	American Society of Anaesthesiologists
ATP	Adenosine-5-Triphosphate
BAT	Brown Adipose Tissue
CCT	Controlled Clinical Trials
CDC	Centres for Disease Control
CI	Confidence Interval
CONSORT	Consolidated Standard of Reporting Trials
CS	Caesarean Section
DPC	Data Protection Commission
DSMB	Data Safety Monitoring Board
EBL	Estimated Blood Loss
Elective LSCS	Elective Lower Segment Caesarean Section
FHS	Faculty of Health Sciences
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HPRA	Health Products Regulatory Authority
I^2	Heterogeneity
ICH	International Conference on Harmonisation
IPH	Inadvertent perioperative hypothermia
IQR	Interquartile Range
ITT	Intention to Treat
IV	Intravenous
MANOVA	Multivariate Analysis of Variance
MD	Mean Difference
MeSH	Medical Subject Headings
n	Sample Size
NCCNSC	National Collaborating Centre for Nursing and Supportive Care
NeoHyp	Neonatal Hypothermia
NICE	National Institute for Health and Care Excellence

NICU	Neonatal Intensive Care Unit
OECD	Organisation for Economic Co-operation and Development
OR	Odds Ratio
OT	Operating Theatre
PACU	Post Anaesthesia Care Unit
PI	Principal Investigator
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROB	Risk of Bias
RR	Relative Risk
SD	Standard Deviation
SMD	Standard Mean Difference
SOP	Standard Operative Procedures
SPSS	Statistical Package for the Social Sciences
SR	Systematic Review
SSC	Skin-to-skin contact
TOR	Terms of Reference
TSC	Trial Steering Committee
TSRF	Trial Screening and Register Form
TTN	Transient Tachypnea of the Newborn
USS	Ultrasound Scan
VIF	Variance Inflation Factor
WHO	World Health Organisation
$\chi 2$	Chi Square test

Chapter 1: Overview of the "NeoHyp" Trial

1.1 Introduction

This thesis is a report of my "NeoHyp" trial, which is a randomised controlled trial (RCT) comparing perioperative administration of warm intravenous (IV) fluids versus room temperature IV fluids, on the temperature of both mothers and their newborns, when skin-to-skin contact (SSC) was initiated immediately after an elective caesarean section (CS). This trial took place in the theatre department of a maternity hospital in Ireland. The primary outcome was to review the occurrence of neonatal hypothermia between the two groups. This chapter gives an overview of the background to the Neonatal Hypothermia (NeoHyp) trial and briefly outlines the focus of the remaining seven chapters of the thesis.

1.2 Study background

The role of a theatre midwife, according to the hospital guidelines, is to attend CS, to ensure neonatal and maternal wellbeing, to establish at birth SSC, to assist in early initiation of breastfeeding and to promote a pleasant experience for pregnant women undergoing elective CS. During my clinical placement as a theatre midwife, SSC was a new practice that the hospital was trying to implement during CS in order to enhance the maternal experience of women. This was to facilitate early initiation of breastfeeding and to promote the beneficial effects of SSC on both mothers and their newborns Hospital guidelines on establishing SSC after vaginal birth are in operation and these same guidelines are also in use with regard to at birth initiation of SSC during CS. However, in my practice I observed repeated occurrences of newborns becoming hypothermic during SSC while in theatre. This occurred while midwives followed the best evidence available on how to prevent heat loss during SSC by covering the newborns and the mothers upper body with warm blankets and towels, keeping the ambient temperature within the WHO (2009) recommended levels (25°C for term babies) and reducing potential drafts which can lead to neonatal heat loss. It is important to highlight that current midwifery practice with regard to SSC and breast feeding is informed by WHO guidelines that are over 20 and 11 years old respectively. The lack of up-to-date guidelines poses limitations in the current provision of health care. A major limitation of these guidelines is that they offer guidance for management of neonatal hypothermia after vaginal birth, a delivery pathway that reflects about the 2/3 of deliveries in many countries around the world (Figures 1.1 and 1.2, page 20). The remaining 1/3 of deliveries are conducted via CS, which as a delivery pathway has a different effect on both neonatal and maternal physiology (Wise 2015) (chapter 2, sections 2.3.1 and 2.6.1). These differences in physiology have not been reflected in the current WHO guidelines, something that could

affect their generalisability among the different delivery methods. Also, taking under consideration the increase in CS rates globally (Philips 2013), this suggests that a larger number of newborns and mothers may receive outdated and potentially inadequate midwifery care. Finally, it is important to highlight that until these guidelines are reviewed to include management of neonatal hypothermia post CS, student midwives around the world will still be taught to adhere to the current guidelines, something that may prolong further the outdated midwifery practice, as the students will keep applying them after their qualification in their own clinical practice.

In my attempt to investigate the prevalence of neonatal hypothermia during CS I conducted three clinical audits and a pilot RCT. Audit number 1 took place in 2012, audit 2 in 2013, audit 3 in 2014. The pilot RCT in 2015 investigated perioperative administration of warm intravenous (IV) fluids versus room temperature IV fluids, on the temperature of both mothers and their newborns, when skin-to-skin contact (SSC) was initiated immediately after an elective caesarean section (CS), which was then followed by the "NeoHyp" trial in 2018. All of the audits showed that both newborns and their mothers were prone to a reduction in their temperature during CS, which led to over 80% of the mothers and over 25% of the newborns eventually becoming hypothermic during/after CS (Vilinsky and McCaul 2017). The evidence-based literature found that prolonged neonatal exposure to conduction, through SSC with a cold mother, would eventually lead to neonatal hypothermia, which in turn could lead to a number of issues that would need to be addressed by the theatre midwives (Lunze *et al* 2013). These issues include separation of the mother from their newborn and discontinuing and disrupting SSC, in order to warm either or both parties, which may take place in different rooms due to the location of the incubator (Lunze *et al* 2013). This separation could cause unnecessary stress and anxiety in the mother, as she would be concerned about the wellbeing of her newborn and because the psycho-neurohormonal responses to stress are altered due to the cessation of SSC (Moore *et al* 2012). Furthermore, subnormal neonatal temperatures could compromise respiratory function in newborns (grunting sound), including laboured breathing and low oxygen saturation levels (Bajwa and Swati 2014). As a result newborns, would have to be removed from their mothers and brought into a separate room where the incubator was located, in order to warm them up.

At the research site, newborns who become hypothermic are placed inside the incubator, on their abdomen and are connected to a saturation probe to monitor their oxygen levels. If the newborn's oxygen levels are sub-standard free flow oxygen would be introduced for as long as needed until oxygen levels are optimal without the use of supplementary

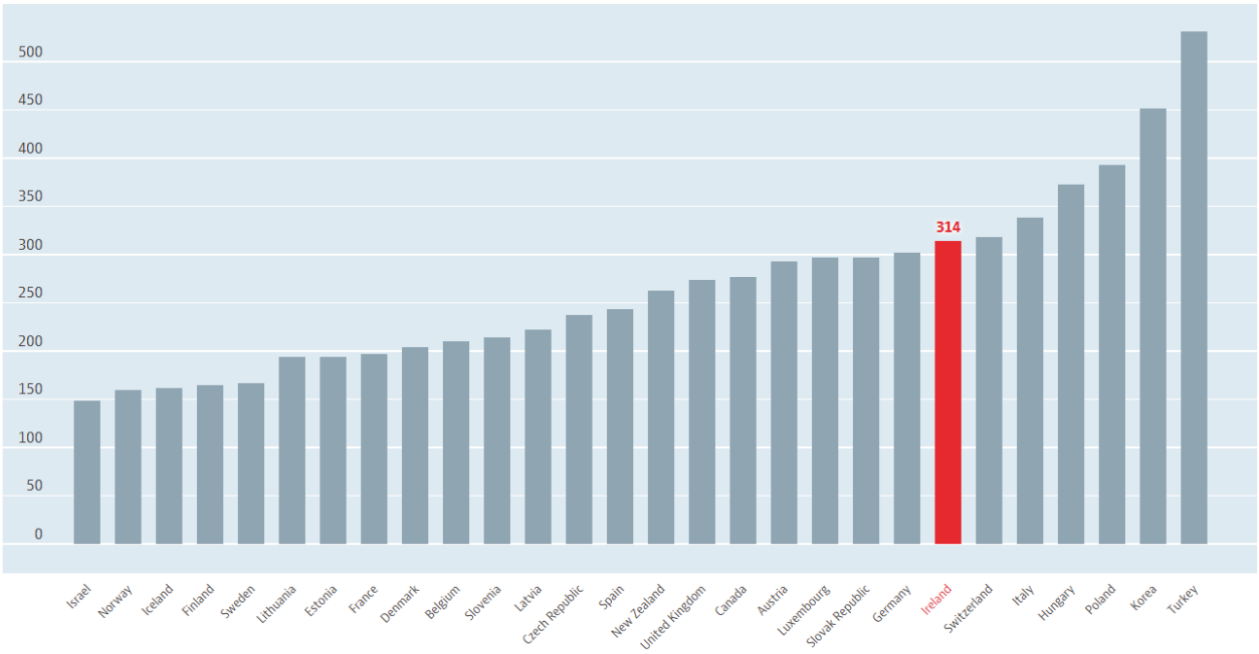
oxygen. If the newborn's temperature remained low or dropped again following this intervention, their blood sugars would be checked as per local hospital protocol, as neonatal hypothermia can cause neonatal hypoglycaemia (Bajwa and Swati 2014) (chapter 2, section 2.4.1). A description of the research site hospital's environment is provided in chapter 5, section 5.2, page 99.

Occasionally, newborns had to be admitted to the Neonatal Intensive Care Unit (NICU) for continuous monitoring of their oxygen levels and for further investigation to ensure that no underlying infection was the cause of this respiratory compromise. This would require blood to be taken, for microbiological investigation and the administration of intravenous prophylactic antibiotics. Furthermore, managing mothers who were hypothermic could potentially cause operational and service delivery issues, including delays in running the theatre list due to mothers staying longer in the Post Anaesthesia Care Unit (PACU) in order to promote heat conservation. This can lead to the next patient's operation being delayed until a space in PACU is available (Reed, 2002). Managing a cold newborn and mother could also have a knock on effect in: the Neonatal Intensive Care Unit (NICU), including preventable neonatal admissions and neonatal bloods being taken to check for blood sugar levels/infection; and in the postnatal departments where it could lead to four hourly monitoring of neonatal vital signs and preventable pre/post feed measurements of newborn blood sugars. These unplanned interventions and delays, if not prevented, could potentially increase healthcare costs and the frontline staff workload (Lunze *et al* 2013). All of the above could be avoided if the temperature of newborns and their mothers were maintained within normal levels. Preventing mothers and newborns from becoming hypothermic could have a positive impact on their physical well-being, the quality of services delivered and the financial costs associated with managing hypothermia in newborns and their mothers.

The observations and issues related to the results of my audits led me to complete a literature review/research proposal as part of my taught M.Sc. in order to understand the theory behind this problem (Vilinsky and Sheridan 2014). This resulted in my completion of a pilot RCT study which investigated the effect of perioperative warm IV fluid administration to mothers and their newborns during/after at birth SSC (Vilinsky *et al* 2016). This pilot study provided the basis for my doctoral studies providing a strong hypothesis and a thirst to further investigate this issue. I received a PhD stipend from Trinity College Dublin to conduct this unique study with the aim of adding to the evidence base.

1.3 The problem statement

SSC is central to midwifery care that is provided to women and newborns due to the many benefits it has for both (Moore *et al* 2012) (chapter 2, section 2.2). Although SSC is well established after vaginal birth, it is not a well-established practice following CS (Phillips 2013) (chapter 2, section 2.2). There are no national or international prevalence figures available with regard to SSC. However, there is a global demand and interest in promoting SSC during CS, especially given the continuing global increase in CS rates, with one in every three women having a CS in Ireland, the UK and USA (Wise 2015), and over one in every two women having CS in countries such as Egypt, Brazil and Turkey (McCarthy 2018) (Figures 1.1 and 1.2). The increasing rates of CS coupled with the associated less practiced SSC with such births, would deprive more women of the beneficial practices of early SSC and breastfeeding if proactive action is not taken by midwifery and nursing staff working in theatre departments.



Source: OECD Health Statistics: Health care utilisation (Data from 2017 or latest available.)

Figure 1.1 Caesarean sections, total per 1 000 live births

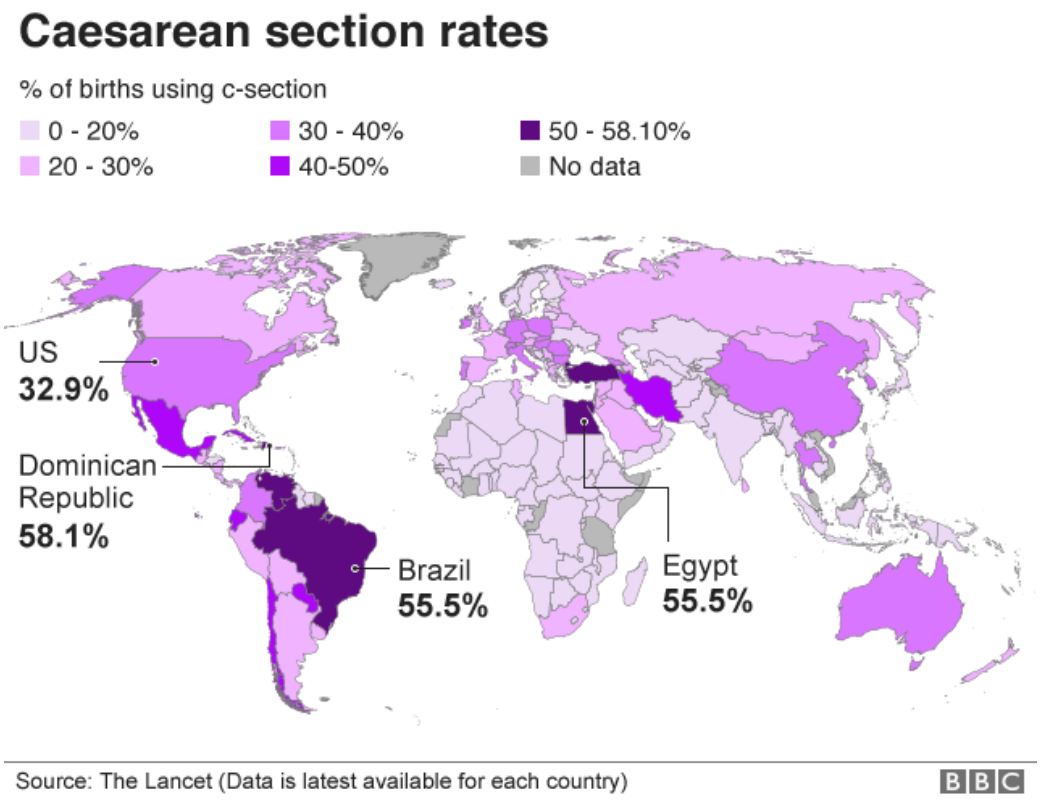


Figure 1.2 Global caesarean sections rates

Moreover, providing care to women who undergo elective CS and their newborns can be challenging when compared to the care provided after vaginal birth due to the nature of the operation. This includes prolonged immobilization of women, anaesthetic agents used and higher maternal blood loss. Such challenges can add additional burden to both theatre staff and mothers attempting to establish early SSC and breastfeeding (Abdolcader 2017).

An additional factor that also needs to be taken into consideration is the attempt to overcome clinical health issues such as preventing perioperative maternal and neonatal hypothermia while SSC is performed. Perioperative hypothermia increases the morbidity of women and newborns, having a major negative impact on their wellbeing (Sultan *et al* 2015, Munday *et al* 2018). The maintenance of maternal and newborn temperature within normal levels can be a daily challenge for both theatre nursing and midwifery staff. My trial is focused primarily on the prevention of neonatal and maternal hypothermia using warm IV fluids during CS, when SSC between mothers and their new-borns was initiated immediately after an elective CS.

Theatre nurses and midwives currently focus on maintaining maternal and newborn temperature within normal levels as preventing the frequency of hypothermia during CS

is not addressed either by hospital guidelines or national/international recommendations. The reason behind the lack of guidelines/recommendations is the lack of studies investigating the prevention of inadvertent perioperative hypothermia (IPH) in this consort of people (NICE 2016). IPH is a common adverse event occurring in people undergoing surgery. There are recommendations on how to prevent IPH on people undergoing general surgical operations (NICE 2016), including the use of warm IV fluids (if more than 500mls of IV fluids will be administered during the operation) and additionally the use of warm forced air devices (especially if the operation is going to last more than 30 minutes). These two methods are considered as the two most suitable methods in preventing IPH (Riley & Andrzejowski, 2018). However, pregnant women and newborns are excluded from this guideline due to lack of studies in this population (NICE 2016). Given this lack of evidence and the aim of promoting early SSC and breastfeeding during CS, I decided to undertake the NeoHyp Trial which evaluated the effectiveness of perioperative active warming by administering warm IV fluids via a Hotline™ device (39°C) to women undergoing elective CS and performing SSC, at term, versus room temperature IV fluids on neonatal and maternal outcomes.

As this thesis describes the conduct of an RCT, the problem statement is in the form of a null hypothesis, which is stated as follows: there is no difference in the frequency of neonatal hypothermia between warmed IV fluids (39°C) and room temperature IV fluids, administered to women undergoing elective CS, at term, who also perform SSC at birth.

1.4 Significance of the study

As outlined, the clinical problem of neonatal and maternal hypothermia affects the clinical health and wellbeing of both newborns and mothers alike. The significance of the study for the mother and infant however, is not just confined to promoting maternal and neonatal clinical health but also enhanced delivery of care and reducing separation of newborns from their mothers at birth. Maternal/newborn separation may lead to the interruption of natural SSC, establishment of early breastfeeding and contribute to maternal postnatal depression (Heidarzadeh *et al* 2013).

Previous studies lack sufficient evidence to provide an answer to the specific issue addressed in this study. Therefore, this study tests in a real-life clinical setting, the implementation of an intervention which is widely accepted in a general surgical population but little tested on pregnant women and their newborns. Any significant results arising from this study will be of clinical value to health care providers. It is also obvious that the chosen population is unique when compared to the general surgical population, due to their different physiology (chapter 2, section 2.5), therefore, this study

will expand the clinical knowledge in this field. Finally, the methods used in this study are not widely used by midwives and as such this study offers some useful methodological findings for the midwifery profession.

1.5 Overview of the thesis chapters

1.5.1 Literature Review

Chapter 2 is a review of the literature on the importance of SSC during birth. Specifically, this chapter discusses hypothermia, thermoregulation, thermogenesis and heat loss mechanisms for both mothers and newborns. Additionally, the effects on neonatal and maternal wellbeing are explained, risk factors that increase the frequency of hypothermia are identified and current evidence on prevention/management approaches are highlighted. Finally, the effect of maternal hypothermia, CS, medication and SSC on neonatal/maternal hypothermia are reviewed. The literature review on perioperative neonatal and maternal hypothermia revealed a number of gaps in the knowledge base as well as a lack of evidence that needs to be addressed through robust research (i.e. RCTs).

1.5.2 Systematic Review

Chapter 3 provides a critical analysis of the worldwide evidence from RCTs on perioperative active warming interventions for the prevention of neonatal and maternal hypothermia of women undergoing elective CS, at term, while undertaking SSC. A total of 3 studies (286 participants) met the inclusion criteria and were reviewed. The review suggests that active warming methods such as warm IV fluids and forced air warming are safe to use on the pregnant population and helps in preventing hypothermia in both mothers and newborns. However, all three of the included studies were found to have unclear and high risk of bias in the reviewed outcomes, had small sample sizes and also had significant clinical and statistical heterogeneity. Also, the overall quality of data was considered as very low based on the GRADE system, which indicates that the findings of the review should be interpreted with caution. Based on the findings of this review it was necessary to conduct a good quality RCT, which required a careful design, which was the foundation of the NeoHyp trial. Additionally, my study is different when compared to the three included studies as it additionally investigated: the effect of maternal active warming on neonatal core temperatures/neonatal hypothermia not only during at birth SSC in OT but also during SSC in PACU, the occurrence of any adverse events on either mothers or newborns, when applying perioperative active warming, the interruption of SSC and breastfeeding during the participant stay in theatre department and the levels of maternal thermal comfort between the two groups.

1.5.3 Trial Methodology and Methods

Chapter 4 focuses on the trial methodology used to conduct the NeoHyp study. In this chapter the specific study design is discussed. Furthermore, the research question, the aim of the study and its objectives are identified. The comparative groups in this study are the intervention group who received warmed IV fluids (set at 39°C) and the control group who received room temperature IV fluids (25°C).

The randomization, the randomised allocation sequence and the allocation concealment, are also explained in this chapter. Specifically, a blocked randomisation sequence generation to control or experimental groups (allocation ratio of 1:1) was used, while allocation concealment was achieved through the use of sequentially numbered sealed opaque envelopes, randomly sequenced by a computer generator. The trial management and the data management are clearly identified and explained. Finally, ethical considerations and the elements of confidentiality, beneficence, non-maleficence and justice are reviewed prior the commencement of the NeoHyp trial. These ethical principles were the foundation of this trial as they assisted me in identifying issues regarding respect, protection and confidentiality of the study participants.

Chapter 5 explores the trial methods used and how this trial was conducted. Trial approval was granted by the Institutional Research Ethics Committee (REC). As this trial was not considered a trial of medicinal products by the Health Products Regulatory Authority (HPRA), HPRA approval was not required to undertake this trial. Also ethical approval from Trinity College Dublin's Faculty of Health Science REC was not sought as this trial was a clinical RCT involving patients and such trials are not within the remit of this Committee. The study population was pregnant women with singleton pregnancies from 37^{+0} up to 41^{+6} weeks of gestation, booked for elective CS, who initiated SSC immediately after their CS. The sample size was estimated, at a total of 150 participants. Details on recruitment, data collection and analysis are also presented in this chapter.

Chapter 6 analyses the results of the NeoHyp trial. Overall, 150 of the 159 eligible participants agreed to participate in my trial, an 94.3% response rate and 5.6% refusal rate. Of these, 75 participants were randomly assigned to the intervention group (warm IV fluids heated at 39°C) and 75 to the control group (room temperature fluids, approximately 25°C). The trial showed a significant difference between the two groups in the prevention of neonatal hypothermia during CS while at birth SSC was performed.

Chapter 7 is the discussion and conclusions chapter of this thesis. Specifically, chapter 7 discusses the findings of the trial in relation to the current literature, outlines future research areas that need to be explored as well as recommendations for clinical practice

to provide the health care professional with answers where currently knowledge gaps exists. The NeoHyp trial is the first RCT of its kind to investigate the effect of maternal active warming on the temperature of the newborn during/after CS while at birth SSC is performed. Additionally, my trial is the first of its kind to review/address adverse events of warm IV fluid administration on mothers and newborns during/after at birth SSC.

Chapter 2: Literature review

2.1 Introduction

SSC is a widely researched technique providing multiple advantages for both mothers and their newborns (Moore *et al* 2016). However, the benefits documented in the literature emerged from studies conducted after a vaginal birth (Moore *et al* 2016), as SSC during/after CS is a relatively new concept, which is being slowly but increasingly being implemented. Although initiation of at birth/early SSC during and after CS has been attempted, there are still many obstacles that can prohibit the promotion and establishment of SSC during and after CS (Smith *et al* 2008, Hung and Berg 2011). One of the obstacles is the increased frequency of neonatal hypothermia noticed after CS within the theatre department. Although the evidence suggests that SSC promotes neonatal normothermia, this evidence is based on studies after vaginal birth and not after CS (Vilinsky and Sheridan 2014). Evidence from three clinical audits has found an increased number of mothers and newborns were hypothermic during/after their CS, especially when no active measures were taken to prevent the development of maternal hypothermia during CS (Vilinsky and McCaul 2017). Suboptimal maternal temperatures could potentially impact the neonatal temperature through physiological heat loss mechanisms which occurs in newborns' bodies (Ringer, 2013). Suboptimal neonatal temperature levels have a huge impact on multiple newborn systems which will be outlined later in this chapter.

This chapter outlines the physiology behind thermoregulation, thermogenesis and heat loss as well as the evidence on neonatal hypothermia and maternal inadvertent perioperative hypothermia and how it can be prevented/managed. Additionally, the effects on neonatal and maternal wellbeing are explained, risk factors that increase the frequency of hypothermia are identified and current evidence on prevention/management approaches are highlighted. Finally, the effect of maternal hypothermia, CS, medication and SSC on neonatal/maternal hypothermia are reviewed.

2.1.1 Search strategy

The search strategy used to identify the relevant literature for this review took place prior to the conduct of this review using a PEOs framework and was repeated after the completion of the study (Figure 2.1). The electronic bibliographic databases searched include: EMBASE, PubMed, CINAHL, Cochrane and Google Scholar. Three separate and thorough searches were conducted. The first search focused on SSC and its benefits both after vaginal birth and CS, in term and preterm newborns. The second search concentrated on the physiology of both adult and newborn thermogenesis, thermoregulation, heat loss mechanisms and hypothermia. The third search was centred

on active warming methods for preventing and managing perioperative maternal and neonatal hypothermia.

The search was limited to publications between 1985 and 2019 that were published in the English language. Studies reviewing the physiology of thermoregulation on fetuses and newborns were initially conducted in the mid-1980s, which explains the reason for including studies from 1985 onwards. MeSH and non-MeSH keywords were used in the above searches which include: Skin-to-skin contact (SSC), Kangaroo Care, neonatal bonding, benefits of SSC, obstacles/barriers for SSC. Additional key words included: fetal/neonatal/maternal thermoregulation, thermogenesis, neonatal hypothermia, maternal hypothermia, inadvertent perioperative hypothermia, prevention of hypothermia, heat loss mechanisms. Other key words included operative birth, Cesarean section (CS), Caesarean section, operative delivery, CS rates in Europe, CS global rates, perioperative active warming, warm IV fluids, forced-air warming device. The above search terms were combined where appropriate using the AND/OR Boolean operators. Following this search 360 articles were identified and reviewed, out of which 108 articles were deemed to be relevant to the research topic. Finally, a review of the reference lists of retrieved papers to identify additional studies that were not retrieved through the electronic database searches, was performed.

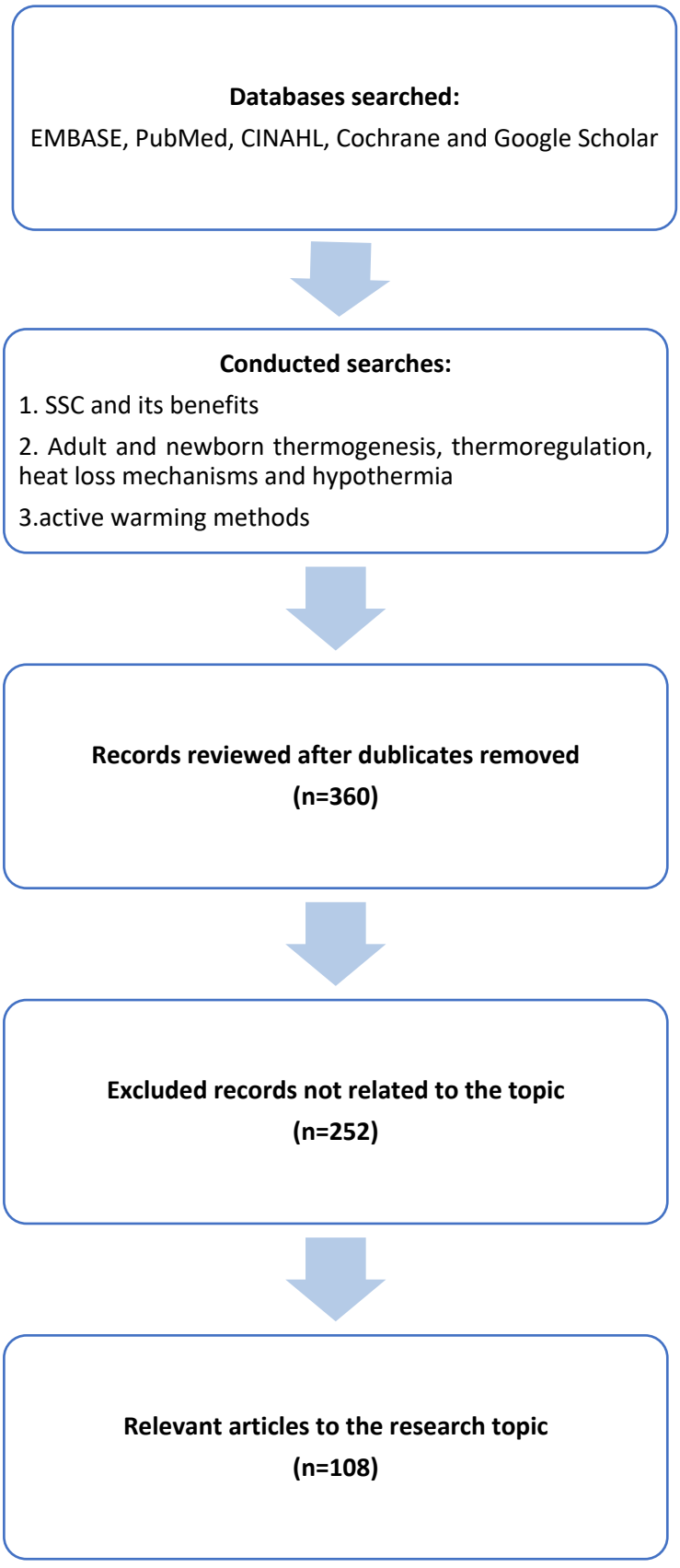

Databases searched:
EMBASE, PubMed, CINAHL, Cochrane and Google Scholar
Conducted searches:
1. SSC and its benefits
2. Adult and newborn thermogenesis, thermoregulation, heat loss mechanisms and hypothermia
3.active warming methods
Records reviewed after dublicates removed
(n=360)
Excluded records not related to the topic
(n=252)
Relevant articles to the research topic
(n=108)

Figure 2.1 Search strategy framework

2.2 Skin-to-skin contact

SSC, also known as kangaroo care, is defined as the practice of positioning the newborn, dressed only with a nappy and a hat, on its mother's bare chest, covered only with warm dry towels/blankets (WHO 2009). This practice has been researched over the past 25 years, after vaginal birth deliveries, and is growing in popularity due to the significant benefits it has for both the newborn and its mother (Moore *et al* 2016). SSC can be described as at birth or immediate SSC (when it is initiated within 10 minutes after birth) and early SSC (initiated between 10 minutes and 24 hours after birth) (Moore *et al* 2016). However, as mentioned in the previous chapter, the current WHO guidelines on SSC and breastfeeding are based after vaginal delivery and they are outdated (20 and 11 years old respectively), something that limits their applicability and effectiveness after CS.

2.2.1 SSC benefits and performance barriers

A recent meta-analysis of 124 studies reviewed the various benefits of SSC in newborns (Boundy *et al* 2016). The method of delivery used in the included studies of this review is not mentioned. One of the main benefits was that SSC lowered the risk of neonatal hypothermia (*n* = 9 studies; RR 0.22, 95% CI, 0.12 to 0.41; p<.01; I^2 = 71%). Also, this meta-analysis found that the mean body temperature of newborns who had SSC was 0.24°C higher compared to the control group (*n* = 14 studies; RR 0.24; 95% CI, 0.15 to 0.33; p<.01; I^2 = 82%). The findings from Boundy *et al* (2016) meta-analysis are in agreement with the Cochrane systematic review by Moore *et al* (2016) who found that axillar temperatures, at 1.5 and 2.5 hours after birth, were higher in the group of newborns who performed SSC (n=6 studies; participants = 558; MD 0.30, 95% CI 0.13 to 0.47; I² = 88%). Boundy *et al* (2016) also found that SSC also significantly reduced the risk of neonatal sepsis (*n* = 8 studies; RR 0.53; 95% CI, 0.34 to 0.83; p<0.01; I^2 = 25%). Furthermore, Boundy *et al* (2016) found that SSC increased exclusive breastfeeding rates at hospital discharge by 50% (*n* = 13 studies; RR 1.50 95% CI, 1.26 to 1.78; p<.01; I^2 = 93%) and increased the rates of exclusive breastfeeding at 1-4 months post-delivery by 39% (*n* = 8 studies; RR 1.39; 95% CI, 1.11 to 1.74; p<.01; I^2 = 60%). This is in agreement with Moore *et al* (2016) findings where SSC increased the exclusive breastfeeding rates at hospital discharge and one month post-delivery (n=6 studies; participants=711; RR 1.30, 95% CI 1.12 to 1.49; I² = 44%) as well as to six months post-delivery (n=7 studies; participants=640; RR 1.50, 95%CI 1.18 to 1.90; p=0.01; I² = 62%). Additionally, Boundy *et al* (2016) suggests that SSC was associated

with lower respiratory rate (*n* = 12 studies; RR -3.17; 95% CI, −5.15 to −1.19; p<0.01; I^2 = 75%) and higher oxygen saturation (*n* = 14 studies; RR 0.90; 95% CI, 0.35 to 1.45; p<0.01; I^2 = 92%). Two studies in this meta-analysis suggested that SSC was significantly reducing the risk of hypoglycaemia in low birth weight infants (RR 0.12; 95% CI, 0.05 to 0.32; p<0.01; I^2 = 0%). It is important to comment that the overall quality of the evidence was not reported by Boundy *et al* (2016). On the other hand, Moore *et al* (2016) suggested that the that the overall quality of the evidence was low to moderate and commented that their results should be interpreted with caution.

A Cochrane systematic review by Moore *et al* (2016) (38 trials with 3472 participants, 30 trials performed SSC after vaginal delivery and eight studies performed SSC after CS), showed that women who performed SSC had longer duration of breastfeeding (n=6 studies; participants=264; MD 64 days, 95% CI 37.96 to 89.50; GRADE: low quality), had higher breastfeeding effectiveness measured with IBFAT (Infant Breastfeeding Assessment Tool) (n=4 studies; participants=384; MD 2.28, 95% CI 1.41 to 3.15; GRADE: low quality; I^2 = 41%) and higher blood sugars at 1.5 hour after birth (n=3; participants=144; MD 10.49 mg/dL, 95% CI 8.39 to 12.59; GRADE: low quality). Furthermore, breast engorgement pain on day three post-delivery was significantly lower in mothers who performed SSC (n=2; participants = 131; SMD -0.41, 95% CI -0.76 to -0.06; I^2 = 8%). Additionally, according to Moore *et al* (2016), SSC reduced feelings of anxiety for mothers **(**n=3; participants= 390; SMD -0.32, 95% CI -0.59 to -0.04; I^2 = 31%). To conclude, Moore *et al* (2016) suggested that the overall quality of evidence of the included studies was borderline adequate, the statistical and clinical heterogeneity of the included studies is moderate to high therefore, the results of their review should be interpreted with caution and future high quality studies are needed on this topic in order to provide sufficient evidence to inform practice recommendations.

Although SSC is beneficial for both mothers and newborns, the vast majority of the studies (n=30) focused on women following vaginal births, with only eight studies in Moore *et al* (2016) performed SSC after CS. This highlights the limited research investigating SSC in women undergoing CS and these studies focused on neonatal and maternal temperatures (Huang *et al* 2006; Gouchon *et al* 2010; Horn *et al* 2014; Paris *et al* 2014; Vilinsky *et al* 2016) and maternal anxiety/stress and birth perception (Nolan and Lawrence 2009, Beiranvand *et al* 2014). One of the main reasons for the limited research in this particular cohort of mothers is that SSC during CS is a new concept with recent attempts being made to implement it in theatres (Phillips 2013, Stevens *et al* 2014). It is also important to highlight that despite the evident benefits of SSC, there are

no available data to demonstrate the national and international rates of SSC, either after vaginal birth or CS.

The drive to introduce SSC in mothers following CS is due to a steadily increasing CS rate, especially in developed countries, with some areas of the USA and Ireland reporting a CS prevalence of 35% (Mangan *et al* 2012, Rotunda 2016). According to the Centres for Disease Control (CDC) (2015), the number of women performing SSC at birth following CS in USA facilities varies between 24%- 83%, suggesting a cohort of women are not receiving the benefits associated with performing SSC at birth during CS, due to the practice not been associated with CS delivery.

Barriers in performing perioperative at birth SSC were described by Mangan *et al* (2012) in their study, including: emergency CS, inability to safely position the newborn on the mothers chest while the mother is lying flat on the operating table, inability of the paediatric nurse to assess the newborn's wellbeing while the newborn is performing perioperative at birth SSC and low ambient temperature in the operating room. Additional barriers in performing SSC post CS include the increased risk for newborn hypothermia secondary to cold operating room temperatures, as well as staffing issues and cost/time concerns which can prevent theatre staff from promoting SSC after CS in theatre departments (Moore *et al* 2016). Common barriers in performing SSC after birth are also reviewed by Seidman's *et al* (2015) (Figure 2.2). Three annual clinical audits, which were conducted in the theatre department at the research site, also showed that over 80% (n=33/40) of mothers become hypothermic during their CS and over 25% (n=26/40) of their newborns became hypothermic as well, despite following the hospital guidelines for SSC (Vilinsky & McCaul 2017). This prevalence of perioperative maternal and neonatal hypothermia during SSC is a barrier to theatre staff in maintaining and establishing undisturbed SSC and early breastfeeding within the theatre department, as in many instances mothers and newborns have to be separated in order to be warmed up, since hypothermia can increase morbidity in both mothers and their newborns (Wilson *et al* 2007, Bajwa and Swati 2014). In order to better understand the concept of hypothermia and its effects of the human body, it is important to explain the physiology of heat production, heat regulation and heat loss.

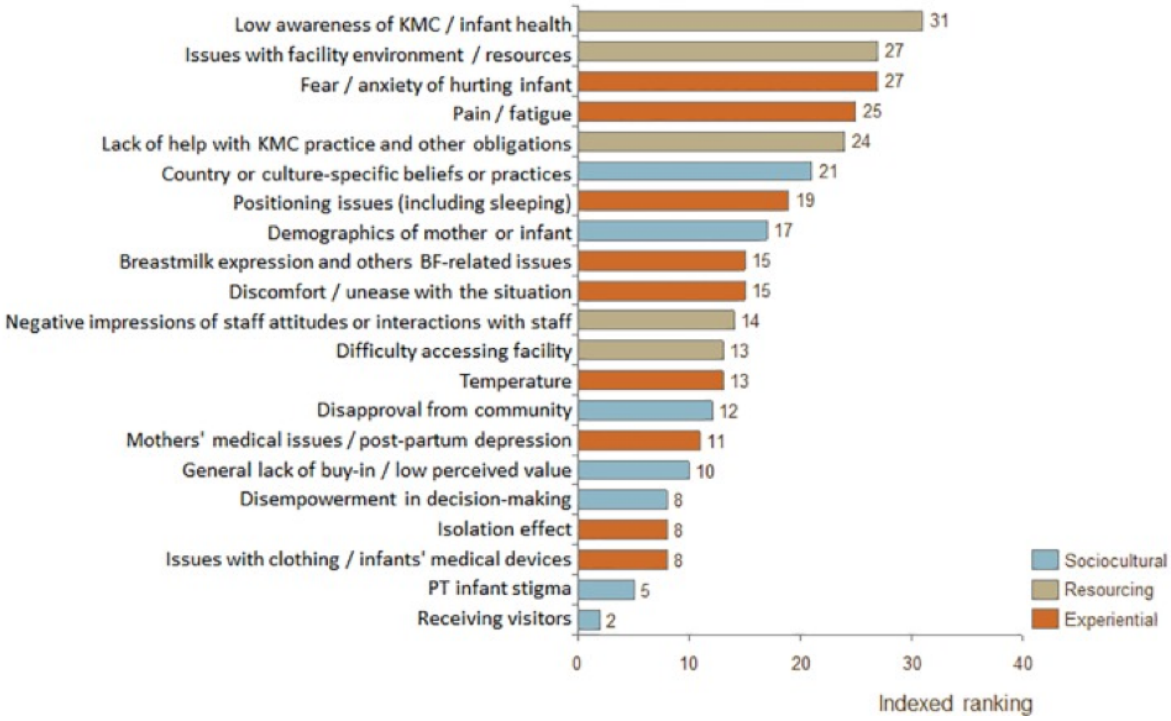


Figure 2.2 Barriers to SSC

Source taken from Seidman *et al* (2015) Barriers and Enablers of Kangaroo Mother Care Practice: A Systematic Review.

2.3 Newborn thermoregulation, thermogenesis physiology, heat loss mechanisms

Humans, as homeotherms, have the ability to balance their heat production and their heat loss in order to maintain their core temperature within certain normal levels. This is defined as thermoregulation (Gardner *et al* 2011, Leduc and Woods 2017).

2.3.1 Foetal and newborn thermoregulation, thermogenesis physiology

Thermoregulation mechanisms are monitored by the hypothalamus and endocrine pathways and are applied differently among adults and newborns (Lunze *et al* 2013). Adult thermoregulation mechanisms include: peripheral vasoconstriction, shivering, reduction of sweating as well as non-shivering thermogenesis. Newborn thermoregulation, in contrast, is heavily depended on environmental temperature, the health status of the newborn and a number of heat production mechanisms (Ringer, 2013). According to the Canadian Paediatric Society, neonatal heat production mechanisms (thermogenesis) include: metabolic processes, voluntarily muscle activity, peripheral vasoconstriction and non-shivering thermogenesis (Leduc & Woods 2017).

The heat source of the metabolic process mechanisms include main organs such as the brain, the heart and the liver, which produce metabolic energy by metabolising glucose, fat and protein (Blackburn 2013). Voluntary muscle activity of the newborn can be generated during restlessness and crying which generates heat through increased muscle activity. Additionally, heat conservation can be achieved when a newborn takes a flexed position, which decreases the skin surface area exposed to the environment. Peripheral vasoconstriction refers to constriction of the blood vessels close to the skin and the extremities as a response to cooling, reducing in that way the blood flow to the skin and therefore decreasing the loss of heat from the skin surface (Leduc & Woods 2017). Finally, with non-shivering thermogenesis Brown Adipose Tissue (BAT) is metabolised in order to generate heat. BAT is a fatty tissue located around the kidneys, the head, neck, heart, great vessels/ adrenal glands and axillary regions. When a newborn gets cold, thermal receptors transmit a signal to the hypothalamus, which in turn stimulates the sympathetic nervous system. When the sympathetic activity is initiated, it increases the levels of norepinephrine and the thyroid-stimulating hormone (T3 and T4). These hormones activate lipase in BAT, which leads to lipolysis and fatty acid oxidation resulting eventually in heat production. This heat production is achieved with releasing the produced energy rather than storing it as Adenosine-5-Triphosphate (ATP) (Knobel *et al* 2010, Volpe *et al* 2017). Unfortunately, in order to activate and maintain non-shivering thermoregulation, a large calorie consumption is needed. It is estimated that if a newborn is left unattended (at room temperature), it may consume approximately 150 kcal per min to cover its heat loss (Soll 2008). This suggests that by not preventing newborn heat loss, excessive calorie consumption will be initiated depriving the newborn of calories required for its optimal growth needs as suggested by the Dietitians of Canada (2010).

Thermogenesis mechanisms are different between the foetus and the newborn. The foetal temperature is directly dependant on its mother's temperature until birth, as maternal heat passes to the foetus through the uterus, the amniotic fluid and the placenta (Lubkowska *et al* 2019). This results in a foetal temperature that is 0.3-0.5°C higher than that of the mother's (Polin *et al* 2016). Most of our current knowledge regarding foetal thermoregulation is based on animal studies conducted in sheep, rats, guinea pigs and cattle, with limited studies being conducted on human foetuses, due to the fact that such studies could have significant adverse event raising ethical considerations for their application to human foetuses (Satoru *et al* 2010). Studies undertaken in sheep foetuses have shown that 85% of the heat produced from the sheep foetus passes through the placenta to its mother and the remaining 15% is further passed to the mother, through

the foetal skin, the amniotic fluid and the uterine wall (Carstens 1994; Laburn *et al* 2002). This mechanism is essential to maintain temperature equilibrium on the foetus. Additionally, heat is passed from the foetus to the placenta via the placental artery. However, some of the heat is returned back to the foetus via the umbilical venous (Gilbert *et al* 1985). Furthermore, the placenta produces heat by itself due to its high metabolical activity, leading to 25% of heat passing from the placenta itself to the mother (Schroder & Power 1997). Based on the above, Gilbert *et al*. (1985) and Schroder and Power (1997) suggest that in order to significantly change the foetal temperature, in utero, compared to its mother, it can only take place by either changing the umbilical flow or the heat production of the foetus itself. This mechanism shows that foetuses are unable to control their own temperature while in utero (Schroder & Power 1997). However, the implications of these animal studies to humans need to be interpreted with caution (Wells 2002) and further data are needed on human foetuses (Gowland & De Wilde 2008).

Finally, the literature suggests that the method of delivery has a direct effect on how newborns regulate their body temperature, with human newborns delivered via elective CS having lower body temperatures compared with newborns delivered via vaginal birth (Topaloglu *et al* 2016, Zulala *et al* 2017). Charafeddine *et al* (2014) in their RCT (n=118 newborns) discovered that the type of delivery had an impact on the difference between rectal and axillar temperatures, with CS newborns having statistically significant lower temperatures than newborns delivered from the vaginal canal (RR= 0.2; 95% CI: 0.02, 0.38). BAT activation, catecholamine plasma levels and thyroid plasma levels are significantly reduced in both human and lamb newborns after elective CS when compared to the ones born vaginally (Polin *et al* 2011). No current studies exist with regard to emergency CS. To summarise, foetuses/newborns do not have the ability to maintain their own temperature and depend on their mothers' temperature both before and after their delivery. As their body temperature is expected to be lower after a CS, while their extra-uterine thermoregulatory response is reduced, it is expected that newborns delivered via CS are prone to temperature drop, hypothermia and slower thermogenesis response in comparison with newborns delivered through the vaginal canal. These physiological factors may have possible implications for the early initiation of SSC during and after CS, especially when combined with maternal low core temperatures, something that will be discussed later in this chapter.

2.3.2 Heat loss mechanisms and neonatal hypothermia risk factors

Newborns are prone to rapid heat loss, resulting in hypothermia, due to a number of reasons. The core temperature can decrease by 0.1°C per minute while skin temperature can decrease by 0.3°C per minute if no actions are taken to prevent it

(Waldron & Mackinnon 2007). The main reason for this rapid heat loss is that newborns have a high surface area to volume ratio, thin skin with blood vessels close to the surface and reduced subcutaneous fat (Leifer 2012; Gibson & Nawab 2015). Additionally, there are four main heat loss mechanisms in the human body; conduction, evaporation, radiation and convection, which effect adults and newborns alike (Leifer 2012; Ringer 2013).

Heat loss via conduction happens when the warm body of a newborn is placed directly on a colder surface, for example placing a newborn immediately after its birth on an unwarmed resuscitation station, scales or even to a hypothermic mother's chest for SSC. Mothers tend to drop their core temperature and become hypothermic during/after their CS, when compared to vaginal births (Zulala *et al* 2017), for a number of reasons which will be outlined later on in this chapter. In this way heat is transferred towards the colder surface in order to heat it up. This mechanism can occur when a warm newborn is placed on the hypothermic mothers' cold bare chest during SSC if maternal hypothermia was not prevented during CS (Zulala *et al* 2017). Evaporation occurs when the liquid that covers the newborn's body (i.e. amniotic fluid) and the mucosa of the respiratory tract vaporise towards the atmospheric air. In that way the body fluids are converted into gas, leading to an approximate 0.6 kcal heat loss for every 1g of fluid evaporated from the body (Guyton & Hall 2006). Radiation occurs when the newborn's heat is lost towards any cold surface around the newborn (including walls and equipment) that is not in direct contact with the newborn's body. According to physics, every warm body radiates its heat in the form of infrared electromagnetic waves towards a colder surface. The same mechanism is applied with radiant heaters mainly used to warm newborns after birth (Ringer 2013).

Finally, convection applies to heat loss from the exposed surface of the newborn's body to the surrounding air. Convection is determined by the temperature difference between the ambient temperature and the newborns surface temperature. For example, neonatal heat loss can occur if the ambient temperature is lower than the newborn's surface temperature. According to Rennie (2012) convective heat loss depends on air speed and can be divided into forced convection and wind chill factor. The first refers to rapid air movement around the newborn's surface while the second refers to the temperature of the air surrounding the newborn's surface. Health care professionals should acknowledge and prevent the above heat loss mechanisms in order to maintain neonatal normothermia post-delivery.

Risk factors that relate to neonatal hypothermia can be categorized into four groups: environmental, physiological, behavioural and socioeconomic (Lunze *et al* 2013). Environmental risk factors are related to: the geographical area, the time of the year and the room temperature in which the baby was born (WHO 1997; Lunze *et al* 2013). Studies investigating neonatal hypothermia in low resource countries, such as India, Uganda and Nepal, showed that the risk of neonatal hypothermia was present notwithstanding the season or the geographical latitude that the babies were born (Kumar *et al* 2009; Mullany 2010).

Although, the occurrence of neonatal hypothermia was higher during the winter months rather than the summer months, neonatal hypothermia was not absent in warm tropical areas. Due to this, the WHO (1997) recommends that the temperature of the delivery room should be kept at a minimum of 25°C for a term baby with normal birth weight and 26-28°C for preterm babies or low birth weight babies, irrespective of the country that the babies are born in. Unfortunately, the above recommended environmental temperatures are not always sustainable within the operative theatres during CS (Sultan *et al* 2017).

The author's audit findings suggest that the majority of OT temperatures were maintained between 21-24 °C. An RCT by Duryea *et al* (2016) (n=809 newborns) suggested that increasing the OT ambient temperature by 3°C (from 20°C to 23°C) significantly reduced the frequency of maternal hypothermia (77% vs. 69%, p=0.008) and neonatal hypothermia (35% vs. 50%, p<0.001). However, there is no reference of the impact of SSC on neonatal hypothermia compared to ambient temperature in the above studies, something that needs to be reviewed in the future.

Physiological risk factors are related to neonatal issues such as: prematurity, neonatal hypoglycaemia and low birth weight (including both babies with intrauterine growth restriction and "small for dates" babies). According to Mullany (2010), female babies are at higher risk of developing hypothermia. These factors usually are combined and gravely increase the risk of neonatal hypothermia (Gardner *et al* 2011, Lunze *et al* 2013).

Behavioural risk factors are identified as any non-evidence based practice undertaken either for cultural reasons and/or lack of adequate training/knowledge, which may result in neonatal hypothermia (Lunze *et al* 2013). An example of such practices, that research has proven to result in neonatal hypothermia, include: bathing babies immediately after birth (sometimes bathed with cold water), removing their vernix caseosa, delayed cutting of the umbilical cord and/or massaging them with essential oils immediately after birth (WHO 1997; Mullany 2010; Onalo 2013). Additionally, babies with delayed breastfeeding (over 24 hours) had 50% higher chance of developing hypothermia (Mullany 2010).

Finally, socioeconomic risk factors are associated with an increased risk of developing neonatal hypothermia, which include mothers of young age, mothers who have already had multiple births, newborns born into families of a low socioeconomic status and/or born in environments which are resource-limited (for example birth facilities that have no thermal protection and/or neonatal warming devices) (Lunze *et al* 2013).

2.4 Neonatal hypothermia

Neonatal hypothermia is defined as a pathological condition in which the newborn's body temperature drops below 36.5 °C (Kumar *et al* 2009, Gupte 2016) and is categorized by the WHO (1997) into three core categories based on the levels of core temperature:

- Mild hypothermia (or Cold stress): 36.0 to 36.4 °C.
- Moderate hypothermia: 32.0 to 35.9 °C.
- Severe hypothermia: <32.0 °C.

It is important to clarify that neonatal hypothermia is a pathological condition that may occur in healthy newborns any time after their birth, which is different to the neonatal therapeutic hypothermia, a term regularly found in the Irish context, which refers to a medical treatment applied to newborns diagnosed with encephalopathy after birth (Meaney *et al* 2018). This thesis focuses on the pathological condition of neonatal hypothermia rather the medical treatment of inducing therapeutic hypothermia to newborns with encephalopathy.

Depending on the level of hypothermia, different actions are required. For example, newborns diagnosed with mild hypothermia need to be warmed and an investigation to discover the reasons for this temperature loss needs to be undertaken. Newborns with moderate hypothermia are in a more urgent state where immediate warming and observations are indicated. Finally, in the rare scenario of severe hypothermia, urgent skilled care is required as untreated severe hypothermia may lead to death (WHO 1993; Gupte 2016).

The WHO (2009) neonatal hypothermia recommendations are not widely used by health care professional around the world (Kumar *et al* 2009). In their review of 20 studies to define hypothermia, Kumar *et al* (2009) concluded that only seven studies used the WHO criteria, nine studies used a cut-off point of <36.0 °C for hypothermia, two studies used <35.5 °C and three studies used <35.0 °C. This variation in the definition of hypothermia may lead to under-recognition and under-management of the problem, increasing the frequency of hypothermia and its adverse effects of this population

(Kumar *et al* 2009). This also suggests an additional challenge in comparing research investigating the effectiveness of preventative strategies as the use of different classifications results in studies that are not comparable.

An additional challenge regarding neonatal hypothermia is that temperature is measured using various devices and from different body sites. Studies argue that temperature measurements may vary depending on the body area that the temperature was measured or with the device used to conduct the measurement (Smith 2014). These differences create further questions as to which site (oral, tympanic, rectal or skin) should be used for a more accurate temperature reading and which device (mercury, digital or infrared thermometers) would be more accurate, as a mismeasurement of neonatal temperature may lead to under-management or over-management of neonatal hypothermia. Specifically, recent studies suggest that newborn axillar temperatures were higher than rectal temperatures (Friedrichs *et al* 2013; Charafeddine *et al* 2014), while other older studies would argue the opposite (Morley *et al* 1992, Hissink *et al* 2008, Hutton *et al* 2009). A SR is required to explore the evidence and quality of evidence in this area. Overall, the site of temperature measurement varies, depending on each hospital's local practices, however, the Canadian Paediatric Society recommends taking the newborns temperature via the axillary route to screen low risk newborns from birth to 2 years (Leduc & Woods 2017).

2.4.1 Effects of hypothermia on neonatal wellbeing

Neonatal hypothermia may affect a number of different systems in the newborn's body including the cardiopulmonary, central nervous and vascular systems (Mank *et al* 2016). Additionally, it may lead to a fall in systemic arterial pressure, decreased plasma volume, decreased cardiac output, and increased peripheral resistance (Knobel & Holditch-Davis 2010). It can also lead to bradycardia and tachypnea, which if left unchecked, can lead to permanent tissue damage, brain damage, or death. Mild hypothermia (cold stress) can lead to vasoconstriction, which reduces blood flow, and therefore the oxygen supply to the skin and other major organs leading to hypoxia and eventually to acidosis (Leifer 2013). This leads to increased oxygen consumption, and an increased respiratory rate to cover the increased oxygen needs (Ramachandrappa *et al* 2008). As a result of the increased oxygen consumption the energy demand increases leading to an increased consumption of glucose, which eventually depletes the glycogen stores and ultimately increases the release of lactic acid in the blood stream resulting in further acidosis (Leifer 2013). At the same time, hypoglycaemia will emerge. According to the Pediatric Endocrine Society (Thornton *et al* 2015), if hypoglycaemia is persistent or reoccurring, it

may lead to: brain injury, cognitive impairment, vision disruption, occipital lobe epilepsy and cerebral palsy. Furthermore, hypothermia may reduce the surfactant production, leading to the collapse of the alveoli and eventually hypoxia (Thornton *et al* 2015). As a result of hypoxia, the ductus arteriosus (foetal circulation) may reopen leading to low diastolic aortic pressure and reduced organ perfusion. Reduced renal perfusion may result in renal failure, which would cause fluid retention, usually associated with congestive heart failure (Volpe *et al* 2017). Likewise, reduced blood flow to the intestines (intestinal ischaemia) may lead to feeding intolerance and necrotizing enterocolitis (Gournay 2011).

Finally, the consumption of BAT to generate heat and raise the body temperature releases fatty acids into the newborn's bloodstream which may interfere with the transport of bilirubin to the liver resulting in hyperbilirubinemia and jaundice (Leifer 2013). This suggests that neonatal hypothermia can and should be prevented after birth. For this to take place, it is important that health care professionals are aware of the risk factors and methods of prevention and management of neonatal hypothermia.

2.4.2 Neonatal hypothermia prevention and management

The WHO World Health Organization (1997) recommendations on room temperature were investigated in an RCT, involving 91 preterm newborns, which reported preterm newborns exposed to an ambient room temperature of 24-26°C when compared to an ambient temperature of 20-23°C had significantly higher rectal temperatures (36.0±0.9 °C vs 35.5±0.8 °C, P<0.01) (Jia *et al* 2013). Similarly, a prospective cohort of 1,764 preterm infants found that a delivery room temperature <25 °C was independently associated with hypothermia at 5 min after birth (OR: 2.13; 95% CI: 1.67–2.28) (de Almeida *et al* 2014). A more recent RCT involving 809 term and preterm infants found that increasing the delivery room temperature from 20 to 23°C showed a reduction in neonatal hypothermia from 50% to 35% (Duryea *et al* 2016). On the other hand, the American Academy of Pediatrics, based on an observational study (n=109 preterm newborns), suggested that a delivery room temperature of 23.5°C, when combined with the use of an exothermic mattress, preheated radiant warmer, saran wrap and warm towels can achieve 94% normothermia in preterm newborns, something that will also maintain the comfort level of theatre staff without compromising the temperature of the preterm newborns (Bhatt 2018).

Prevention of neonatal hypothermia can also occur with the use of various techniques, which are separated into two main categories: passive and active warming (Holtzclaw 2008). Passive warming includes all of the man-made instruments that work as barriers to heat loss such as: newborn caps and plastic bag wraps made of various materials

(Vilinsky & Sheridan 2014). These devices are frequently used to prevent hypothermia in pre-term babies and are recommended by the American Academy of Paediatrics. A recent meta-analysis by McCall *et al* (2018) suggested that newborns exposed to bags/wraps, had significantly higher core temperatures and lower frequency of hypothermia compared to the newborns, MD 0.58°C (95%; CI: 0.50 to 0.66; 13 studies, 1633 infants) and RR0.67 (95% CI:0.62 to 0.72; 10 studies, 1417 infants), respectively.

Active warming refers to any method used to directly warm the newborn. The active warming methods mentioned in literature include: radiant heaters, exothermic mattresses and SSC (Holtzclaw 2008). Radiant warmers are devices which spread heat through radiation, while exothermic mattresses are devices which heat the newborn through conduction. According to the meta-analysis by McCall *et al* (2018) (n=25 studies, participants= 2433, type of delivery not mentioned in this review), SSC significantly reduced the risk of hypothermia when compared with conventional incubator care for low birth infants (RR 0.09; 95% CI; 0.01 to 0.64). Thermal (transwarmer) mattress kept infants ≤ 1500g significantly warmer (MD 0.65°C, 95% CI 0.36 to 0.94) and reduced the frequency of hypothermia on admission to the NICU, with no significant difference in hyperthermia risk.

A comparison of thermal mattresses versus plastic wraps or bags in the same meta-analysis (two studies, n=77 preterm infants) found no significant differences in core body temperature, frequency of hypothermia and/or hyperthermia (McCall *et al* 2018). McCall *et al* (2018) suggest that a combination of plastic bags and exothermic mattresses compared to plastic bags alone (two studies, n=119 preterm infants) had significant higher core temperature but also an increase in hyperthermia.

2.5 Adult thermoregulation during pregnancy

Adult thermoregulation is the balance between heat loss and heat production in the human body (Blackburn 2013). Heat is produced from complex metabolic processes of the human body in conjunction with muscular activity and environmental factors. Thermoregulation is controlled by the hypothalamus, thyroid hormones and the sympathetic nervous system. The anterior hypothalamus controls the heat loss mechanisms while the posterior hypothalamus controls the heat production or dissipation. Specifically, when the environmental temperature changes, the peripheral and central receptors (free nerve endings on the skin, spinal cord, internal organs) send impulses (through afferent nerve fibers) to the hypothalamus. The hypothalamus can either conserve or produce heat (via vasoconstriction, shivering/non shivering thermogenesis vasodilatation, sweating and respiration) (Blackburn 2013).

Furthermore, the human body has two main areas that control the body temperature, a core thermal compartment (organs and tissues) and a peripheral compartment (arms and legs). The organs of the core thermal compartment are usually well perfused leading to a constant temperature, managed by neuro-thermoregulatory mechanisms. The temperature of the peripheral compartment, can be 2.0°C to 4.0˚C lower than the core thermal temperature, it is regulated by central structures. Therefore, human homeothermy, uses internal mechanisms to control/balance heat loss and gain in order to maintain normal temperature (Ivanov 2006).

During pregnancy, the metabolic process and the hormonal balance changes have a direct effect on maternal temperature. In pregnant women, the body temperature tends to slightly increase, especially after the first trimester (Cowlin 2002). This temperature increase is balanced by increased perspiration in pregnant women and this balances their body temperature within normal levels (Cowlin 2002). Specifically during the early antepartum period, the heat production increases up to 35% due to the thermogenic effects of progesterone (Blackburn 2013). The additional heat tends to spread through the body and dissipate via vasodilation to the environment. This additional heat production can increase the pregnant woman's core temperature by 0.5°C with vasodilation making the women's skin warmer (Blackburn 2013). However, heat production decreases towards the end of pregnancy possibly because of the reduction of progesterone levels and less physical activity of the pregnant women (due to the natural loosening of the pelvic ligaments, which can cause mild to significant discomfort to the pregnant women) (Macdonald & Johnson 2017).

Women's temperature during labour can increase by an average of 1°C due to increased physical activity (i.e. uterine contractions) and increased hypothalamic activity (i.e. oxytocin release) which is at the centre of thermoregulation (Blackburn 2013). However, these elements are not applicable in women undergoing elective CS, since their physical activity is reduced. A temporary cold sensation and drop of core temperature can be experienced by most women in the immediate postpartum period (after the delivery of the baby and/or the placenta) for reasons that still remain unknown (Blackburn 2013).

Heat generation occurs independently of the central thermoregulation processes. Muscular exercise is considered the most common source of heat generation. Heat generation aims to restore thermal imbalance, and can be classified as shivering and non-shivering. Shivering can increase heat production, with 80% of the produced heat being retained by the body, compared to 50% from voluntary exercise according to the National Collaborating Centre for Nursing and Supportive Care (NCCNSC) (2008). Non-

shivering heat generation in adults increases the basal rate of metabolism in different tissues (i.e. liver) which promote further heat generation (NCCNSC 2008).

The same heat loss mechanisms that apply to the newborn also apply to pregnant women with 75% of heat loss in adults occurring via conduction, convection and radiation. A quarter of heat is lost through evaporation, which includes sweating (major cause of heat loss) and through the respiratory tract.

2.5.1 The effect of medication on thermoregulation in mothers

Anaesthetic drugs used for spinal/epidural anaesthesia, during CS, lower the thermoregulatory set point of the hypothalamus which initiates shivering (Hess *et al* 2005). Additionally, they block the natural blood vessel reaction to cold (peripheral vasoconstriction), increasing the core-to-peripheral heat redistribution and the heat loss through the blood flow to the skin (peripheral vasodilatation) (Campbell *et al* 2015, Cobb *et al* 2018). This heat redistribution mainly takes place during the first hour following anaesthesia and is one of the main causes of hypothermia in short surgical procedures, such as CS. These heat loss mechanisms, result in rapid heat loss immediately after the administration of anaesthesia, and a later more gradual heat loss while the anaesthetic effects persist (Campbell *et al* 2015). An observational study by Hilton *et al* (2015) (n=40) focused on the effect of phenylephrine, a pharmacological agent, on mother's core temperature during CS. Phenylephrine, which causes vasoconstriction, was shown in this study to potentially decrease core temperatures by 0.29°C. However, notwithstanding of the drop in temperature, there was no occurrence of maternal hypothermia reported in this study (Hilton *et al* 2015).

Anaesthetic drugs, especially opioids, may also inhibit the newborn's thermoregulation system in the same way as in adults (Bajwa & Swati 2014). Although the effects of opioids administered to the mother during CS on the newborn's temperature have not been explored in detail, it is known that fentanyl, a drug regularly used in spinal anaesthesia, passes through the placenta to the foetus, which could lower the thermoregulatory set point of a newborn's hypothalamus and increase its peripheral vasodilatation, resulting in an additional cause for neonatal temperature drop and hypothermia during/after CS (Loftus *et al* 1995, Sedgwick *et al* 2005).

2.6 Maternal hypothermia

The definition of hypothermia, the stages that it is divided into and the symptoms of each stage vary in the current literature. Hypothermia in pregnant women is defined as a core temperature below 36°C (Desgranges *et al* 2017). It is divided into five stages with a

gradual increase of severity of its symptoms as the core temperature drops (Wilson *et al* 2007). Specifically, hypothermia is divided into the following stages:

1. *Mild hypothermia*: temperature ranges between 35.9°C and 35°C. Common phenomenon among patients undergoing surgical operations. Usual symptoms include shivering, hyperventilation, tachycardia, vasoconstriction and painful peripheral body parts.
2. *Moderate hypothermia*: temperature ranges between 34.9°C and 32.5°C. Common symptoms include sinus bradycardia, central depression of ventilation, disorientation, exhaustion and drop of muscular tone.
3. *Severe hypothermia*: temperature ranges between 32.4°C and 28.1°C. Symptoms include bradyrhythmia, bradypnoea, unconsciousness and paralysis.
4. *Life threatening hypothermia*: core temperature below 28°C. Clinical signs are similar to apparent death (vita reducta).
5. *Profound hypothermia*: core temperature below 18°C, is usually an induced hypothermia for operations that require circulatory arrest.

Mild hypothermia is a frequent occurrence among pregnant women undergoing CS (Munday *et al* 2014; Desgranges *et al* 2017) an issue also identified in my clinical audits (Vilinsky & McCaul 2017) and which informed the direction of my study. The other stages of hypothermia are extremely rare and do not apply in healthy pregnant women undergoing elective CS. For this reason, this thesis will focus on the common phenomenon of mild maternal hypothermia and its prevention.

2.6.1 Effects of hypothermia on maternal wellbeing and neonatal temperature

Perioperative and postoperative hypothermia may increase the morbidities experienced by mothers after CS (Sultan *et al* 2015). It is evident that more than 60% of women who have a CS will develop hypothermia (Cobb *et al* 2016). Shivering, experienced by patients as an unpleasant feeling, is the most common postoperative incident (Campbell *et al* 2015). Additionally, hypothermia may delay wound healing, increase the risk of wound infection (Melling *et al* 2001, Cobb *et al* 2018) and increase the risk of haemorrhage because it decreases platelet activity (Rajagopalan *et al* 2008). Additional effects of perioperative hypothermia include longer post-anaesthetic recovery, longer stay in hospital (Karalapillai 2013), altered drug metabolism (McSwain *et al* 2015) and patient thermal discomfort (Alfonsi *et al* 2003).

The effect of maternal hypothermia on neonatal temperature is another area not adequately researched. There are limited studies investigating this area. A systematic review (SR) was undertaken as part of my PhD study investigating the effect of perioperative active warming of pregnant women who perform at birth SSC on the

maternal and neonatal temperature. Its findings are described in detail in the following chapter.

2.6.2 Inadvertent perioperative hypothermia (IPH)

Inadvertent perioperative hypothermia (IPH) is defined as a body core temperature below 36°C in adults during their perioperative period (NICE 2015). IPH is a common complication among patients undergoing surgery, with a 50-90% occurrence in operative theatres (OT) and post-anaesthetic care units (PACU) (Fatemi *et al* 2016). IPH should be distinguished from therapeutic induced hypothermia, since the second is purposefully induced by medical experts as part of medicinal treatment. IPH is divided into three phases (NICE 2008), which are:

- Preoperative phase: up to one hour before the administration of anaesthesia.
- Intraoperative phase: starting from the administration of anaesthesia until the completion of the operation.
- Postoperative phase: starting from the admission to PACU including the time of transfer and stay on the ward.

Generally, adults are prone to drop their temperature below normal levels within the first 30-40 minutes after the administration of anaesthesia. An RCT (n=156) involving pregnant women undergoing CS under regional anaesthesia suggest that intraoperative shivering, due to hypothermia, can occur in at least 55% of the women (Anaraki & Mirzaei 2012). There are three main causes of IPH in pregnant women during CS (Chung *et al* 2012), which are;

- Spinal anaesthesia leads to redistribution of heat from the core of the body to the periphery.
- Heat is lost from the skin surface, starting below the level of the spinal anaesthesia block, due to peripheral vasodilatation as an effect of spinal anaesthesia.
- Spinal anaesthesia alters the thermoregulation, leading to a temperature drop of 0.5°C by decreasing shivering threshold and vasoconstriction.

Additional causes of IPH (NICE 2008) include:

- Temperature drop while patients are waiting for their surgery,
- Body exposure to environmental factors (i.e. room temperature, air draft) during surgery,
- Dehydration before anaesthesia (fasting up to 12 hours before the operation) and
- Use of unwarmed intravenous or irrigation solutions.

As the anaesthetic agent interferes with the ability of the brain to trigger thermoregulation responses, it can take between 2-5 hours for the anaesthetic medication to wear off and thermoregulation to be re-established (Sessler 2000). During that period, IPH is evident and normothermia can gradually be restored after this period. Since, redistribution of heat from the core to the periphery of the body is difficult to treat naturally, it is recommended to prevent it with the use of perioperative active warming (Chung *et al* 2012).

Risk factors for IPH, according to NICE (2008) and (ASA 2016) include:

- Smokers,
- Obesity (30<BMI),
- Pregnant women,
- Patient preoperative temperature below 36.0°C,
- Preoperative warming is not possible (i.e. emergency operation),
- Undergoing combined general and regional anaesthesia,
- Undergoing major or intermediate surgery (CS are considered a major/complex surgery as per the Royal Australasian College Of Surgeons (RACS 2015),
- Patients are at risk of cardiovascular complications and
- Administration of unwarmed IV fluids, blood or irrigation fluids.

All patients should be assessed preoperatively for their risk factors of IPH by members of the perioperative team and should be considered/managed as high risk if two or more of the above risk factors apply to them. As pregnant women undergoing CS are considered high risk patients of IPH, preventative management of IPH should be included in their perioperative care by theatre staff, to prevent adverse effects related to IPH. These adverse effects are similar to the effects of hypothermia on maternal wellbeing, which were explained in the previous paragraph.

As shown above, mothers undergoing CS, without any preventative management of IPH, have a high risk of developing low core temperature and even lower skin temperature (see section 2.5). As previously discussed, newborns delivered via CS are at higher risk of neonatal hypothermia (see section 2.3.1). When you combine these risk factors, placing a newborn at risk of hypothermia on the skin of a mother (SSC) with IPH escalates the risk of neonatal hypothermia.

2.6.3 Perioperative warming mechanisms

The use of preoperative warming alone is not adequate to prevent maternal hypothermia during and after CS, therefore, a combination of perioperative active warming should be considered (Munday *et al* 2018). Intraoperative warming of the pregnant women

undergoing CS could take place either with the use of active warming devices or with thermal insulation devices (NCCNSC 2008). Active warming is defined as a method of transferring heat to a patient (NCCNSC 2008). There are a number of active warming devices documented in the literature including fluid warmers, forced air warming, electric heated mattresses and water mattress.

A fluid warmer involves actively warming IV fluids with the use of various fluid warming devices prior to fluid IV administration to the patient. In forced air warming a specially designed blanket is applied over the pregnant woman's half body (upper or lower) and warm air is forced through the device to the equipped blanket for as long as the device is activated. A similar method of forced air warming is the thermal gown, which can be worn by women before the operation and can be used as a forced air blanket during the operation. A meta-analysis by Sultan *et al* (2015) involving 13 RCT studies (n=789 pregnant women undergoing elective CS) compared the use of perioperative active warming versus no warming. The findings of this meta-analysis suggested that the use of warm IV fluids and forced air-warming, administered within 30 minutes from the administration of neuraxial anaesthesia, reduced maternal temperature change (SMD: −1.27°C; CI 95%; −1.86, −0.69; P=0.00002), had higher end of surgery temperatures (MD: 0.43 °C; CI 95%; 0.27, 0.59; P<0.00001), reduced shivering (RR 0.58; CI 95%; 0.43, 0.79; P=0.0004), increased thermal comfort (SMD 0.90; CI 95%; 0.36, 1.45; P=0.001) and decreased maternal hypothermia (RR 0.66; CI 95%; 0.50, 0.87; P=0.003). Neonatal temperatures were only reviewed at delivery in some of the included studies, where no statistical difference between the groups was found. However, the above meta-analysis did not investigate if SSC at birth was performed, the effect maternal active warming had on newborn temperatures or the frequency of neonatal hypothermia during and after SSC was discontinued.

It is evident that the perioperative active warming methods used on pregnant women undergoing elective CS, include the use of warm IV fluids and upper or under body forced air warming devices. The use of other active warming devices such as: electric heated mattress, water mattress, heating gel pads, radiant heater, heated-humidifiers, heat and moisture exchange and thermal insulation have not been investigated yet on the pregnant population undergoing elective CS, therefore no findings are available on their effectiveness. It is clear that there is a lack of evidence on the effect of perioperative maternal active warming during elective CS on neonatal hypothermia when SSC at birth is performed, suggesting the need for the conducting of a systematic review in this field. Such a SR was performed and will be explained in detail in chapter three.

2.6.4 International guidelines on inadvertent perioperative hypothermia

Guidelines on the prevention of IPH are available from NICE (2015), however, they are focused on the prevention/management of IPH in the general adult surgery population and exclude pregnant women and children/newborns. As part of my fieldwork I contacted NICE via e-mail (on 24/8/2016) seeking clarification as to why pregnant women were excluded from their guideline and what advice or suggestions they would have regarding a method of active warming that could be used to prevent hypothermia in this population. Their response was:

> "Pregnant women were excluded from the scope of the guideline because of the different physiology of the population and it was felt that would be too complex to include this patient group. It is worth noting that our guidelines cannot always cover every group, however in this case where relevant data on this patient group was identified it was considered as indirect evidence for reviews, where there is insufficient direct evidence. When we last undertook a surveillance review to see if an update to this guideline was warranted, the possibility of expanding the scope of the guideline to include obstetric patients was raised by a member of the original guideline development group. However, it was concluded that given the complexity of the task and the lack of available direct evidence compared to other issues raised, it was not a priority at this time".

Following a search of the NICE Evidence Services I could not find any additional or relevant guidelines pertaining to pregnant women developed by other organisations. A database search of the literature (PubMed, CINAHL, Embase), including a google search for additional national/international guidelines in this area was also futile, with only local hospital guidelines/protocols been identified. This dearth of evidence suggests that each hospital has its own method of dealing with this issue, based on individual hospitals policy rather than evidence based practice.

2.7 Conclusion

This chapter's key outcome is to outline the physiology behind thermoregulation, thermogenesis and heat loss as well as the evidence on neonatal hypothermia and maternal inadvertent perioperative hypothermia and how it can be prevented/managed. This literature review suggests that although SSC is a beneficial practice after vaginal birth, it is still not well established during CS due to a number of obstacles within the theatre departments. At the same time, this chapter suggests a trend in promoting SSC during CS, particularly as the global rates of CS are increasing and more women show their interest in having SSC during their operation. The review also suggests that women and newborns are prone to becoming hypothermic during their operation if no preventative methods are offered by theatre staff. This subsequently increases mother and newborn morbidity as well as causing separation of mother and newborn in order to treat the persons affected by the hypothermia. Hypothermia is a preventable adverse

event, commonly associated with CS and neuraxial anaesthesia and can cause harm to both mothers and newborns. It was evident from this chapter that in order for SSC to be safely promoted during CS, maternal and neonatal hypothermia needs to be prevented which in turn would reduce the occurrence of maternal/newborn separation. Prevention of maternal hypothermia could be managed with the use of perioperative active warming methods. By keeping the mothers warm and placing a newborn for SSC on a warm mother, we could potentially reduce the risk of neonatal heat loss via conduction and therefore reduce also the occurrence of perioperative neonatal hypothermia during SSC.

The review identified that there is insufficient research to show the perioperative maternal hypothermia effect on neonatal hypothermia during/after SSC at birth in women undergoing CS. There are also insufficient studies investigating different methods of active warming to support which method of active warming is better, safer and most cost-effective, to prevent neonatal and maternal hypothermia during CS, without interrupting at birth SSC. Additionally, current international guidelines on prevention of IPH focus on the general surgical population, while pregnant women and newborns have been excluded from these guidelines due to lack of evidence on the safety and efficiency of perioperative active warming in this specific population. An up to date SR and meta-analysis of RCTs comparing the effect of various maternal perioperative active warming methods versus no warming on the occurrence of neonatal hypothermia, while at birth SSC is performed, is warranted in order to address this gap in the evidence. The SR strategy and the findings of its meta-analysis are explored in chapter three.

Chapter 3: Perioperative active warming versus no active warming of women performing at birth skin-to-skin contact during/after caesarean section, at term, for preventing neonatal hypothermia: a systematic review.

3.1 Introduction

This chapter focuses on a systematic review (SR), investigating the randomised controlled trial (RCT) evidence on the effect of perioperative maternal active warming versus no warming on the frequency of neonatal hypothermia for newborns who have at birth SSC during CS. This SR was undertaken from 2016 to 2019 and was guided by a predetermined protocol registered in Prospero (registration number CRD42016039003); the conduct of the review was guided by the Cochrane Handbook on Systemic Reviews (Higgins *et al* 2011). This SR offers an insight as to the evidence that exists on this specific topic; if maternal active warming during CS is effective in preventing neonatal hypothermia during SSC; if a particular perioperative maternal active warming method is most effective, compared to others, and if active warming is safe for both mothers and newborns. Furthermore, findings of this SR add to the evidence that will inform national and international guidelines. The findings of this SR guided the direction and focus of my study.

3.2 Review Objectives

This SR of the worldwide evidence aims to assess the effectiveness of perioperative active warming, using any recognised warming mechanism (for example;. forced air warming blanket, warmed IV fluids or warmed underbody pad) versus no active warming of women performing at birth SSC, during/after elective CS at term (from 37 completed weeks) on maternal and neonatal outcomes.

3.3 Review Methods

3.3.1 Criteria for considering studies for this review

Type of studies: Randomised controlled trials (RCTs), including cluster trials and controlled clinical trials (CCTs), published in any language were considered for inclusion in the review. All other study designs were excluded.

Type of participants:

Inclusion criteria: Women who received an intervention to prevent or minimise perioperative heat loss, and their babies who experienced SSC during their elective caesarean section at or after term gestation. To be eligible for inclusion, studies must have performed at birth SSC, as defined by WHO (1997), during or after the elective caesarean section. Mothers should have received regional anaesthesia (spinal,

combined spinal epidural) prior to their elective caesarean section because mothers will be awake and therefore able to hold their baby during SSC.

Exclusion criteria: Participants, who were greater than 42 weeks gestation, undergoing any type of operation or surgical procedure other than an elective (planned) CS, including emergency CS, and who had a multiple pregnancy (twins or more), were excluded.

Type of interventions: Studies evaluating any form of perioperative active warming intervention versus no active warming of women during CS were included. Active warming interventions may include forced air warming devices, warmed IV fluids, warmed mattresses and warmed coverings, used on their own or in any combination, and applied before, during or after the CS regardless of the duration used. Studies that evaluated interventions in any combination, and applied during the CS regardless of the duration were included only if they extrapolated and reported data specific to each intervention. Non active warming, or standard care, may include the use of unheated blankets or administration of room-temperature IV fluids. For inclusion in the review, all the women and newborn participants of the studies must have performed at birth SSC. Studies were excluded if at birth SSC and perioperative active warming were not performed.

Types of outcome measures:

Primary outcome

1. Neonatal hypothermia during and after SSC (defined as temperature < 36.5^0C, as measured by any method, device or location)
2. Maternal hypothermia during and after SSC (defined as temperature < 36^0C, as measured by any method, device or location)

Secondary outcomes

1. Maternal and neonatal core temperatures, and room temperature before, during and after SSC (measured by any method, device or location);
2. Duration of SSC, including total time of SSC for example, from the start time to the end;
3. Timing of initiation of first feed, including type of feed and, if breastfeed, length of feed;
4. Neonatal jitteriness (yes/no);
5. Neonatal blood sugar level two hours after birth;

6. Maternal satisfaction (as measured by trial authors);
7. Umbilical cord blood analysis (arterial and venous cord pH);
8. Apgar Scores at 1 and 5 minutes;

Core temperature is defined as the temperature of internal organs (for example heart, liver) (Miller-Keane 2003), which is the most common temperature measured in the clinical setting via different locations (for example rectal, axillar, oral). Peripheral temperature (for example skin temperature) can be an average of 3.3°C lower than the core temperature . For this reason, data on participants' core temperature measurements only, were extracted for this review.

3.4 Search methods for identification of studies

3.4.1 Electronic searches

In March 2016, a search of CENTRAL, Prospero and PubMed revealed that no similar SR was conducted, planned or in progress. Following the primary search, an SR protocol was developed and as previously discussed registered with PROSPERO. Following assistance from a subject Librarian in developing search terms, a search was undertaken to identify eligible RCTs and CCTs. The electronic bibliographic databases searched were: EMBASE, Scopus, Web of Science, CINAHL, PubMed and Maternity and Infant Care. Trials registries for example ISRCTN registry https://www.isrctn.com/ and https://clinicaltrials.gov/ and open grey literature database in Europe (http://www.opengrey.eu/search) were also searched. A second, third and fourth search was performed in December 2017, March 2018 and March 2019, using the same databases and following the same search terms (Appendix 3.1). Finally, a search was performed of the reference lists of retrieved papers to identify potentially eligible studies that were not retrieved through the electronic database searches.

3.5 Data collection and analysis

3.5.1 Selection of studies

Citations retrieved were managed in EndNote reference manager (version X7). Duplicate citations from across the different databases were removed. The remaining citations were uploaded to Covidence© (Covidence, 2019) and independently screened, initially by title and abstract, by two review authors (AVR and MMC). Potentially eligible studies were forwarded for full text review. Full text review was also independently performed by the same pair of reviewers. Reasons for excluding studies following full text review were documented for each study (Appendix 3.2). Any disagreements were resolved by discussion or involving a third assessor (MB). The selection process was

recorded in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 3.1).

3.5.2 Data extraction

A data extraction form (Appendix 3.3) was designed primarily based on the review's primary and secondary outcomes. Two reviewers independently extracted the data (AVR and MMC). It was planned in advance that articles published in any other language than English would be translated before the data extraction. Any additional information needed for the review was obtained by contacting the correspondent author of each article via e-mail. Any disagreements were resolved by discussion or involving a third assessor (MB). It was planned to collate multiple reports of the same study so that each study would be the unit of interest in the review rather than each report.

3.5.3 Assessment of risk of bias in included studies

Two reviewers (AVR, MMC) independently assessed the quality of included studies using the Cochrane Risk of Bias (ROB) assessment tool (Higgins *et al* 2011). Any disagreements were resolved by a third reviewer (MB).

The ROB criteria (appendix 3.4) used to assess included studies were: selection bias (randomisation and allocation process), blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias) and other sources of bias (bias due to other problems not covered above). Judgements were made (for example high, low or unclear risk of bias) for each of the seven criteria, followed by an overall risk of bias judgement for each included study. Specifically, the ROB criteria used to assess included studies were:

1) Random sequence generation (selection bias)

The method used to randomly allocate participants to their groups was described to allow for assessment as to whether or not sequence generation was sufficiently performed to produce comparable groups. Methods were assessed as low risk of bias where true random allocation was used (e.g. computer random number generator); high risk of bias when non-random allocation was used (e.g. allocation by date of birth or days of week) and unclear risk of bias when there was insufficient information provided in the study report to make a clear judgement.

2) Allocation concealment (selection bias)

The method used to randomly allocate participants to their groups, was described to allow for assessment as to whether or not allocation concealment was sufficiently

performed. Methods were assessed as low risk of bias where adequate concealment was used (e.g. sequentially numbered opaque sealed envelopes); high risk of bias when inadequate concealment was used (e.g. non-sequentially numbered envelopes) and unclear risk of bias when there was insufficient information provided in the study report to make a clear judgement.

3) Blinding of participants and personnel (performance bias)

Blinding of staff or participants to the type of intervention being studied was not possible. However, methods were assessed as low risk of bias (e.g. no blinding or incomplete blinding but the authors judge that the outcome was not influenced by the lack of blinding); high risk of bias (e.g. no blinding or incomplete blinding and the outcome was influenced by the lack of blinding) and unclear risk of bias when the authors did not address this outcome.

4) Blinding of outcome assessment (detection bias)

Methods used to blind outcome assessors from knowing which intervention was given to each participant were assessed in details, including the possibility of bias when blinding was not possible. Methods were assessed as low risk of bias (e.g. no blinding of outcome assessment but the authors judge that the outcome was not influenced by the lack of blinding), high risk of bias (e.g. no blinding of outcome assessment and the outcome was influenced by the lack of blinding) and unclear risk of bias (e.g. the authors did not address this outcome).

5) Incomplete outcome data (attrition bias)

Whether attrition or exclusions, and their reasons, were reported, the numbers included in the analysis at each stage and whether missing data were balanced across groups or were related to outcomes were also assessed. Methods were assessed as low risk of bias (e.g. missing outcome data were balanced across groups), high risk of bias (e.g. where attrition or exclusions was high) and unclear risk of bias (e.g. insufficient reporting of attrition and exclusions to allow judgement of “low” or “high” risk).

6) Selective reporting (reporting bias)

Whether outcomes of interest were reported or not in the included study was assessed. Methods were assessed as low risk of bias (e.g. protocol is available or not available, but all pre-specified outcomes were reported), high risk of bias (e.g. one or more pre-specified outcomes were not reported) and unclear risk of bias (e.g. insufficient information to allow judgement of “low” or “high” risk).

7) Other sources of bias (bias due to other problems not covered above)

Any concerns about other possible sources of bias, for example, any baseline imbalances between groups included in the trials, were also assessed and described. Methods were assessed as low risk of bias (e.g. the study appears to be free of other sources of bias), high risk of bias (e.g. potential source of bias due to study design used) and unclear risk of bias (e.g. insufficient evidence to identify a problem that would cause bias).

Finally, to enhance methodological rigour, the results of the ROB assessment from both reviewers were reviewed by a third assessor (MB).

3.5.4 Measures of treatment effect

For continuous outcomes, for example, temperature and birth weight, the mean values and standard deviations, for each group, were extracted and standardised mean differences (SMD) with 95% confidence interval (CI), as measures of treatment effect, were calculated as studies used different outcome measurement scales. For binary outcome measures, for example, neonatal hypothermia, relative risks (RR) with 95% CIs as estimates of treatment effects across included trials were calculated. Where it was not feasible to undertake a meta-analysis of review outcomes, we provided a narrative analysis

3.5.5 Dealing with missing data

The corresponding author from one of the included studies (Horn *et al* 2014) was contacted with a request for information about missing data from their publication but there was no reply to the email. However, although not all of the data on the trial's pre-specified outcomes were presented in the study report, data on outcomes that were measured in the trial and pre-specified for this review, were available. These outcome data were extracted and analysed as presented in the authors' study report.

3.5.6 Assessment of heterogeneity

Heterogeneity refers to any kind of variation across the included studies and can be divided into clinical and statistical heterogeneity (Daly *et al* 1991). Clinical heterogeneity is associated with differences among the participants, interventions or outcomes of the studies while statistical heterogeneity is associated with differences on how the studies were conducted (Ryan & Hill 2016). Clinical and statistical heterogeneity across included studies was assessed using RevMan software and the I^2 test and Chi^2 test, as recommended by Higgins and Green (2007). According to the Cochrane handbook, a guide to interpret heterogeneity among studies is;

- 0% to 40%: might not be important;

- 30% to 60%: moderate heterogeneity;
- 50% to 90%: substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

3.5.7 Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality on the results of the review. However, since there were only three studies included, all of them having unclear and/or high risk of bias, no sensitivity analysis was conducted. In any future version of this systematic review and if further studies are included, sensitivity analysis will be considered. Studies judged as high risk of bias on concealment of allocation, high attrition rates, or both, would have been analysed separately from studies judged as having low risk of bias, so as to assess whether this would make any difference to the overall result.

3.5.8 Data synthesis

Data was entered into RevMan software (RevMan 2012) and the random-effects model was used to pool the data. The reason for using the random-effects model rather the fixed effect model is to allow for the possibility that the true effect would vary between the included studies rather than assuming that there is only one true effect size between the included studies (Borenstein *et al* 2007). One of the studies (Paris *et al* 2014) had three comparison arms, two intervention arms and one control arm. In the review, the two intervention arms were merged together for the main synthesis, using the statistical formula provided by the Cochrane Handbook on Systematic Reviews (Higgins *et al* 2011) for combining the means and standard deviations (SD) from two different groups (chapter 7.7.3.8, table 7.7).

3.5.9 Subgroup analysis

In this systematic review, we conducted a subgroup analysis comparing a subset of two of the included studies (Paris *et al* 2014; Vilinsky *et a*l 2016) based on the Cochrane guidelines (Higgins *et al* 2011). As the three included studies used different methods of active warming, it was beneficial to conduct a subgroup analysis comparing the only active warming method that was common in two of the studies. In the subgroup analysis, the warm IV fluid intervention was compared with the control group (no warming) in the two studies that used this method of active warming (Paris *et al* 2014; Vilinsky *et al* 2016).

3.5.10 Assessment of the quality of the evidence using the GRADE approach

We used the GRADEpro software (Grades of Recommendation, Assessment, Development and Evaluation Working Group) to assess the quality of evidence arising from the included studies that contributed to the meta-analysis of the specified outcomes

and prepared a summary of findings table for review outcomes. This assessment was based on five criteria; risk of bias (ROB), inconsistency, indirectness, imprecision and publication bias, to assess the quality of the body of evidence for each outcome. The evidence could be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments of these five criteria. Any disagreements were resolved by discussing or involving MB. This review assessed the quality of evidence relating to the following outcomes.

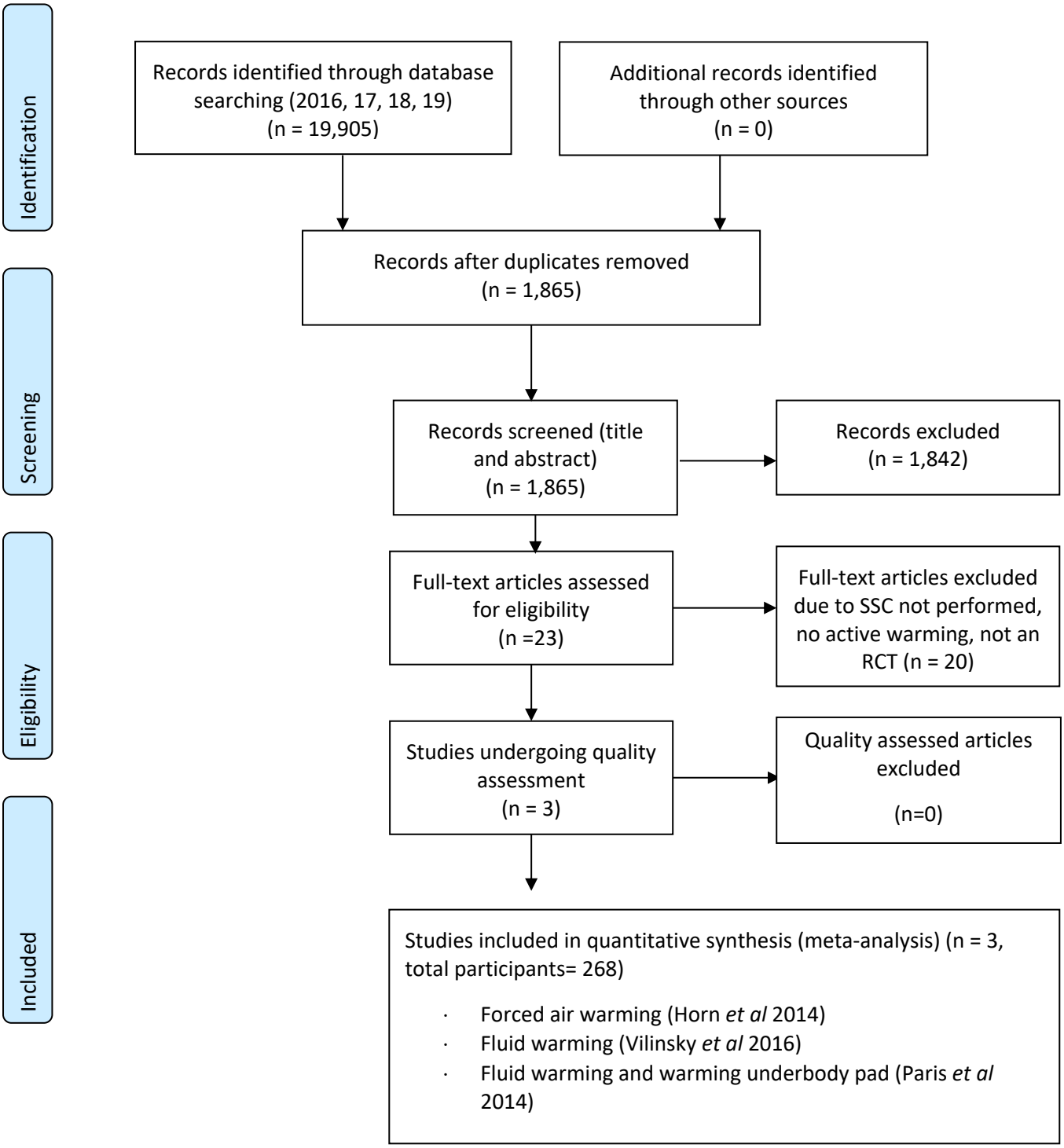
- Neonatal hypothermia in OT.
- Maternal hypothermia in OT.
- Neonatal temperature at the end of SSC in OT (assessed with: axillar thermometer; Scale from: 35.5°C to 38°C).
- Maternal temperature before SSC (assessed with: tympanic thermometer; Scale from: 35.5°C to 38.5°C).
- Maternal temperature during SSC (assessed with: tympanic thermometer; Scale from: 35.5°C to 38.5°C).
- Maternal temperature after SSC (assessed with: tympanic thermometer; Scale from: 35.5°C to 38.5°C).
- Maternal hypothermia in PACU.

3.6 Results

3.6.1 Results of the search

The search of the predetermined databases revealed a total of 19,905 records out of which 18,040 were duplicates. Of the remaining 1,865 records, 1,842 were excluded at title and abstract screening level as they were clearly not relevant to the review. Of the 23 papers that were assessed at full text level, three met the inclusion criteria. Figure 3.1 presents a flow diagram of the results of the search and selection strategy.

Figure 3.1: Flow diagram of the total results of the search and selection strategy



3.6.2 Description of included studies

Three RCTs (total participants 268) met the inclusion criteria (Horn *et al* 2014; Paris *et al* 2014; Vilinsky *et al* 2016). Horn *et al* (2014) study, undertaken in Germany, recruited 40 participants. The intervention group (n = 19) received an active forced-air warmed cover, set at 44°C, while the control group (n = 21) received passive insulation (no active warming). Paris *et al* (2014) was a three armed RCT, conducted in the US and included 226 participants. The first group (n=77) received an underbody pad treatment, set at 40.3°C, the second group (n=73) received warm IV fluids, set at 41°C and the control group (n=76) received no active warming. Finally, Vilinsky *et al* (2016) was a pilot RCT study, conducted in Ireland with 20 participants. The intervention group (n=10) received warm IV fluids, set at 39°C, while the control group (n=10) received room temperature fluids. The characteristics of the included studies are summarised in table 3.1.

3.6.3 Description of excluded studies

Of the 22 remaining studies that were evaluated at full text level, six were excluded as the intervention was different to that been evaluated in this review, (Huang *et al* 2006, Nolan & Lawrence 2009, Gouchon *et al* 2010, Keshavarz *et al* 2010, Chung e*t al* 2012, Beiranvand *et al* 2014). Eleven studies were excluded as no at birth SSC was performed (Horn *et al* 2002, Fallis *et al* 2006, Butwick *et al* 2007, Woolnough *et al* 2009, Yokoyama *et al* 2009, Goyal *et al* 2011, Oshvandi *et al* 2011, Chakladar *et al* 2014, Cobb *et al* 2016, de Bernardis *et al* 2016, Chebbout *et al* 2017). One study was excluded as they used a general adult population instead of pregnant women (Rowley *et al* 2014) and another study (Munday *et al* 2018) was excluded as it used the wrong comparator (Appendix 3.2).

Table 3.1: Summary characteristics of the included studies

Study	**Horn *et al* (2014)**	**Paris *et al* (2014)**	**Vilinsky *et al* (2016)**
Design	Two-group parallel RCT	Three-group RCT	Two-group parallel pilot RCT
Country	Germany	USA	Ireland
Participants	Women, >18 years of age, scheduled for elective CS under spinal anaesthesia at term. All neonates underwent 20mins of SSC commencing 5 minutes after birth when neonatal assessments were complete. N= 40 mother/newborn dyads	Women, with singleton, scheduled for elective CS during the study period. All neonates had SSC but it is unclear when SSC commenced. N= 226 mother/newborn dyads	Women, > 18 years of age, scheduled for elective CS under regional anesthesia at term; neonates had SSC during and after the CS. N = 20 mother/newborn dyads
Interventions	Active warming using an upper body forced-air cover (44°C) during the operation (n=19), including for duration of SSC	Active warming using a warm underbody foam pad (40.3°C) during the CS (n=77); Warmed fluids (41°C) (n=73) during the operation	Warmed IV fluids using hotline to 39°C (n = 10)
Comparisons	Pre-warmed cotton blankets (from a 40°C heating cabinet) (n=21) during the CS, including for duration of SSC	Usual care (no active warming) (n=76)	Room temperature IV fluids (25°C) (n = 10)
Outcomes	Newborn rectal temperature (continuous), newborn mean skin temperature	Maternal core temperature (urethral/oral), maternal	Newborn axillar temperature, maternal tympanic

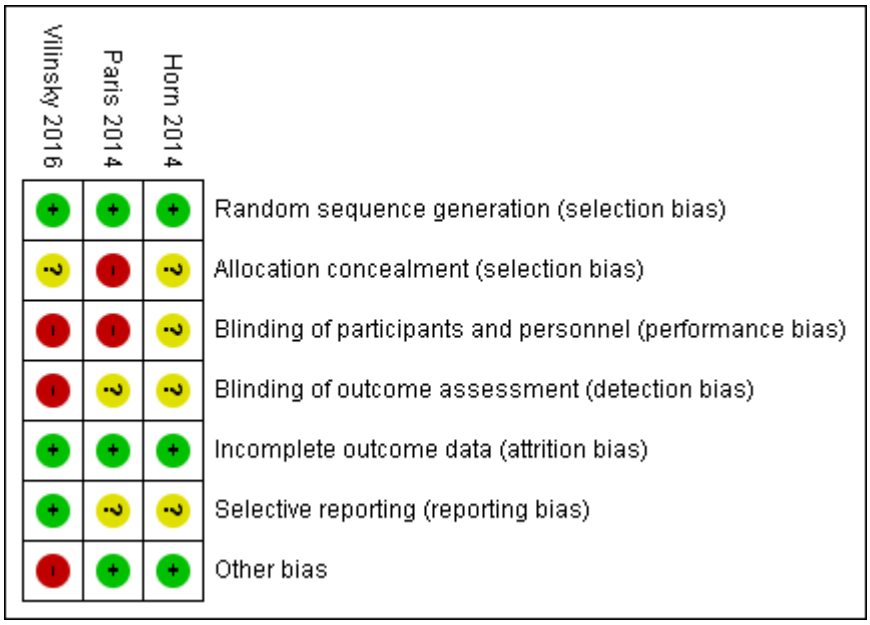
	(5mins after birth and at end of SSC), newborn length and weight, maternal core temperature (sublingual), maternal skin temperature, maternal thermal comfort (100mm VAS; 0mm = thermally neutral, -50mm = worst imaginable cold and +50mm = insufferably hot), peripheral oxygen saturation, maternal heart rate, maternal mean arterial BP, maternal shivering (0 = no shivering, 1 = intermittent, low-intensity shivering, 2 = moderate shivering, 3 = continuous, intense shivering).	hypothermia, maternal thermal comfort, maternal shivering, maternal estimated blood loss, post-operative pain score, observed maternal-neonatal bonding, maternal comfort score, use of rescue blankets, first neonatal temperature, Apgar scores and cord Ph.	temperature, room temperature, duration SSC, newborn weight.
Notes	All women performed 20 minutes of SSC with their baby during the CS. At the end of the CS babies were dressed and handed back to their mothers in the PACU. Outcome measurements stopped at the end of the CS.	All women performed SSC at some point after their baby's birth as per authors email correspondence. No further details were given as to where/when SSC was initiated.	SSC started during the CS and continued until after transfer to the post-natal ward. Maternal and newborn temperatures were measured at different times up to 2 hours post-delivery

3.7 Risk of bias of included studies

Overall, no trial met all criteria for low risk of bias. All three included studies had unclear reporting for one or more domains. Two out of three studies also had high risk of bias for two or more domains. All three trials were best at reporting randomization methods, while the lack of blinding of participants, personnel and outcomes assessors were considered the highest risk of bias across the three included studies.

Risk of bias refers to limitations in the study design of the included studies which would reduce our confidence in the estimate of the treatment effect (Schünemann *et al* 2013). A summary of risk of bias judgements for the three included studies as created in RevMan is provided in table 3.2.

Table 3.2. Risk of bias summary of included studies.



Random sequence generation was judged as low risk of bias in all three included studies as coin tossing allocation (Horn *et al* 2014, Vilinsky *et al* 2016) and computer generated randomisation (Paris *et al* 2014) were employed.. Allocation concealment was judged as unclear in Horn *et al* (2014) and Vilinsky *et al* (2016) studies given the lack of discussion on allocation concealment, while Paris *et al* (2014) was judged as been high risk of bias as the author did not discuss the type of envelope used and who made up the envelopes, something that could potential impact adequate concealment.

Blinding of participants, researchers or outcome assessors were not discussed in Horn *et al* (2014) study so it is unclear what actions the researchers took to reduce the risk of bias related to blinding. In Vilinsky *et al* (2016) and Paris *et al* (2014) studies, although the participants were blinded, the researcher (Vilinsky *et al* 2016) and the study nurses

(Paris *et al 2014)* were involved in recruitment, revealed the assigned treatment, provided primary care and collected data. Therefore, blinding of participants and outcome assessors was judged as high risk of bias. No participants were lost to follow up in any of the included studies, therefore, we judged this criterion as low risk of bias. Additionally, the incomplete outcome data was judged as low risk of bias, for Vilinsky *et al (2016)*, since all pre-specified outcomes were reported, but the studies of Horn *et al* (2014) and Paris *et al* (2014) were judged as unclear risk of bias as both authors did not report all the outcomes. Finally, regarding other risk of bias, we judged this outcome as low risk of bias for Horn *et al* (2014) and Paris *et al (2014)* because we could detect any other source of bias in these studies. However, Vilinsky *et al* (2016) was judged as high risk of bias due to the difference between the room temperatures in the study groups.

3.8 Main Analysis

3.8.1 Primary outcomes

Neonatal hypothermia in the operation theatre

Neonatal hypothermia in the OT was reported by Horn *et al* (2014) and Vilinsky *et al* (2014). The occurrence of neonatal hypothermia was significantly less in neonates of women receiving active warming as compared to those receiving no active warming (2 studies, 60 participants, RR 0.14; 95%CI 0.03 to 0.75; Figure 3.2). I^2 is 28% indicating not important heterogeneity in this analysis.

Maternal hypothermia in the operation theatre

Maternal hypothermia in the OT was reported in all three included studies after the initiation of SSC. The occurrence of maternal hypothermia did not differ between mothers receiving active warming and those receiving no active warming (3 studies, 286 participants, RR 0.35; 95%CI 0.11 to 1.17; Figure 3.2). I^2 is 56% indicating moderate heterogeneity in this analysis.

Maternal hypothermia in the Post Anaesthesia Care Unit (PACU)

Maternal hypothermia in the PACU was reported by Paris *et al* (2014) and Vilinsky *et al* (2016) while SSC was still being performed. The occurrence of maternal hypothermia was not significantly different between mothers receiving active warming and those receiving no active warming (2 studies, 246 participants, RR 0.47; 95%CI 0.09 to 2.40) (Figure 3.2). I^2 is 64% indicating moderate heterogeneity in this analysis.

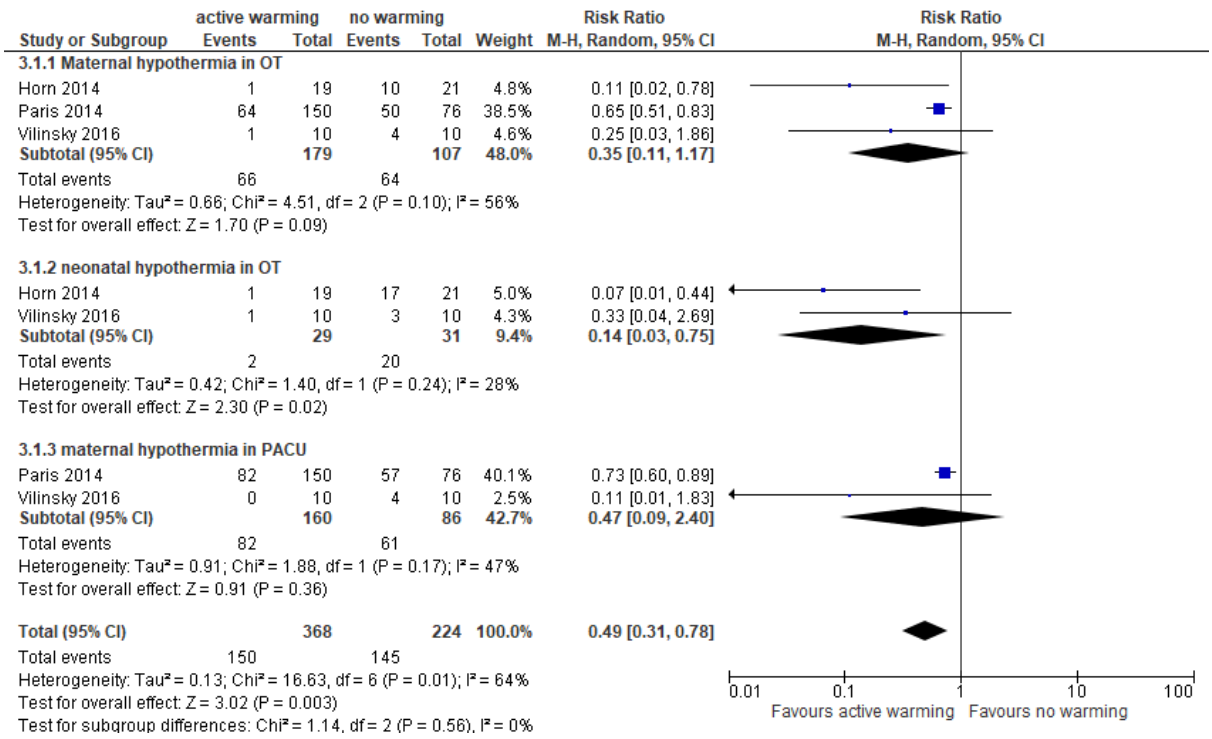


Figure 3.2: Active warming versus no active warming on frequency of hypothermia

3.8.2 Secondary outcomes

Neonatal core temperature before SSC

It was not feasible to undertake a meta-analysis of this outcome due to the lack of data across the three studies. Specifically, Horn *et al* (2014) did not report the mean and SD values for each group. Vilinsky *et al* (2016) did not measure temperatures at that time, while Paris et al. (2014) measured the neonatal birth temperature once only, but it is unclear as to when this was conducted in relation to SSC.

Neonatal core temperature during SSC

Neonatal core temperatures were measured by Horn *et al* (2014); Vilinsky *et al* (2016) in the first five minutes of SSC. However, the data (mean, SD) documented by Horn *et al* (2014) were not identifiable in the article. Vilinsky *et al* (2016) found that the mean neonatal core temperatures was 36.8°C for the intervention group and 36.55°C for the control group, however, no SD were documented; therefore no meta-analysis was conducted for this outcome.

Neonatal core temperature at the end of SSC in OT

At the end of SSC neonatal core temperatures were measured by Horn *et al* (2014) and Vilinsky *et al* (2016). There was no significant difference in the neonatal temperatures at the end of SSC between those receiving active warming and no active warming (2 studies, 60 participants, SMD 1.03; 95%CI -1.58 to 3.64). I^2 is 95% indicating considerable heterogeneity in this analysis (Figure 3.3).

Maternal core temperature before SSC

Maternal core temperature before SSC was measured in all three studies and meta-analysis found no difference in maternal temperature measurements between active warming and no active warming participants (3 studies, 286 participants, SMD -0.01. 95% CI -0.70 to 0.69). I^2 is 77% indicating substantial statistical heterogeneity in this analysis (Figure 3.3).

Maternal core temperature during SSC

All three studies also reported maternal core temperature during SSC. The analysis found significant difference in maternal temperature during SSC, in those receiving active warming versus no active warming interventions (3 studies, 286 participants, SMD 0.75, 95%CI 0.50 to 1.01). I^2 is 0% indicating no statistical heterogeneity (Figure 3.3).

Maternal core temperature after SSC

Pooling of data from the three studies showed no difference between active warming and no active warming in maternal temperatures at the end of SSC (3 studies, 286 participants, SMD 0.64; 95% CI -0.28 to 1.56). I^2 is 85% indicating substantial statistical heterogeneity (Figure 3.3).

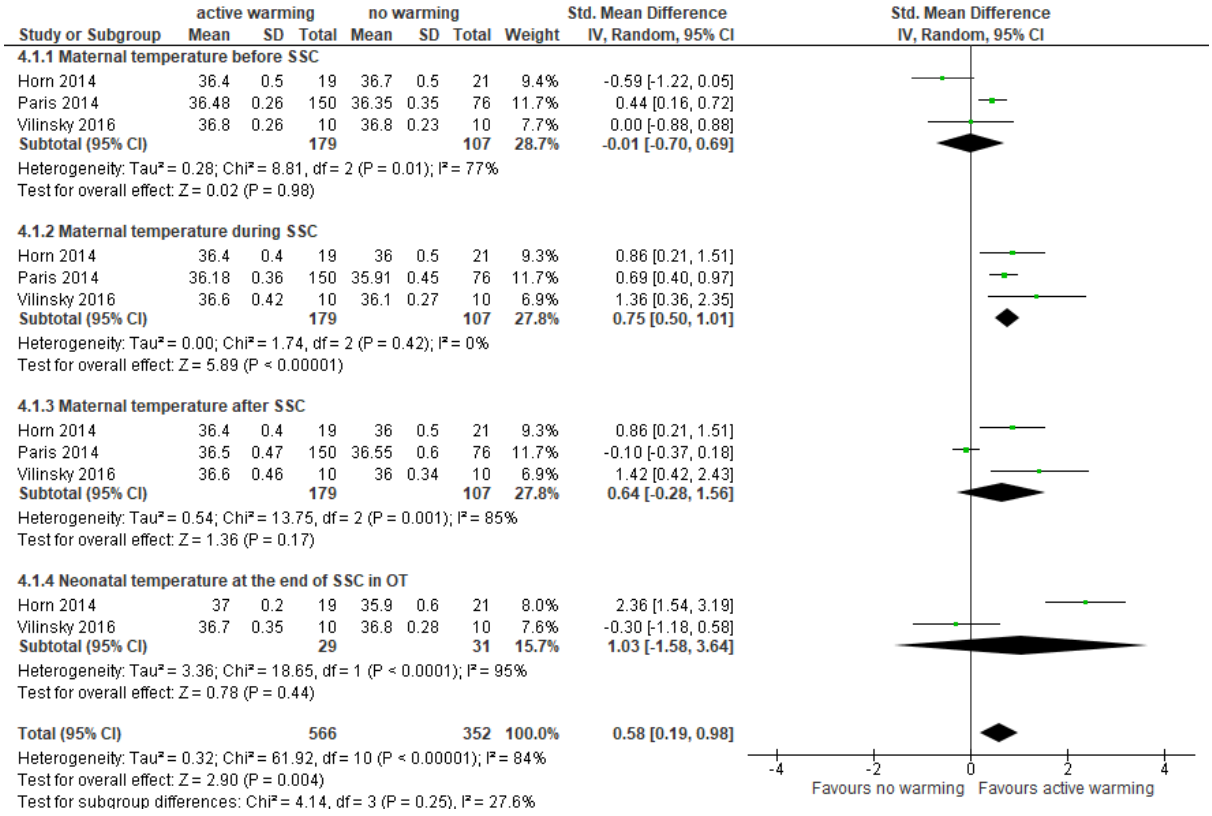


Figure 3.3: Active warming versus no active warming on core temperatures

Room temperature before, during and after SSC

The ambient operating room temperature was reported in all three studies, however, none of the studies reported with precision the time that the temperature was measured, therefore pooling of data was not appropriate.

Duration of skin-to-skin contact including total time of SSC

Horn *et al* (2014) reported that each newborn received a total of 20 minutes SSC in both groups, without reporting any SD. Vilinsky *et al* (2016) reported an average of 81.3 minutes of SSC in the intervention group and an average of 82 minutes of SSC for the newborns in the control group without reporting any SD. In correspondence with Paris *et al* (2014), she mentioned that SSC was performed in all the participants but the duration of SSC was not documented in her article or her correspondence. Due to missing data no meta-analysis was performed.

Other secondary outcomes

Umbilical cord blood analysis was only measured by Paris *et al* (2014); findings suggest that arterial pH were 7.32 (SD=0.8) for the control group, 7.33 (SD=0.7) for the warm IV fluid group and 7.31 (SD=0.6) for the warmed underbody pad group. Similarly, the venous pH were 7.37 (SD=0.6) for the control group, 7.39 (SD=0.5) for the warm IV fluid group and 7.37 (SD=0.6) for the warmed underbody pad group. Apgar scores were reported by Horn *et al* (2014) and Paris *et al* (2014). Horn *et al* (2014) reported a mean Apgar score of nine in the first minutes and ten in the fifth minute. In contrast, Paris *et al* (2014) reported the lowest first minute and fifth minute Apgar scores. The low first minute Apgar score was 8 (SD=10.5), 2 (SD=2.7) and 4 (SD=5.2) for the control, warm IV fluid and warmed underbody pad groups, respectively. The low five minute Apgar score was 1 (SD=1.3) for the control group, 0 for the warm IV fluid group and 2 (SD=2.6) for the warmed underbody pad group. Due to the lack of data, no meta-analysis was performed on these outcomes.

3.8.3 Non reported secondary outcomes

The following outcomes were not reported: maternal satisfaction, type/timing and duration of newborn feeding, neonatal jitteriness and neonatal blood sugar level two hours after birth.

3.9 Subgroup analysis

A subgroup analysis was performed, evaluating studies which used warm IV fluids as an intervention versus no active warming (Paris *et al* 2014; Vilinsky *et al* 2016). A meta-analysis found a significant difference in maternal hypothermia in OT between warm IV fluids and no active warming participants (2 studies, 169 participants, RR 0.57, 95%CI 0.41 to 0.79) (Figure 3.4). I^2 is 0% therefore there was no statistical heterogeneity. However, no difference was found in maternal hypothermia in PACU between participants receiving warm IV fluids and those receiving no active warming (2 studies, 169 participants, RR 0.47, 95%CI 0.08 to 2.77) (Figure 3.4). I^2 is 52% therefore there was a moderate statistical heterogeneity.

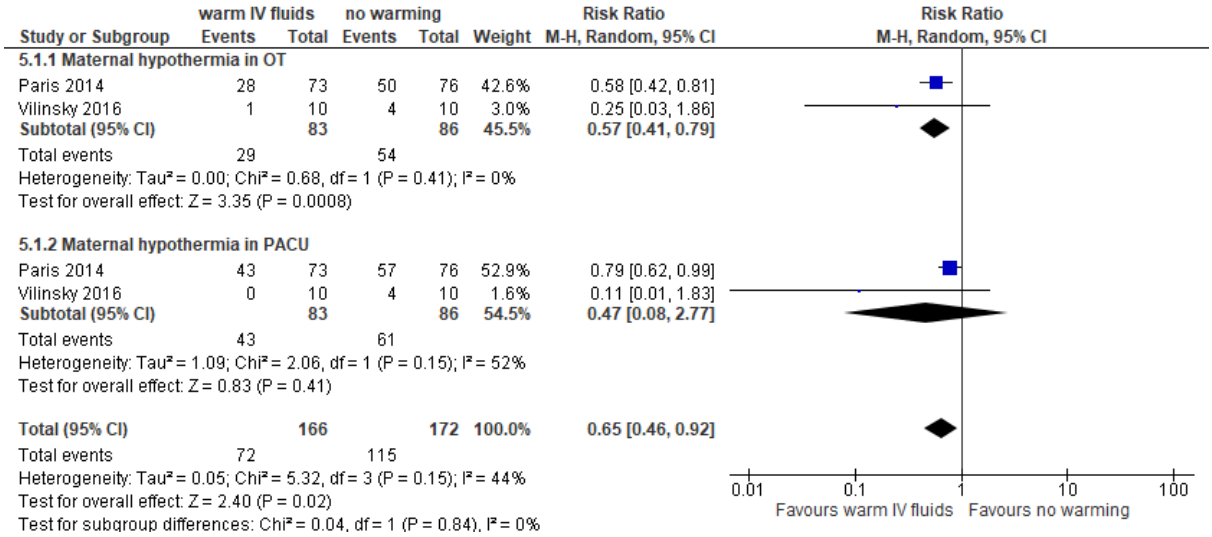


Figure 3.4: Subgroup analysis maternal hypothermia (warm IV fluids only)

There was a significant difference in the maternal core temperature before SSC (2 studies, 169 participants, SMD 0.40, 95%CI 0.10 to 0.71) (I^2 =0%) and during SSC (2 studies, 169 participants, SMD 0.80, 95%CI 0.04 to 1.57) (I^2 =58%) in participants receiving warm IV fluids when compared to those receiving no active warming (Figure 3.5). Maternal core temperature after SSC did not differ between warm IV fluids and no active warming participants (2 studies, 169 participants, SMD 0.57, 95%CI -0.94 to 2.43) (Figure 3.5). I^2 is 88% therefore it represents substantial statistical heterogeneity.

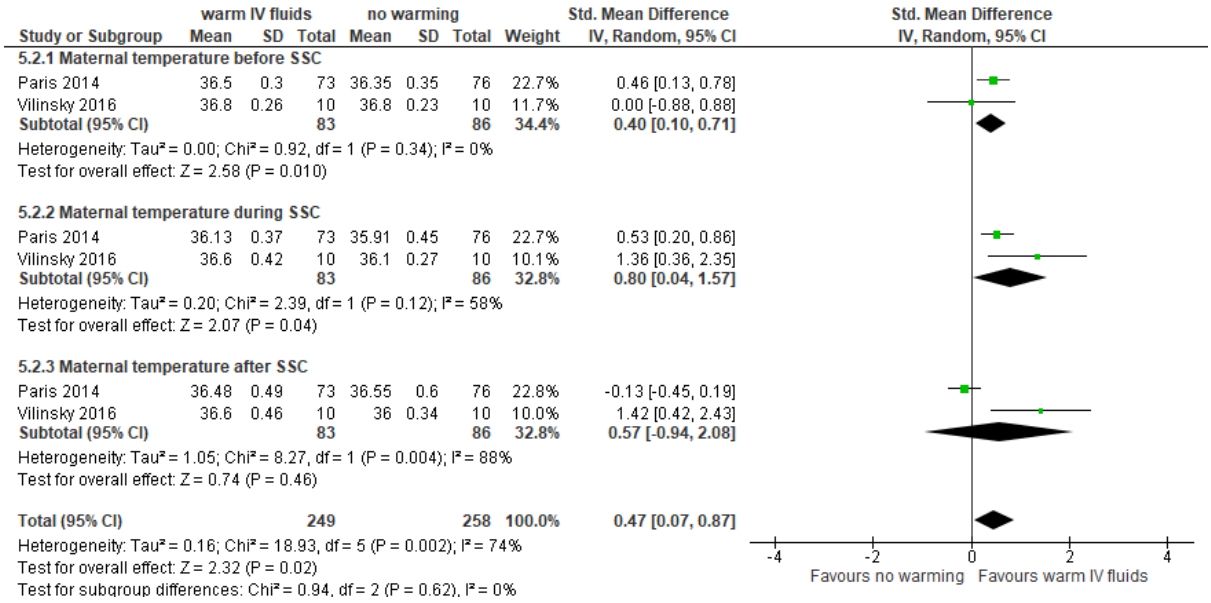


Figure 3.5: Subgroup analysis on maternal core temperatures (warm IV fluids only)

3.10 Discussion

The main finding of this review is that maternal perioperative active warming reduced the occurrence of neonatal hypothermia while at birth SSC was performed (2 studies; Horn *et al* 2014; Vilinsky *et al* 2016; 60 participants; RR 0.14; 95%CI 0.03 to 0.75; P=0.02). This finding suggests that the risk of neonatal hypothermia during elective CS and while at birth SSC is performed is 14% times higher in newborns whose mothers do not receive perioperative active warming than those whose mothers received active warming. This is the first SR investigating the effect of perioperative maternal active warming on neonatal hypothermia while at birth SSC was performed.

Maternal hypothermia during SSC (in OT), was reported in all three included studies with no differences found between mothers receiving active warming and those receiving no active warming (Horn *et al* 2014; Paris *et al* 2014; Vilinsky *et al* 2016; 286 participants). Furthermore, maternal hypothermia after SSC (in PACU), was not significantly different between mothers receiving active warming and those receiving no active warming (2 studies; Paris *et al* 2014; Vilinsky *et al* 2016; 246 participants). This lack of differences between the two groups may be due to the use of additional active warming methods offered in hypothermic mothers during their stay in PACU in both studies.

Neonatal core temperatures at the end of SSC in OT were not significantly different between those receiving active warming and no active warming (2 studies; Horn *et al* 2014; Vilinsky *et al* 2016; 60 participants). Similarly, maternal core temperature before SSC did not differ between active warming and no active warming participants (3 studies; Horn *et al* 2014; Paris *et al* 2014; Vilinsky *et al* 2016; 286 participants). However, the

meta-analysis found significant difference in maternal temperature during SSC, in those receiving active warming versus no active warming interventions (3 studies; Horn *et al* 2014; Paris *et al* 2014; Vilinsky *et al* 2016; 286 participants). Finally, pooling of data from the three studies showed no difference between active warming and no active warming in maternal temperatures at the end of SSC (3 studies; Horn *et al* 2014; Paris *et al* 2014; Vilinsky *et al* 2016; 286 participants).

None of the studies reported the following outcomes: room temperature during and after SSC; duration of SSC; timing of initiation of first feed, including type of feed and length of feed; neonatal jitteriness; neonatal blood sugar level two hours after birth; maternal satisfaction.

A subgroup analysis comparing warm IV fluids as an intervention versus no active warming (Paris *et al* 2014; Vilinsky *et al* 2016) found significant differences in maternal hypothermia and core temperature during SSC in OT between participants recieving warm IV fluids and participants with no active warming (2 studies; Paris *et al* 2014; Vilinsky *et al* 2016; 169 participants). No difference was found in maternal hypothermia and core temperature after SSC in PACU between participants receiving warm IV fluids intervention and those receiving no active warming (2 studies; Paris *et al* 2014; Vilinsky *et al* 2016; 169 participants). This could be clinically interpreted due to the use of additional active warming methods offered to hypothermic mothers during their stay in PACU in both studies.

To conclude, the subgroup analysis suggests that perioperative administration of warm IV fluids in women undergoing elective CS and performing at birth SSC has the potential to decrease the risk of maternal perioperative hypothermia in this group of women compared to those receiving no active warming. Further studies comparing warm IV fluids versus no active warming are needed given the limited number of outcomes explored including the impact on neonatal hypothermia. Furthermore further studies are needed comparing air warming versus fluid warming and a combination of air warming and fluid warming versus other warming methods, to determine which method would offer the best thermal protection of women undergoing elective CS and performing at birth SSC.

3.10.1 Overall completeness and applicability of evidence

The review findings suggest that maternal active warming during elective CS is more effective when compared with no active maternal warming for reducing the frequency of neonatal hypothermia during SSC. The same effect was seen in relation to maintaining maternal core temperature within normal levels during SSC, however, these effects were

not evident after SSC. A possible explanation for this is the methodological differences between the three studies. Specifically, maternal temperatures at the end of SSC were recorded at different time frames in the three included studies, for example in Horn *et al* (2014) the maternal core temperature at the end of SSC was measured 20 minutes after initiation SSC in OT. In Vilinsky *et al* (2016) maternal core temperature at the end of SSC was measured before the PACU discharge, approximately within one hour following the end of the operation while in Paris *et al* (2014) maternal core temperature at the end of SSC was measured two hours after the CS. It is unclear, in all three studies, if the maternal temperature measurements at the end of SSC were performed after the discontinuation of SSC or while SSC was still performed. If the maternal temperature measurements at the end of SSC were performed after the discontinuation of SSC, this may suggest that the measurements were not actually linked to SSC but rather the location of the mother. Additionally, in Horn *et al* (2014) and Vilinsky *et al* (2016) maternal active warming was performed during CS and discontinued at the end of the operation, while in Paris *et al* (2014) active warming was provided up to two hours after the operation. Furthermore, Horn *et al* (2014) did not provide any information during participants stay in PACU, while Vilinsky *et al* (2016) and Paris *et al* (2014) continued SSC and further maternal/neonatal measurements were obtained during the stay in PACU. Moreover, Vilinsky *et al* (2016) provided additional active warming to mothers who were hypothermic in PACU something that would impact on the maternal core temperature measurements in PACU.

Only two studies compared the administration of perioperative warm IV fluids to room temperature fluids (Paris *et al* 2014; Vilinsky *et al* 2016). Paris *et al* (2014), measured neonatal temperatures only once, immediately after birth, before initiating SSC and no further neonatal temperatures were recorded in their study, especially during/after the conduct of SSC and following the end of the intervention. This suggests that my pilot study (Vilinsky *et al* 2016) was the only identified study comparing the administration of perioperative warm IV fluids to room temperature fluids and measuring the intervention effect on neonatal temperatures/hypothermia while at birth SSC was performed not only during CS but also during maternal/newborn stay in PACU.

It is important to note that, through the literature search, many studies were identified which measured maternal hypothermia during CS, but few studies measured neonatal hypothermia and conducted SSC. From these few studies only the three included studies measured neonatal hypothermia as an outcome, while only two studies (Horn *et al* 2014; Vilinsky *et al* 2014) had neonatal hypothermia during at birth SSC as their primary concern. Additionally, only these two studies measured neonatal temperatures while at

birth SSC was performed in more than one occasions, while Paris *et al* (2014) measured neonatal temperatures only once and that was before SSC was initiated. The small number of studies investigating the frequency of neonatal hypothermia during CS while at birth SSC is performed suggest that additional research is required for definitive confirmation of the true effects of perioperative maternal active warming on neonatal temperatures while at birth SSC is performed including the use warmed IV fluids. Another issue related to perioperative maternal active warming is the cost-effectiveness of the intervention. None of the included studies addressed the costs to delivering their interventions versus the costs of managing maternal and neonatal hypothermia when no maternal perioperative active warming is provided. Due to the lack of evidence, it is not possible to support or oppose the treatment effect of perioperative maternal active warming and/or its economic benefits for the theatre departments/hospitals.

3.10.2 Quality of evidence

As previously discussed GRADEpro software (Grades of Recommendation, Assessment, Development and Evaluation Working Group) was used to assess the quality of evidence arising from the included studies. This assessment was based on five criteria; risk of bias, inconsistency, indirectness, imprecision and publication bias (table 3.3 and appendix 3.5).

The assessor's judgement for risk of bias was considered as very serious, which, as a result, led to downgrading by one point, due to the fact that all three studies suffered from major limitations which would result in a biased assessment of the intervention effect (Schünemann *et al* 2013).

Inconsistency refers to a detected heterogeneity of the study results which cannot be explained by the assessors. Heterogeneity (I^2) rising from the statistical analysis with RevMan software suggested the existence of substantial heterogeneity which the assessors could not explain from the analysis of the articles. Due to the substantial heterogeneity in all of the reported outcomes, the assessors' judgement was considered as very serious and the results were downgraded by one point for inconsistency. Indirectness is associated with how well the results of the included trials apply to the review question and is divided into two types: the indirect population/intervention/comparator/outcome and the indirect comparison (Ryan & Hill 2016). The first type refers to included studies which were limited to particular participants/interventions - the comparators were not very applicable and/or the study outcomes were not the best way of measuring the effects of the intervention. The second type of indirectness refers to applicability (or not) of a direct comparison between the interventions. Evidence based on an indirect comparison of the interventions is usually

a sign of a lower quality of evidence (Ryan & Hill 2016). Based on the above terms, the included studies do not appear to be indirect to the review question, therefore, no downgrading took place.

Imprecision refers to studies which include few participants or where there is a significant variation among the participants, something that can be seen in wide confidence intervals (CI) around the effect estimate (Ryan & Hill 2016). The two elements reviewed when assessing for imprecision are: a) the sample size to be of sufficient size to detect a precise estimate of the effect and b) the CI to be able to estimate a meaningful effect or no effect at all. Following the Cochrane handbook guidance (Higgins *et al* 2011) in grading imprecision in a review, the evidence were downgraded by one point (some imprecision exists) as the combined sample size was less than 400 participants.

Publication bias refers to the availability of the data of the included studies and/or to the presence of selective publication of the studies (Ryan & Hill 2016). A common reason to downgrade a review is due to an un-representable sample of studies, for example studies that were not officially reported due to their findings (Ryan & Hill 2016). Additionally, reviews that include only small sample size studies may be prone to publication bias, however that is not always the case since the small sample studies may reflect a risk of bias or imprecision rather than publication bias (Ryan & Hill 2016). In this review, although all three studies have a small sample size, they were all published in peer reviewed journals and were not considered to have publication bias, therefore no downgrading took place for this criterion.

The selected studies were downgraded by one level for the outcome of neonatal hypothermia in OT, based on their very serious risk of bias inconsistency and imprecision, while indirectness and publication bias were assessed as not serious, leading to a final GRADE score of “very low” quality of evidence. The GRADE assessment of the maternal hypothermia in OT outcome was scored as very serious risk of bias, serious inconsistency and imprecision, while indirectness was found not serious, leading to a final GRADE score of “very low” quality of evidence. The same applied to the outcomes of: maternal temperature before and after SSC. Additionally, the GRADE assessment of the neonatal temperature at the end of SSC in OT outcome was scored as very serious risk of bias, inconsistency and imprecision, while indirectness was found not serious, leading to a final GRADE score of “very low” quality of evidence. The same applied for the outcomes: maternal temperature during SSC and maternal hypothermia in PACU. Overall, these GRADE scores indicate that we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate

of effect (Higgins *et al* 2011).This led us to the conclusion that the quality of studies is insufficient to allow definitive conclusions to be drawn based on these data.

Table 3.3 GRADE quality of evidence

Active warming of pregnant women compared to no warming for preventing neonatal hypothermia during CS, for term babies performing SSC					
Patient or population: preventing neonatal hypothermia during CS, for term babies performing SSC **Intervention**: active warming of pregnant women **Comparison**: no warming					
Outcomes	**№ of participants (studies) Follow-up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with no warming	**Risk difference with active warming of pregnant women**
neonatal hypothermia in OT	60 (2 RCTs)	⊕◯◯◯ VERY LOW [a,b]	**RR 0.14** (0.03 to 0.75)	**Low**	
				30 per 100 [c]	**26 fewer per 100** (29 fewer to 8 fewer)
				High	
				81 per 100 [c]	**70 fewer per 100** (79 fewer to 20 fewer)
maternal hypothermia in OT	286 (3 RCTs)	⊕◯◯◯ VERY LOW [b,d,e]	**RR 0.35** (0.11 to 1.17)	**Low**	
				40 per 100 [f]	**26 fewer per 100** (36 fewer to 7 more)
				High	

Active warming of pregnant women compared to no warming for preventing neonatal hypothermia during CS, for term babies performing SSC

Patient or population: preventing neonatal hypothermia during CS, for term babies performing SSC

Intervention: active warming of pregnant women

Comparison: no warming

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no warming	Risk difference with active warming of pregnant women
				66 per 100 [f]	**43 fewer per 100** (59 fewer to 11 more)
neonatal temperature at the end of SSC in OT assessed with: axilar thermometer Scale from: 35.5 to 38	60 (2 RCTs)	⊕◯◯◯ VERY LOW [a,b,g]	-	-	SMD **0 SD** (0 to 0)
maternal temperature before SSC assessed with: tympanic thermometer Scale from: 35.5 to 38.5	286 (3 RCTs)	⊕◯◯◯ VERY LOW [b,d,e]	-	-	SMD **0.01 SD lower** (0.7 higher to 0.69 higher)
maternal temperature during SSC assessed with: tympanic thermometer Scale from: 35.5 to 38.5	286 (3 RCTs)	⊕◯◯◯ VERY LOW [b,d]	-	-	SMD **0.75 SD higher** (0.5 higher to 1.01 higher)

Active warming of pregnant women compared to no warming for preventing neonatal hypothermia during CS, for term babies performing SSC

Patient or population: preventing neonatal hypothermia during CS, for term babies performing SSC

Intervention: active warming of pregnant women

Comparison: no warming

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no warming	Risk difference with active warming of pregnant women
maternal temperature after SSC assessed with: tympanic thermometer Scale from: 35.5 to 38.5	286 (3 RCTs)	⊕◯◯◯ VERY LOW b,d,e	-	-	SMD **0.64 SD higher** (0.28 higher to 1.56 higher)
maternal hypothermia in PACU	246 (2 RCTs)	⊕◯◯◯ VERY LOW b,h	**RR 0.47** (0.09 to 2.40)	**Low**	
				40 per 100 i	**21 fewer per 100** (36 fewer to 56 more)
				High	
				75 per 100 i	**40 fewer per 100** (68 fewer to 105 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

Active warming of pregnant women compared to no warming for preventing neonatal hypothermia during CS, for term babies performing SSC

Patient or population: preventing neonatal hypothermia during CS, for term babies performing SSC

Intervention: active warming of pregnant women

Comparison: no warming

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no warming	Risk difference with active warming of pregnant women

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

3.10.3 Potential biases in the review process

This review was based on a predetermined registered protocol (Prospero registration number: CRD42016039003) and a search strategy that had no language restrictions. The quality assessment of the included studies was robust and based on the Cochrane guidelines and standards. Quality of evidence was determined using the GRADEpro GDT software 2015. In order to minimise the risk of bias in the review, two reviewers conducted each stage of the review independently, and a third reviewer, experienced in conducting systematic reviews, reviewed the systematic review during each stage to ensure that it was conducted rigorously.

The review findings were limited by the variation of different warming interventions, the instruments used for measuring maternal and neonatal temperatures and the body locations used for measurements of the participant's core temperatures. We were not able to explore a number of our secondary outcomes (e.g. maternal satisfaction, on the type, timing and duration of newborn feeding, on neonatal jitteriness and neonatal blood sugar level two hours after birth) as they were not the focus of the included studies. Due to the high risk of bias, the small sample size of the studies and the significant clinical and statistical heterogeneity, we considered the quality of data as very low.

Overall, using the GRADE Working Group grade of evidence there is a very low certainty with regard to the review findings i.e. we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect, therefore the findings of the studies should be interpreted with caution. Overall, evidence from the included studies is of very low quality and insufficient to guide clinicians and nursing/midwifery staff working in operating theatre departments.

3.10.4 Agreements and disagreements with other studies or reviews

Although most of the excluded studies provided maternal active warming interventions, they did not perform SSC and/or did not measure neonatal outcomes. This SR is the first meta-analysis that reviewed neonatal outcomes of RCTs comparing perioperative active warming vs no active warming methods in mothers performing at birth skin-to-skin contact during/after CS. The inclusion criteria required measurements of neonatal outcomes such as neonatal core temperatures and neonatal hypothermia during and after SSC, duration of SSC, type and duration of feeding and neonatal jittering and blood sugars.

In my review of the current literature, I found only two SR which reviewed the effect of maternal active warming during CS. Munday *et al* (2014) SR of 12 RCTs investigated the effectiveness of warming interventions for women undergoing SSC during CS.

Overall, this SR suggested that maternal administration of warm IV fluids during CS was effective at maintaining maternal temperatures within normal levels and preventing maternal shivering. Alternative warming devices such as forced air warming and under-body carbon polymer mattresses were also found to be effective at preventing maternal hypothermia. Additionally, this SR found that preoperative warming devices improved neonatal temperatures at birth, but warm IV fluids during CS did not improve neonatal temperatures, and the effectiveness of any warming intervention on umbilical pH remains unclear. However, this SR reviewed the findings of neonatal temperatures only once (immediately after birth), while no SSC was performed and no additional neonatal temperature measurements were reviewed during the newborn stay in OT and PACU. Additionally, the only other neonatal outcomes reviewed were Apgar Scores and umbilical pH.

A meta-analysis by Sultan *et al* (2015) of 13 RCTs (789 participants) on the effect of maternal warming during CS (not focusing on SSC) on maternal and neonatal outcomes concluded that maternal active warming reduced the frequency of maternal hypothermia, increased the maternal end of surgery temperatures, reduced maternal shivering, improved maternal thermal comfort and increased the umbilical artery pH. This review found no difference in neonatal temperature at birth and Apgar Scores between the intervention and comparator groups. No additional neonatal outcomes were included in this meta-analysis including the impact of SSC on maternal and neonatal outcomes.

Both Munday *et al* (2014) and Sultan *et al* (2015) recommend the use of maternal active warming during CS as an effective way of reducing maternal hypothermia and shivering however it is unclear if the quality of the included studies is sufficient to allow definitive conclusions to be drawn based on these data. Additionally, neither SR reviewed additional neonatal outcomes or investigated the impact of SSC on neonatal or maternal outcomes, which was in the focus of our SR.

Although the current literature suggests that SSC can reduce the occurrence of neonatal temperature drop and maintain neonatal normothermia after vaginal birth (Yokoyama *et al* 2009; Keshavarz *et al* 2010) this is not the case for newborns having SSC after CS (Cobb *et al* 2016). Our review suggests that women performing at birth SSC during CS maybe prone to dropping their core temperature during their operation unless active warming was applied. This may have a direct effect on the occurrence of neonatal hypothermia in OT for the group of women who did not receive an active warming intervention.

Neonatal and maternal hypothermia can cause significant co-morbidities both to newborns and women postoperative (Sultan *et al* 2015; Abdolcader *et al* 2017). In our review, active warming of mothers during their operation, when compared to no warming, was associated with reduced risk of neonatal hypothermia, for women undergoing SSC. Administration of warm IV fluids helped maintaining maternal core temperature within normal levels during SSC in OT, reducing in this way maternal hypothermia in OT compared to no active warming. There was no evidence of harm related to active warming measured in any of the included studies. Additionally, there was no difference in maternal hypothermia in PACU between the groups. Similarly, there was no difference in the neonatal and maternal core temperatures at the end of SSC or after SSC between the two groups.

None of the included studies assessed maternal satisfaction, newborn feeding, neonatal jitteriness and neonatal blood sugar level two hours after birth. How much of the active warming effect on neonatal temperature through SSC alone, compared with no warming, remains unclear due to the dearth of details/findings of the included studies as well as the variety of different active warming techniques, their duration, their temperature settings and the difference in the measurements of core temperatures, both in location of temperature measurement and the device used for the measurement. Unfortunately, due to the small amount of included studies, it was not possible to conduct a subgroup analysis comparing the different active warming methods and/or the difference between locations of temperature measurements (i.e. rectal, axillar, tympanic and skin). Finally, no meta-analysis was feasible on the impact of active warming on maternal/neonatal temperatures when compared with the duration of SSC because the included studies recorded different duration of SSC.

Key issues arising from my review include: insufficient quality of studies; small number of relevant studies; variation in methodological design; and insufficient evidence on the longitudinal measurement of the intervention effect on both maternal and neonatal temperatures. Consequently, there is insufficient high-quality evidence to permit conclusions about the effects of maternal active warming on the frequency of neonatal hypothermia during CS, while at birth SSC is performed, as well as during the PACU stay. This lack of high quality evidence in this field suggest the need to conduct a well-designed large RCT to explore the effect of maternal active warming on the frequency of neonatal hypothermia during elective CS while at birth SSC is performed, so adding to the evidence base.

3.11 Implications

In summary, this meta-analysis of three trials identified a potential relationship between perioperative active warming of women undergoing CS and a reduction of neonatal hypothermia and maintenance of maternal core temperature within normal levels, during SSC. No difference was found between maternal hypothermia in OT/PACU, maternal core temperatures before and after SSC and neonatal temperatures at the end of SSC.

3.11.1 Implications for practice

Perioperative active warming of mothers and newborns who had SSC during CS may be beneficial, but given the quality of the included studies, there is very low certainty with regard to these findings. As a result, there is insufficient evidence to advise healthcare professionals and service providers about the effectiveness of maternal active warming during CS while at birth SSC is performed on the prevention of neonatal hypothermia. Clinicians, managers and policy makers must balance possible potential benefits and harms, and the cost of providing the active warming products involved.

3.11.2 Implications for research

Future high quality trials with larger samples are required and should report maternal and newborn outcomes similar to those reported in this review and also include additional outcomes such as: type and duration of feeding, duration of SSC, maternal thermal comfort, maternal blood loss, length of maternal stay in PACU, additional maternal warming, adverse events and unexpected neonatal admission to the neonatal intensive care unit.

Given the findings from the subgroup analysis, which suggest that warmed IV fluids are more effective than room temperature IV fluids at preventing maternal hypothermia, there is a need for an RCT to investigate warmed IV fluids versus room temperature IV fluids in the prevention of neonatal hypothermia during and after SSC as this particular focus was only investigated by Vilinsky *et al* (2016) pilot study (20 participants).

It is evident that this pilot study had a very small sample size and it was assessed as very low quality which reduces our confidence in its findings. Furthermore, the study of Paris *et al* (2014) while comparing warmed IV fluids versus room temperature IV fluids, as a secondary outcome, only measured the neonatal temperature once and this measurement was obtained before SSC was initiated (to be precise the temperature was measured after birth when the newborn was under the ohio, and after being checked by the paediatricians). No additional neonatal temperature measurement was done in this study. Based on this gap in the evidence, we recommend a high quality RCT with a large sample size to investigate warmed IV fluids compared to room temperature IV fluids for

the prevention of neonatal hypothermia during SSC. Such an RCT would compare maternal administration of warm IV fluids during CS versus maternal administration of room temperature IV fluids:

- while at birth SSC is conducted and continued within PACU;
- to include subgroups (for example: use of additional warming for mothers and newborns, separation of mother/newborn dyads);
- to review potential harms/side effects of the intervention on mothers/newborns and
- to review any correlation between maternal and neonatal temperature while SSC is performed which would provide an explanation for the treatment effect of the intervention.

As other active warming interventions become available, further studies need to be conducted comparing these to currently available active warming products and the use of no active warming products to determine their efficacy and cost effectiveness.

3.12 Conclusion

This SR identified that perioperative active warming over no warming of pregnant women undergoing elective CS while performing at birth SSC, had a significant effect on maintaining neonatal temperatures within normal levels. However, this SR identified the lack of quality evidence to inform decisions about the effectiveness of maternal active warming on neonatal hypothermia during elective CS while at birth SSC is performed. The review recommends an RCT investigating warmed IV fluids compared to room temperature IV fluids for the prevention of neonatal hypothermia during SSC which is the focus of this unique PhD study.

This PhD study aims to add to the evidence base that will contribute to future national and international guidelines on preventing Inadvertent Perioperative Hypothermia during CS and SSC. The use of “real life research” is recommended by policy-makers and researchers when comparing clinical interventions preventing adverse events, and therefore, this PhD study will focus on the comparison of a particular active warming intervention versus no active warming and its effectiveness for the prevention of neonatal and maternal hypothermia during/after elective CS, while at birth SSC was performed in a real world operating theatre. Furthermore, a pragmatic trial design will ensure this PhD study is focused on the “real life effectiveness” of the intervention. Chapter 4 and 5 will outline the methodology and methods undertake as part of this PhD.

Chapter 4. Trial Methodology

4.1 Introduction

My study (NeoHyp trial) is an open label single-centre, parallel, randomised controlled trial (allocation 1:1) comparing the effectiveness of perioperative active warming by administering warm IV fluids to women undergoing elective CS and performing SSC, at term, versus room temperature IV fluids on neonatal and maternal outcomes. Participants in the intervention group received an active warming technique (administration of warm IV fluids heated to 39°C via a Hotline™ device) before and during their SSC. Participants in the control group received room temperature IV fluids, which is the usual care provided in the hospital. The only difference between the two groups was the temperature of the fluids that participants were randomly assigned to receive. A randomised controlled trial (RCT) was chosen over other designs (for example case control study) as it is the most reliable design to assess the effect of a different intervention including the benefits and harms of same (Hariton & Locascio 2018).

This trial, although based on the same concept as my previous pilot study, was conducted according to the standards of Good Clinical Practice guidelines and as if it was a medicinal product trial. This contributed to a number of differences in the methods used to conduct this trial so as to ensure strict adherence to the GCP standards (chapter 5, sections 5.6, 5.7, 5.13 and 5.14).

The reporting of the NeoHyp trial was based on the Consort statement (Consolidated Standard of Reporting Trials). This chapter focuses on the trial design of the NeoHyp trial, while the following chapter will analyse the methods/conduct of this trial. The theoretical perspective of the trial design and research approach are also discussed in this chapter.

4.2 Research Question

What are the effects of perioperative active warming by administering warm IV fluids via a Hotline™ device (39°C) to women undergoing elective CS and performing SSC, at term, when compared to the administration of room temperature IV fluids (25°C) on neonatal and maternal outcomes?

4.3 Aim of the study

The aim of the study is to compare the effectiveness of perioperative active warming by administering warmed IV fluids to women undergoing elective CS and performing SSC, at term, versus room temperature IV fluids, on neonatal and maternal outcomes.

4.4 Null Hypothesis

There is no difference in the frequency of neonatal hypothermia between warmed IV fluids and room temperature IV fluids, administered to women undergoing elective CS, at term, who also perform SSC at birth.

4.5 Study Objectives

Primary Objective

To compare the effect of warmed IV fluids to room temperature IV fluids on:

- Neonatal hypothermia (defined as a temperature < 36.5^0C, assessed immediately prior to transfer to PACU in newborns undertaking SSC).

Secondary Objectives

To compare the effects of warmed IV fluids to room temperature IV fluids on:

- Maternal hypothermia (defined as a temperature <36^0C) and assessed prior to transfer to PACU)
- Maternal tympanic temperature, measured on four occasions (on admission as a baseline measure, and on three occasions post-intervention using an adult tympanic (ear) thermometer as per current hospital practice
- Neonatal axillar temperatures measured on two occasions using a neonatal axillar (under-arm) thermometer as per current hospital practice
- Maternal shivering (yes/no)
- Maternal thermal comfort scale measurement, measured using a 1-5 scale from cold, cool, neutral, warm and hot
- Use of additional warming of mothers (Bair Hugger™) and the temperature setting of the device
- Use of additional warming of newborn (incubator) and the temperature setting of the device
- Occurrence of adverse events (for both newborn and mother)
- Interruption to SSC and breastfeeding.

Although there is some literature on the effect of preoperative fasting on patient temperature, suggesting that a patient fasting for eight hours before their operation is more likely to develop perioperative hypothermia (Webb 2003), there is no current literature on the effect of preoperative fasting on pregnant women temperatures who are undergoing CS. This factor, although important, was not included in my study outcomes

but could be included in a wider multicentre trial on this topic as part of my post-doctoral studies.

4.6 Methodology

Methodology is defined as a way to solve the research problem in a systematic fashion using a strategy that a researcher will adopt in order to study his/her research problem (Kothari 2004). In order to determine which methodology and methods should be used in a study, it is important to determine which theoretical perspective has the ability to answer the research question (Gray 2017).

4.6.1 Theoretical perspective and research methodology

Theory and research are naturally linked together, however this link is not always straightforward. Theory offers a rationale for conducting the research and at the same time provides a framework of how the researcher understands the social phenomena and how to interpret the research findings (Bryman 2012). In order to achieve this link, the researcher needs to ask his/herself what form of theory his/her research question is answering and if the data collected is testing or creating theories (Bryman 2012).

As my study aims to test if active warming methods versus no warming methods are more efficient for preventing perioperative neonatal and maternal hypothermia, the use of a deductive approach through empirical experimentation was deemed appropriate. With a deductive approach a hypothesis is developed based on a current theory. In order to test this hypothesis, a detailed research strategy is designed (Wilson 2010). Empirical experimentation means that information is gained by experiment, which was at the core of this study. Therefore, conducting an experiment (use of perioperative active warming versus non active warming) provided information that tested the developed hypothesis (prevention of neonatal and maternal hypothermia during SSC) (Gray 2017).

The theoretical perspective of this study came from an epistemological position called positivism. Epistemology helps us to understand the nature and the ways to gain knowledge, while positivism guides us to apply the methods of the natural sciences to my study (Bryman 2012).

Based on the chosen theoretical perspective, the research methodology supporting the trial design and aims of this study was a quantitative research approach, specifically, experimental quantitative research. In experimental research, the independent variable (active warming of pregnant women) was actively manipulated and its effect on the dependent variable (newborns temperature) was observed.

4.6.2 True experimental design

True experimental design, most commonly known as a RCT, is considered the 'gold standard' in research and the best method to evaluate proposed changes in health care, due to its effectiveness and simplicity of its design (DePoy & Gitlin 2013; Torgerson & Torgerson 2008). The three key components of RCTs are manipulation, randomisation and control; the utilisation of all three can determine a cause and effect relationship between the independent and dependent variable (Park *et al* 2014). In order for manipulation of the independent variable to take place, two or more experimental conditions are usually created by the researcher (Houle 2015). Randomisation of study participants, refers to the random (by chance) allocation of study participants to either the experimental (intervention) group(s) or the control group (no intervention or placebo or usual care) (Lee & Kang 2015). The control group, is also a very important element in an RCT since it is used as a baseline to compare the two groups and also allows the researcher to assess the effect of the study intervention (Pithon 2013; Lee & Kang 2015). Therefore, an RCT, through the use of the control group as a comparison baseline, controls known and unknown variables to establish a causal relationship between the study intervention and the outcome(s) (Torgerson & Torgerson 2008; DePoy & Gitlin 2013).

There are many different types of RCT designs: in this study a two arm parallel group design was used. This design is one of the most commonly used RCT designs used to test the efficacy of two or more treatments. With the two arm parallel group design, study participants were randomly allocated to one of two groups (intervention or usual care group). Following the conclusion of the trial, the results of both groups were compared. The main advantage of this design is that it minimises the risk of bias affecting the study. There is a risk of variability between participants in the intervention and control group but using a robust randomisation strategy ensures that any imbalances between the groups are due to chance through randomisation and not due to manipulation of the assignment. Additional limitations may include the use of this design in the real clinical environment and the feasibility of controlling the external variables which exist is such an environment. Finally, there is a possibility that the nursing staff may provide enhanced care to the participants of the study because they are aware the care is being examined closely (usually referred to as the Hawthorne effect). All the above limitations were considered in the NeoHyp trial design and strategies were set to minimise their effect on the validity of the trial (Chapter 5, section 5.7).

Concluding, this trial is a two-arm parallel group RCT in which the intervention (warm IV fluids set at 39 °C) was offered to participants of the intervention group, while participants

assigned to the control group received the usual care provided by the hospital (room temperature IV fluids set at 25°C) during their elective CS, while at birth SSC was performed. At the end of the participant's stay in the Theatre Department, the results in the newborn/maternal temperature of both groups were reviewed to evaluate the effect of warm IV fluids on the occurrence of newborn/maternal hypothermia.

4.6.3 Pragmatic approach

Clinical trials can be described as pragmatic, explanatory or a mix of both approaches (Sedgwick 2014; Yoong *et al* 2014). Explanatory trials usually measure the efficacy of an intervention under an 'ideal' controlled environment (Sedgwick 2014) while pragmatic trials test the effectiveness of an intervention under 'real life' conditions, in this scenario in a real clinical setting (Yoong *et al* 2014). Pragmatic trials tend to be more flexible with their procedures in the sample selection and the delivery of their intervention and they focus more on the external validity (Thorpe *et al* 2009). Additionally, pragmatic trials aim to support the clinicians choice between options for therapy in a real life clinical setting through a comparison of usual care against an alternative intervention (Thorpe *et al* 2009). Pragmatic trials tend to have higher heterogeneity, compared to explanatory trials, which could dilute the effect of the intervention. In order to overcome this obstacle pragmatic trials must have a larger sample size (a factor that would increase the power for detecting smaller effects) and should have a simple design (Patsopoulos 2011). This was taken under consideration during the calculation of the sample size of this trial. This trial used a pragmatic design in order to evaluate the effectiveness of active warming versus usual care in a real clinical environment and on real people to help health care professionals choose the best treatment in preventing neonatal and maternal hypothermia.

4.7 Adverse effects expected in the trial

According to the Irish Health Products Regulatory Authority (HPRA) this trial is not considered to be a trial of medicinal products (Appendix 4.1), however, I followed the same monitoring standards as if my trial was a medicinal product for human use. This monitoring is based on the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 (regulation 17 of S.I. No. 374/2006) which requires ongoing safety monitoring of the study participants. Participant safety monitoring was facilitated through continuous participant assessment for adverse events/reactions, reviewing their seriousness and reporting to the trial principal investigator, the Trial Steering Committee (TSC) and the Data Safety Monitoring Board (DSMB). A Standard Operating Procedure (SOP) was also developed to provide a clear guide on the safety monitoring and reporting of such events. Specifically, an adverse event is defined in

Article 2(m) of Directive 2001/20/EC as: 'Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment'. An adverse event is defined in Article 2(m) of Directive 2001/20/EC as: 'all untoward and unintended responses to an investigational medicinal product related to any dose administered'.

Although the three RCTs included in the SR (chapter 3 section 3.6.2) did not monitor for adverse events or reactions, there is a rare possibility that active warming might make some participants feel uncomfortably warm during their operation. In order to monitor the occurrence of such an adverse event all participants were asked by the theatre nursing/midwifery staff during active warming if they felt comfortably or uncomfortably warm. Any participant that felt uncomfortably warm had her temperature checked and asked if she wanted to discontinue the intervention. In the event that a participant's temperature indicated hyperthermia, after the initiation of active warming, the intervention was discontinued and the participant's temperature closely monitored. If neonatal hyperthermia was noted in the newborns of the intervention group, active warming would be discontinued, the newborn allowed to cool naturally while its temperature was closely monitored. If the temperature of the newborn remained high or increased, despite appropriate management, the paediatrician would be called to review the newborn and investigate the possibility of alternative factors (outside the study) causing the hyperthermia (i.e. infection). The possibility of hyperthermia after active warming (39°C IV fluids) has not been identified in any studies where warm fluids were used on participants during CS (Sultan *et al* 2015). Any adverse events were documented on the Adverse Event Recording Form (AERF) (Appendix 4.2), while the Principal investigator (PI) was immediately informed about the incident for consideration. The PI had the power to consider if the adverse event was related to the trial or not and make the decision to escalate the adverse event to the TSC and DSMB if needed.

4.8 Trial management

4.8.1 Principal investigator

In accordance with ICH-GCP and ISO 9001, no sponsor was required for the oversight of my clinical trial. Although I developed the concept and early design of this study, the research site stipulated that the PI, who must be an authorised medical professional, should be in charge of the trial conduct within the clinical research site. A consultant anaesthetist with experience in RCTs accepted the role of the PI in July 2017. After a meeting with the PI it was advised to invite a second co-investigator to support the role of the PI on the days that he was not present at the study site. A registrar anaesthetist,

with research experience, accepted the role of the co-investigator toward the end of July 2017. All tasks and duties relating to the trial were delegated to me.

The leadership role of this trial was provided by the principal investigator, who offered guidance/support with any clinical/scientific issue that arose during the trial. I, as the lead researcher managed all day-to-day activities related to the trial. Communication between the PI and the lead researcher was achieved via email and face-to-face meetings, which were archived in the Trial Master File.

4.8.2 Lead researcher

I managed all day-to-day activities related to the trial. Communication between the PI and myself was achieved via emails, which were archived in the Trial Master File.

4.8.3 Trial Steering Committee (TSC)

A designated TSC was formed for the purpose of this study. The TSC of this trial consisted of six members. The areas of expertise of TSC members included trial statistical analysis, obstetrics, clinical midwifery, nursing, neonatology and anaesthesiology expertise. The TSC role was to ensure that the trial was conducted in a rigorous way. The TSC members approved the study protocol, monitored and supervised the trial throughout its duration and considered the recommendations of the DSMB.

4.8.4 Data Safety Monitoring Board (DSMB)

The DSMB consisted of three independent experts who were not directly involved with either the study or the lead investigator. The role of the DSMB was to assess the study protocol and the study progress, as well as to review/advise on un-blinded interim analysis of outcome data and adverse event reports. The areas of expertise of the DSMB members included an academic with experience in conducting clinical trials and trial statistical analysis, neonatology and anaesthesiology expertise. If the DSMB had any concerns about the study it could make recommendations to the TSC with regard to the continuation of the study, or its cessation, or if the investigator needed to modify areas of the study.

4.8.5 Trial Protocol

A clinical trial should be described in a clear manner through a detailed trial protocol (RCSI 2016). The trial protocol provides structure to a trial, promotes adherence of the study to procedures and processes and minimizes the risk of selective reporting of study outcomes. The trial protocol was discussed with academic supervisors and members of the TSC and DSMB. Once all members agreed on the final version of the protocol, it was submitted to the research ethics committee of the hospital. Older versions of the trial protocol are securely kept within the trial master file.

4.8.6 Standard operating procedures

Standard Operating Procedures (SOP) were created, to satisfy compliance requirements and guide the trial. SOPs were offered to both TSC and DSMB members, along with the protocol, so that the suggested amendments from these committees could be made to trial documents prior to seeking trial ethical approval. Both TSC and DSMB approved the SOPs and based their trial monitoring on the accepted SOPs.

For this trial, seven SOP documents were created (Appendix 4.3) including:

- SOP1 Archiving of Essential Documents
- SOP2 Trial Master File
- SOP3 Document Control
- SOP4 Safety Reporting
- SOP5 Adverse Events Report Forms Completion
- SOP6 Informed Consent
- SOP7 Participant Recruitment

4.8.7 Clinical indemnity and Good Clinical Practice

The PI and I were hospital employees at the time of the trial and covered to undertake the trial, by the hospital's insurance and the Clinical Indemnity Scheme. This study was conducted in accordance with Good Clinical Practice (GCP), although it was not a clinical trial of a medicinal product, as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and 2005/28/EC. According to article 1.2 of the Directive 2001/20/EC, GCP refers to 'a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible'. Since my trial involved human participants, it was important to conduct the trial based on these high standards. To ensure that all the GCP standards were followed, I attended the GCP study day on the 20th July 2017. The application of these standards to my trial are explained later in this chapter.

4.9 Data protection and management

Data protection in my study was guided by the eight principles of the General Data Protection Regulation (GDPR) suggested by the Data Protection Commission (DPC) . These include:

- Process the data in a lawful, fair, and transparent manner;

- Collect data only for specified, explicit and legitimate purposes;
- Ensure data is adequate, relevant and limited to what is necessary for the purpose of the study;
- Keep data accurate and up-to-date and erase/rectify any inaccurate data without delay;
- Keep data in a way that allows their identification, do not retain data longer than necessary;
- Keep data secure by using appropriate technical/organisational security measures;
- Be able to demonstrate the compliance with the above principles; and
- Respond to requests by individuals seeking to exercise their data protection rights.

Data management ensured the right collection, verification and organisation of all the anonymised data.

Microsoft Excel was used to keep track of the flow of participant entry, with the use of assigned trial number. This ensured that all anonymised data collection forms were available for statistical analysis. Data management procedures included:

- Creation of a Trial Master File and a SOP guideline on how to use it.
- Predetermination of who would collect the data and who would complete the data collection forms.
- Informing theatre staff about data collection both verbally (theatre meetings) and in writing (instruction manual, announcements on theatre communication book/board).
- Ensuring all data collection forms were kept in order.
- Inputting collected data into SPSS on a daily basis.
- Maintaining anonymised accounts of ineligible patients, eligible patients who refused to participate and participants who withdrew from the study.

I was responsible for data protection and management, as this study was undertaken as part of my academic qualification. All hardcopies of the anonymised data collection were chronologically organised and kept in the Trial Master File, which is securely kept within the hospital premises. All anonymised data were manually entered into IMB SPSS Version 20 software, by me and a person with IT expertise who was independent from the study, in a designated secure computer provided by the hospital, located within the

hospital premises. Collected data were processed and securely stored, for seven years after the completion of the study, as per GDPR guidelines (2018).

4.10 Trial approval

As this study was not a clinical trial of a medicinal product, as confirmed by the HPRA on the 27th of June 2017, no authorisation by the HPRA was required. Additionally, no authorisation was required by the Faculty of Health Sciences (FHS), Trinity College Dublin Research Ethics Committee (REC), as the remit of this committee does not extend to intervention trials involving patients, as confirmed by FHS on the 7th of July 2017. Ethical approval could only be granted by a REC authorised by the Department of Health (Government of Ireland 2004), which in this case was the Research site REC, which granted ethical approval on the 28th of September 2017 (REC-2017-018, Appendix 4.4).

4.11 Pilot study

A pilot study was conducted in 2015 after receiving approval from the hospital REC. This pilot study helped me to review and refine any problems with the research design, the selection/enrolment procedures and the data collection/analysis phase of the trial. Additionally, it offered invaluable feedback from both clinical staff and participants in respect of the research process. Also, this pilot was conducted to determine the sample size of the main trial. A number of amendments were made to the main study as a result of the pilot study. These amendments include more rigorous methods in areas such as:

- Sequence generation
- Allocation concealment
- Allocation assignment
- Safety monitoring
- Data management
- Trial management

Specifically, the pilot study used a coin toss (by an independent person, on the day of participant operation) as a method of sequence generation, allocation concealment and allocation assignment. Although this simple method is widely used in past RCTs, it has the potential to create bias, as people could potentially manipulate the result of the coin toss, and therefore it was not used in the main trial. Instead, sequence generation, allocation concealment and allocation assignment for the main study was achieved by three different individuals, who were independent from the study and the research team.

In the pilot study there were minimal strategies in place for safety monitoring of the trial and data management. This informed the planning and implementation of more rigorous

procedures for the main study ensuring the trial and data were monitored more robust using clear procedures, for example, regular staff information sessions, SOPs and the use of an adverse event form. Furthermore, a TSC and DSMB were established for the main study (which were not present in the pilot) to monitor participant safety and methodology rigour.

4.12 Study validity

Validity is an important element of an RCT, since many factors in a clinical trial can have implications that can effect relationships (Fortin & Smith 2013). Such factors include: uncontrolled extraneous variables, which can cause biases.

Since there are many different types of validity (Bryman 2012) such as: statistical conclusion validity, internal validity, construct validity and external validity, different strategies were put in place to deal with potential risks that would reduce these types of validity. Statistical conclusion validity refers to the correct use of statistics. Incorrect use of statistics could lead to violation of the assumptions of statistical tests, fishing for results and reduction of the reliability of intervention implementation (intervention fidelity). In my trial, in order to increase statistical conclusion validity, the right statistical tests were predetermined in the protocol and were performed by three different people, two of which were experts in conducting statistical tests, to ensure that the tests were ran correctly. Intervention fidelity was assured by providing theatre staff with information leaflets and education sessions on implementing the trial interventions and collecting the study data using the same methods.

Another possible issue that could cause different group composition, despite the fact that at the beginning of the trial both groups were equivalent, is the participant attrition rate (Kennedy-Martin *et al* 2015). Since my study was a pragmatic RCT, it had an increased risk of attrition. In theory, if attrition was similar between the two groups, there would be no bias. However, in the real clinical setting this theory is not always applicable. In order to minimise bias caused by participant attrition, intention-to-treat (ITT) analysis was used (Gupta 2011). To achieve ITT, any attrition rate was documented, including why participants withdrew from the trial.

An additional threat to internal validity is instrumentation, which refers to different methods that the dependent variable was measured during the trial. In order to improve instrumentation, an information leaflet and education sessions were offered to theatre staff on how to use the data collection tools and how to measure the dependent variables. Also, I was the only person who collected the data from the e-charts, which

reduced any bias linked to the use of multiple data collectors. Furthermore, construct validity refers to the possibility that staff behaviour and perception of how they should behave may be influenced by the presence of the trial, this is known as the Hawthorne effect (McCambridge *et al* 2014; Henry *et al* 2015). It was anticipated that staff education and monitoring would minimise the Hawthorne effect during the trial. Finally, external validity refers to the generalisability of the study findings to similar patient populations and settings (Steckler & McLeroy 2008). The study was conducted in a large teaching maternity hospital in Ireland. The inclusion of this site reflects the main providers of maternity care in Ireland, eliminating in this way the threat of not being able to generalise study findings to other Irish maternity care settings.

4.13 Blinding

Blinding refers to the concealment of group allocation from the study participants, clinicians, data collectors and outcome assessors (Karanicolas *et al* 2010). Blinding of the participants and staff members is a key methodological procedure to reduce bias according to Hróbjartsson (2014). The intervention was administered by the hospital anaesthetists who were not blinded to the intervention allocation; however they were not involved in the temperature measurements of the participants. The anaesthetists, after attending training sessions delivered by me, connected all trial participants to the fluid warmer device using the Hotline™ device, but only turned on the device for those participants assigned to the intervention. This move blinded participants and theatre nurses and midwives who were measuring the initial temperatures within the OT to the allocated assignment. The participants were not informed of their group allocation, neither could they identify to which group they were allocated due to the blinding conducted by the anaesthetists. However, in the unlikely event that participants could determine their allocation due to the temperature of the administered IV fluids, this would have no effect on their temperature measurement since they could not change their own core temperature during their operation. PACU staff were also unaware of participants' allocation assignment, as the intervention ceased before the transfer of the participant into the PACU room. Although I was occasionally present in the trial room, my lack of blinding could not cause any bias as I was not involved in any of the data measurements.

4.14 Clinical Trial Registration

Clinical trial registration has been strongly advocated by journals and editors, especially in the past 12 years and is now mandatory for publication by most medical journals (Tiffin & Nickerson 2013). Information about the study design and conduct of a clinical trial can be published on web-based clinical trial registries, which can be publicly accessed. A clinical trial needs to be registered prior to recruitment of the first participants, and this

is based on the Declaration of Helsinki as recorded by the World Medical Association (2013). Therefore, my trial was registered prior to participant recruitment on the 'clinicaltrials.gov' website with registration number: NCT03316716.

4.15 Ethical Considerations

4. 15.1 Clinical equipoise

Clinical equipoise refers to the uncertainty among the health care experts about the harms and benefits of the interventions compared in an RCT (Hey *et al* 2017) . This uncertainty was evident before the conduct of my trial, as the health care community was uncertain if perioperative active warming was beneficial in preventing neonatal hypothermia during CS while at birth SSC was performed (chapter 3 section 3.10.1). This 'clinical equipoise' existed before my trial and justified the need for such an RCT. Additionally, clinical equipoise means that there is not enough evidence to suggest one intervention is better than another (chapter 3 section 3.10.1). This suggests that participants can enrol in the trial without being disadvantaged and a health care professional can refer participants without violating their duty of care (Hey *et al* 2017).

4. 15.2 Respect for persons & informed consent

Since this study involved research on human subjects, it was very important that it was conducted in accordance with the ethical principles of the Declaration of Helsinki (WMA 2013). All of the following principles were applied in this study to ensure that participants' rights, wellbeing and respect were promoted. These ethical principles were:

- "The physician has a duty to protect the health, well-being and rights of patients who are involved in medical research;
- Medical progress is based on research that ultimately must include studies involving human subjects;
- The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments);
- Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights;
- While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects;
- It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects;

- Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards;
- Medical research should be conducted in a manner that minimises possible harm to the environment;
- Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications;
- Groups that are underrepresented in medical research should be provided appropriate access to participation in research;
- Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value;
- Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured".

(WMA 2013)

Furthermore, according to the Belmont Report (1979), people have the right to participate in a study voluntarily. Their decision can be autonomous only if they are fully informed and aware of their decision (WMA 2013). In order to achieve this in my trial, women received an information leaflet prior (Appendix 4.5) to their hospital admission, giving them adequate time (a minimum of two weeks) to make an informed decision on partaking in the study and to give informed consent. The information leaflet my contact information, and I was available to answer any queries that potential participants may have had prior to their admission to the hospital.

An additional component of informed consent is full disclosure. In order for this element to be achieved, information was not only provided in writing (information leaflet) but also orally. The admission midwife (independent from the study), approached the participants, checked if they were eligible to participate and answered any additional questions regarding this study, that participants may have had prior to giving their consent on the day of their operation.

Informed written consent (Appendix 4.6) was obtained by the admission midwife, on the admission of the participant in the hospital, which takes place on the day of the operation. Prior to any study-related screening procedures being performed on the participant, the informed consent statement was reviewed, signed and dated by the participant and the admission midwife.

4. 15.3 Confidentiality and privacy

Confidentiality and privacy of trial participants is an important ethical issue that was addressed before the start of the trial to protect the dignity of each study participant (WMA 2013). Participant confidentiality was achieved with the allocation of a unique trial identification number to each study participant. This allocated number was used in all NeoHyp trial documentation of each participant, apart from the signed consent forms. Trial documentation was only accessible by the PI and myself.

All hard copies of the data collection forms were stored in a locked cabinet in a locked room within the hospital premises. All electronic data were password protected. Data will be kept for seven years as per GDPR (2018) data protection policy. After this period I will ensure that all hard copies are shredded and electronic data erased.

4. 15.4 Beneficence

The ethical principle of beneficence was based on the idea that study participants would gain the maximum benefits from the study with potential harms being reduced to a minimum (Belmont 1979). The principle of beneficence affects not only the participant but also society, obliging the researcher to give thorough forethought to both the short-term and long-term benefits and harms of the novel study.

In order to address this principle I anticipated short-term and long-term benefits/harms during the planning phase of my study. In relation to benefits, actively warming women using warm IV fluids (39°C) could potentially reduce the temperature drop participants may experience during CS and SSC. However, there was no guarantee that the trial intervention would prevent neonatal temperatures dropping which may lead to neonatal hypothermia.

Regarding the minimization of study related harms, I included strategies that would address potential harms/discomforts caused to participants during the study. A basic strategy was a frequent assessment/documentation of women's and newborns temperatures (see data collection booklet, appendix 4.7), which involved theatre nurses/midwives closely monitoring participants' wellbeing. Additionally, women were directly asked about their thermal comfort level, measured on a scale from hot(5) to cold(1), with their answers being documented and nursing interventions implemented in cases where the patients would feel uncomfortably hot or cold.

For example if a woman from the intervention group felt uncomfortably hot, regardless of her temperature measurement being normal, the intervention would be discontinued and frequent temperature measurement would take place to ensure that she would not develop pyrexia. In situations where a pyrexia occurred, it was planned for a doctor to

review the participant and an adverse event form completed. If a woman felt cold and/or she was shivering, additional active warming would be provided using a forced air warming device (Bair Hugger™) and her temperature monitored until either she become normothermic and/or the shivering/feeling cold disappeared. Similarly, if a newborn's temperature was lower than the accepted normal levels, the newborn would be placed in an incubator until the temperature was within normal levels and this would be documented within the newborn's chart and data collection form.

Alternatively, if a newborn's temperature was higher than the normal, the newborn would be allowed to cool down by removing the blankets/towels and exposing its skin to the ambient temperature. Any additional interventions would be documented in each participant's medical chart and the data collection booklet and a paediatrician would be informed and assess any newborn that theatre staff would have any concerns about. Finally, additional strategies used in the trial to minimize harm was the formation of an independent DSMB, a TSC and reporting of any adverse events to the TSC, DSMB, the PI and the Research site REC.

4. 15.5 Justice

Justice is another ethical principle referred to in the Belmont (1979) report, and focuses on the recruitment process of participants. This ethical principle ensures that all participants will be treated fairly and none will be exploited. In order to achieve this principle within my study, I made sure that the eligibility criteria were broad enough and at the same time relevant to the topic of the study. Therefore, there would be no discrimination against people and patients would be excluded only if they did not match the inclusion criteria or could not give informed consent.

4.16 Discontinuation/withdrawal of subjects from study protocol

Participants had the right to voluntarily withdraw from the study at any time and for any reason, without any consequences. The investigator had the right to discontinue a subject from study treatment or withdraw a participant from the study at any time if it was in the best interest of the participant.

Participants were withdrawn from the study if any of the following issues arose:

- Withdrawal of consent by the participant.
- Any medical condition that the investigator determined could jeopardize the participant's safety.
- Ineligibility, having been overlooked at screening.
- An adverse event which required discontinuation of the study.

All participants who discontinued or withdrew from the trial complied with protocol specified follow-up procedures. The reason for withdrawal was documented in the subject case report form. If a participant withdrew due to an adverse event, I would follow-up the participant until the adverse event had been resolved.

4.17 Definition of End of Trial

The end of trial is the date of the last visit of the last subject. The end of the study was reported to the REC of the hospital, in writing, 90 days after the recruitment of the last participant. A summary report of the study was provided to the REC within 1 year of the end of the study as this was a legal requirement.

4.18 Summary

My trial, using a true experimental design, compared the effectiveness of perioperative active warming by administering warm IV fluids via a Hotline™ device (39°C) to women undergoing elective CS and performing SSC, at term, versus room temperature IV fluids on neonatal and maternal outcomes. Although my trial was not a trial of a medicinal product, as per HPRA feedback, it followed the National and EU clinical trial legislation and was guided by the trial protocol and SOPs documents.

As my trial was not a trial of a medicinal product, no trial sponsor was needed, but a medical practitioner with experience in quantitative research and anaesthetic background agreed to act as the trial's principal investigator. Trial approval was sought and granted by the trial site REC. The trial was registered on a clinical trials website and managed by a trial steering committee group and a data safety monitoring board. Finally, this trial was conducted in accordance with GDPR and ethical principles that protected participants' confidentiality, wellbeing and which ensured that participants would be treated fairly and with respect throughout this trial.

5.1 Introduction

The methods and conduct of my trial (NeoHyp trial) are explained in this chapter. The structure of the methods/conduct of the trial were based on the Consort statement. This chapter explores issues relating to research site, the sample size, recruitment and randomisation, preparation of the research site, intervention, trial compliance, trial deviations and outcomes and data analysis. All the challenges faced during this trial and how they were overcome are discussed in this chapter.

5.2 Trial Research Site

The research site of the trial was the theatre department of a large maternity hospital in Dublin, Ireland. This urban research site offers services to public, semi-private and private clients. It has three available theatres, two identical theatres for elective and emergency cases and one dedicated to emergency cases. It also has one PACU with three bed capacity. It is important to highlight the fact that this hospital is located in a very old building with limited space, resulting in equipment, such as the neonatal incubator in the theatre department, being located outside the operating theatres and the PACU, something that results in separation of newborns from their recovering mothers in case of treating neonatal hypothermia after CS. The hospital has a total of 212 adult beds and 39 neonatal beds (in NICU). The hospital's 2017 annual report showed that 2,796 CS were undertaken in the hospital; 1,379 were emergency CS and 1,417 were elective CS. Only one study site was used as there are a large number of CS every year in this site and therefore the sample size required could be guaranteed. The standard practice with regard to booking and undertaking elective CS is that women attending their antenatal visit and after consultation with the attending doctor are booked for elective CS at least two weeks in advance of their surgery. The reasons for booking an elective CS include: previous CS (943 repeat CS were undertaken in 2017), fetal malpresentation (for example breech/oblique/transverse presentation with 238 cases in 2017), medical disorders (for example maternal hypertension, preeclampsia, fetal growth restriction with 153 cases in 2017), previous third or fourth degree tear (41 cases), placenta praevia (37 cases) and maternal request (5 cases). It is worth mentioning that the theatre department of the research site has no standard practice with regard to keeping mothers warm before/during elective CS. If a mother develops hypothermia after the CS, diagnosed in PACU, then the standard practice is to apply a forced air warmer (see section 5.9.4) to the hypothermic mother until the temperature returns to normal. Once the woman is normothermic and stable, then she and her newborn can be transferred to the postnatal ward.

The hospital has a baby friendly philosophy promoting early initiation of SSC and breastfeeding, immediately after birth. This philosophy is a standard hospital practice after vaginal birth and since 2011 is standard hospital practice after elective CS (and whenever is applicable after emergency CS). The philosophy for SSC after vaginal birth suggests that all healthy newborns are placed naked on their mothers' abdomen immediately after their birth, dried and positioned for SSC. All wet towels are removed and the newborns covered with one prewarmed towel, two prewarmed blankets and a hat while undertaking SSC for at least one hour after birth. Delayed cord clamping and early breastfeeding initiation is also hospital policy. Practices that require discontinuation of SSC such as weighing of the newborn, newborn examination and dressing of the newborn are postponed until after the first hour of SSC. This SSC practice might be delayed in the event that the newborn requires resuscitation and/or the mother develops a postnatal complication, such as an excessive bleeding/ fainting episode.

SSC after elective CS has a slightly different process in order to facilitate the nature of the operation. For example, the delivered newborn is handed to the theatre midwife by the surgeon, who immediately transfers the newborn to the heated resuscitaire. There the newborn is dried with prewarmed towels, assessed, resuscitated if needed, weighted, vitamin K given. Once the newborn is stable, a warm hat and nappy is applied and the newborn is transferred to the mother for SSC. This whole process, until the SSC is established lasts approximately 5 minutes. During SSC newborns are again covered with a prewarmed towel and two prewarmed blankets as per hospital protocol. The initial SSC within the operating theatre lasts until the wound of the mother is sutured. SSC is then interrupted and the newborn is transferred to its father in a waiting area until the mother is cleaned and is stable to be transferred to PACU. If the neonatal temperature is suboptimal the newborn is placed in the theatre incubator until the temperature reaches normal levels.

Once the mother is admitted to PACU, she is assessed by the staff that she is well to receive her newborn to continue SSC and start breastfeeding. If the maternal temperature on admission is suboptimal and/or the mother is shivering excessively a forced air warmer is applied until the mother recovers. The use of active warming for either mothers and/or their newborns is a common reason for delaying the SSC and breastfeeding within the PACU. Once both mothers and newborns are well and warm, SSC and breastfeeding is initiated in PACU which would last until the discharge of the dyad from the PACU. This practice was part of the department's usual care, which was also applied in my clinical audits and the pilot study.

5.3 Permission to access the research site

Permission to access the research site was granted by the Director of Nursing and Midwifery and the Master of the Hospital (10/2/2016). Additional access to the site was granted by the CMM3 of the Theatre Department (10/7/2017). I arranged to meet the theatre staff, in face-to-face meetings, closer to the initiation of the trial, to inform them about the trial and gain their support for conducting the trial. I also continuously engaged with the theatre staff during the different phases of my trial. Additionally, study information leaflets were offered to each individual theatre staff to provide more information about the trial and their role (appendix 5.1). I personally handed these information leaflets to every member of theatre staff, allowing them time to review them and ask me queries they might have had about the trial. My face-to-face approach was successful as the theatre staff were happy to support me in my trial, since they could physically see and have access to me on the premises. Laminated posters were placed in visible areas in the theatre department to remind nursing and medical staff about the trial (appendix 5.2). Clinical managers in the postnatal wards, outpatient department, private clinic and NICU were informed in person by me about the trial. The managers of the outpatient department and private clinic were particularly supportive by contacting me when they needed additional patient information leaflets for dissemination.

Furthermore, access to patients was requested and granted by the Obstetrical and Anaesthetic consultants of the hospital. The consultant obstetricians were informed about the NeoHyp trial by the Master of the Hospital at one of their monthly meetings which (January 2018). Similarly, the consultant anaesthetists were informed about the trial by the Head of Anaesthesia, at their monthly meeting in January 2018. It is important to mention that medical staff in grades other than consultants have new hospital placements every six months to a year. Therefore, the meeting with new obstetricians and anaesthetist took place in January 2018 and before the initiation of the trial.

Overall, there was no resistance to assessing the site and the potential participants. The CMM3 of the theatre department was also supportive as long there was no additional workload to the theatre staff. No additional workload on theatre staff was ensured as they would only need to measure and document the neonatal/maternal temperatures and use of additional warming, which is documented as part of their standard daily practice. Such reassurance was provided in writing and through face to face meetings but also in writing e-mail correspondence. Some concern was raised by three consultant anaesthetist and one consultant paediatrician regarding the lack of a trial sponsor, as they believed the trial was a clinical trial of medicinal product and as such, should follow a different process. However, following confirmation from the HPRA that my trial was not

a trial of a medicinal product (appendix 4.1) and after the Hospital REC approved the conduct of my trial (appendix 4.4), the specific consultants were reassured and no further concern was evident.

5.4 Target population

5.4.1 Eligibility and exclusion criteria

Women and their newborns were eligible to participate in the study if they met the following criteria:

- Aged 18 years or over,
- Able to provide informed consent for themselves and their newborn,
- Had a singleton pregnancy between 37^{+0} and 41^{+6} weeks gestation,
- Foetus/new-born was alive/born alive, and had no risk factors such as congenital or cardiovascular anomalies (Appendix 5.3, TSRF),
- Received spinal or combined spinal anaesthesia for their CS,
- Had an elective CS,
- understand and communicate in English,
- Willing and able to perform skin-to-skin contact.

Women were excluded from this study if they had:

- Pyrexia (> 37.5C) on admission to the ward,
- A maternal medical disease (i.e. spinal abnormalities, coagulation abnormalities, maternal serology positive, congestive heart failure, severe renal function impairment),
- General anaesthesia,
- A newborn who had a congenital anomaly (i.e. spina bifida, anencephaly, hydrocephaly, cardiovascular anomalies, anomalies of nervous system, defects of anterior abdominal wall),
- A newborn who has abnormal Doppler artery velocimetry,
- A stillbirth newborn,
- Not speaking English,
- A recent USS (ultrasound scan) estimating the foetal weight less than 2000g.

5.5 Sampling and Sample Size Calculation

In order to estimate the sample size, a previous pilot RCT (Vilinsky *et al* 2016) study which investigated neonatal hypothermia in women performing SSC at CS, was used. After discussions with clinicians from the clinical site, the PI of the study, the hospital statistician, academic supervisors and members of the DSMB and TSC, it was agreed

that the use of the previous pilot study would be appropriate to estimate the sample size of the current study, since the intervention, setting, equipment and environment were the same as the pilot study. The frequency of neonatal hypothermia from the pilot study was 30% in the control group and 10% in the intervention group, therefore, the absolute reductions achieved by perioperative active warming in Vilinsky *et al* (2016) was 20% (from 30% to 10%) . The sample size required to have a sufficient 80% power of detecting a difference in the frequency of neonatal hypothermia between the two groups, with alpha level set at 0.05, is 124, was 62 women per group. Those calculations were made using ClinCalc statistical package (http://clincalc.com/Stats/SampleSize.aspx) with an enrolment ratio of 1 (which indicated equal participant enrolment in both groups).

The hospital statistician ran a separate calculation to test the accuracy of the statistical package. He used SPSS software to calculate a measure of effect size (Cramer's V) and the result was 0.250. He then used this to estimate a sample size using a software application called G*Power. He used an alpha level of 0.05, a power of 80% and df=1. His result was 126 participants, which is 63 women per group, which was very similar to the original sample size. Clinical trials may have a high participants' dropout rate, a 20% attrition was allowed after discussion with the PI, leading to a total sample size of 150 participants, 75 women per group. The 20% attrition rate mark has been adopted by studies in the literature as a rule of thumb to reduce the risk of bias due to attrition rates (Amico 2009; Cramer *et al* 2016).

The general population of women who underwent caesarean section in 2015 was 1,364 with the numbers steadily increasing since 2005 according to the Hospital's Annual Clinical Report (2015). Assuming that approximately 50% of these would be eligible and that about half would agree to take part in the trial, it was estimated that 307 women could be recruited over 12 months (or 26 women approx. per month). Therefore it was anticipated that the recruitment period for the trial would be seven months, allowing for one month contingency. The number of participants recruited were monitored on a monthly basis.

5.6 Recruitment and Randomisation

5.6.1 Process of recruitment and eligibility assessment

The information and consent process took place in two stages. Primarily, women were given a study information leaflet (Appendix 4.5) during their antenatal visit to the outpatients department or private clinic when they were booked for their CS, at 32-40 weeks gestation. At that stage, women were informed in writing, of: the purpose of the study, the potential benefits and harms, their right to withdraw anytime from the study without this impacting on their care, participant confidentiality, the data collection

procedures, the time commitment and the voluntary nature of participation. The women could contact me to answer any questions they had regarding the trial. Recruitment took place over a six month period.

Allocation to intervention or control took place during a woman's admission for her elective CS. The designated midwife who admitted all women for their planned elective CS completed a Trial Screening and Register Form (TSRF) (Appendix 5.3) on women who had received the study information leaflet and assessed their eligibility to take part in the study. Eligible women were invited to take part in the study and asked to sign a written consent form (Appendix 4.6). These consent forms were printed in booklets with three copies of each form: one scanned into the woman's electronic chart, one provided to the woman for her own record, and the third stored securely in a designated folder in the admission ward office to be collected and filed in the Trial Master File. Study numbers were pre-printed on the consent forms, so that once a woman signed the form she was allocated a study number which became her trial identifier on all other trial documentation from that point onwards. Recruiting participants in this study was a relatively straight forward procedure. The only minor problem faced was that some women had also participated in other clinical trials. In such a scenario, every woman was free to decide if she wanted to participate in more than one clinical trial at the same time, since there are no such restrictions applicable by the REC of the hospital.

5.6.2 Process of randomisation and allocation concealment

Blocked randomisation sequence to control or experimental groups (allocation ratio of 1:1) was generated by the hospital statistician using computer software. The copy of the sequence generation was handed by the statistician to myself and I gave them to a midwife who was independent from the study, to conduct the allocation concealment. Allocation concealment was achieved through use of sequentially numbered sealed opaque envelopes, where each sequential envelope contained the group allocation. The sealed envelopes had an ascending study number printed on the front of each envelope. The independent midwife added a pre-designed allocation card to the envelope as per the allocation sequence while I was present to ensure the accuracy of the randomisation process. My presence at this stage was not considered as a bias since the researcher was not involved in the sequence generation nor in the participant's eligibility/consent and allocation stage. The sealed opaque numbered envelopes were handed to the admission midwife who stored in a secure locker within the theatre department.

Every day, the admission midwife picked the next available sequenced numbered envelope for the eligible participant who consented to participate in the study. When the admission midwife met an eligible participant who was willing to participate in the trial,

she opened the envelope and documented the envelope number, the allocation and the study number on the participant's TSRF. The group allocation was also noted on the participants consent form, which was stored for me to collect. This alerted the midwife to those who had been randomised and to enable cross-validation of adherence to the trial protocol.

For women who were screened ineligible, or screened eligible but declined to participate in the study, the TSRFs was stored securely in the designated folder for collection on a daily basis, by me. Retaining the TSRFs was important to the study for assessing the proportion of women ineligible compared to eligible, and the proportion of women eligible and non-consenting compared to those eligible and consenting. For women screened eligible and consenting to take part, the TSRF was handed to the anaesthetist in charge of the operation, by the admission midwife, the anaesthetist was able to review and offer the correct intervention to each participant. The anaesthetist returned the TSRF to myself and I safely stored them in the Trial Master File. The above measures were taken to reduce the risk of missing any participants throughout the study.

Once the participant was admitted to the operative theatre, the anaesthetist checked the TSRF and initiated the intervention or provided usual care. The intervention commenced prior to the insertion of regional anaesthesia and was continued during the operation. All women who had an elective CS at the hospital site, and who were at a low risk for maternal/neonatal complications performed a period of SSC with their newborns at birth. The SSC within theatre department takes place within 5-10mins after birth and lasts until the participant's transfer to PACU as standard practice for the hospital. SSC is then temporarily interrupted until the participant's stability is confirmed by the PACU staff and then it is resumed in PACU and lasts until the dyad transfer to the postnatal wards or until the mother requests to discontinue it earlier (something that was not evident during the NeoHyp trial).

5.7 Blinding

No issues emerged in the blinding process (Chapter 4 section 4.13). After the end of the intervention I was asked by participants and staff as to which group they were allocated, something that clearly indicated the sound blinding of participants and theatre personnel.

5.8 Preparation of research site and staff

In order to be successful, the trial was dependent on the support and participation of clinical nurse managers and theatre staff, as well as maintaining their motivation and interest through the duration of the study. The literature suggest some factors that could limit the progress of RCTs such as untrained and unsupported staff (Elliot *et al* 2017).

Also staff that are differently trained could use different measurement techniques that could potentially cause bias in my study (Deaton & Cartwright 2018). Given that there are many ways to measure maternal and neonatal temperatures, to conduct SSC and to initiate breastfeeding, staff were offered education and training sessions in order to standardise temperature measurements and SSC/ breastfeeding practices within theatre department. This minimised differences in care that may cause variation in study. Nursing and midwifery staff in the research site are competent in measuring maternal and neonatal temperatures with either the tympanic or axillar thermometers. However, in order to ensure that all staff would use the tympanic or axillar thermometers in a similar and effective way, I went over the basics with the staff including the temperature tool and route that would be used in the trial. Furthermore, training was given on how to conduct efficient SSC and breastfeeding during and after the CS. In addition to their skills, all staff received information workshops regarding the background, purpose and methods of the study. Staff attendance at this meeting was recorded to ensure that all staff received this information. Any staff that were unable to attend that meeting were approached on separate occasions and individual information sessions were provided. These workshops began two months before the commencement of the study and were repeated on a monthly basis until the completion of the study.

Overall, this RCT would not have been successfully completed without the clear and continuous communication between me as the researcher and the hospital staff. I ensured that every aspect of the clinical trial, as seen above, was clearly explained to every member of hospital staff involved with the study, both in writing but also face-to-face. The fact that I was a long-term employee of the hospital, with very good interpersonal relation with the other staff members was crucial in establishing a good communication and cooperation environment, which eventually supported the smooth conduct of the RCT. I was able, not only to discuss the methods that the research would be conducted through, but also was available on a daily basis to support the staff in their involvement with the study while ensuring that trial would be conducted in a rigorous way without adding any burden to the busy clinical departments and staff.

5.9 Trial Intervention/Control

5.9.1 Trial intervention/control and its administration

Control group

Participants randomised to the control group received the current standard of care in the hospital which is the perioperative administration of room temperature IV fluids (25°C) consisting of Hartman's solution initiated prior to the insertion of regional anaesthesia and administered until the woman was discharged from PACU. On arrival to theatre,

once the anaesthetist confirmed that a woman was allocated to the control group, he/she connected a room temperature IV Hartman's solution bag to the Hotline™ device, which was not turned on so blinding participants and theatre staff to assigned intervention. Any additional IV fluids (i.e. antibiotics, IV paracetamol) were also given at room temperature. The majority of women received up to two litres of Hartman's during their stay in the operation theatre.

Intervention group

Women randomised to the intervention group were administrated warm IV fluids (39°C) consisting of Hartman's solution with the use of the theatre's Hotline™ device (Figure 5.1). The Hotline™ device was set to 39°C in which the Hartman's solution bag was infused to the participants perioperatively. On arrival to theatre, once the anaesthetist confirmed that a woman was allocated the intervention, he/she connected an IV Hartman's solution bag with the Hotline™ device. The IV administration of Hartman's commenced before the administration of the regional anaesthesia and was continued during the operation. Any additional IV fluids (i.e. antibiotics, IV paracetamol) were given at room temperature. The majority of women received up to two litres of Hartman's during their stay in the operation theatre. The hospital has two Hotline™ devices which were available for the needs of this study. The Hotline™ device was controlled and pre-set at 39°C by the anaesthetist and no other person had authority to change the devices settings.

All women who had an elective CS at the hospital site, and who were at a low risk for maternal/neonatal complications, performed a period of SSC with their newborns at birth as standard practice for the hospital. In order to facilitate early SSC after birth, newborns are placed for SSC immediately after being dried and checked by the theatre midwives under the resuscitaire (Figure 5.2). Once the midwives ensure that the newborn is dried and stable (within the first five minutes of life), they commence SSC while the mother is still being operated on. SSC during CS lasts until the operation is over. The newborn is then temporarily removed from SSC, in order for the theatre staff to clean the woman and prepare her for the PACU. On PACU admission and as long as the woman was stable, the second stage of SSC and also the initiation of breastfeeding took place in PACU.

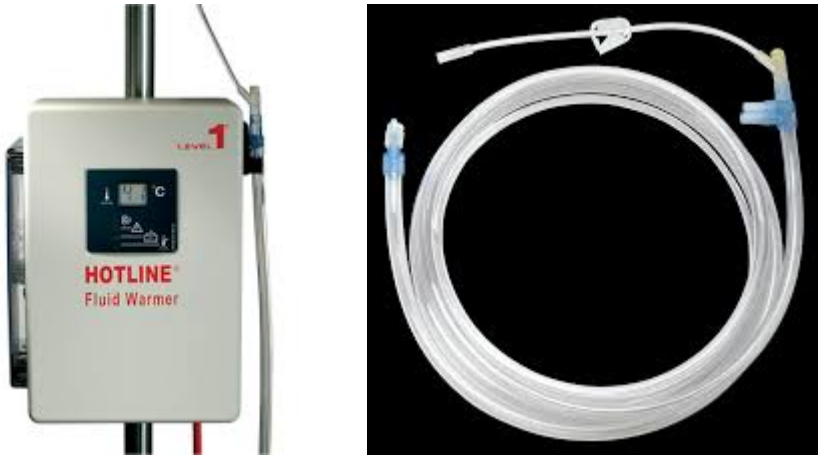


Figure 5.1. Hotline™ device and giving set

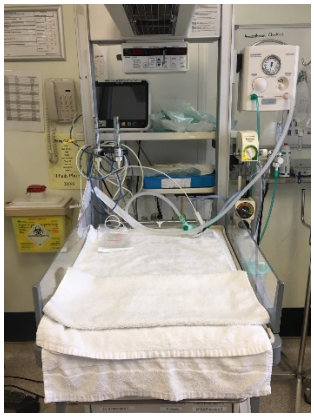


Figure 5.2. Neonatal resuscitaire (ohio)

5.9.2 Hospital IV fluid practice

The IV fluid Hartmann's is a solution administered, free flow, to every woman who undergoes elective CS at the hospital (approximately 2 litres). It is indicated as a source of water and electrolytes. According to Schmitz (2017), the components of the Hartmann's IV are: sodium chloride (6g/L), sodium lactate (3.22g/L), potassium chloride (0.4g/L), and calcium chloride dihydrate (0.27g/L). A multiple electrolyte intravenous solution, like Hartman's solution, is used for hydration by restoring water and the electrolyte balance in the body, something that normalises the pH of the acid-base balance of the body (Baxter, 2014). Sodium chloride controls the balance between water and electrolytes and the osmotic pressure of body fluids. Sodium lactate slowly metabolises to bicarbonate and water. Potassium chloride regulates the nerve conduction and muscle contraction, particularly in the heart. Calcium chloride maintains the functional integrity of nervous, muscular, and skeletal system and cell membranes (Baxter 2014). Hartmann's solution is contraindicated in patients with hypersensitivity to sodium lactate, congestive heart failure or severe impairment of renal function and in

cases where the administration of sodium and chloride is harmful (Baxter 2014). Such conditions are extremely rare in the maternity setting and if such a case was present these women would not have met the inclusion criteria for the study.

According to the Baxter Healthcare Corporations' information leaflet for the IV Hartmann's solution, VIAFLEX plastic containers (used in the hospital) can be warmed once at a temperature not exceeding 40°C for up to 14 days without any effects on the quality of the solution (Schmitz 2017). The hospital stores the Hartman's plastic containers in a cool environment away from sunlight and humidity as per hospital guidelines, following the manufacturer's instructions. The Hotline™ device is pre-set to warm fluids at 39°C and is able to constantly give the fluids at this specific temperature through the infusion of the IV solution. Specifically, the Hotline™ device is only attached to a specific, single use, sterile giving set, which is connected to the Hartmann's container. The room temperature fluid is warmed to 39°C inside the Hotline™ device and is administered at this temperature directly to the woman's vein. The administered temperature of the fluid (39°C) is within the allowed limit (40°C) by the manufacturer, for warming the product without changing its consistency.

5.9.3 Environmental Considerations

The research site has two theatres used for elective CS. Both theatre rooms are identical with each room's doors and windows being closed during each operation as an infection control standard. Potential opening of the doors during the operation might occur, although they are aimed to be minimal. An open door is something that could create a small air draft which could interfere with the newborns temperature, especially for a preterm newborn. However, this study involved healthy term babies so such issues would have a minimum impact on newborns in comparison with preterm babies. Additionally, the theatre room and recovery room temperature are kept at 25°C for all CS term newborns and between 26-28° for preterm newborns. Each theatre room (including PACU) has a digital wall thermometer from which the room temperature was monitored. As the air-conditioning system was controlled from the manager's office, the theatre manager had control over the adjustment of the room temperature. All of these environmental factors were taken under consideration and possible small discrepancies were expected to occur with regard to the different seasons and outside weather conditions. These potential discrepancies were beyond my control or the control of theatre staff, reflecting the pragmatic nature of this study. Furthermore, participants of both groups had an equal chance of experiencing these environmental factors, therefore it was expected that exposure to these factors would be balanced between the groups.

5.9.4 Other concurrent treatments

It was the intention in this study that mothers, in either the intervention or control group, whose temperatures were below normal levels and/or were shivering, would be offered a Bair Hugger™. A Bair Hugger™ is a warming device that covers patients from their neck to their toes. This device is connected to a machine that fills the plastic cover with warm air. Warm air can be manually set at either 32, 38 or 43°C by the PACU nurse who is caring for the woman. The temperature settings chosen by each PACU nurse is informed by their clinical judgement and the severity of symptoms experienced by participants. As Bair Huggers™ can be used on any patient that has symptoms of hypothermia (core temperature below normal levels and/or shivering), it was expected that a number of study participants may receive this additional intervention.

This additional warming method may likely change the hypothermic temperatures of study participants which could impact on the study's findings. Additionally, it is a common safety practice in the hospital that women who receive post-operative active warming with a Bair Hugger™ do not undergo any SSC or breastfeeding in order to reduce the risk of neonatal suffocation and/or hyperthermia of the newborn who would otherwise be totally covered from the warm plastic cover during SSC in PACU. However, it would be unethical to withhold such an intervention from any hypothermic woman, given the effects of hypothermia on the woman's physical wellbeing (chapter 2 section 2.13). For that reason, where relevant the use of the Bair Hugger™ was documented in the participant's data collection booklet. This data has the potential to illustrate how delayed warming of women can have an additional impact in early breastfeeding and mothers' bonding time with their newborns.

Additional concurrent treatment that may be implemented is the use of a warming incubator for any infant who becomes hypothermic at any stage after their birth and before their transfer to the postnatal department. This additional treatment could alter the temperature findings of the newborns who received this warming method and change the final results of the study. It is clear that it would be unethical to withhold warming of any hypothermic newborn, as the effects of hypothermia can be even more significant to the newborn's wellbeing (chapter 2 section 2.4). For that reason, the use of the incubator where relevant was documented in the participant's data collection form.

The use of the above concurrent interventions could lead to bias in the findings and reduce the internal validity of the study. A solution to this problem is the use of intention-to-treat analysis, although the treatment effect may be conservative due to the noncompliance dilution of the study.

5.10 Site visits

I visited the research site on a daily basis during the entire recruitment and data collection phase, in order to keep the staff motivated and support them with any queries and/or problems with the process. During my presence in the theatre department, no additional queries/issues were raised by staff and my presence in theatre was welcome as the staff felt supported and confident to assist me with the trial. All theatre staff were informed of the progress of the trial on a monthly basis at staff meetings. Staff members were encouraged to provide feedback regarding the trial and to discuss with me any potential problems they encountered. My regular presence in the study site was appreciated by the staff and also increased the awareness of the trial, something I believe enhanced the smooth flow of the day to day conduct of my study.

5.11 Compliance and Trial Deviations

Protocol deviation refers to any non-adherence to procedures, intervention and/or evaluation, as specified in the protocol, which could happen either from participants or hospital staff (ICH 2016). Deviations were categorised according to their severity as:

- Minor (no impact on the evaluation of the intervention/it's effectiveness)
- Major (this deviation cannot always be prevented and may have some impact on the study)
- Protocol violation (this deviation could have been prevented and may affect the results of the study (ICH 2016))

To ensure that protocol compliance was achieved, theatre staff were offered monthly information sessions through face-to-face meetings. Also written information on which data to collect and when to collect them, was offered to all staff in the theatre communication book. Additionally, study information posters were demonstrated in each room within the theatre department to ensure staff complied with the study protocol at all times. Finally, I monitored theatre staff compliance, during the daily site visits, by supervising the administration of the right intervention and reminding the staff to collect and document the data.

Finally, since this was a pragmatic designed trial and conducted in a real clinical environment, it was expected that some deviations might occur irrespective of the compliance efforts (ICH 2016). For that reason, intention-to-treat analysis was performed, with which all trial participants were included in the analysis of the results, regardless of their compliance to the study protocol.

5.12 Trial Outcomes

As discussed in chapters 2 (section 2.4), 3 (section 3.8) and 4 (section 4.5), the most clinically important outcomes for women undergoing elective CS and initiating at birth SSC are neonatal and maternal hypothermia, as a result of neonatal and maternal temperature loss. Taking under consideration the effects that hypothermia has on newborn and maternal health and wellbeing (chapter 2, section 2.4), the dearth of research conducted so far in relation to prevention of neonatal and maternal hypothermia during CS while at birth SSC is performed (chapter 3, section 3.11) and the lack of recommendations/guidelines related to this issue, informed the trial's outcomes.

Primary outcome

To compare the effects of warmed IV fluids to room temperature IV fluids on neonatal hypothermia in newborns undertaken SSC (defined as a temperature < 36.5^0C, assessed immediately prior to transfer to PACU). Neonatal axillar temperatures were measured on two occasions using a neonatal axillar (under-arm) thermometer as per current hospital practice. The first temperature was measured by the theatre midwife in charge of each delivery, which took place after the initial at birth SSC in OT was discontinued and before the newborn was transferred to PACU to continue SSC and start breastfeeding with its mother. The second newborn temperature was measured by PACU staff before the discharge of the newborn from PACU. All newborn temperatures were measured with the use of axillar digital thermometer (SureTemp® Plus; Figure 5.3). These thermometers were used in measuring neonatal temperatures on a daily basis and were also frequently calibrated by hospital technicians.

Figure 5.3. Newborn digital thermometer (SureTemp® Plus)

Secondary outcomes

Secondary outcomes included the comparison of the effects of warmed IV fluids to room temperature IV fluids on: maternal hypothermia, maternal tympanic temperature, neonatal axillar temperatures, maternal shivering, maternal thermal comfort, use of additional warming for mothers and newborns, occurrence of adverse events for mothers and newborns and Interruption to SSC and breastfeeding. The secondary outcomes are important to study participants, as their prevalence would result in substantial morbidity and could have a negative impact on their overall CS experience.

Maternal hypothermia (defined as a temperature $<36^0$C) was assessed by the anaesthetist in charge, by measuring the tympanic maternal temperature, while at birth SSC was performed during the CS. These tympanic thermometers are the usual method of measuring women's temperatures in the hospital. Maternal temperatures were measured with the use of tympanic digital thermometer (COVIDIEN Genius 2; Figure 5.4). These thermometers were frequently calibrated by hospital technicians, in order to maintain the accuracy and good working condition of the devices.

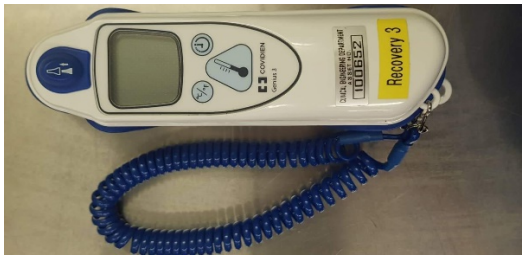


Figure 5.4. Maternal digital thermometer (COVIDIEN Genius 2)

Maternal tympanic temperature was measured on four occasions (on admission as a baseline measure, and on three occasions perioperatively using an adult tympanic (ear) thermometer as per current hospital practice). The first maternal temperature was measured by the admission midwife while she was preparing the mothers for their CS in the postnatal wards. The second measurement was collected by the anaesthetist in charge during at birth SSC and while the participant was having the CS. The third/fourth measurement was done by the PACU staff on participant PACU admission and prior to PACU discharge to the postnatal wards. The maternal digital thermometer (COVIDIEN Genius 2) is the only available thermometer used in adults around the hospital.

Maternal shivering (yes/no) was recorded by PACU staff in the e-chart, at the time of the participant's admission in PACU. At the same time, PACU staff graded the participants' thermal comfort by asking the participants if they felt cold, cool, neutral, warm or hot. A maternal thermal comfort scale was used, which has a 1-5 scale from cold, cool, neutral, warm and hot. If a participant's temperature was below normal levels, or if the mother

was shivering and was feeling cool or cold on her thermal comfort scale, then the PACU staff applied additional warming to the participants (Bair Hugger™; Figure 5.5). There are two types of Bair Hugger™ available in the theatre department of the hospital: a full body forced air warming blanket and an upper body forced air warming blanket. During the trial, the upper body forced air blankets was the only type available, due to storage capacity shortage of the full body forced air warming blanket. This was an additional benefit for the study as all the participants who received active warming received the same type. Bair Hugger™ devices are set on the highest temperature (43°C) at the beginning of the treatment and as the woman's temperature improves the temperature setting gradually reduces until it is discontinued once the woman becomes normothermic again.

Figure 5.5. Bair Hugger™

According to hospital policy, all women and newborns can to be transferred back to their postnatal wards as long as their vital signs are stable after their operation (including their temperature measurements). If a temperature measurement is suboptimal additional warming needs to be applied to either the mother or the newborn until normothermia is reached prior to PACU transfer. If a newborn's temperature measured below normal levels, the midwife in charge of the delivery would place the newborn inside an incubator (Figure 5.6) pre-set to 37°C, which is located outside the PACU, until the newborn temperature returned to normal levels. Only once the newborn was normothermic was it removed from the incubator and was brought back to its mother in PACU to resume SSC and initiate breastfeeding. Additional newborn warming could take place at any time after its delivery until before their PACU discharge. Recurring neonatal hypothermia in the same newborn was escalated by the midwife in charge to the hospital paediatrician, who would then review the newborn and would determine if the newborn would be admitted to NICU for further monitoring, especially since neonatal hypothermia has a direct effect on the newborns cardiac, respiratory and metabolic systems (chapter 2, section 2.4.1).

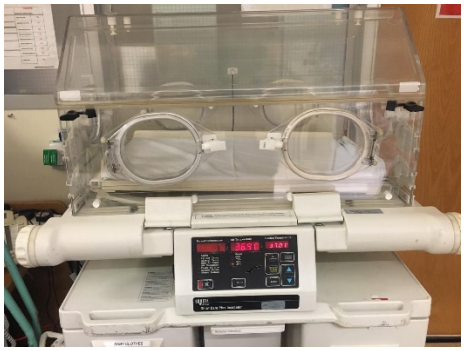


Figure 5.6. Newborn incubator

Unexpected events associated with neonatal and/or maternal hypothermia were also documented as adverse events. Additional adverse events could also include the potential effect of active warming on mothers and newborns, but also unexpected neonatal admissions to NICU, postpartum haemorrhage after CS and unexpected maternal/neonatal collapse. The occurrence of adverse events (for both newborn and mother) were documented directly by the researcher in the pre-designed adverse event form, who was notified directly by the theatre staff on the day the adverse event took place. All adverse events were escalated to the PI and if there was a possible relation to the intervention, the DSMB was also informed. Finally, interruption to SSC and breastfeeding was also documented especially in cases were additional neonatal warming was performed, since the newborns had to be warmed in the incubator which is stationed outside PACU and therefore away from the reach and view of their mothers. Additional information regarding interruption to SSC and breastfeeding was also collected from the nursing and midwifery notes within the participants' e-chart, in which the time and duration of SSC/breastfeeding were documented as per hospital policy. Additional information found in the e-charts were unexpected admissions to NICU something that would also interrupt the SSC and breastfeeding.

5.13 Data Collection

5.13.1 Baseline characteristics

The following baseline characteristics were collected on all study participants. These data are important to assess for baseline balance between groups at the end of the trial/during data analysis:

- Maternal age (date of birth)
- Anaesthetic received
- Duration of gestation (gestational age)
- Apgar score
- Birth weight

- Pre-theatre admission temperature of the women (measured during the admission in the postnatal departments, prior their transfer to OT for CS)
- OT and PACU ambient temperatures
- Total IV fluid volume administered
- Estimated blood loss (EBL)
- Skin to skin contact duration
- Breastfeeding
- Neonatal complications/type of complications and
- Maternal complications/type of complications.

Maternal age and gestational age were documented in the e-chart of each participant and were collected retrospectively. The admission temperature of the women was measured with the standard adult digital thermometer provided by the hospital, by the admission midwife and it was also documented in the participant's e-chart by the admission midwife. Additionally, birth weight of the participants' newborns, the EBL of the participants, the OT and PACU ambient temperatures and the SSC duration was documented in each participant's e-chart by the theatre midwives. Finally, the IV fluid volume was documented in each e-chart by any personnel who administered IV fluids and medication as per hospital policy. I was then able to retrospectively document all the above measured data in the data collection form (appendix 5.9).
Data collection tools included:

- Trial register form,
- Data collection booklet and
- Adverse event form (appendix 4.2).

Potential problems in data collection included:

- Incomplete data due to carelessness in data entry,
- Inter-observer variability and
- Participant withdrawal mid-way of the study.

The only problem experienced were incomplete documentation of data in some occasions, possibly caused by theatre personnel carelessness in data entry. As some data were not adequately documented in some e-charts, it was not feasible to retrospectively record them in the data collection booklet. This issue was addressed by offering staff support on how to successfully document/save the data to the e-charts and also by reminding the staff to document their measurements as per hospital policy. No

inter-observer variability was noted during the trial and no participant withdrew from the study.

Table 5.1. Data collection intervals

	Data Collection Interval			
	Start of study	Daily	When occurs	End of study
Trial screening and register form	√			
Data collection form		√		√
Adverse event form			√	√

5.13.2 Quality assurance

Quality assurance efforts ensured that high quality data are collected. Strategies to minimise potential problems in data collection included:

- Developing a manual of procedures guide. This manual included information on case definitions, inclusion and exclusion criteria for the trial, and the outcome events forms used to collect relevant data.
- Developing data collection forms based on other similar forms in past RCTs.
- Developing a protocol which gave instructions on how to fill out the data collection form.
- Providing information sessions about the study to all theatre staff.
- Cross checked the data collected during the study.
- Verified that the correct intervention was given by being present in theatre during the operation of the participant. Verification was documented in the data collection form (appendix 4.7). On two occasions, were the researcher was not present, the anaesthetist in charge administered room temperature fluids in participants originally allocated in the warm IV fluid group. There were no other times when the correct intervention was not given.

5.14 Safety Monitoring and Reporting During Trial

This trial was monitored by a TSC and DSMB. Additional mechanisms facilitating monitoring and reporting, included the development of SOPs and the assessment of participants for any adverse events. There were no adverse events anticipated in this study, but a process was in place if such events occurred. According to GCP, a document that recorded adverse events was created in anticipation of such events (ICH 2016).

5.14.1 Trial Steering Committee

Face to face meetings with the TSC took place on two occasions during the study; before the beginning of the trial (13th of October 2017) and midway through the trial (21st of March 2018). Minutes of these meetings were kept by me and then I filed them in the Trial Master File. Further communication was achieved via emails, copies of which were filed in the Trial Master File. A copy of a Terms of Reference (TOR) was provided to each TSC member (Appendix 5.4). Safety reports were submitted every four months to Institutes Research Ethics Committee (REC). Additionally, a declaration form announcing the end of the trial has been submitted.

Deadlines were approached in a timely manner, with a reminder being sent to individual TSC members 4 days before the deadline. The only issue that was highlighted in the first TSC meeting was the concern of the theatre managers of any potential additional workload that could apply to theatre staff because of the trial. Reassurance was given once again that the staff would engage in their daily activities as usual without any additional task being added to their workload. The theatre staff were requested to perform their usual measurements and provide the usual care to the women/newborns irrespectively as to whether they are participating in the trial or not. Finally theatre staff were required to document all their measurement and care provided in the e-chart as per hospital policy. No further issues were addressed and overall both TSC meetings were uneventful.

5.14.2 Data Safety Monitoring Board

The DSMB met three times during the trial. All DSMB members were contacted via e-mail by me requesting their participation in the DSMB and offered a copy of the study protocol and the TOR (Appendix 5.5). Once all members of DSMB accepted their invitation, the first official DSMB meeting was arranged. The first meeting took place on the 9th of October 2017, before the Trial started. The DSMB and researcher discussed the study protocol, TOR, schedule/format of future meetings and interim reports. During the second meeting (18th of March 2018) unblinded interim results were discussed, with a particular focus on the safety, rights and well-being of trial participants. This meeting took place after the trial had commenced. Data for the interim analysis included accrual and dropout rates, baseline data, data relating to compliance with interventions and outcome data comparing the effects in the intervention and control groups (Appendix 5.6). The final meeting discussed the findings of the trial (Appendix 5.7) and took place at the end of the trial (20th of April 2018). Before the final meeting one of the DSMB members withdrew due to increased workload. The final meeting was carried out with the remaining DSMB members as it was too late for a replacement member to be found.

5.15 Data Analysis

Statistical tests were two-tailed, while a p-value below .05 was considered statistically significant. ITT was used for the data analysis, for all the outcomes of the trial.

ITT was used for primary analysis to increase the external validity of the collected data. With this type of analysis, all collected data, from all the participants, were analysed, whether or not the participants continued their intervention or if there were missing data among the groups. Thankfully, no participants withdrew from the trial, however the intervention was discontinued on three participants, one because she felt uncomfortably warm (although her temperature was within normal levels) and the last two because their temperature during the intervention was 37.6°C. There were also some missing data noted during the data collection phase. A number of newborn temperatures during PACU discharge were not documented (total *n*=18, 8 from intervention group and 10 from comparator group), either because the newborns were transferred to the NICU or because they were not adequately documented on the e-charts by the PACU staff. Additionally, there were n=11 maternal temperatures (n=4 in the intervention group and n=7 in the comparator group) not documented by the anaesthetists during at birth SSC. Despite the above described missing data, ITT would help to keep the balance between the two groups of the study and also to estimate the treatment effect. The main disadvantage of ITT is that although it helps to reduce bias, it could dilute the estimates of treatment effects (Torgerson & Torgerson, 2008). To prevent that from happening, sensitivity analysis was used, especially in outcomes were data were missing (chapter 6, section 6.4 and 6.5.1).

All collected data were anonymised, and were inputted first into Excel software, which was available on the department's computer, and then it was transferred by me (on a designated password protected USB) to my own laptop on which I had installed the SPSS software (version 25). Since all the data were anonymised from the beginning of the process, it was impossible to identify the identity of the participants, something that is compatible with the data protection guidelines. Descriptive statistics were initially used, followed by inferential statistics. Descriptive statistics describe the data collected from the sample (i.e. mean and SD), whereas, inferential statistics were used to make predictions based on these data and be able to generalise the findings of the sample to the general population.

Categorical data of the study (such as: neonatal and maternal hypothermia, type of feeding) were analysed by counting the occurrence of participants with an event. The difference between groups was analysed using a Chi-square (x^2) test (non-parametric

test). This test would prove that the effectiveness of the treatment was not due to chance. The assumptions underpinning the chi-square test include: there should be two categorical variables, the data should be counts or frequencies not percentages, the study groups must not be related, the expected value of the cell must be five or more but not less than one and each subject must have data for only one cell (McHugh 2013). When the value of the cell was five or more Fisher's exact test was used instead (Kim 2017). The results of dichotomous data were analysed with the use of Relative risks (RR), with 95% confidence intervals (CIs). RR to compare the chance of an event occurring between two groups (Andrade, 2015).

Continuous data from the study (neonatal and maternal temperatures, neonatal weight, gestational age, maternal age) were analysed using mean, standard deviation and interquartile range (where appropriate). To compare mean differences between the groups, two-sample independent t-test (parametric test) or Mann-Whitney U test (non-parametric test) was used. The independent t-test was used to determine if the mean of the dependent variables (shown above) are similar between the two independent groups of this study. Specifically, this test showed if the mean difference between the groups was due to the treatment effect rather than chance. In order to use an independent t-test, six assumptions must be met; the dependant variables should be continuous, independent variable should involve two categorical, independent groups (active warming, no warming), there should be independence of each observation, there should be no significant outliers, data should be approximately normally distributed and there should be homogeneity of variances (Field, 2013). In my trial, some of the data were not normally distributed (maternal tympanic temperature at the end of SSC in OT, neonatal axillary temperature at the end of SSC in OT and on PACU discharge), violating in this way one of the assumptions and for that reason the equivalent non-parametric test Mann-Whitney U test was used instead. Mann-Whitney U test, similar to independent t-test, is used to compare two sample means from the same population and test whether these two means are equal or not. However, unlike the independent t-test it has less assumptions which include: the sample of the population has to be random, there should be independence of each observation and independent variable should involve categorical data. The difference in reporting the findings of Mann-Whitney U test, compared to independent t-test, is that it presents the results in group rank differences rather than group mean differences (Field 2013). In my study, the p values of Mann-Whitney U test reflect those reported using the independent t test (Chapter 6, section 6.5.2).

Analysis of variance (ANOVA) calculates any statistically significant differences between the means of three or more independent (unrelated) groups. Since this study compared only two groups, ANOVA was not applicable to use (Field 2013). However, Pearson's correlation (correlation coefficient) was used instead to investigate the relationship between two continuous variables, which in my trial investigated the correlation between maternal temperatures and neonatal temperatures. The assumptions of the Pearson's correlation test include; each variable has to be continuous (Spearman correlation should be used, if one or both of the variables are ordinal), each observation should have a pair of values, absence of outliers in either variable, normality of variables, linearity (a "straight line" should be formed on the scatterplot between the variables), and homoscedasticity (which refers to the distance between the points to that straight line seen on the scatterplot) (Schober *et al* 2018). MANOVA (multivariate analysis of variance) calculates any differences between independent groups on more than one continuous dependent variable. The MANOVA assumptions include: the sample should be random and independent from the population, each dependent variable has to be continuous and they should be normally distributed, the independent variables has to be categorical. In my trial MANOVA was planned to calculate the impact of active warming on neonatal and maternal temperatures, but it was not applicable in my trial since the data on neonatal and maternal temperatures were not normally distributed and there is no non parametric test available to do this calculation instead of MANOVA (French *et al* 2008) .

Finally, all possible regressions model of logistic regression analysis was used to understand the relationship between the independent variable and the dependent variables of the study, since it helps to predict the likelihood of an event happening. The reason that the all possible regressions model was used over other models of logistic regression was the fact that the literature recommends its use if the study has 15 or less independent variables (NCSS 2019). Specifically, all possible regressions analysis was used to understand the relationship between the neonatal hypothermia (at the end of SSC in OT and before PACU discharge) and a number of predictors of the likelihood of neonatal hypothermia in my study. These variables included: maternal temperature/ maternal hypothermia at the end of SSC in OT, OT and PACU ambient temperatures, SSC duration, type of feeding, infants weight, IV fluid volume, Estimated Blood Loss, gestational age and additional maternal/neonatal warming. As logistic regression analysis helps in understanding relationships and predicting outcomes, it is a useful tool to improve decision-making and support health care professionals to provide preventative care (Field 2013). When the dependent variables are categorical,

the model of logistic regression analysis used is binary regression. If the dependent variables are continuous, then multinomial regression analysis was used. In my study, binary regression was used to predict if maternal hypothermia during SSC in OT would predict the likelihood of neonatal hypothermia. Additionally, binary regression was used to predict if additional warming of the mothers/newborns would predict the likelihood of neonatal hypothermia happening. In order to use logistic regression analysis the following assumptions should be met: a linear relationship between the outcome and each predictor variables should be present, there are no outliers and no multicollinearity in the continuous data (Field 2013). In order to review the existence or not of multicollinearity, the variance inflation factor (VIF) was calculated with the use of Excel in each of the above mentioned dependant variables.

The collected data were documented by the theatre staff on the electronic charts of each woman. Subsequently I accessed each participants electronic chart and documented the collected data in the trial data collection booklet. The collected data were then inputted in Microsoft Excel, within the hospital premises, using the study number given to each participant to ensure their anonymity. The collected data were inserted in the data collection booklet and Excel by myself and an anaesthetic registrar to ensure that all data were inputted correctly from the e-charts to the data collection booklet and then to the Excel software. As they were anonymised all the collected data in Excel were transferred safely from the hospital premises to my password protected laptop, using of a password protected USB stick. This was done to ensure that the data were protected during each phase of data collection and analysis, in accordance with the agreement made with the REC of the hospital. I inputted and analysed all anonymised collected data from Excel to the IBM SPSS statistic software version 25. At the same time the anonymised data were also offered to the hospital statistician, who also analysed the data independently of myself. The findings of these two separate analyses were then compared to ensure the rigour and accuracy of the data findings.

The anonymised data, in Excel format, were also submitted for analysis to the principal investigator who performed an independent analysis. My analysis was compared with the results of the PI as another measure to ensure rigour and accuracy of the data analysis. Three independent meetings took place with each of the above members and the findings were compared with each person/group individually. The first meeting was organised with the hospital statistician on the 11th of July 2018, during which some minor corrections took place as to how to more effectively use the IBM SPSS statistic software (version 25). Based on these corrections, the lead researcher repeated the SPSS findings, reaching the same outcomes with the statistician. The second meeting took

place on the 20th of July 2018 with the PI where the individual findings were also compared. The PI used a different statistical software (SigmaStat 4.0) and his findings were similar to the SPSS findings. Finally, the findings of study were reviewed in the third meeting with the DMSB members.

5.15.1 Assessing normality

One of the most important aspects in statistics is to ensure that the assumption of normality applies to the collected data. The distribution of data offers a clear idea of which statistical test should be performed in each situation in order to achieve the best results (Daly *et al* 1991). An assessment of the normality of the data included examination of the baseline characteristics and primary/secondary outcomes including neonatal temperatures (T_1 and T_2) and maternal temperatures (T_1, T_2, T_3 and T_4). Due to the sample size in the study, the normality was assessed with the Shapiro-Wilk test. This test is used when the database has less than 2000 data to assess normality (http://www.maths-statistics-tutor.com/normality_test_pasw_spss.php accessed on 21/05/2018). Once the p-value of this test is below .05 then the null hypothesis can be rejected and the data are considered non-normally distributed, allowing us to use non-parametric tests to analyse the data in this scenario. Finally, no assessment of normality was performed on dichotomous data where Chi^2 test was applied, as assumption of normality is not relevant to this type of analysis. These data include maternal hypothermia (defined as temperature $<36^0$C), maternal shivering (yes/no), use of additional warming of mothers (Bair Hugger™) and use of additional warming of new-born (incubator).

5.16 Conclusion

In this chapter information on the methods of conduct of the trial were discussed. The trial was approved by the REC of the trial site. Permission was also granted by the Director of Nursing and Midwifery of the trial site and the Consultant Obstetricians and Anaesthetists. The population of the study was pregnant women and their newborns who were booked for elective CS and willing to part take in SSC. Trial eligibility of the participants was assessed by an independent midwife, who was admitting/preparing the women prior to their operation. The randomisation sequence was generated by the hospital statistician with the use of a computer randomisation software and participants were assigned to either the intervention or control group using sequenced opaque sealed numbered envelopes, which ensured allocation concealment. Participants in the intervention group received administration of warm IV fluids heated at 39°C with the use of Hotline™ device while the participants in the control group received the administration of room temperature IV fluids (25°C) with the use of Hotline™ device that was not switch

on (to achieve blinding of participants and staff). All records related to the trial conduct were kept in the Trial Master File.

Blinding of participants and theatre personnel was done by the theatre anaesthetists, who were independent from the study, by applying the hotline giving sets to all participants, but activating the device for only those participants assigned to the intervention group. Compliance with the trial protocol was monitored by myself during daily on-site visits. The primary outcome of the study was the occurrence of neonatal hypothermia between the two study groups. Data relevant to trial outcomes were collected and recorded by theatre midwives and nurses in participants' hospital's e-charts. The data was then transferred to the data collection booklet. Adverse events were monitored and reported based on the guidance of a SOP document. A TSC and a DSMB were assembled prior the commencement of the trial to assess the trial progress, review the trial interim analysis and ensure that the study was conducted in a safe manner following the protocol and to identify any potential reasons which would lead to a discontinuation of the trial. Finally, the strategy used for the data analysis was explained.

Chapter 6. Findings of NeoHyp Trial

6.1 Introduction

In this chapter the findings of the NeoHyp trial are presented based on an 'intention to treat' analysis. Findings are presented for the comparison of warm IV fluid administration (39°C) via Hotline™ device (intervention group) versus room temperature IV fluids (approximately 25°C) (comparator group) which is the normal care provided in the hospital. These findings are presented based on the CONSORT guidelines for reporting parallel group randomised trials (Moher *et al* 2010).

Two-tailed statistical tests were used, with a p value of <0.05 considered statistically significant. Categorical data are reported with the use of frequencies (numbers and percentages) relative risk and absolute risk reduction. Differences between group proportions were analysed using Chi^2 and Fisher's Exact tests, where appropriate (Chapter 5, section 5.15). Continuous data are reported with the use of means and standard deviations (SD) and, where appropriate, with median and interquartile ranges. Two sample independent *t*-test (for normally distributed data), Mann-Whitney test (where normal distribution of data was rejected), logistic regression analysis and Pearson correlation were also calculated (chapter 5, section 5.15). Finally, confidence intervals are also reported, where applicable.

The results of trial recruitment and randomisation are discussed first, followed by findings relating to baseline characteristics, primary outcomes, secondary categorical and continuous outcomes, logistic regression and additional findings of my trial.

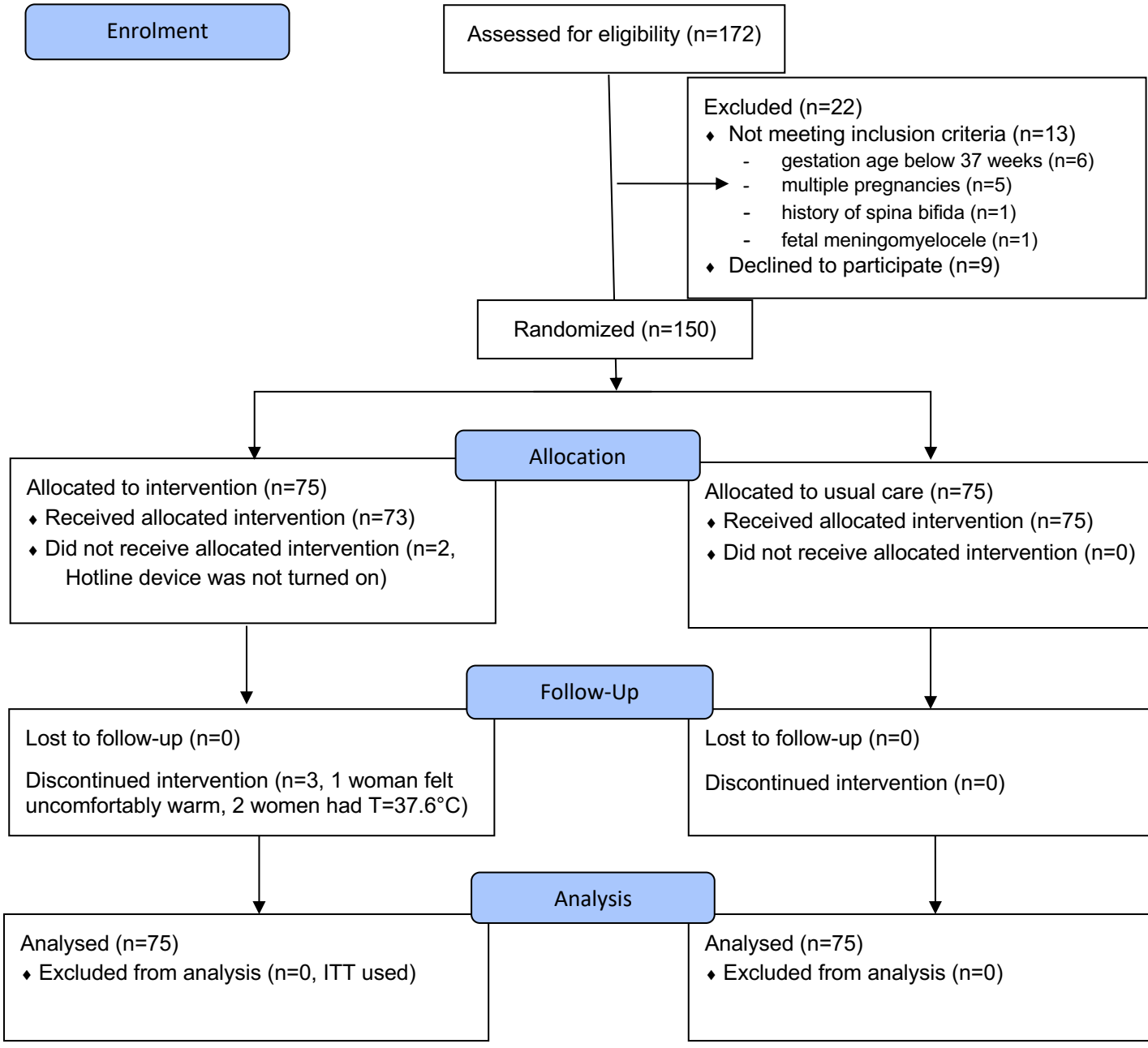
6.2 Recruitment and Randomisation

A total of 172 pregnant women undergoing elective CS were assessed by the staff for trial eligibility between February 2018 and May 2018. Following this eligibility assessment, 13 (7.5%) women were excluded as they did not meet the inclusion criteria (Figure 6.1). After the eligibility assessment, 159 women were eligible for the trial. A total of 150 (94.3%) women agreed to participate with a refusal rate of 5.6% (n=9). Following randomisation, 75 women were assigned to the intervention group and 75 to the control group.

All women in the comparator group received fluids that were at room temperature, two women from the intervention group did not receive their intervention as the Hotline device was not switched on due to human error. Additionally, three women from the

intervention group had their intervention discontinued as two developed a temperature of 37.6°C, while the third stated that they felt uncomfortably warm (though her recorded temperature was 37.2°C, which is within the normal levels). All three cases where recorded as adverse events. No women were lost to follow up. All women were included in the data analysis as ITT was used.

Figure 6.1: NeoHyp Trial Flow Diagram



6.3 Baseline Characteristics of Participants

All trial participants (100%) had spinal anaesthesia. The mean maternal age of the intervention group and the comparator group was 35.5 years old (SD 5.51) and 34.4 (SD 5.14, p=0.46), respectively, with the majority of women over the age of 35 (n=80, 53.34%). Table 6.1 outlines the baseline characteristics for both groups. The mean gestational age in the intervention group and the comparator group was 38.95 weeks (SD 0.93) and 38.5 weeks (SD 4.24, p=0.03), respectively. Newborns of women who received warm IV fluids had a mean birth weight of 3470 grams (SD 486.48; median 3490 and IQR 660 grams) similar to the comparator newborn birth weight (3479.5 grams, SD 540.86; median 3570 and IQR 653 grams). Differences between groups were not significant (t [147] =-0.11, p=0.33; Mann-Whitney test (U=2976.5, z= 0.53, p=0.44). The pre-theatre admission temperature for women in the intervention group was lower (36.45°C, SD 0.29; median 36.5°C and IQR 0.4°C) than the comparator group (36.56°C, SD 0.34; median 36.4°C and IQR 0.5°C). While this difference was significant with the t-test (t [149] =-2.12, p<0.00) it was not significant using the Mann-Whitney test (U=2482, z= -1.12, p=0.26).

Table 6.1. Baseline characteristics

Baseline characteristics Warm IV fluids Vs Room temperature fluids Mean (SD)				
	Warm IV fluids (n=75)	**Room temperature fluids (n=75)**	**P[1]**	**Overall total mean (SD)**
Maternal age	35.5 (5.51)	34.4 (5.14)	0.46	34.95 (5.32)
Gestational age	38.95 (0.93)	38.5 (4.24)	0.03	38.72 (2.58)
Birth weight (gr)	3470 (486.48)	3479.5 (540.86)	0.33 (0.44[#])	3474 (513.67)
Pre-theatre admission temperature of the women	36.45 (0.29)	36.56 (0.34)	0.00 (0.26[#])	36.48 (0.31)
OT ambient temperature	23.87 (1.75)	23.73 (1.30)	0.65	23.8 (1.52)
PACU ambient temperature	23.73 (0.57)	24.01 (0.84)	0.73 (0.00[#])	23.87 (0.7)

P[1], p-value t-test; [#] p-value independent two sample t-test (Mann-Whitney Test).

The ambient OT temperature for both groups was comparable: 23.87°C (SD 1.75) for the intervention group and 23.73°C (SD 1.3, p=0.65) for the comparator group. The ambient PACU temperature for the intervention group was lower (23.73°C, SD 0.57; median 36.5°C and IQR 0.4°C) than the comparator group (24.01°C, SD 0.84; median

36.4°C and IQR 0.5°C). Difference between groups was not significant with the t-test (t [144] =-2.33, p=0.73) but significant with the Mann-Whitney test (U=2549, z= -.17, p<0.00).

In general, there were no significant differences between the main comparison groups with respect to baseline characteristics except for gestational age, pre-theatre admission temperature for women and PACU ambient temperature. The data on the pre-theatre admission temperature for women and PACU ambient temperature outcomes showed a difference in p values between the t-test and the Mann-Whitney test. However, since the data in these outcomes were non-normally distributed (due to the presence of outliers), the t-test is not reliable (as it assumes normality) and the non parametric test (Mann-Whitney test) is more reliable for non-normally distributed data (Chapter 5, section 5.15).

6.4 Primary Outcome

The proportion of newborns with neonatal hypothermia (defined as a temperature < 36.5^0C) assessed at the end of SSC in OT was significantly lower in participants receiving warmed IV fluids (*n*=4/75, 5.3%) than participants who received room temperature IV fluids (*n*=14/75, 18.7%; RR 0.28, 95% CI 0.09 to 0.82; p=0.02; Table 6.2). Regarding the number of newborns with neonatal hypothermia before PACU discharge to the post-natal ward there was no statistical difference between the two groups (*p*=0.3). Specifically, there were no hypothermic babies in the intervention group (*n*=0/75, 0%) and only one hypothermic baby in the comparator group (*n*=1/75, 1.5%; RR 0.33, 95% CI 0.01 to 8.05).

Table 6.2: Primary outcomes

Neonatal Hypothermia **Warm IV fluids Vs Room temperature fluids (N %)**						
	Warm IV fluids (n=75)	**Room temperature fluids (n=75)**	**P[1]**	**Relative Risk (95% CI)**	**Absolute Risk Reduction (95% CI)**	**Total (n=150 N (%)**
At the end of SSC in OT	4 (5.3%)	14 (18.7%)	.02	0.28 (0.09 to 0.82)	13.3 (3.15 to 23.51)	18
Before PACU discharge	0 (0%)	1 (1.5%)	.30	0.33 (0.01 to 8.05)	1.3 (-1.26 to 3.92)	1

[1] p-value chi-square (Pearson's test).

There was no missing data for the primary outcome related to neonatal hypothermia at the end of SSC in OT. However, a sensitivity analysis (table 6.3) was carried out to assess the potential impact on newborns (total *n*=18, 8 from intervention group and 10

from comparator group), whose temperatures were not documented before PACU discharge regarding the primary outcomes analysis for before PACU discharge. Using the worst case scenario, it was assumed that all newborns whose data were not documented before PACU discharge developed hypothermia (scenario one). Based on this scenario there were n=8/75 (10.66%) newborns who become hypothermic in the intervention group and n=11/75 (14.66%) in the comparator group (RR 0.72, 95% CI 0.31 to 1.70), the difference between the groups was not statistically significant (p=0.46). Furthermore, an 'Intervention worst, comparator best' scenario (scenario two) and an 'intervention best, comparator worst' scenario (scenario three) was also presumed for newborns of the intervention group and the comparison group, whose data regarding neonatal hypothermia were not documented in the e-charts before PACU discharge. Based on scenario two, there were n=8/75 (10.66%) newborns who become hypothermic in the intervention group and n=1/75 (1.3%) in the comparator group (RR 8.0, 95% CI 1.02 to 62.39), the difference between the groups was statistically significant (p=0.04). Finally, based on the third scenario, there were n=0/75 (0%) newborns who become hypothermic in the intervention group and n=11/75 (14.66%) in the comparator group (RR 0.04, 95% CI 0.0026 to 0.72), the difference between the groups was statistically significant (p=0.02).

This sensitivity analysis suggests that the results of the primary outcomes are robust, when all the missing data in both groups were assumed as cases of hypothermia, because the results are not sensitive to a large increase in the number of events in both groups and/or in the comparator group. If scenario two was correct, then the intervention group would do significantly worse than the comparator group. However, this scenario is very unlikely to be true if we take under consideration the physiology of neonatal thermogenesis for newborns delivered from mothers whose core temperature was optimal (Chapter 2, section 2.3.1). If scenario three was correct then the comparator group would do significantly worse than the intervention group, something that would support the theory that administration of warm IV fluids has a longer lasting effect in the prevention of neonatal hypothermia after the end of the intervention.

Table 6.3. Sensitivity analysis on missing data

Neonatal Hypothermia (before PACU discharge) **Warm IV fluids Vs Room temperature fluids (N %)**						
	Warm IV fluids (n=75)	**Room temperature fluids (n=75)**	**P[1]**	**Relative Risk (95% CI)**	**Absolute Risk Reduction (95% CI)**	**Total (n=150 N (%)**

Scenario one	8 (10.66%)	11 (14.66%)	0.46	0.72 (0.31 to 1.70)	4 (-6.62 to 14.62)	19
Scenario two	8 (10.66%)	1 (1.3%)	0.04	8.0 (1.02 to 62.39)	-9.3 (-16.78 to -1.88)	9
Scenario three	0	11 (14.66%)	0.02	0.04 (0.0026 to 0.72)	14.7 (6.66 to 22.67)	11

[1] p-value chi-square (Pearson's test).

6.5 Secondary Outcomes

6.5.1 Categorical outcomes

Maternal hypothermia, defined as temperature < 36^0C, assessed during SSC in OT occurred significantly less frequently in women receiving warmed IV fluids (*n*=2/75, 2.6%) compared to women receiving room temperature IV fluids (*n*=13/75, 17.3%; RR 0.15, 95% CI 0.03 to 0.65; p=.0027; Table 6.4). Similar significant differences between the intervention group *n*=10/75, (13.3%) and the comparator group were recorded for the proportion of women with maternal hypothermia on PACU admission (*n*=26/75, 34.6%; RR 0.38, 95% CI 0.2 to 0.74, p= .0022). Also, before PACU discharge to the postnatal ward, although clinically more participants receiving usual care experienced hypothermia than participants in the intervention group, there was no statistical difference between the two groups; *n*=5/75 (6.6%) and *n*=0/75 (0%; RR 0.09, 95% CI 0.005 to 1.61, p=.10). Furthermore, the proportion of women experiencing maternal shivering was significantly higher in women receiving room temperature IV fluids (30/75, 40%) than in women receiving warmed IV fluids (3/75, 4%; RR 0.1, 95% CI 0.03 to 0.31; p= .0001).

The need for additional warming for mothers and newborns during their stay in PACU (chapter 5, section 5.12), was also explored. Additional warming was needed by a significantly higher percentage of mothers in the comparator group (42/75, 56%) compared to mothers in the intervention group (13/75, 17.3%; RR 0.31, 95% CI 0.18 to 0.52; p=.0001). The use of additional warming in newborns whose mothers received room temperature IV fluids (27/75, 36%) was also significantly higher than newborns whose mothers received warm IV fluids, (8/75, 10.6%; RR 0.29, 95% CI 0.14 to 0.6; p= .0009).

Maternal thermal comfort described as "feeling cool" was observed in a higher percentage of mothers in the comparator group (24/75, 32%) than mothers in the intervention group (2/75, 2.6%). Furthermore, maternal thermal comfort described as "feeling neutral" was comparable across both groups, 56% (42/75) in the comparator group and 54.6% (41/75) in the intervention group. Finally, maternal thermal comfort described as "feeling warm" was observed in a lower percentage of mothers in the comparator group (9/75, 12%) than mothers in the intervention group (32/75, 42.6%).

No women in either group said that they felt too cold or too hot during their stay in PACU. Based on the above number of participants who reported “feeling cool” and “feeling warm”, a 2x2 chi-square test of independence was conducted. This showed that the thermal comfort of women who were administered warm IV fluids (34/75, 45.3%) was not statistically different to women who received room temperature fluids (33/75, 44%; RR 1.03, 95% CI 0.72 to 1.47; p= 0.86).

Table 6.4. Secondary categorical outcomes

Secondary categorical outcomes Warm IV fluids Vs Room temperature fluids (N %)						
	Warm IV fluids (n=75)	**Room temperature fluids (n=75)**	**P[1]**	**Relative Risk (95% CI)**	**Absolute Risk Reduction (95% CI)**	**Total (n=150 N (%)**
Maternal hypothermia during SSC in OT	2 (2.6%)	13 (17.3%)	p= .0027	0.15 (0.03 to 0.65)	14.7 (5.35 to 23.97)	15
Maternal hypothermia on PACU admission	10 (13.3%)	26 (34.6%)	p= .0022	0.38 (0.2 to 0.74)	21.3 (8.09 to 34.57)	36
Maternal hypothermia on PACU discharge	0 (0%)	5 (6.6%)	p= .10	0.09 (0.005 to 1.61)	7.1 (1.11 to 13.17)	5
Maternal shivering	3 (4%)	30 (40%)	p= .0001	0.1 (0.03 to 0.31)	36 (24.05 to 47.94)	33
Additional maternal warming	13 (17.3%)	42 (56%)	p= .0001	0.31 (0.18 to 0.52)	38.7 (24.53 to 52.79)	55
Additional newborn warming	8 (10.6%)	27 (36%)	p= .0009	0.29 (0.14 to 0.6)	25.3 (12.41 to 38.24)	35
Maternal thermal comfort	34 (45.3%)	33 (44%)	p= .86	1.03 (0.72 to 1.47)	-1.3 (-17.24 to 14.57)	67
Newborn adverse events	1 (1.33%)	0 (0%)	p= .49	3 (0.12 to 72.48)	0.01 (0.013 to 0.013)	1
Maternal adverse events	3 (4%)	0 (0%)	p= .19	7 (0.36 to 133.22)	-4 (-8.43 to 0.43)	3
Interruption to SSC	8 (10.6%)	27 (36%)	p= .0009	0.29 (0.14 to 0.6)	25.3 (12.41 to 38.24)	35

Interruption to breastfeeding	5 (6.6%)	17 (22.6%)	p=.0076	0.27 0.10 to 0. 71)	0.31 (0.31 to 0.32)	22
Breastfeeding	53 (70.6%)	53 (70.6%)	p=1.0	1 (0.81 to 1.22	0 (-14.57 to 14.57)	106
Maternal complications	2 (2.6%)	6 (8%)	p= .16	3.3 (0.06 to 1 .59)	6 (-1.67 to 13.58)	8
Neonatal complications	4 (5.3%)	5 (6.6%)	p= .73	0.8 (0.22 to 2 .86)	-4 (-11.57 to 3.57)	9

[1]p-value chi-square (Pearson's).

There was n=1/75 (1.33%) newborn adverse events in the intervention group and n=0/75 (0%) in the comparator group (RR 3, 95% CI 0.12 to 72.48; p=.499). The type of neonatal adverse event documented in the intervention group was the newborn of the mother whose intervention was discontinued early as she felt uncomfortably warm. This newborn developed a temperature of 37.6°C possibly because it was kept under the neonatal resuscitaire (ohio) for a longer period of time.

Additionally, there were n=3/75 (4%) maternal adverse events in the intervention group and n=0/75 (0%) in the comparator group (RR 7, 95% CI 0.36 to 133.22; p=0.19). The type of maternal adverse events documented in the intervention group included two women who developed a temperature of 37.6°C and one woman who felt uncomfortably warm during the administration of warm IV fluids.

Overall, only 10.6% (8/75) of participants who received warm IV fluids had interruption to SSC compared to 36% (27/75) who received room temperature IV fluids (RR 0.29, 95% CI 0.14 to 0.6) the difference between the groups was statistically significant (p= .0009). In addition, participants who received warm IV fluids experienced less interruption to breastfeeding (5/75, 6.6%) than participants receiving room temperature IV fluids (17/75, 22.6%; RR 0.27, 95% CI 0.10 to 0.71) the difference between the groups was statistically significant (p=.0076). Both groups were comparable in the proportion of participants who breastfeed their newborns (n=53/75, 70.6%; RR 1, CI 95% 0.81 to 1.22 p=1.0).

There were no differences between the intervention and comparator group in the number of neonatal complications: 5.33% (n=4/75) and 6.6% (n=5/75, RR 0.8, 95% CI 0.22 to 2.86; p=.73), respectively. The type of neonatal complications in the comparator group included newborns requiring minor resuscitation immediately after birth (n=2), a newborn admitted to NICU due to low SPO_2 (n=1), a newborn who was hyperthermic (37.8°C) and kept for a prolonged period of time under the ohio while its mother was treated for PPH (n=1) and a newborn was kept longer under the ohio for observations

due to grunting (n=1). On the other hand, the type of neonatal complications in the intervention group included four newborns admitted to NICU due to Transient tachypnea of the newborn (TTN).

Maternal complications were lower in those women receiving IV warm fluids (n=2/75, 2.6%) than those women receiving usual care (n=6/75, 8%; RR 3.3, 95% CI 0.06 to 1.59). However, this difference was not significant (p= .16). The type of maternal complications in the intervention group were two cases of PPH. On the other hand, the type of maternal complications that occurred in the comparator group included four cases of PPH, one woman fainted due to low BP post anaesthesia and n=1 woman had a bowel injury during her CS.

A sensitivity analysis (table 6.5) was carried out to assess the potential impact of maternal hypothermia, on those participants whose data were not documented during SSC in OT. Using the worst case scenario, it was assumed that all mothers whose data were not documented during SSC in OT (n=4 in the intervention group and n=7 in the comparator group) developed hypothermia (scenario one). Based on this scenario there were n=6/75 (8%) participants who become hypothermic in the intervention group and n=20/75 (26.6%) in the comparator group (RR 0.3 95% CI 0.12 to 0.70). The difference between the groups was statistically significant (p= .0057).

Furthermore, an 'Intervention worst, comparator best' scenario (scenario two) and an 'intervention best, comparator worst' scenario (scenario three) was also presumed for participants of the intervention group and the comparison group, whose data regarding maternal hypothermia were not documented in the e-charts during SSC in OT discharge. Based on scenario two, there were n=6/75 (8%) participants who become hypothermic in the intervention group and n=13/75 (17.3%) in the control group (RR 0.46, 95% CI 0.18 to 1.14). The difference between the groups was not statistically significant (p=.0969; Table 6.5).

Finally, based on the third scenario, there were n=2/75 (2.6%) participants who became hypothermic in the intervention group and n=20/75 (26.6%) in the comparator group (RR 0.1, 95% 0.02 to 0.41). The difference between the groups was statistically significant (p=.0015).

This sensitivity analysis suggests that the results of the secondary outcomes are robust, when all the missing data in both groups were assumed as cases of hypothermia, because the results are not sensitive to a large increase in the number of events in both groups and/or in the control group. If scenario three was correct, then the comparator group would do significantly worse than the intervention group.

Table 6.5. Sensitivity analysis on missing data

Maternal Hypothermia (during SSC in OT) Warm IV fluids Vs Room temperature fluids (N %)						
	Warm IV fluids (n=75)	**Room temperature fluids (n=75)**	**P[1]**	**Relative Risk (95% CI)**	**Absolute Risk Reduction (95% CI)**	**Total (n=150 N (%)**
Scenario one	6 (8%)	20 (26.6%)	p=.0057	0.3 (0.12 to 0.70)	27.7 (13.3 to 42.01)	26
Scenario two	6 (8%)	13 (17.3%)	p=.09	0.46 (0.18 to 1.14)	12.3 (0.15 to 24.39)	23
Scenario three	2 (2.6%)	20 (26.6%)	p=.0015	0.1 (0.02 to 0.41)	33.6 (20.37 to 46.87)	22

[1] p-value chi-square (Pearson's test).

6.5.2 Secondary Continuous Outcomes

The maternal mean tympanic temperature during SSC in OT for the intervention group was 36.42 °C (SD 0.44; median 36.2°C and IQR 0.6°C) and for the comparator group 36.48 °C (SD 0.43; median 36.6°C and IQR 0.57°C). The difference between groups was not significant with t-test (t [139] =1.97, p=0.79) but was significant with the Mann-Whitney test (U=2409, z= 0.84, p<0.00). The maternal mean tympanic temperature on PACU admission for participants receiving warm IV fluids was 36.27°C (SD 0.42) and for comparator participants 36.27°C (SD 0.45; p=1.00). Also, the maternal tympanic temperature on PACU discharge of the intervention group was 36.54 °C (SD 0.33) and for control participants was 36.39 °C (SD 0.36; p= 0.35).

The neonatal mean axillary temperature at the end of SSC in OT for the intervention group was 36.84°C (SD 0.34; median 36.8°C and IQR 0.38°C) and for the comparator group was 36.89°C (SD 0.24; median 36.9°C and IQR 0.3°C). The difference between groups was not significant with the t-test (t [150] =1.98, p=0.15) but was significant with the Mann-Whitney test (U=2812, z= 1.19, p=0.02). Finally, the neonatal mean axillary temperature on PACU discharge of the intervention group was 36.9°C (SD 0.21; median 36.9°C and IQR 0.2°C) and for the comparator group was 36.95°C (SD 0.27; median 37°C and IQR 0.3°C). The difference between groups was not significant (t-test, t [132] =1.98, p=0.11; Mann-Whitney test, U=2170, z= 1.41, p=1.18).

Furthermore, the mean duration of SSC was 22 minutes (SD 8.84) for intervention group newborns and 24.33 minutes (SD 10.90, p=0.81) for newborns in the comparator group. The total mean IV fluid volume that intervention participants received during their stay in OT was lower (1092.46mls, SD 532.26; median 1000mls and IQR 300mls) than comparator participants (1240.13mls, SD 473.42; median 1000mls and IQR 475mls). The difference between groups was significant with the t-test (t [149] =-2.29, p<0.00) but

not significant with the Mann-Whitney test (U=3103, z= 2.25, p=0.51). The total mean estimated blood loss (EBL) for participants receiving warm IV fluids was 444.52mls (SD 240.75; median 400mls and IQR 100mls) as compared to 473.02mls (SD 203.05; median 400mls and IQR 150mls) for those receiving usual care. The difference between groups was not significant (t [147] =0.13, p=0.89 and Mann-Whitney test; U=2937, z= 1.59, p=0.2).

In general, there were no significant differences between the main comparison groups except for maternal mean tympanic temperature during SSC in OT, neonatal mean axillar temperature at the end of SSC in OT and mean total IV fluid volume (SD), which showed a difference in p values between the t-test and the Mann-Whitney test. However, since the data in these outcomes were not normally distributed (due to the presence of outliers), the t-test is not reliable (assumes normality) and the non-parametric test (Mann-Whitney test) is more reliable for non-normally distributed data (Chapter 5, section 5.15).

Table 6.6. Secondary continuous outcomes

Secondary continuous outcomes Warm IV fluids Vs Room temperature fluids Mean (SD)				
	Warm IV fluids (n=75)	**Room temperature fluids (n=75)**	**P[1]**	**Overall total mean (SD)**
Maternal tympanic temperature during SSC in OT	36.42 (0.44)	36.48 (0.43)	p= 0.79 (p< 0.00)[#]	36.45 (0.43)
Maternal tympanic temperature on PACU admission	36.27 (0.42)	36.27 (0.45)	p=1.00	36.27 (0.43)
Maternal tympanic temperature on PACU discharge	36.54 (0.33)	36.39 (0.36)	p= 0.35	36.46 (0.34)
Neonatal axillar temperature at the end of SSC in OT	36.84 (0.34)	36.89 (0.24)	p=0.15 (p=0.02)[#]	36.86 (0.29)
Neonatal axillar temperature on PACU discharge	36.9 (0.21)	36.95 (0.27)	p=0.11 (p=1.18)[#]	36.92 (0.24)

Mean SSC duration	22 (8.84)	24.33 (10.90)	p=0.81	23.16 (9.87)
Mean total IV fluid volume	1092.46 (532.26)	1240.13 (473.42)	p=0.00 (0.51[#])	1166.29 (502.84)
Mean estimated blood loss	444.52 (240.75)	473.02 (203.05)	p=0.89 (0.20[#])	458.77 (221.9)

P[1], p-value t-test; [#] p-value independent two sample t-test (Mann-Whitney Test).

6.6 Additional findings

6.6.1 Impact of active warming on maternal and neonatal temperatures

It was intended to use a repeated measures test to investigate the impact of active warming on maternal temperatures (during CS, on PACU admission and before PACU discharge) and on neonatal temperatures (at the end of SSC in OT and before PACU discharge). However, the data were not normally distributed on the initial analysis, something that would require the use of an equivalent non-parametric test to perform repeated measures. Unfortunately, there is no existing non-parametric test to conduct this comparison, therefore, it was not possible to obtain any results for these outcomes (chapter 5, section 5.15).

6.6.2 Logistic regression analysis

Logistic regression analysis (chapter 5, section 5.15), was used to understand the relationship between the neonatal hypothermia (at the end of SSC in OT and before PACU discharge) and a number of predictors of the likelihood of neonatal hypothermia in my study. These variables included: maternal temperature/ maternal hypothermia at the end of SSC in OT, OT and PACU ambient temperatures, SSC duration, type of feeding, infants weight, IV fluid volume, Estimated Blood Loss, gestational age and additional maternal/neonatal warming. Logistic regression analysis was applicable as all of the assumptions were met. Multicollinearity is one of the assumptions that must be met before proceeding to the regression analysis. One way to measure multicollinearity was to measure the variance inflation factor (VIF) of each of the predictors. If the VIF was close to one, then no factors correlated. If the VIF is between five and ten, this is an indication that a high correlation is present, which could be problematic, a VIF of more than 10 indicates a very high correlation (Field 2013). Any predictor variable that had high levels of VIF was not included in the logistic regression as the regression coefficients would be poorly estimated due to multicollinearity (appendix 6.1). In addition, since the logistic regression analysis is based on logarithms, odds ratios (OR) were used to interpret the findings, as the coefficient is measured in log-odds units. If in OR the 95% confidence interval includes 1 then it is an indication that the odds ratio is not statistically significant, compared to the RR where if the 95% confidence interval includes 0 then the RR it is not statistically significant.

Table 6.7. Logistic regression analysis on neonatal hypothermia (At the end of SSC in OT)

Neonatal Hypothermia (At the end of SSC in OT) Logistic Regression Analysis (Binary)					
Predictors	**Coefficient of the constant (B)**	**Standard Error (S.E.)**	**P[1]**	**Exponentiation of the B coefficient**	**Odds Risk (95% CI)**
Maternal temperature (during SSC in OT)	0.62	1.08	p=0.37	2.61	0.11 (0.31 to 22.14)
Maternal hypothermia (during SSC in OT)	-0.39	0.95	p=0.68	0.67	3.75 (0.1 to 4.37)
OT ambient temperature	0.02	0.2	p=0.9	1.02	0.82 (0.68 to 1.54)
SSC duration	0.06	0.03	p=0.9	1.06	0.97 (0.98 to 1.14)
Infants weight	0.00	0.00	p=0.99	1.00	0.99 (0.99 to 1.00)
Additional IV fluid volume	0.00	0.00	p=0.54	1.00	0.99 (0.99 to 1.00)
EBL	0.00	0.00	p=0.98	1.00	0.99 (0.99 to 1.00)
Gestational age	0.32	0.38	p=0.69	1.38	1.32 (0.64 to 2.65)

P[1], p-value binary regression

Table 6.7 highlights the lack of correlation between neonatal hypothermia and the above-mentioned predictors. No correlation was found between neonatal hypothermia at the end of SSC in OT and: maternal temperature during SSC in OT (OR 0.11, 95% CI 0.31 to 22.14, p=0.37), maternal hypothermia during SSC in OT (OR 3.75, 95% CI 0.1 to 4.37, p=0.68), OT ambient temperature (OR 0.82, 95% CI 0.68 to 1.54, p=0.9), SSC duration (OR 0.97, 95% CI 0.98 to 1.14, p=0.9), infants weight (OR 0.99, 95% CI 0.99 to 1.00, p=0.99), additional IV fluid volume (OR 0.99, 95% CI 0.99 to 1.00, p=0.54), EBL (OR 0.99, 95% CI 0.99 to 1.00, p=0.98) and gestational age (OR 1.32, 95% CI 0.64 to 2.65, p=0.69).

Table 6.8. Logistic regression analysis on neonatal hypothermia (Before PACU discharge)

Neonatal Hypothermia (Before PACU Discharge) Logistic Regression Analysis (Binary)

Predictors	Coefficient of the constant (B)	Standard Error (S.E.)	P[1]	Exponentiation of the B coefficient	Odds Risk (95% CI)
PACU ambient temperature	-57.19	1.18	p=0.07	2.11	8.25 (0.80 to 84.44)
SSC duration	-8.23	0.09	p=0.23	0.00	1.11 (0.92 to 1.34)
Type of Feeding: Breastfeeding	17.84	7154.11	p=0.99	0.00	37629.64 (0.00 to n/a*)
Type of Feeding: Formula	-13.63	7154.11	p=0.99	0.00	0.00 (0.00 to n/a*)
Additional maternal warming	-17.96	6325.70	p=0.99	0.00	0.00 (0.00 to n/a*)
Additional neonatal warming	-17.77	7929.68	p=0.99	79395132.07	0.00 (0.00 to n/a*)

P[1], p-value binary regression, *n/a, not applicable.

A second logistic regression analysis was conducted that focused on neonatal hypothermia before PACU discharge and the following predictors PACU ambient temperature, SSC duration, breastfeeding, formula feeding, additional maternal and neonatal warming. As seen in Table 6.8, no correlations were found between neonatal hypothermia before PACU discharge and PACU ambient temperature (OR 8.25, 95% CI 0.80 to 84.44, p=0.07), SSC duration (OR 1.11, 95% CI 0.92 to 1.34, p=0.23), breastfeeding (OR 37629.64, 95% CI 0.00 to n/a, p=0.99), formula feeding (OR 0.00, 95% CI 0.00 to n/a, p=0.99), additional maternal warming (OR 0.00, 95% CI 0.00 to n/a, p=0.99) and additional neonatal warming (OR 0.00, 95% CI 0.00 to n/a, p=0.69).

6.7 Conclusion

The NeoHyp clinical trial investigated the impact active warming using warm IV fluids had on neonatal hypothermia during CS when SSC was performed at birth. A total of 172 women and their newborns were assessed for trial eligibility and 150 of them entered the trial. Following randomisation, 75 women were allocated to the intervention group (warm IV fluids at 39°C) and 75 to the comparator group (room temperature fluids approx. 25°C). No women were lost to follow-up in either group.

No significant differences were noted in the baseline characteristics between the two groups, with the exception of the gestational age of the new-borns (p= .03) and the mean PACU ambient temperature (Mann-Whitney test p<.00). This difference between the groups was due to chance alone since robust methods for allocation sequence generation and concealment were in place.

Regarding the primary outcome of the trial, the analysis shows that administration of warm IV fluids significantly reduced the risk of neonatal hypothermia at the end of SSC in OT (p=0.02) compared to newborns whose mothers received room temperature IV fluids. Overall, only four (5.3%) newborns became hypothermic at the end of SSC in the OT in mothers receiving warm IV fluids, 3.5 times lower than newborns in the comparator group (14/75, 18.7%). Since there were a number of missing data on the neonatal hypothermia before PACU discharge (some data were not successfully recorded by the PACU staff), a sensitivity analysis was undertaken. Overall, the analysis indicates that the main results for the intervention group are robust to missing data (RR 0.72, 95% CI 0.31 to 1.70, p=0.46), but in the highly unlikely worst-case scenario the intervention group would fare worse than the control group.

The use of warm IV fluids significantly reduced the number of women experiencing maternal hypothermia during SSC in OT (p=0027), PACU admission (p=0.0022). Since there were a number of missing data on maternal hypothermia during SSC in OT (some data were not successfully recorded by the theatre anaesthetists), a sensitivity analysis was undertaken. Overall, the analysis indicates that the main results for the intervention group are robust to missing data (p= .0057) because the results are not sensitive to a large increase in the number of events in both groups and/or in the control group, but in the highly unlikely worst-case scenario the comparator group would fare worse than the intervention group.

Maternal shivering (p=.0001) and the need for additional maternal warming (p= .0001) were significantly higher in women in the comparator group than women who received warm IV fluids. The use of additional warming in newborns whose mothers received room temperature IV fluids was also significantly higher than newborns whose mothers received warm IV fluids (p=.0009). The maternal thermal comfort of women who were administered warm IV fluids was not significantly different to women who received room temperature fluids (p=.86).

There was no statistical difference in the number of newborn adverse events (p=.499) nor in the number of maternal adverse events (p=.19) between the two groups. The type of neonatal adverse event documented in a single case in the intervention group occurred in the newborn whose mother was discontinued early from the intervention as she felt uncomfortably warm. This newborn developed a temperature of 37.6°C possibly because it was kept under the ohio for a longer period of time. No newborn adverse events were documented in the comparator group.

The type maternal adverse events documented in the intervention group included women who developed a temperature of 37.6°C (n=2) and one woman who felt uncomfortably warm during the administration of warm IV fluids. All adverse events resolved shortly after the discontinuation of the intervention. No maternal adverse events were documented in the comparator group.

There was a statistical difference in the interruption to SSC (p=.0009) and breastfeeding (p=.0076) between two groups. There was no statistical difference in neonatal (p=.73) nor maternal complications (p=.16) between two groups. The type of neonatal complications in the comparator group included newborns requiring minor resuscitation immediately after birth (n=2), one newborn was admitted to NICU due to low SPO_2, another newborn was hyperthermic (37.8°C) as was kept for a prolonged period of time under the ohio while its mother was treated for PPH and one newborn was kept longer under the ohio for observations due to grunting.

On the other hand, the type of neonatal complications in the intervention group included n=4 newborns who were admitted in NICU due to TTN. The type of maternal complications that occurred in the intervention group were two cases of PPH. On the other hand, the type of maternal complications occurred in the comparator group were four cases of PPH, one woman fainted due to low BP post anaesthesia and one woman had a bowel injury during her CS.

In general, there were no significant differences between the main comparison groups except for maternal tympanic temperature during SSC in OT, neonatal axillar temperature at the end of SSC in OT and mean total IV fluid volume (SD), which showed a difference in p values between the t-test and the Mann-Whitney test. However, since the data in these outcomes were not normally distributed (due to the presence of outliers), the t-test is not reliable (assumes normality) and the non parametric test (Mann-Whitney test) is more reliable for non-normally distributed data (Chapter 5, section 5.15).

The use of repeated measures test to investigate the impact of active warming on maternal temperatures (during CS, on PACU admission and before PACU discharge) and on neonatal temperatures (during the initial SSC in OT and before PACU discharge) was not feasible. This is because there is no existing non-parametric test to conduct these comparisons, since the data were not normally distributed on the initial analysis (chapter 5, section 5.15).

There was no correlation between neonatal hypothermia (at the end of SSC in OT) and; maternal temperature (during SSC in OT) (p=0.37), maternal hypothermia (during SSC

in OT) (p=0.68), OT ambient temperature (p=0.9), SSC duration (p=0.9), infants weight (p=0.99), additional IV fluid volume (p=0.54), EBL (p=0.98) and gestational age (p=0.69).

There was also no correlation between neonatal hypothermia (before PACU discharge) and, PACU ambient temperature (p=0.07), SSC duration (p=0.23), breastfeeding (p=0.99), formula feeding (p=0.99), additional maternal warming (p=0.99) and additional neonatal warming (p=0.69). The regression analysis did not clearly indicate any other predictive variable for the cause of neonatal hypothermia in this study, therefore one could assume that the only explanation for the difference in neonatal hypothermia is the effectiveness of warm IV fluids.

To conclude, this study suggests that the administration of warm IV fluids during CS when SSC was performed at birth reduces the risk of neonatal and maternal hypothermia, interruption in SSC and breastfeeding, as well as maternal shivering. It is also evident that when active warming is not performed during the operation, there is an increased need for additional active warming in PACU for both mothers and newborns. This fact, in combination with the very low case of adverse events to the treatment (3/75 women and 1/75 newborn) suggests that the administration of warm IV fluids is a safe procedure for both mother and newborns and could be used safely as a preventative measure against neonatal and maternal hypothermia during CS.

This is the first study to prove that perioperative maternal active warming (with the use of warm IV fluids) is a safe practice for both newborns and mothers, with no long term side effects, which would allow the establishment of at birth SSC and early initiation of breastfeeding within the theatre departments, since it would reduce the need for additional neonatal/maternal warming something that by itself increases the risk of neonatal/maternal separation (due to the nature of additional warming within the theatre department).

Chapter 7: Summary and Discussion

7.1 Introduction

This final chapter of the thesis discusses the findings of the 'NeoHyp' trial in the context of the international literature. This chapter provides a reprise of the aim and objectives, key findings of the study and discusses the implications of the findings for practice, education and research. The aim of this study was to compare the effectiveness of perioperative active warming, by administering warmed IV fluids to women undergoing elective CS and performing SSC at birth, at term, versus the administration of room temperature IV fluids, on neonatal and maternal outcomes.

As discussed in chapters 4 and 5 my study was a pragmatic RCT investigating how perioperative maternal administration of warm IV fluids during elective CS while at birth SSC was performed, could decrease the occurrence of neonatal and maternal hypothermia in order to minimize the separation of mother/newborn dyads. This separation would inevitably happen due to the need to warm up hypothermic mothers/newborns. Reducing the maternal/newborn separation supports theatre staff to promote SSC within the theatre department and initiate early breastfeeding. As discussed in chapter 2 (section 2.2.1), decreasing the frequency of hypothermia and increasing the initiation and duration of SSC/breastfeeding has significant health benefits for both mothers and newborns. In this pragmatic RCT, eligible participants were randomly allocated to two groups, comparator and intervention. Comparator participants were administered room temperature IV fluids (approximately 25°C), which is the usual practice within the research site, while the intervention group received warm IV fluids (39°C), Hartmann's solution, with the use of the theatre's Hotline™ device.

This chapter discusses the trial findings within the context of the wider evidence based literature. The strengths and weaknesses of my trial are also presented. The final section of this chapter addresses the contribution of my study to the current knowledge on prevention of neonatal hypothermia during CS while at birth SSC is performed, together with a conclusion and recommendations for future clinical practice and research.

7.1.1 Uniqueness of Trial

My trial is the first high quality study to explore the effectiveness of perioperative maternal administration of warm IV fluids on neonatal hypothermia while SSC was performed in OT and in PACU. Over the course of six months, data collected from 150 participants and analysed using ITT (chapter 6, section 6.2) found that the use of warm IV fluids had a number of health benefits for both mothers and newborns, when compared to the comparator group. These benefits include:

- a significant reduction in the number of newborns experiencing neonatal hypothermia at the end of SSC in OT in those mothers who received warm IV fluids.
- a significant reduction in maternal hypothermia during SSC in OT and on PACU admission
- significantly lower interruption to SSC and breastfeeding in the intervention group and
- significantly lower use of additional warming for mothers and newborns in the intervention group.

Given these findings, the null hypothesis that there was no difference in neonatal hypothermia between warmed IV fluids (39°C) and room temperature IV fluids, administered to women undergoing elective CS, at term, who also performed SSC at birth, was rejected.

Key findings from the groups of my trial are explored within the context of similar arms in other perioperative maternal active warming studies, which performed at birth SSC (Table 7.1). However, only two studies compared the administration of perioperative warm IV fluids to room temperature fluids (Paris *et al* 2014; Vilinsky *et al* 2016); but, Vilinsky *et al* (2016), which was the pilot study for this PhD study, recorded neonatal hypothermia at the end of at birth SSC and before PACU discharge. Paris *et al* (2014), measured neonatal temperatures only once, immediately after birth, and no further neonatal temperatures were recorded in their study, especially during/after the conduct of SSC and following the end of the intervention. A third study (Horn *et al* 2014) compared a forced air-warming device to no warming and all IV fluids were administered at room temperature. Horn *et al* (2014) did not measure any neonatal/maternal data following the end of the intervention for example there was no follow up of the participants in the PACU.

Table 7.1 'NeoHyp trial' compared to studies with similar trial arms

Study	Warm IV Fluids	Warm IV Fluids	P[1]
	Neonatal hypothermia (n) at the end of at birth SSC	Neonatal hypothermia (n) at the end of at birth SSC	
Vilinsky *et al* (2016)	1/10 (10%)	3/10 (30%)	p=.3125

Paris *et al* (2014)	not measured	not measured	not measured
The 'NeoHyp' trial	4/75 (5.3%)	14/75 (18.7%)	p=.02

The majority of international research studies (n=14) focused mainly on maternal outcomes during elective CS while active warming was performed, but SSC was not performed. Eight studies reviewed the use of warm IV fluids (Chan *et al* 1989; Woolnough *et al* 2009; Yokoyama *et al* 2009; Oshvandi *et al* 2011; Goyal *et al* 2011; Chakladar *et al* 2014; Cobb *et al* 2016; de Bernardis *et al* 2016; Cobb *et al* 2018). Two studies reviewed the use of forced air warming (Horn *et al* 2002; Butwick *et al* 2007) and two studies reviewed the combined use of forced air warming with warm IV fluids (Fallis *et al* 2006; Chung *et al* 2012). Two studies compared perioperative active warming to no warming in maternal groups, both using warm IV fluids and forced air warming, however they recorded only a small number of newborns using SSC (Chebbout *et al* 2017; Munday *et al* 2018). In contrary, in my study at birth SSC was performed in all newborns and continued in PACU until discharge to the postnatal wards.

Additionally, in my study, only nine eligible women declined to participate in the trial (9/159, 5.6% refusal rate). The reasons for their refusal include: not interested in participating in trials (n=3), already participating in other clinical studies (n=4) and two women declined to give a reason for declining to participate. The refusal rate in this study was lower compared to other similar studies. For example, Horn *et al* (2014) had 18 eligible women who declined to participate in their trial (18/63, 28% refusal rate) the reasons for refusal were not explored in the article. Neither Paris *et al* (2014) or Vilinsky *et al* (2016) discussed participant refusal rates or reasons for non-participation, therefore no comparison can be made. The higher participation rate in my study may be explained by the early and clear information provided to the women about the purpose of the trial, the promotion of early SSC/breastfeeding of the newborns and the low risk that the intervention would impose on them and their newborns.

This study is unique as it is the first known RCT focused on SSC, comparing warm IV fluids to room temperature IV fluids which measured the following outcomes: neonatal hypothermia during SSC in OT and while in PACU, maternal and neonatal complications and adverse events, the prevalence of maternal and neonatal separation and its impact on SSC/breastfeeding interruption. It was also the first RCT to explore if there were any other factors, other than warm IV fluids, to have a correlation with neonatal hypothermia while at birth SSC was performed.

7.2 Overview of the study primary outcome 'Neonatal Hypothermia'

The administration of warm IV fluids to mothers undergoing elective CS was designed to reduce perioperative neonatal hypothermia while at birth SSC was performed in the OT and continued in PACU until dyad discharge to the postnatal ward. This is achieved in part by increasing the maternal core temperature and therefore, reducing maternal hypothermia during and after elective CS. By keeping maternal core temperatures within normal levels, the risk of the neonatal temperature dropping, via conduction, while at birth SSC was performed was reduced (chapter 2, section 2.3.2).

The findings of "NeoHyp" study showed that neonatal hypothermia at the end of SSC in OT was significantly higher in newborns whose mothers received room temperature IV fluids 14/75 (18.7%) than mothers who received warm IV fluids 4/75 (5.3%) (RR 0.28, 95% CI 0.09 to 0.82, p=0.02). A similar beneficial effect was reported by Horn *et al* (2014) who also used active warming devices during CS while at birth SSC was performed, in which a significantly higher proportion of newborns (17/21, 81%) became hypothermic in the comparator group compared to newborns in the intervention group (1/19, 5%; p< 0.0001). Differences between my study and Horn *et al* (2014) include using a different method of active warming (they used forced air warming) and a three times smaller sample size (40 participants compared to 150). Additionally, a different site and tool was used to measure the neonatal core temperatures. Horn *et al* (2014) used a rectal probe (IntelliVue MP50; Philips) while my study used an axillary digital thermometer (SureTemp® PLUS). These difference in the tools used and the different sites that the temperatures were measured in these studies could potentially influence the final results of this comparison (Jacqueline Smith 2014) (chapter 2, section 2.4).

Similarly, the occurrence of neonatal hypothermia at the end of SSC in OT between the two groups was significant different in my PhD study compared to the pilot study (Vilinsky *et al* 2016), which found no difference between the comparator (3/10, 30%) and intervention groups (1/10, 10%; p= .31). The occurrence of neonatal hypothermia at the end of SSC in OT in the Paris *et al* (2014) study could not be compared with my study as Paris *et al* (2014) measured immediately after the delivery of the newborns and before any SSC was performed, therefore the results of the two studies are not comparable. Finally, the occurrence of neonatal hypothermia before the PACU discharge was not measured by Horn *et al* (2014), Paris *et al* (2014) or Vilinsky *et al* (2016), therefore no comparison between the studies could take place.

My study differs from Paris *et al* (2014) and Horn *et al* (2014) as it measured the effects of maternal warming on neonatal hypothermia over a longer period of time (until PACU

discharge). This enabled SSC to be performed not only at birth (during the CS) but also to be continued within PACU, something that was not evident in the studies by Paris *et al* (2014) and Horn *et al* (2014). This is also important as continuing SSC in PACU enabled the participants to initiate the first newborn feeding within the theatre department, which again is something that was not measured in the studies by Paris *et al* (2014) or Horn *et al* (2014). The study intervention focused on promoting SSC and breastfeeding during elective CS by reducing the occurrence of neonatal and maternal hypothermia, which would lead to maternal/newborn separation in order to warm up participants and/or their newborns.

Overall, it is evident from my study findings, when compared to the current literature, that maternal active warming reduces the occurrence of neonatal hypothermia at the end of SSC in OT. This finding is important as it allows the mother/newborn dyads to stay longer together by doing SSC without any interruptions (for example hypothermic newborn being separated from their mothers/ SSC as they need to be warmed up with a neonatal active warming device) and allowing early breastfeeding to be initiated.

7.3 Overview of secondary outcomes

In this study, the administration of perioperative warm IV fluids to mothers undergoing elective CS while performing at birth SSC, had a number of positive effects on neonatal and maternal secondary outcomes. The intervention reduced the: frequency of maternal hypothermia, frequency of maternal shivering, use of additional warming for mothers/newborns, interruption of SSC and breastfeeding, while it increased maternal thermal comfort.

7.3.1 Maternal hypothermia and maternal shivering

Participants allocated to the intervention group in "NeoHyp" study were administered warm IV fluids instead of the current practice of room temperature fluids. Administration of perioperative warm IV fluids significantly reduced maternal hypothermia at the end of SSC in OT (RR 0.15, 95% CI 0.03 to 0.65, p= .0027) and in PACU admission (RR 0.38, 95% CI 0.2 to 0.74, p= .0022). The findings of "NeoHyp" study are in agreement with a recent meta-analysis, which reviewed perioperative maternal active warming without the performance of SSC, on the occurrence of maternal hypothermia at the end of CS (13 RCTs, n=789 women) (Sultan *et al* 2015). The studies of Paris *et al* (2014) and Horn *et al* (2014) were included in this meta-analysis, therefore no individual comparison between them and my study will take place. This meta-analysis suggested that maternal hypothermia at the end of CS was statistically higher in the control group compared to the intervention group (RR 0.66, 95% CI 0.50 to 0.87, p<0.00), which aligns with my trial findings. However, it is worth mentioning that this meta-analysis did not explore the

frequency of maternal hypothermia during the PACU stay and/or before PACU discharge.

There is insufficient evidence from the wider literature regarding the duration of maternal active warming and its effect on mothers. “NeoHyp” study is therefore unique since it measured the effects of maternal active warming on maternal hypothermia from the immediate period after the CS, within PACU and on discharge from PACU and adds to the evidence base of this under researched patient outcome. It is important to note that it is during the PACU stay that many early postoperative complications occur (Eichenberger *et al* 2011) and therefore investigating the effect of maternal active warming on early postoperative complications specifically on women after an elective CS and performing SSC, adds to the knowledge base in this field (see chapter 2, section 2.6.1).

Also, according to “NeoHyp” my study findings, shivering was significantly higher in women who received room temperature fluids compared to women who received warm IV fluids (RR 0.1, 95% CI 0.03 to 0.31, p= .0001). This aligns with findings reported in Sultan *et al* (2015) systematic review, which suggest that maternal shivering is significantly reduced when different methods of maternal active warming were performed compared to no warming (13 studies, n= 789, RR 0.58, 95% CI 0.43 to 0.79, p=.0004).

7.3.2 Use of additional warming for mothers/newborns

“NeoHyp” study suggested that the use of additional warming in women who received room temperature IV fluids (42/75, 56%) was significantly higher than women who received warm IV fluids (13/75, 13%, RR 0.31, 95% CI 0.18 to 0.52, p= .0001). The trial findings are similar to those reported by Paris *et al (*2014), which was the only study that reviewed the use of additional maternal warming on women undergoing an elective CS and performing at birth SSC. Paris *et al* (2014) found that the use of additional warming was significantly higher in the control group (76/226, 34.2%) compared to the warm IV fluid group (73/226, 12.5%) and the warmed underbody pad group (77/226, 18.2%).

Similarly, “NeoHyp” study showed that the use of additional warming in newborns whose mothers received room temperature IV fluids was significantly higher than newborns whose mothers received warm IV fluids, (RR 0.29, 95% CI 0.14 to 0.6, p= .0009). I found no other studies that investigated the prevalence of additional neonatal warming in women undergoing an elective CS and performing at birth SSC. Therefore, “NeoHyp” study is the first RCT to review the need of additional neonatal warming when perioperative administration of warm IV fluids was compared to no warming.

7.3.3 Interruption of SSC and breastfeeding

"NeoHyp" study found that the mean duration of at birth SSC was 23.16 minutes (SD 9.95). Also, this study showed that interruption of SSC in the intervention group was significantly lower when compared to the control group (RR 0.29, 95% CI 0.14 to 0.6, p= .0009). "NeoHyp" study also found that 106/150 (70.66%) women breastfed their newborns within theatre department while the remaining women (43/150, 28.66%) formula fed their newborns. "NeoHyp" study findings regarding the interruption of breastfeeding showed that interruptions were significantly lower in the intervention group compared to the control group (RR 0.27, 95% CI 0.10 to 0.71, p=0.0076). These findings are also significant, from a midwifery perspective, considering the number of women who wish to breastfeed their newborns, something that could be more feasible if mothers and newborns are prevented from becoming hypothermic with the use of warm fluids. To the best of my knowledge no other studies investigated the interruption of SSC and breastfeeding postoperatively, highlighting the uniqueness of "NeoHyp" study which is the first RCT to explore interruption of SSC and breastfeeding when perioperative maternal active warming is performed. It is important that future studies review, among their outcomes, newborn and maternal separation during CS to compare their findings with "NeoHyp" study.

7.3.4 Adverse Events

A critical review of the literature on perioperative maternal active warming found no evidence of adverse events measured in studies that reviewed perioperative maternal active warming versus no warming. "NeoHyp" study is unique as it monitored and documented the adverse events that occurred in both mothers and newborns during the trial. In total, there were three (4%) maternal adverse events in the intervention group and zero events in the comparator group, the difference between the groups was not statistically significant (p=0.19). The types of adverse events experienced by women in the intervention group included one woman reporting that she felt uncomfortably warm (while her temperature was within normal levels) while two women developed a temperature of 37.6°C during their operation. The intervention administered to all three women was immediately discontinued, their temperature returned to normal levels shortly after the discontinuation of the intervention and caused no additional adverse events to the women and/or newborns involved. The Principal Investigator and Data Safety Monitoring Board were informed about these events and approved the continuation of the trial. This suggests that administration of warm IV fluids is a safe intervention for both mothers and their newborns and as long as the maternal temperatures are monitored closely during the CS, any increase of maternal temperature

above recommended levels can be managed effectively with the discontinuation of the intervention.

Finally, there was one (1.33%) newborn who had an adverse event in the intervention group and none in the control group, however the difference between the groups was not statistically significant (RR 3, 95% CI 0.12 to 72.48, p=0.49). The neonatal adverse event documented in the intervention group was the newborn of the mother whose intervention was discontinued early as she felt uncomfortably warm. This newborn developed a temperature of 37.6°C possibly because it was kept under the ohio for a longer period of time that the other newborns.

7.3.5. Predicators for Neonatal Hypothermia

"NeoHyp" study is also unique as it is the first trial to run a logistic regression model, to check if there were any other predictive factors for neonatal hypothermia other than the intervention itself. The findings of the study highlight the lack of correlation between neonatal hypothermia and other possible predictors. Specifically, there was no correlation found between neonatal hypothermia at the end of SSC in OT and: maternal temperature during SSC in OT (p=.37), maternal hypothermia during SSC in OT (p=.68), OT ambient temperature (p=.9), SSC duration (p=.9), infants weight (p=.99), additional IV fluid volume (p=.54), EBL (p=.98) and gestational age (p=.69). Also, there was no correlation found between neonatal hypothermia before PACU discharge and PACU ambient temperature (p=.0754), SSC duration (p=.2339), breastfeeding (p=.99), formula feeding (p=.99), additional maternal warming (p=.99) and additional neonatal warming (p=.69). This is a very important finding as it suggests that maternal administration of warm IV fluids is the only predictive factor in preventing neonatal hypothermia during elective CS, while at birth SSC was performed.

7.4 Strengths and limitations of the study

One of the strengths of "NeoHyp" study is the use of a methodologically robust designed RCT. During the development of the study protocol, I followed the CONSORT guidelines to ensure that the study was designed to a high standard and that measures were taken prospectively in order to avoid any issues which could lead to a potential downgrading of this study in a future systematic review (SR). Specifically, I aimed to minimize risk of bias, which included the following elements: random sequence generation; allocation concealment; blinding; incomplete accounting of patients and outcome events; selective outcome reporting; and other bias.

In order to ensure that random sequence generation was achieved, a statistician based at the research site and independent to the trial created a computer generated

randomisation sequence. For allocation concealment, the trial used sequenced numbered opaque sealed envelopes, opened by hospital admission midwives who were independent from the trial. In order to blind participants, personnel and outcome assessors all participants received their IV fluids using the theatre's Hotline™ device. The anaesthetist in charge of the CS operation only activated the warming device for women assigned to the intervention group. These anaesthetists were independent from the study and not involved in the data collection process. As a result, participants and theatre personnel involved in measuring the maternal/neonatal outcomes were unaware of the allocation of each woman. Each intervention lasted approximately 30 minutes from the initiation of anaesthesia until the end of the elective CS and as a result the dropout rate of participants and the loss of their follow up was minimal, which in turn minimized the attrition bias of the study.

My aim was also to ensure that all collected data (collected by theatre staff independent from the study), would be documented in the patients electronic charts by the staff managing the participants, which would allow easy access to collect the relevant data for follow up analysis. At the time of undertaking the trial a new electronic chart system was introduced in the hospital system. As a result, some outcome data was missing including; n=18 on neonatal hypothermia (before PACU discharge) and n=11 on maternal hypothermia (during SSC in OT). This may have occurred due to errors in operating the new chart system or errors in inputting the data by the staff. The problem of missing data was anticipated and was managed using ITT during the data analysis phase.

Women who required emergency CS were also excluded. This study was, therefore, unable to investigate the effect of the intervention on this cohort of people. An additional limitation is that this is not a multicentre study, but rather undertaken in one large urban maternity hospital. The main disadvantage of a single centre trial is that they may only recruit a small number of participants which could increase the risk of type II error. Also, single centre trials have the potential of not recruiting a sufficient number of participants which may have an impact on the clinical trial viable size. However, the sample size of my trial was carefully estimated to be representative of the population before the trial was conducted and the hospital annual elective CS rate was sufficient to allow the sample size to be recruited within the time limits agreed in the trial protocol. This approach was effective in minimising the limitations of a single centre study, however, a multicentre study would offer advantages such as providing a better basis for the generalisation of its findings, due to the recruitment of participants from a wider population and testing the intervention in a broader range of clinical settings. Multicentre

studies could be conducted in different countries which would facilitate generalisability to a greater extend. Therefore, a similar future study should be multicentre including maternity hospitals from different countries to allow further generalisability of the trial findings.

Overall, this was the first RCT to target a reduction in neonatal hypothermia during and after elective CS while at birth SSC was initiated in the OT and continued until PACU discharge, while maternal administration of warm IV fluids was used as an intervention. In addition, it was the first RCT to prove the effectiveness of the intervention in newborns who performed prolonged perioperative SSC. Consequently, this study contributes to the body of evidence and knowledge as it provides robust evidence that perioperative neonatal hypothermia can be reduced using warm IV fluids ensuring that uninterrupted SSC and breastfeeding within OT and PACU premises can be safely performed. This study may change the way that perioperative nursing/midwifery practice is currently provided, while allowing mothers and newborns benefit from the early initiation of SSC and breastfeeding without the co-morbidities associated with perioperative maternal and neonatal hypothermia.

7.5 Summary

Pregnant women are at increased risk of developing hypothermia during elective CS due to peripheral vasodilatation, the effects of neuraxial analgesia on the heat redistribution and alteration of their thermoregulation (chapter 2, sections 2.5.1 and 2.5.2). Newborns delivered via elective CS by women who are hypothermic and who perform at birth SSC, are at an increased risk of developing hypothermia due to their decreased thermoregulation abilities and their dependence on the surrounding environment and care provided to them by the healthcare professional to prevent their temperature from dropping. Preventing maternal and neonatal hypothermia while allowing the performance of at birth SSC and early initiation of breastfeeding is a very important factor in keeping mothers and newborns safe and well.

Prevention of perioperative maternal and neonatal hypothermia depends on the deployment of active warming techniques and hospital policies/strategies, which are evidence-based. This trial compared the effectiveness of perioperative active warming by administering warmed IV fluids in women undergoing elective CS and performing SSC, at term, versus room temperature IV fluids on neonatal and maternal outcomes. The trial proved that perioperative administration of warm IV fluids was more effective in decreasing neonatal and maternal hypothermia than the current hospital practice, which is the administration of room temperature IV fluids.

Maternal shivering was reduced and thermal comfort higher in women receiving warm IV fluids compared to participants in the comparator group. It was also evident that additional warming of mothers and newborns was significantly less in participants of the intervention groups than the comparator group. There was also a statistical significant difference in the interruption of SSC and breastfeeding between the two groups, with mothers and newborns of the comparator group who received room temperature IV fluids, having a higher rate of cessation of their SSC and early feeding since hypothermic mothers and newborns had to be warmed separately prior to their transfer to the postnatal wards. Adverse events in the trial were observed in only three women in the intervention group, while no adverse events were experienced in the women of the control group. Thermal comfort was restored after the discontinuation of the intervention in all three women. This has minor implications for patient acceptability of this particular intervention.

It is evident, both nationally and internationally, that approximately 1/3 of women deliver their newborns via CS (chapter 2, sections 2.2.1). These women are less likely to enjoy the benefits of at birth SSC and early breastfeeding compared to women who had a vaginal delivery, due to a number of clinical barriers (chapter 2, sections 2.2.1). Taking under consideration the increasing CS rates, it is important to overcome any barriers that prevent women/newborn dyads undergoing at birth SSC and early breastfeeding during/after CS. By overcoming these barriers, especially by promoting active warming to prevent perioperative neonatal and maternal hypothermia, theatre midwives and nurses would enhance the normalisation of CS, while enabling new mothers and their newborns to enjoy the benefits of at birth SSC and early breastfeeding during/after CS. The findings of the NeoHyp study support the normalisation of CS by successfully providing a safe solution (intraoperative use of warm IV fluids) to overcome the separation barriers usually associated with CS deliveries (chapter 6, sections 6.7).

The next section discusses implications and recommendations for future practice and research that arise from the findings of the NeoHyp trial. This part is a very important element of any research activity conducted, including the NeoHyp trial.

7.6 Implications, Recommendations and Conclusion

Although a systematic review and an RCT were conducted to provide further evidence of the effect of maternal perioperative active warming methods versus no warming on neonatal hypothermia, while at birth SSC is performed, there are further gaps in the current literature that need to be addressed.

7.6.1 Implications for practice

Offering optimal care to mothers and newborns during an elective CS, while promoting at birth SSC and breastfeeding, is dependent on promoting knowledge built on evidence based practice, but the current practice is suboptimal and not widely applied due to a lack of sufficient guidelines (chapter 2, section 2.2). Continuous in-service training/education for all clinical staff involved with the provision of care to mothers and newborns during elective CS is needed.

Findings from the SR (chapter 3, section 3.10.1) were inconclusive to suggest that perioperative administration of warm IV fluids to pregnant mothers during elective CS could be beneficial in reducing maternal hypothermia. On the other hand, my SR showed that providing maternal active warming during elective CS was more effective for reducing the occurrence of neonatal hypothermia during SSC (2 studies; Horn *et al* 2014; Vilinsky *et al* 2016; 60 participants), however these findings should be interpreted with caution due to the small sample size and the very low quality of the included studies. Additionally, in my trial active warming reduced shivering of mothers in PACU, which suggests that active warming could potentially be a good practice for PACU staff to perform to reduce the frequency of the uncomfortable but preventable postoperative complication.

Theatre managers need to ensure that guidelines in preventing and managing maternal and neonatal hypothermia during elective CS while at birth SSC is performed are available in their department and that all theatre staff are aware of them. Although national and international guidelines are not yet available for this cohort of the population, it is recommended that scientific and government bodies should pursue the creation of such guidelines to promote optimal care to this group of health care users. A clear communication of the findings of this thesis to national and international stakeholders could form part of the solution to this problem. In particular, policy makers and clinical effectiveness programmes could be a key target audience.

The trial findings (chapter 6) demonstrate that administration of warm IV fluids reduces maternal and neonatal hypothermia while allowing at birth SSC to be promoted and early neonatal breastfeeding to be established when compared to women who received no active warming during their CS. Promotion of early SSC and breastfeeding, within the theatre department, could have long term benefits for the maternal and newborn population who undergo elective CS as demonstrated by the current literature (chapter 2, section 2.2). For mothers and newborns who remain normothermic during and after their elective CS there could be a decrease in the co-morbidities of IPH and neonatal hypothermia which in turn could minimize the unnecessary neonatal admissions to NICU

and promote maternal and neonatal emotional and physical wellbeing by establishing early SSC and breastfeeding. Based on my trial findings, the administration of warm IV fluids would promote a better quality of care of mothers/newborns without causing harm.

7.6.2 Implications for research

The initiation of at birth SSC and early breastfeeding, during and after elective CS is still in its infancy not only in Ireland, but also around the world, with one of the most common barriers being the separation of mothers and newborns during elective CS (chapter 2, section 2.2.1),. The lack of robust randomised control evidence supporting perioperative practice guidelines is also highlighted in this chapter, which suggests that further good quality RCTs are needed in perioperative care of mothers and newborns in order to promote early initiation of SSC and breastfeeding.

"NeoHyp" trial found that the administration of warm IV fluids on pregnant mothers undergoing elective CS reduced the occurrence of both neonatal and maternal hypothermia, while allowing the early initiation and establishment of SSC and breastfeeding as well as reducing the maternal/newborn separation due to the need for additional warming. However, prolonged PACU stay and preventable neonatal admissions to NICU and their impact on theatre and NICU nurses' workload lack investigation in current research and warrant attention. Finally, further studies could: compare different active warming methods to find the most effective intervention; investigate if there are any long-term effects on the duration/interruption of SSC and breastfeeding; and review maternal satisfaction and thermal comfort levels during and after elective CS while at birth SSC is performed. Furthermore, no studies were found that investigated maternal and neonatal hypothermia during emergency CS. Finally, future studies could include a cost-analysis as there is insufficient evidence from the current literature as to which method of perioperative maternal active warming is the most cost-effective. Such studies would help to address the gaps in the current literature and provide sufficient evidence as to the most appropriate warming method to be promoted in clinical settings.

7.6.3 Recommendations for practice

Midwifery and nursing practice:

- Theatre staff caring for pregnant women undergoing elective CS and their newborns may consider using warm IV fluids to prevent mothers becoming hypothermic perioperative while promoting at birth SSC (chapter 3);

- The perioperative administration of warm IV fluids on pregnant women is a safe practice for both mothers and newborns and should be used to prevent perioperative IPH (chapter 6);
- SSC can be safely performed within theatre department and, in combination with maternal active warming, has greater effect in preventing neonatal hypothermia (chapter 6);

Midwifery and nursing education:

- Continuous education within theatre departments on prevention of perioperative maternal and neonatal hypothermia, while SSC is performed (chapter 2);
- Schools of midwifery and nursing should include in their teaching curriculum how to establish at birth SSC and early breastfeeding safely within theatre departments (chapter 6);
- Schools of midwifery and nursing should include in their teaching curriculum the importance/benefits of perioperative maternal active warming and methods of applying this practice, based on the current evidence (chapter 6).

Maternity care policy:

- Local and national standards should be developed to establish prevention of perioperative maternal and neonatal hypothermia, while promoting SSC and breastfeeding in theatre departments based on the current evidence (chapter 6);
- Given the growing evidence in this area of care there is now a need for an update of the WHO and NICE guidelines to include prevention of perioperative maternal and neonatal hypothermia, while promoting SSC and breastfeeding in theatre departments after CS. (chapter 6).

7.6.4 Recommendations for research

- Explore alternative perioperative active warming methods and compare them to warm IV fluids, for preventing maternal and neonatal hypothermia while SSC is performed (chapter 2);
- Systematic Review if perioperative SSC reduces the risk of neonatal hypothermia (in mothers receiving perioperative active warming) when compared with conventional incubator care (chapter 2);

- Investigate the prevalence of maternal and neonatal hypothermia during emergency CS while no active warming is performed;
- Future RCTs could also compare the effectiveness of:
    - Warm IV fluids versus forced air warming no treatment;
    - Electric heated mattresses versus warm IV fluids versus no treatment;
    - Water mattresses versus warm IV fluids versus no treatment;
    - Heating gel pads versus warm IV fluids versus no treatment;
    - Radiant heater versus warm IV fluids versus no treatment;
    - Heated-humidifiers versus warm IV fluids versus no treatment;
    - Heat and moisture exchange versus warm IV fluids versus no treatment; and
    - Thermal insulation versus warm IV fluids versus no treatment; (chapter 2);
- A future SR needs to be conducted to explore the evidence and quality of evidence as to which site (oral, tympanic, rectal or skin) should be used for a more accurate temperature reading and which device (mercury, digital or infrared thermometers) would be more accurate, as a mismeasurement of neonatal temperature may lead to under-management or over-management of neonatal hypothermia (chapter 2);
- Surveillance programmes across Irish maternity theatre departments could allow stakeholders to conduct national comparisons (chapter 2);
- An up to date SR of RCTs investigating the use of alternative perioperative active warming methods for preventing maternal and neonatal hypothermia while at birth SSC is performed, in which my trial would be included and would make an important contribution (chapter 3);
- Investigate the impact on theatre and NICU nurses' workload of the prolonged PACU stay and preventable neonatal admissions to NICU (chapter 7); An economic evaluation and analysis should be performed to review the cost-effectiveness of the different perioperative active warming methods on maternal and neonatal hypothermia while SSC is performed (chapter 7);
- A mixed methods study to investigate barriers in using perioperative active warming devices (chapter 7);

- Investigate the use of different active warming practices in Ireland and the rates of perioperative SSC with surveys provided in hospitals which provide maternity services across the country (chapter 6);
- A longitudinal mixed methods study which would follow up issues such as maternal depression, ongoing bonding, family functioning etc. in both groups (chapter 7).

7.6.5 Reflexivity

Throughout the duration of this PhD journey, there were a number of challenges upon which I would like to reflect on, in order to fully understand what I have learned and how I developed as a researcher, not only for myself but also for the readers of this thesis. My PhD was based on my personal and professional curiosity and passion to find a solution to a clinical problem that intrigued me. This clinical problem along with the pursuance of understanding it and potential solutions further, encouraged me to become involved in focused research, even prior to the commencement of my PhD. Working as a clinical midwife for eight years in both the delivery suite and the theatre department, during a time when an attempt was being made to implement SSC, I discovered a number of obstacles that made me question the current evidence on how SSC can be safely performed to allow the promotion of at birth SSC during CS.

As a midwife, I could see that a frequent issue raised by many women who were undergoing CS, was their fear that they would not have the opportunity to perform SSC and initiate breastfeeding during/after their operation. Although these practices were well established after vaginal birth, their implementation during CS had many obstacles. These obstacles were even more obvious during the first year that SSC was promoted within the theatre department. These obstacles almost resulted in the ceasing of this practice. However, as a midwife I was willing to promote the naturalization of CS especially since I was aware that one in every three women have a CS, and therefore at risk of being deprived of the benefits of SSC and breastfeeding if the naturalization of CS is not promoted.

During these early years, and after a number of trial and errors to successfully establish SSC during/after CS, I commenced my initial steps as a novice researcher. I started with learning about and performing clinical audits, followed by a clinical pilot RCT with the help and support of theatre staff, managers and doctors alike. The pilot RCT was conducted, with the knowledge that I had at that time and with some guidance by medical personnel who had previous experience in clinical research. My current reflection on the pilot RCT, after all the knowledge and experience that I gained through my PhD journey,

is that although it was a genuine attempt to conduct a robust clinical trial, I had performed without knowing, a number of biases that may have impacted on the quality of the study's findings.

Now I can clearly see that these early attempts shaped the methodological framework that I would perfect during my PhD journey and which informed my research question. My early research endeavours, which were published in peer reviewed journals, supported the promotion and establishment of SSC during CS in the hospital I was working in. This early research activity highlighted to me the gap in the literature in the subject area, the need for more robust trial evidence which guided my interest in clinical research. This interest culminated in securing funding for a PhD and the conducted of a full clinical RCT on the topic of SSC in CS. Additionally, during these early years, I managed to achieve the unofficial title of perioperative SSC champion and I was entrusted by my hospital managers at that time to educate theatre staff and managers of a second large maternity hospital to promote and perform SSC in their department.

Once I successfully secured funding for my PhD, the real task started, as I had to build on my existing skills and experience, including how I conducted a literature search, how to perform a rigorous systematic review (a brand new concept for me at the time) and eventually how to conduct a high quality clinical RCT. Although at the time all these steps seemed to me to be disconnected, now I can see how they are all linked together in a coherent and logical thought process. All the chapters of my thesis are the proof that everything I did through my PhD journey was based on the best practice, not only to identify the gaps in current knowledge around my topic, but also supported the rational for conducting this RCT and the methodology that underpinning the RCT.

With my current knowledge, I can identify the enormous difference in the ways of thinking between M.Sc. and PhD level, as well as the challenges that a clinician and a researcher may face. Although at times it was very difficult for me to separate my role as a clinical midwife and a clinical researcher, I eventually managed to utilize these two different roles interchangeably, eventually allowing them to complement each other in a meaningful and productive way. However, my biggest challenge in the merging of these two different roles was not to allow one role over influence the other, therefore I learned how to find a balance between research and clinical practice, by mindfully trying to identify which role was needed every time and focusing on applying interchangeably each role when it was indicated. Additionally, I aimed to remain detached from the study and I followed a robust predetermined research strategy to achieve rigorous hypothesis testing, which are the core elements of positivism (the theoretical framework widely used in RCTs and

specifically followed in my pragmatic RCT). This resulted in minimizing potential biases of my clinical research, something that allowed me to maintain a high standard in my trial. To conclude, as a clinical midwife and researcher, I consider myself as a pragmatist with a traditional positivism mind frame, which shaped not only this PhD but will also influence my future studies.

7.6.6 Conclusion

The uniqueness of the NeoHyp trial lies in the fact that it not just compares the effectiveness of perioperative active warming by administering warmed IV fluids to women undergoing elective CS, at term, versus room temperature IV fluids on neonatal and maternal outcomes but also focuses on at birth SSC in all newborns whose mothers participated in the trial. This trial is the first to investigate multiple neonatal outcomes when active warming was administered to women undergoing an elective CS, while at birth SSC was performed and was continued until participant discharge from PACU. My trial is very relevant, not only to theatre midwives and nurses, but also to anaesthetists, obstetricians, paediatricians and neonatal nurses as it focuses on a topic that tackles an important element of a routine operation in the obstetric population. This trial contributes to evidence based knowledge that will assist members of the multidisciplinary team involved in the provision of care during elective CS. It will inform their decision making when choosing an active warming technique in order to prevent maternal and neonatal hypothermia, while ensuring that SSC can be established at birth with no further complications or delays to the whole duration of stay in the theatre department for both mothers and their babies.

My thesis also contributes to the knowledge base on perioperative maternal and neonatal safety. It highlights the impact warm IV fluids have on reducing the separation between mothers and newborns, promoting early initiation and establishment of breastfeeding in a consort of people deprived of this practice and identifies areas of clinical practice that need research. Therefore, my study has an added value for the development of national and international guidelines for the management of hypothermia during CS and how to promote SSC for mothers undergoing CS. These guidelines would have the potential to change midwifery practice in maternity hospitals around the world and also be integrated in the midwifery curriculum in midwifery/nursing colleges around the globe.

This trial compared the effectiveness of perioperative active warming by administering warmed IV fluids to women undergoing elective CS and performing SSC, at term, versus room temperature IV fluids on neonatal and maternal outcomes. The trial proved that perioperative administration of warm IV fluids was more effective in reducing maternal

and neonatal hypothermia compared to the current hospital practice, which was the administration of room temperature IV fluids. Perioperative maternal and neonatal hypothermia was lower than that found in other studies and could be explained by the robust methods used in this trial. Maternal shivering was also reduced while thermal comfort of mothers during their stay in PACU was higher in women who were administered with warm IV fluids compared to those who received room temperature IV fluids.

It was also evident that the requirement for additional warming of mothers and newborns was significantly less in participants receiving the active warming intervention than those who received no active warming. There was also a significant impact on SSC and breastfeeding between the two groups, with mothers and newborns of the comparator group having a higher number of interruptions to SSC and early feeding as hypothermic mothers and newborns had to be warmed separately prior to their transfer to the postnatal wards.

To conclude, this is the first study to prove that administration of warm IV fluids on pregnant women undergoing elective CS is a safe practice for both mothers and newborns, which would allow the performance of uninterrupted at birth SSC and early initiation of breastfeeding within the theatre departments. My study's contribution to the evidence highlights the positive impact of this active warming intervention in women undergoing an elective CS, while at birth SSC was performed. It reduces the occurrence of maternal and neonatal hypothermia, reducing the need for additional maternal/neonatal warming, which in turn reduces the need for maternal/newborn separation and allows for uninterrupted at birth SSC and early breastfeeding to take place immediately after an elective CS.

7.6.7 Study Dissemination

The results of this trial were disseminated to the members of the multidisciplinary team in the research site. Consultant obstetricians, anaesthetists and neonatologists, clinical midwifery managers, theatre nurses and midwifery staff were invited to attend the presentation. The importance of implementing maternal active warming at clinical level was discussed. To date, some of the thesis findings have been disseminated through three different conference presentations:

- A pragmatic randomized controlled trial involving women undergoing elective CS: from an idea, to overcoming challenges in its implementation. Lisbon, Portugal (September 2018)
- Programme for Translational Paediatric Research Day. Trinity College Dublin (October 2018)

- Presentation at the Annual Research Conference. Trinity College Dublin (March 2019)

Currently, three manuscripts have been prepared for submission to peer reviewed journals:

- Perioperative active warming versus no active warming of women performing at birth skin-to-skin contact during/after caesarean section, at term, for preventing neonatal hypothermia: a systematic review.
- Perioperative active warming versus no active warming of women performing at birth skin-to-skin contact during/after caesarean section, at term, for preventing neonatal hypothermia: a randomized controlled trial.
- Skin to Skin Contact Following Caesarean Section – A Narrative Review.

The international peer reviewed journals in which the above articles will be submitted are: BIRTH, British Journal of Obstetrics and Gynaecology, Anaesthesia and Analgesia.

References

Abdolcader S. (2017) *Newborn Kangaroo Care Immediately after Cesarean Birth.* Unpublished Masters Thesis, University of San Francisco, San Francisco.

Alfonsi P., Nourredine K. E., Adam F., Chauvin M. & Sessler, D. I. (2003) Effect of postoperative skin-surface warming on oxygen consumption and the shivering threshold. *Anaesthesia 58*(12), 1228-1234.

Amico K. R. (2009) Percent total attrition: a poor metric for study rigor in hosted intervention designs. *American journal of public health 99*(9), 1567-1575.

Anaraki A. N. & Mirzaei K. (2012) The Effect of Different Intrathecal Doses of Meperidine on Shivering during Delivery Under Spinal Anesthesia. *International Journal of Preventive Medicine 3*(10), 706-712.

Andrade C. (2015) Understanding relative risk, odds ratio, and related terms: as simple as it can get. *J Clin Psychiatry 76*(7), e857-861.

American Society of Anaesthesiologists (2016) Practice Guidelines for Obstetric AnesthesiaAn Updated Report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology*. *Anesthesiology 124*(2), 270-300.

World Medical Association (2013) 'World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects'. Fortaleza, Brazil.

Bajwa S.J.S, & Swati. (2014) Perioperative hypothermia in pediatric patients: diagnosis, prevention and management. *Anaesthesia, Pain & Intensive Care, 18*(1), 97-100.

Baxter (2014) *Product information: compound sodium lactate (hartmann's) and modified hartmann's solution intravenous infusion*, Baxter Healthcare.

Beiranvand S., Valizadeh F., Hosseinabadi R. & Pournia, Y. (2014) The effects of skin-to-skin contact on temperature and breastfeeding successfulness in full-term newborns after cesarean delivery. *International journal of pediatrics 1, 1-7*.

National Research Act (1979) *The Belmont Report: Ethical Principles nand Guidelines for the Protection of Human Subjects of Research*. Department of Health, Education, and Welfare, USA. Retrieved from https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html on 10 June 2018.

Bhatt D. R. (2018) Delivery Room Temperature at 74 degree F can achieve the Normothermia in extremely low birth weight infants: A single unit multidisciplinary QI project. *Pediatrics, 142*(1), 143-143.

Bigelow A., Power M., MacLellan-Peters J., Alex M. & McDonald C. (2012) Effect of mother/infant skin-to-skin contact on postpartum depressive symptoms and maternal physiological stress. *J Obstet Gynecol Neonatal Nurs, 41*(3), 369-382.

Blackburn S. (2013) *Maternal, Fetal, & Neonatal Physiology, 4th edn.* Elsevier, London.

Borenstein M., Hedges L., & Rothstein H. (2007) Meta-Analysis Fixed effect vs. random effects Retrieved from https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf on 11 September 2019

Boundy E. O., Spiegelman D., Fawzi W. W., Missmer S. A., Kajeepeta S., Wall S. & Chan G. J. (2016) Kangaroo Mother Care and Neonatal Outcomes: A Meta-analysis. *Pediatrics* 137(1), 1-16.

Bryman A. (2012) *Social research methods,* 4th edn. Oxford University Press, Oxford.

Butwick A. J., Lipman S. S. & Carvalho B. (2007). Intraoperative forced air-warming during cesarean delivery under spinal anesthesia does not prevent maternal hypothermia. *Anesth Analg* 105(5), 1413-1419.

Campbell G., Alderson P., Smith A. F. & Warttig S. (2015) Warming of intravenous and irrigation fluids for preventing inadvertent perioperative hypothermia. *Cochrane Database Syst Rev* 4, 1-62.

Carstens G. E. (1994) Cold Thermoregulation in the Newborn Calf. *Veterinary Clinics of North America: Food Animal Practice, 10*(1), 69-106.

CDC (2015) *CDC National Survey: Maternity Practices in Infant Nutrition and Care (mPINC*. Retrieved from https://www.cdc.gov/breastfeeding/data/mpinc/state-reports-2015-508.html on 18 April 2017.

Chakladar A., Dixon M. J., Crook D. & Harper C. M. (2014) The effects of a resistive warming mattress during caesarean section: A randomised, controlled trial. *Int J Obstet Anesth 23*(4), 309-316.

Chan V. W., Morley-Forster P. K. & Vosu H. A. (1989) Temperature changes and shivering after epidural anesthesia for cesarean section. *Reg Anesth 14*(1), 48-52.

Charafeddine L., Tamim H., Hassouna H., Akel R. & Nabulsi M. (2014) Axillary and rectal thermometry in the newborn: do they agree? *BMC Research Notes 7*, 584.

Chebbout R., Newton R. S., Walters M., Wrench I. J. & Woolnough M. (2017) Does the addition of active body warming to in-line intravenous fluid warming prevent maternal hypothermia during elective caesarean section? A randomised controlled trial. *Int J Obstet Anesth 31*, 37-44.

Chung S. H., Lee B. S., Yang H. J., Kweon K. S., Kim H. H., Song J. & Shin D. W. (2012) Effect of preoperative warming during cesarean section under spinal anesthesia. *Korean Journal of Anesthesiology 62*(5), 454-460.

Cobb B., Abir G. & Carvalho B. (2018) Preoperative anterior thigh temperature does not correlate with perioperative temporal hypothermia during cesarean delivery with spinal anesthesia: Secondary analysis of a randomized control trial. *Int J Obstet Anesth 33*, 40-45.

Cobb B., Cho Y., Hilton G., Ting V. & Carvalho B. (2016) Active Warming Utilizing Combined IV Fluid and Forced-Air Warming Decreases Hypothermia and Improves Maternal Comfort during Cesarean Delivery: A Randomized Control Trial. *Anesth Analg 122*(5), 1490-1497.

Covidence (2019) Covidence systematic review software. Melbourne, Australia: Veritas Health Innovation. Retrieved from www.covidence.org on 23 March 2017.

Cowlin A. F. (2002) *Women's Fitness Program Development*, 1st edn. Human Kinetics, Yales.

Cramer H., Haller H., Dobos G. & Lauche R. (2016) A Systematic Review and Meta-Analysis Estimating the Expected Dropout Rates in Randomized Controlled Trials on Yoga Interventions. *Evidence-Based Complementary and Alternative Medicine 1*-7.

Daly L. E., Bourke G. J. & MCGilvray J. (1991) *Interpretation and uses of medical statistics,* 4th edn. Blackwell scientific publications, Oxford.

De Almeida M. F. B., Guinsburg R., Sancho G. A., Rosa I. R. M., Lamy Z. C., Martinez F. E. & Silveira R. d. C. (2014) Hypothermia and Early Neonatal Mortality in Preterm Infants. *The Journal of Pediatrics 164*(2), 271-275.

De Bernardis R. C., Siaulys M. M., Vieira J. E. & Mathias L. A. (2016) Perioperative warming with a thermal gown prevents maternal temperature loss during elective cesarean section. A randomized clinical trial. *Braz J Anesthesiol 66*(5), 451-455.

Deaton A., & Cartwright N. (2018) Understanding and misunderstanding randomized controlled trials. *Social Science & Medicine 210*, 2-21.

DePoy E. & Gitlin L. N. (2013) *Introduction to Research: Understanding and Applying Multiple Strategies,* 5th edn, Elsevier, St. Louis.

Desgranges F. P., Bapteste L., Riffard C., Pop M., Cogniat B., Gagey A. C., Bouvet L. (2017) Predictive factors of maternal hypothermia during Cesarean delivery: a prospective cohort study. *Can J Anaesth 64*(9), 919-927.

Dietitians Of Canada (2010) Promoting Optimal Monitoring Of Child Growth In Canada: Using The New Who Growth Charts. Paediatric Child Health 15(2): 77–79.

Duryea E. L., Nelson D. B., Wyckoff M. H., Grant E. N., Tao W., Sadana N., Leveno K. J. (2016) The impact of ambient operating room temperature on neonatal and

maternal hypothermia and associated morbidities: a randomized controlled trial. *American Journal of Obstetrics & Gynecology 214*(4).

Eichenberger A.-S., Haller G., Cheseaux N., Lechappe V., Garnerin P. & Walder B. (2011) A clinical pathway in a post-anaesthesia care unit to reduce length of stay, mortality and unplanned intensive care unit admission. *European Journal of Anaesthesiology 28*(12), 859-866.

Elliott D., Husbands S., Hamdy F. C., Holmberg L. & Donovan J. L. (2017) Understanding and Improving Recruitment to Randomised Controlled Trials: Qualitative Research Approaches. *European Urology 72*(5), 789-798.

Evidence Prime (2015) *GRADEpro GDT: GRADEpro Guideline Development Tool*, McMaster University.

Fallis W. M., Hamelin K., Symonds J. & Wang X. (2006) Maternal and newborn outcomes related to maternal warming during cesarean delivery. *J Obstet Gynecol Neonatal Nurs 35*(3), 324-331.

Fatemi S. N. L., Mohammad R. A., Zeydi A. E., Soleimani A. & Kiab i. F. H. (2016) Inadvertent Perioperative Hypothermia: A Literature Review of an Old Overlooked Problem. *ACTA FACULTATIS MEDICAE NAISSENSIS 33*(1), 5-11.

Field A. (2013). *Discovering Statistics Using IBM SPSS Statistics,* 4th edn, Sage, London.

Fortin M. & Smith S. M. (2013) Improving the external validity of clinical trials: the case of multiple chronic conditions. *Journal of Comorbidity 3*, 30-35.

French A., Macedo M., Poulsen J., Waterson T. & Yu A. (2008) Multivariate analysis of variance (MANOVA). *San Francisco State University, San Francisco*.

Friedrichs J., Staffileno B. A., Fogg L., Jegier B., Hunter R., Portugal D., Peashey J. M. (2013) Axillary temperatures in full-term newborn infants: using evidence to guide safe and effective practice. *Adv Neonatal Care 13*(5), 361-368.

Gardner S. L., Carter B. S., Enzman-Hines M. I. & Hernandez J. A. (2011) *Merenstein & Gardner's Handbook of Neonatal Intensive Care, 7th* edn). Mosby Elsevier, Missouri: USA.

GDPR (2018) General Data Protection Act. Retrieved from https://www.dataprotection.ie/en/legal/data-protection-legislation on 2 July 2017.

Gibson E. & Nawab U. (2015) Hypothermia in Neonates. Retrieved from http://www.merckmanuals.com/professional/pediatrics/perinatal-problems/hypothermia-in-neonates on 8 November 2017.

Gilbert R. D., Schroder H., Kawamura T., Dale P. S. & Power G. G. (1985) Heat transfer pathways between fetal lamb and ewe. *J Appl Physiol 59*(2), 634-638.

Gouchon S., Gregori D., Picotto A., Patrucco G., Nangeroni M. & Di Giulio P. (2010) Skin-to-skin contact after cesarean delivery: an experimental study. *Nurs Res 59*(2), 78-84.

Gournay V. (2011) The ductus arteriosus: Physiology, regulation, and functional and congenital anomalies. *Archives of Cardiovascular Diseases 104*(11), 578-585.

Gowland P. A. & De Wilde J. (2008) Temperature increase in the fetus due to radio frequency exposure during magnetic resonance scanning. *Phys Med Biol 53*(21), 15-18.

Goyal P., Kundra S., Sharma S., Grewal A., Kaul, T. K. & Singh M. R. (2011) Efficacy of intravenous fluid warming for maintenance of core temperature during lower segment cesarean section under spinal anesthesia. *Journal of Obstetric Anaesthesia and Critical Care 1*(2), 73.

Gray D. E. (2017) *Doing Research in the Real World*. 4th edn. Sage, London.

Gupta S.K. (2011) Intention-to-treat concept: a review. *Perspectives in clinical research* **2**(3), 109.

Gupte S. (2016) *The Short Textbook of Pediatrics, 12th edn. Blackwell's, London.*

Guyton A. & Hall J. (2006) *Textbook of medical physiology,* 11th edn. Saunders, London.

Hansen D. J. (1991) *The Work Environment: Occupational Health Fundamentals* (Vol. 1). Lewis Publishers, United States of America.

Hariton E. & Locascio J. J. (2018) Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG : an international journal of obstetrics and gynaecology 125*(13), 1716-1716.

Heidarzadeh M., Hosseini M. B., Ershadmanesh M., Gholamitabar T. M. & Khazaee S. (2013) The Effect of Kangaroo Mother Care (KMC) on Breast Feeding at the Time of NICU Discharge. *Iranian Red Crescent medical journal 15*(4), 302-306.

Henry S. G., Jerant A., Iosif A.M., Feldman M. D., Cipri C. & Kravitz R. L. (2015) Analysis of threats to research validity introduced by audio recording clinic visits: Selection bias, Hawthorne effect, both, or neither? *Patient Education and Counseling 98*(7), 849-856.

Hess P., Snowman C. & Wang J. (2005) Hypothermia after cesarean delivery and its reversal with lorazepam. *Int J Obstet Anesth 14*(4), 279-283.

Hey S. P., London A. J., Weijer C., Rid A. & Miller F. (2017) Is the concept of clinical equipoise still relevant to research? *BMJ 359*.

Higgins J. P. T., Altman D. G., Gøtzsche P. C., Jüni P., Moher D., Oxman A. D., Sterne J. A. C. (2011).The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *The BMJ, 343*.

Higgins J. P. T. & Green S. (2006) *Cochrane Handbook for Systematic Reviews of Interventions.* Wiley & Sons.

Hilton E. J., Wilson S. H., Wolf B. J., Hand W., Roberts L. & Hebbar L. (2015) Effect of Intraoperative Phenylephrine Infusion on Redistribution Hypothermia During Cesarean Delivery Under Spinal Anesthesia. *Journal of Clinical Anesthesia and Management 1*(1), 1-4.

Hissink Muller P. C., van Berkel L. H. & de Beaufort A. J. (2008) Axillary and rectal temperature measurements poorly agree in newborn infants. *Neonatology 94*(1), 31-34.

Holtzclaw B. J. (2008) Managing Inadvertent and Accidental Hypothermia. *Online Journal of Clinical Innovations 10*(2), 1-58.

Horn E. P., Bein B., Steinfath M., Ramaker K., Buchloh B. & Hocker J. (2014). The incidence and prevention of hypothermia in newborn bonding after cesarean delivery: a randomized controlled trial. *Anesth Analg 118*(5), 997-1002.

Horn E. P., Schroeder F., Gottschalk A., Sessler D. I., Hiltmeyer N., Standl T. & Am Esch J. S. (2002) Active warming during cesarean delivery. *Anesth Analg 94*(2), 409-414.

Houle S. (2015) An introduction to the fundamentals of randomized controlled trials in pharmacy research. *The Canadian journal of hospital pharmacy 68*(1), 28-32.

Hróbjartsson A., Emanuelsson F., Skou Thomsen A. S., Hilden J. & Brorson S. (2014) Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. *International Journal of Epidemiology 43*(4), 1272-1283.

Huang Y. Y., Huang C. Y., Lin S. M. & Wu S. C. (2006) Effect of very early kangaroo care on extrauterine temperature adaptation in newborn infants with hypothermia problems. *Journal of Nursing, 53*(4), 41-48.

Hung K. J. & Berg O. (2011) Early Skin-to-Skin After Cesarean to Improve Breastfeeding. *The American Journal of Maternal/Child Nursing 36*(5), 318 - 324.

Hutton S., Probst E., Kenyon C., Morse D., Friedman B., Arnold K. & Helsley L. (2009) Accuracy of different temperature devices in the postpartum population. *J Obstet Gynecol Neonatal Nurs, 38*(1), 42-49.

ICH (2016) *ICH GCP Guidelines for Good Clinical Practice*. Retrieved from https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice on 28 October 2018.

Ivanov K. P. (2006) The development of the concepts of homeothermy and thermoregulation. *journal of thermal biology 31*, 24-29.

Jia Y. S., Lin Z. L., Li Y. M., Green R. & Lin J. (2013) Effect of delivery room temperature on the admission temperature of premature infants: a randomized controlled trial. *J Perinatol 33*(4), 264-267.

Karalapillai D., Story D., Hart G. K., Bailey M., Pilcher D., Schneider A., Bellomo R. (2013) Postoperative hypothermia and patient outcomes after major elective non-cardiac surgery. *Anaesthesia 68*(6), 605-611.

Karanicolas P. J., Farrokhyar F. & Bhandari M. (2010) Practical tips for surgical research: blinding: who, what, when, why, how? *Canadian journal of surgery. 53*(5), 345-348.

Kennedy-Martin T., Curtis S., Faries D., Robinson S. & Johnston J. (2015) A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials* **16**(1), 495.

Keshavarz M. & Bolbol Haghighi N. (2010) Effects of kangaroo contact on some physiological parameters in term neonates and pain score in mothers with cesarean section. *koomesh, 11*(2), 91-98.

Kim H.-Y. (2017) Statistical notes for clinical researchers: Chi-squared test and Fisher's exact test. *Restorative dentistry & endodontics 42*(2), 152-155.

Knobel R. & Holditch-Davis D. (2010) Thermoregulation and Heat Loss Prevention After Birth and During Neonatal Intensive-Care Unit Stabilization of Extremely Low-Birthweight Infants. *Advances in Neonatal Care, 10*, S7-S14.

Kotharin C. R. (2004) *Research Methodology: Methods and Techniques.* 3rd edn. New Age International, New Delhi.

Kumar V., Shearer J. C., Kumar A. & Darmstadt G. L. (2009) Neonatal hypothermia in low resource settings: a review. *Journal of Perinatology 29*(6), 401-412 412p.

Laburn H. P., Faurie A., Goelst J. & Mitchell D. (2002) Effects on fetal and maternal body temperatures of exposure of pregnant ewes to heat, cold, and exercise. *J Appl Physiol* (92), 802-808.

Leduc D. & Woods S. (2017) Temperature measurement in paediatrics. Retrieved from https://pdfs.semanticscholar.org/122a/a8f3aa45790e3203638cfa723950dcd64baa.pdf on 15 November 2017.

Lee S. & Kang H. (2015) Statistical and methodological considerations for reporting RCTs in medical literature. *Korean Journal of Anesthesiology 68*(2), 106-115.

Leifer G. (2012) *Maternity Nursing: An Introductory Text.* 11th edn. Elsevier Health Sciences, St. Louis, Missouri.

Leifer G. (2013) *Maternity Nursing: An Introductory Text.* 11th edn. Elsevier, Canada.

Loftus J. R., Hill H. & Cohen S. E. (1995) Placental transfer and neonatal effects of epidural sufentanil and fentanyl administered with bupivacaine during labor. *Anesthesiology 83*(2), 300-308.

Lubkowska A., Szymański S. & Chudecka M. (2019) Surface Body Temperature of Full-Term Healthy Newborns Immediately after Birth Pilot Study. *International Journal of Environmental Research and Public Health 16*(8), 1312.

Lunze K., Bloom D. E., Jamison D. T. & Hamer D. H. (2013) The global burden of neonatal hypothermia: systematic review of a major challenge for newborn survival. *BMC Medicine 11*, 24-24.

Macdonald S. & Johnson G. (2017) *Mayes' Midwifery.* 14th edn. Elsevier, London.

Mangan S., Mosher S. & Scheans P. (2012) Challenges to Skin-to-Skin Kangaroo Care: Cesarean Delivery and Critically Ill NICU Patients. *Neonatal Network* (4) 259-261.

Mank A., van Zanten H. A., Meyer M. P., Pauws S., Lopriore E. & Te Pas A. B. (2016) Hypothermia in Preterm Infants in the First Hours after Birth: Occurrence, Course and Risk Factors. *PLoS One, 11*(11).

McCall E. M., Alderdice F., Halliday H. L., Vohra S. & Johnston L. (2018) Interventions to prevent hypothermia at birth in preterm and/or low birth weight infants. *Cochrane Database of Systematic Reviews*.

McCambridge J., Witton J. & Elbourne D. R. (2014) Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *Journal of Clinical Epidemiology 67*(3), 267-277.

McCarthy N. (2018). Which Countries Conduct The Most Caesarean Sections? Retrieved from https://www.forbes.com/sites/niallmccarthy/2018/10/15/which-countries-conduct-the-most-caesarean-sections-infographic/#4b132ec718ea on 5 May 2017.

McHugh M. L. (2013) The chi-square test of independence. *Biochemia medica 23*(2), 143-149.

McSwain J. R., Yared M., Doty J. W. & Wilson S. H. (2015) Perioperative hypothermia: Causes, consequences and treatment. *World J Anesthesiol 4*(3), 58-65.

Meaney S., McGinley J., Horkan S., Corcoran P., Greene R.A. & Murphy J. (2018) *Neonatal Therapeutic Hypothermia in Ireland*. National Perinatal Epidemiology Centre, Cork.

Melling A. C., Ali B., Scott E. M. & Leaper D. J. (2001) Effects of preoperative warming on the incidence of wound infection after clean surgery: a randomised controlled trial. *The Lancet 358*(9285), 876-880.

Miller-Keane (2003) *Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health.* 7th edn. Saunders, Elsevier, London.

Moher D., Hopewell S., Schulz K. F., Montori V., Gøtzsche P. C., Devereaux P. J., Altman D. G. (2010) CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ 340*, c869.

Moore E. R., Anderson G. C., Bergman N. & Dowswell T. (2012) Early skin-to-skin contact for mothers and their healthy newborn infants. *Cochrane Database Syst Rev, 5*(3).

Moore, E. R., Bergman, N., Anderson, G. C., & Medley, N. (2016). Early skin-to-skin contact for mothers and their healthy newborn infants. *Cochrane Database Syst Rev, 6*(3).

Morley C. J., Hewson P. H., Thornton A. J. & Cole T. J. (1992) Axillary and rectal temperature measurements in infants. *Archives of Disease in Childhood 67*(1), 122-125.

Mullany L. C. (2010) Neonatal hypothermia in low-resource settings. *Seminars in perinatology 34*(6), 426-433.

Munday J., Hines S., Wallace K., Chang A. M., Gibbons K. & Yates P. (2014) A systematic review of the effectiveness of warming interventions for women undergoing cesarean section. *Worldviews on Evidence-Based Nursing 11*(6), 383-393.

Munday J., Osborne S., Yates P., Sturgess D., Jones L. & Gosden E. (2018) Preoperative Warming Versus no Preoperative Warming for Maintenance of Normothermia in Women Receiving Intrathecal Morphine for Cesarean Delivery: A Single-Blinded, Randomized Controlled Trial. *Anesthesia & Analgesia 126*(1), 183-189.

Munday J., Osborne S., Yates P., Sturgess D., Jones L. & Gosden E. (2018) Preoperative Warming Versus no Preoperative Warming for Maintenance of Normothermia in Women Receiving Intrathecal Morphine for Cesarean Delivery: A Single-Blinded, Randomized Controlled Trial. *Anesth Analg 126*(1), 183-189.

National Collaborating Centre for Nursing and Supportive Care (2008). *Inadvertent perioperative hypothermia: full guideline*. Retrieved from https://www.nice.org.uk/guidance/cg65/update/CG65/documents/perioperative-hypothermia-inadvertent-guideline-full-guideline-part-12 on 16 February 2018.

NCSS (2019) *All Possible Regressions*. Retrieved from https://www.ncss.com/software/ncss/regression-analysis-in-ncss/#Subset on 13 September 2019.

National Institute for Health and Care Excellence (2008) *The Management of Inadvertent Perioperative Hypothermia in Adults NICE Clinical Guidelines, No. 65.* Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK53797/ on 16 February 2018.

National Institute for Health and Care Excellence (2015) *Hypothermia: prevention and management in adults having surgery*. Retrieved from https://www.nice.org.uk/guidance/cg65/update/CG65/documents/perioperative-hypothermia-inadvertent-review-consultation on 16 February 2018.

National Institute for Health and Care Excellence (2016) *Hypothermia: prevention and management in adults having surgery.* Retrieved from https://www.nice.org.uk/guidance/cg65 on 16 February 2018.

Nolan A. & Lawrence C. (2009) A pilot study of a nursing intervention protocol to minimize maternal-infant separation after Cesarean birth. *J Obstet Gynecol Neonatal Nurs 38*(4), 430-442.

Organisation for Economic Co-operation and Development (2020) *Caesarean sections (indicator)*. Retrieved from https://data.oecd.org/healthcare/caesarean-sections.htm on 05 March 2020.

Onalo R. (2013) Neonatal hypothermia in sub-Saharan Africa: A review. *Nigerian Journal of Clinical Practice 16*, 129-138.

Oshvandi K., Shiri F. H., Safari M., Fazel M. R., Salavati M. & Tehrani T. H. (2011) Effect of pre-warmed intravenous fluid therapy on prevention of postoperative shivering after caesarean section. *HAYAT 17*(4), 5-15.

Paris L. G., Seitz M., McElroy K. G. & Regan M. (2014) A Randomized Controlled Trial to Improve Outcomes Utilizing Various Warming Techniques during Cesarean Birth. *JOGNN: Journal of Obstetric, Gynecologic & Neonatal Nursing 43*(6), 719-728 710p.

Park T., Usher K. & Foster K. (2014) The Challenges of Conducting a Nurse-Led Intervention in a Randomized Controlled Trial with Vulnerable Participants. *Nursing Research and Practice* 6.

Patsopoulos N. A. (2011) A pragmatic view on pragmatic trials. *Dialogues in clinical neuroscience 13*(2), 217-224.

Phillips R. M. (2013) The Sacred Hour: Uninterrupted Skin-to-Skin Contact Immediately After Birth. *Newborn and Infant Nursing Reviews 13*(2), 67–72.

Pithon M. M. (2013) Importance of the control group in scientific research. *Dental Press Journal of Orthodontics 18*, 13-14.

Polin R. A., Fox W. W. & Abman S. H. (2011) *Fetal and Neonatal Physiology: Expert Consult,* 4th edn Vol. 2. Saunders, New York.

Polin R.A., Abman S.H., Rowitch D. & Benitz W.E. (2016) *Fetal and Neonatal Physiology*. 5th edn. Elsevier, California.

Royal Australasian College of Surgeons (2015) Morbidity Audit and Logbook Tool: Procedure list for SET and IMG General Surgery. Retrieved from https://www.surgeons.org/ on 22 March 2018.

Rajagopalan S., Mascha E., Na J. & Sessler D. I. (2008) The effects of mild perioperative hypothermia on blood loss and transfusion requirement. *The Journal of the American Society of Anesthesiologists 108*(1), 71-77.

Ramachandrappa A. & Jain L. (2008) Elective cesarean section: its impact on neonatal respiratory outcome. *Clinics in Perinatology 35*(2), 373-vii.

Reed H. (2002) *Guidelines from the Association of Anaesthetists of Great Britain and Ireland state that criteria need to be in place in all recovery units to ensure the safe discharge of patients to surgical wards.* Retrieved from https://www.nursingtimes.net/clinical-archive/public-health/criteria-for-the-safe-discharge-of-patients-from-the-recovery-room/205256.article on 22 March 2018.

Rennie J. M. (2012) *Rennie & Roberton's Textbook of Neonatology E-Book.* 5th edn. Elsevier, Edinburgh.

RevMan (2012) Review Manager (RevMan) [Computer program]. (Version Version 5.2). Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration.

Riley C. & Andrzejowski J. (2018) Inadvertent perioperative hypothermia. *BJA Education 18*(8), 227-233.

Ringer S. A. (2013) Core Concepts: Thermoregulation in the Newborn Part I: Basic Mechanisms. *NeoReviews 14*(4), e161-e167.

Rotunda (2016) *The Rotunda Hospital, Dublin Annual Report 2016*. Retrieved from https://rotunda.ie/rotunda-pdfs/Clinical%20Reports/Rotunda%20Annual%20Report%202016.pdf on 19 March 2018.

Rotunda Hospital (2013) *Receiving the baby at Caesarean Section.* Hospital guideline Doc No: CD-OT-010.

Rowley B., Kerr M., Van Poperin J., Everett C., Stommel M. & Lehto R. H. (2014) Perioperative Warming in Surgical Patients A Comparison of Interventions. *Clinical nursing research* 24(4):432-41.

Royal College of Surgeons Ireland (2016) *Introduction to Clinical research and Good Clinical Practice including intergrated addendum to GCP guidelines (E6 (R2)* Retrieved from https://ichgcp.net/ on 30 August 2018.

Ryan R. & Hill S. (2016) *How to GRADE the quality of the evidence. Cochrane Consumers and Communication Group*. Retrieved from https://colorectal.cochrane.org/sites/colorectal.cochrane.org/files/public/uploads/how_to_grade.pdf on 2 July 2018.

Satoru K., Kazuyuki S., Masaharu T. & Koichi I. (2010) Temperature elevation in the fetus from electromagnetic exposure during magnetic resonance imaging. *Physics in Medicine & Biology 55*(8), 2411.

Schmitz D. M. (2017) *Information regarding the intentional warming of both irrigation and intravenous solutions in plastic bag containers and irrigation solutions in plastic pour bottle containers manufactured by Baxter Healthcare Corporation (Baxter).* Retrieved from https://ecatalog.baxter.com/ecatalog/loadproduct.html?cid=20016&lid=10001&hid=20001&loadroot=true&categoryId=&pid=822192 on 5 June 2017.

Schober P., Boer C. & Schwarte L. A. (2018) Correlation Coefficients: Appropriate Use and Interpretation. *Anesthesia & Analgesia 126*(5), 1763-1768.

Schroder H. J. & Power G. G. (1997) Engine And Radiator: Fetal And Placental Interactions For Heat Dissipation. *Experimental Physiology* (82), 803-414.

Schünemann H., Brożek J., Guyat G. & Oxman A. (2013) *GRADE handbook for grading quality of evidence and strength of recommendations.* Retrieved from https://gdt.gradepro.org/app/handbook/handbook.html on 2 July 2018.

Sedgwick J.A., Schenbeck J.L. & Eghtesady P. (2005) Harmful effects of fentanyl on the fetus and placenta? *American Journal of Obstetrics & Gynecology* **193**(1), 303-304.

Sedgwick P. (2014) Explanatory trials versus pragmatic trials. *British Medical Journal 349*.

Seidman G., Unnikrishnan S., Kenny E., Myslinski S., Cairns-Smith S., Mulligan B. & Engmann C. (2015) Barriers and Enablers of Kangaroo Mother Care Practice: A Systematic Review. *PLoS ONE* 10(5), e0125643.

Sessler D. I. (2000) Perioperative heat balance. *Anesthesiology 92*(2), 578-596.

Smith J. (2014) Methods and Devices of Temperature Measurement in the Neonate: A Narrative Review and Practice Recommendations. *Newborn and Infant Nursing Reviews 14*(2), 64-71.

Smith,J., Plaat F. & Fisk N. M. (2008) The natural caesarean: a woman-centred technique. *BJOG 115*(8), 1037-1042.

Soll R. F. (2008) Heat loss prevention in neonates. *J Perinatol 28*(S1), S57-S59.

Steckler A. & McLeroy K. R. (2008) The importance of external validity. *American journal of public health 98*(1), 9-10.

Stevens J., Schmied V., Burns E. & Dahlen H. (2014) Immediate or early skin-to-skin contact after a Caesarean section: a review of the literature. *Matern Child Nutr 10*(4), 456-473.

Sultan P. & Carvalho B. (2018) Does the addition of active body warming to in-line intravenous fluid warming prevent maternal hypothermia during elective caesarean section? A randomised controlled trial. *Int J Obstet Anesth 35*, 115-116.

Sultan P., Habib A. S. & Carvalho B. (2017) Ambient operating room temperature: mother, baby or surgeon? *British Journal of Anaesthesia 119*(4), 839-839.

Sultan P. H., A.S. Cho Y. Carvalho B. (2015) The Effect of patient warming during Caesarean delivery on maternal and neonatal outcomes: a meta-analysis. *Br J Anaesth 115*(4), 500-510.

Thornton P. S., Stanley C. A., De Leon D. D., Harris D., Haymond M. W., Hussain K., Wolfsdorf J. I. (2015) Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. *J Pediatr 167*(2), 238-245.

Thorpe K. E., Zwarenstein M., Oxman A. D., Treweek S., Furberg C. D., Altman D. G., Chalkidou K. (2009) A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *Journal of Clinical Epidemiology 62*(5), 464-475.

Tiffin N. H. & Nickerson J. (2013) Clinical trials registration. *Canadian journal of respiratory therapy : CJRT = Revue canadienne de la therapie respiratoire : RCTR 49*(4), 20.

Topaloglu N., Binnetoglu F. K., Yildirim S., Tekin M., Kaymaz N., Aylanc H., Hanci V. (2016) Effect of delivery mode on postpartum neonatal body temperatures. *J Matern Fetal Neonatal Med 29*(3), 385-388.

Torgerson D. J. & Torgerson C. J. (2008) *Designing Randomised Trials in Health, Education and the Social Sciences; An Introduction* (Vol. 1st). Palgrave MacMillan, New York.

Vilinsky A. & McCaul C. (2017) Διερεύνηση της περιεγχειρητικής μητρικής και νεογνικής υποθερμίας. *Eleutho 1*(1).

Vilinsky A. & Sheridan A. (2014) Hypothermia in the newborn: An exploration of its cause, effect and prevention. *British Journal of Midwifery 22*(8), 557-562 556p.

Vilinsky A., Sheridan A. & Nugent L. E. (2016) Preventing peri-operative maternal and neonatal hypothermia after skin-to-skin contact. *Journal of Neonatal Nursing 22*(4), 163-170.

Volpe,J. J., Inder T. E., Darras B. T., de Vries L. S., du Plessis A. J., Neil J. & Perlman J. M. (2017) *Volpe's Neurology of the Newborn.* 6th edn. Elsevier, Washington.

Waldron S. & Mackinnon R. (2007) Neonatal thermoregulation. *Infant 3*(3), 101-104.

Wells J. C. K. (2002) Thermal Environment and Human Birth Weight. *Journal of theoretical biology* (214), 413-425.

Webb K. (2003) What are the benefits and the pitfalls of preoperative fasting? *Nursing Times* 99(50), 32

World Health Organisation (1993) *Thermal control of the newborn; a practical guide*. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/60042/WHO_FHE_MSM_93.2.pdf?sequence=1&isAllowed=y on 9 April 2016.

World Health Organisation (1997) *Thermal protection of the newborn: a practical guide*. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/63986/WHO_RHT_MSM_97.2.pdf?sequence=1 on 9 April 2016.

World Health Organisation & Unicef (2009) Baby-friendly hospital initiative: revised, updated and expanded for integrated care. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/272943/9789241513807-eng.pdf?ua=1 on 9 April 2016.

Wilson J. (2010) *Essentials of Business Research: A Guide to Doing Your Research Project. 2nd edn.* SAGE, London.

Wilson W. C., Grande, C. M., & Hoyt, D. B. (2007). *Trauma: Emergency Resuscitation, Perioperative Anesthesia, surgical management* Vol. first volume.

Wise, J. (2015) Rates of caesarean vary widely across Europe. *British Medical Journal 350*, h1332.

World Medical Association (2013) *World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects*. 64th WMA General Assembly, Fortaleza, Brazil.

Woolnough M., Allam J., Hemingway C., Cox M. & Yentis S. M. (2009) Intra-operative fluid warming in elective caesarean section: a blinded randomised controlled trial. *Int J Obstet Anesth 18*(4), 346-351.

Yokoyama K., Suzuki M., Shimada Y., Matsushima T., Bito H. & Sakamoto A. (2009) Effect of administration of pre-warmed intravenous fluids on the frequency of

hypothermia following spinal anesthesia for Cesarean delivery. *J Clin Anesth 21*(4), 242-248.

Yoong S. L., Wolfenden L., Clinton-McHarg T., Waters E., Pettman T. L., Steele E. & Wiggers J. (2014) Exploring the pragmatic and explanatory study design on outcomes of systematic reviews of public health interventions: a case study on obesity prevention trials. *Journal of Public Health 36*(1), 170-176.

Zulala N. N., Sitaresmi M. N. & Sulistyaningsih (2017) *Vaginal delivery to reduce the risk of hypothermia to newborn.* Paper presented at the AIP Conference Proceedings, India.

Appendices

Appendix 3.1: Search strategy

PubMed *(1960-2019)*

1. Randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomized controlled trials as topic[MeSH Terms]
2. Passive warming[Title/Abstract] OR usual care[Title/Abstract] OR standard care[Title/Abstract] OR non active warming[Title/Abstract] OR active warming[Title/Abstract] OR active forced air warming[Title/Abstract] OR peri-operative heating[Title/Abstract] OR warming patients[Title/Abstract] OR warming devices[Title/Abstract] OR pre-warmed fluids[Title/Abstract] OR heating blanket[Title/Abstract] OR maternal warming[Title/Abstract]
3. Pregnancy[MeSH Terms] OR obstetrics[MeSH Terms] OR delivery, obstetric[MeSH Terms] OR method, kangaroo mother care[MeSH Terms] OR pregnant women[MeSH Terms] OR infant, newborn[MeSH Terms] OR anestesia, obstetric[MeSH Terms] OR anesthesia, obstetrical[MeSH Terms]
4. **1 AND 2 AND 3.**

EMBASE *(<1966-2019)*

1. 'randomized controlled trial':it OR 'controlled clinical trial':it OR 'randomized controlled trials as topic':de OR 'random' OR 'trial':de OR 'randomized':de OR 'randomly':de OR 'controlled clinical trial'/de OR 'randomized controlled trial'/de
2. 'passive warming':ab OR 'usual care':ab OR 'standard care':ab OR 'non active warming':ab OR 'active warming':ti OR 'active forced air warming':ab OR 'peri-operative heating':ab OR 'warming patients':ab OR 'warming devices':ab OR 'pre-warmed fluids':ab OR 'heating blanket':ab OR 'maternal warming':ab
3. 'pregnancy':de OR 'obstetrics':de OR 'delivery, obstetric':de OR 'method, kangaroo mother care':de OR 'pregnant women':de OR 'infant, newborn':de OR 'anestesia, obstetric':de OR 'anesthesia, obstetrical':de
4. **1 AND 2 AND 3.**

CINAHL *(1986-2019)*

1. TX operative delivery OR TX infant OR TX new-born OR TX newborn OR TX childbirth OR TX perinatal care OR TX perinatal OR TX peripartum OR TX perioperative OR TX peri-operative OR TX cesar* OR TX caesar* OR TX c-

section* OR TX skin-to-skin contact OR TX skin to skin contact OR TX SSC OR TX kangaroo mother care method OR TX regional anaesthesia OR TX anesthesia OR TX anaesthasia OR TX spinal anaesthesia OR TX spinal anesthesia

2. TX passive warming OR TX usual care OR TX standard care OR TX non active warming OR TX active warming OR TX active forced air warming OR TX peri-operative heating OR TX warming patients OR TX warming devices OR TX pre-warmed fluids OR TX heating blanket OR maternal warming
3. PT randomized controlled trial OR PT controlled clinical trial OR TX (random* AND trial*) OR TX randomized OR TX randomised OR TX randomly
4. **1 AND 2 AND 3.**

Web of Science *(1945-2019)*

1. TS=(operative delivery OR infant OR new-born OR newborn OR childbirth OR perinatal care OR perinatal OR peripartum OR perioperative OR peri-operative OR c-section OR skin-to-skin contact OR skin to skin contact OR SSC OR kangaroo mother care method OR regional anaesthesia OR anesthesia OR anaesthasia OR spinal anaesthesia OR spinal anesthesia)
2. TS=(passive warming OR usual care OR standard care OR non active warming OR active warming OR active forced air warming OR peri-operative heating OR warming patients OR warming devices OR pre-warmed fluids OR heating blanket OR maternal warming)
3. TI=(randomized controlled trial)
4. **1 AND 2 AND 3.**

Scopus *(1960-2019)*

1. title-abs-key (**operative delivery**) or title-abs-key (**infant**) or title-abs-key (**new-born**) or title-abs-key (**newborn**) or title-abs-key (**childbirth**) or title-abs-key (**perinatal care**) or title-abs-key (**perinatal**) or title-abs-key (**peripartum**) or title-abs-key (**perioperative**) or title-abs-key (**perioperative**) or title-abs-key (**caesarean**) or title-abs-key (**cesarean**) or title-abs-key (**skin to skin contact**) or title-abs-key (**skin-to-skin contact**) or title-abs-key (**kangaroo mother care method**) or title-abs-key (**ssc**) or title-abs-key (**regional anesthesia**) or title-abs-

key (**epidural anesthesia**) or title-abs-key (**anesthesia**) or title-abs-key (**anaesthesia**) or title-abs-key (**c-section**) or title-abs-key (**cesarean section**) or title-abs-key (**caesarean section**) and subjarea (**mult** or **medi** or **nurs** or **vete** or **dent** or **heal**)

2. (title-abs-key (**passive warming**) or title-abs-key (**usual care**) or title-abs-key (**standard care**) or title-abs-key (**non active warming**) or title-abs-key (**active warming**) or title-abs-key (**active forced air warming**) or title-abs-key (**peri-operative heating**) or title-abs-key (**warming patients**) or title-abs-key (**warming devices**) or title-abs-key (**pre-warmed fluids**) or title-abs-key (**heating blanket**) or title-abs-key (**maternal warming**)) and subjarea (**mult** or **medi** or **nurs** or **vete** or **dent** or **heal**)
3. (title-abs-key (**randomized controlled trial**) or title-abs-key (**controlled clinical trial**) or title-abs-key (**randomized controlled trials as topic**) or title-abs-key (**random**)) and subjarea (**mult** or **medi** or **nurs** or **vete** or **dent** or **heal**)
4. 1 AND 2 AND 3.
5. **Then limited fields to article and randomized controlled trial.**

Maternity and infant care (MIDIRS) *(1971-2019)*

1. (operative delivery or infant or new-born or newborn or childbirth or perinatal care or peripartum or perioperative or peri-operative or caesarean section or cesarean section or c-section or skin to skin contact or skin-to-skin contact or kangaroo mother care method or regional anaesthesia or anesthesia or anaesthesia or epidural anesthesia).af.
2. (passive warming or usual care or standard care or non active warming or active warming or active forced air warming or peri-operative heating or warming patients or warming devices or pre-warmed fluids or heating blanket or maternal warming).af.
3. (randomized controlled trial or clinical controlled trial).pt. or randomized controlled trial.af. or randomly.af.
4. **1 AND 2 AND 3.**

Opengrey;

Kangaroo mother care method OR skin to skin contact OR c-section OR caesarean section AND active warming OR non active warming AND randomised controlled trial. Search within medicine field

Clinicaltrials;

Kangaroo mother care method OR skin to skin contact OR c-section OR caesarean section AND active warming OR non active warming AND randomised controlled trial. Fields searched; completed recruitment, interventional studies, female population

Trinity College Library; Kangaroo mother care method OR skin to skin contact OR c-section OR caesarean section AND active warming OR non active warming AND randomised controlled trial. Fields searched; TCD thesis

Four Searches has been conducted: first was completed on 30/06/16, second on 20/11/17, third on 31/03/18 and the fourth on 30/03/19.

Summary Table of total citations and retrieval results

Database	**No. of citations resulting from search**	**No. retrieved for full text review**	**No. included in the review**
PubMed	3,449	18	3
CINAHL	3,170	12	3
EMBASE	1,556	6	1
Scopus	5,377	14	3
MIDIRS	584	6	1
Web of Science	2,421	11	3
Opengrey.eu/search	302	0	0
Clinicaltrials.gov	2,398	4	2

Trinity College Dublin library (thesis)	649	0	0

Appendix 3.2: Excluded studies

No.	Excluded studies during full text screening	Reasons for exclusions agreed by two independent reviewers (AV and MMC)
1	(Beiranvand *et al* 2014)	The intervention was SSC not maternal active warming
2	(Butwick *et al* 2007)	SSC was not performed
3	(Chakladar *et al* 2014)	SSC was not performed
4	(Chung *et al* 2012)	SSC was not performed
5	(Fallis *et al* 2006)	SSC was not performed
6	(Horn *et al* 2002)	SSC was not performed
7	(Goyal *et al* 2011)	SSC was not performed
8	(Nolan & Lawrence 2009)	The intervention was SSC not maternal active warming
9	(Rowley *et al* 2014)	The population was general adults undergoing various operations and not pregnant women undergoing caesarean
10	(Woolnough *et al* 2009)	SSC was not performed
11	(Yokoyama *et al* 2009)	SSC was not performed
12	(Keshavarz & Bolbol Haghighi 2010)	The intervention was SSC not maternal active warming
13	(Cobb *et al* 2016)	SSC was not performed
14	(Huang *et al* 2006)	The intervention was SSC not maternal active warming
15	(Gouchon *et al* 2010)	The intervention was SSC not maternal active warming
16	(Munday *et al* 2018)	SSC was performed in half of the newborns
17	(Chebbout *et al* 2017)	SSC was performed in half of the newborns
18	(de Bernardis *et al* 2016)	SSC was not performed
19	(Oshvandi *et al* 2011)	SSC was not performed
20	(Cobb *et al* 2018)	SSC was not performed

Appendix 3.3: Data extraction form for included studies

Record Number	
Author	
Journal	
Year of review	
Study method	
Setting	

Inclusion Criteria

Study Design	
RCT	Yes ☐ No ☐
Clinical Controlled trial	Yes ☐ No ☐
Participants	
Elective CS	Yes ☐ No ☐
Regional Anaes	Yes ☐ No ☐
Baby: Skin-to-skin contact min 10 mins	Yes ☐ No ☐
Intervention	
Active Warning	Yes ☐ No ☐
Type of active warning	
Air warming devices	Yes ☐ No ☐
Warmed IV fluids	Yes ☐ No ☐
Warmed Mattress	Yes ☐ No ☐
Warmed coverings	Yes ☐ No ☐
Other	_____
On own	Yes ☐ No ☐

Combined	Yes ☐ No ☐
Control intervention	
Routine care	Yes ☐ No ☐
Unheated blankets	Yes ☐ No ☐
Room temp IV fluids	Yes ☐ No ☐
Other	_____
On own	Yes ☐ No ☐
Combined	Yes ☐ No ☐

Include Yes ☐ No ☐

Characteristics of included studies

	Descriptions as stated in report/paper	**Location in text or source** *(pg & ¶/fig/table/other)*
Aim of study *(e.g. efficacy, equivalence, pragmatic)*		
Design *(e.g. parallel, crossover, non-RCT)*		
Method of Recruitment		
Total no randomised		
Method of Randomisation		
Unit of allocation *(by individuals, cluster/ groups or body parts)*		
Withdraws and exclusions/missing participants		
Baseline imbalances		
Start date		
End date		

Duration of participation / duration of follow-up *(from recruitment to last follow-up)*			
ITT	☐ Yes ☐ No ☐ Unclear		
Subgroups measured			
Subgroups reported			
Ethical approval needed/ obtained for study	☐ Yes ☐ No ☐ Unclear		
Informed consent obtained	☐ Yes ☐ No ☐ Unclear		
Notes:			

Participants

	Intervention group	Control group
Number in group		
Mean maternal age		
Gestation in weeks		
Anaesthetic type		
Excluded patients		
Patients who left the study and why		

Interventions

	Intervention group	**Control group**

Method of warming		
Length of warming		
Duration of treatment period (include sufficient detail for replication, e.g. content, dose, components)		
Timing (e.g. occurrence, duration of each episode)		
Delivery (e.g. mechanism, medium, intensity, fidelity)		
Providers (e.g. no., profession, training, ethnicity etc. if relevant)		
Co-interventions		
Integrity of delivery		
Compliance		

Outcomes

SR Primary Outcomes	**Intervention group**		**Control group**	
	No with event	Total in Group	No with event	Total in Group
Mode of temperature measurement (mother/baby)				
Maternal core temperature before SSC (numerical)				
Maternal core temperature during SSC (numerical)				
Maternal core temperature after SSC (numerical)				
New-born core temperature before SSC (numerical)				
New-born core temperature during SSC (numerical)				
New-born core temperature after SSC (numerical)				

Ambient theatre temperature before SSC (numerical)				
Ambient theatre temperature during SSC (numerical)				
Ambient theatre temperature after SSC (numerical)				
Duration of skin-to-skin contact including total time of SSC (mins)				
Maternal satisfaction (tool)				
Hypothermia definition (mother/baby) (definition				
Neonatal hypothermia (Yes/No)				
Maternal hypothermia (Yes/No)				

Secondary outcomes	**Intervention group**		**Control group**	
	No with event	Total in Group	No with event	Total in Group
Timing of initiation of first feed (mins)				
Type of feed (breast/bottle)				
Length of feed if breast fed (mins)				
Apgar Score 1 min (numerical)				
Apgar Score 5 min (numerical)				
Umbilical cord analysis (numerical)				
Arterial pH (numerical)				
Base excess (numerical)				

Neonatal jitteriness (Yes/No)				
Neonatal blood sugar levels 2 hours after birth (numerical)				
Other outcomes discussed in study				

Risk of Bias assessment

(See Handbook Chapter 8*. Additional domains may be added for non-randomised studies.)*

Domain	Risk of bias Low High Unclear	Support for judgement *(include direct quotes where available with explanatory comments)*	Location in text or source *(pg & ¶/fig/table/other)*
Random sequence generation *(selection bias)*	☐ ☐ ☐		
Allocation concealment *(selection bias)*	☐ ☐ ☐		
Blinding of participants and personnel *(performance bias)*	☐ ☐ ☐		
Blinding of outcome assessment *(detection bias)*	☐ ☐ ☐		
Incomplete outcome data *(attrition bias)*	☐ ☐ ☐		
Selective outcome reporting? *(reporting bias)*	☐ ☐ ☐		
Other bias	☐ ☐ ☐		
Notes:			

Other information

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

Include **Yes** ☐ **No**

Appendix 3.4. Risk of bias assessments using the Cochrane Collaborations ROB tool

Risk of Bias (Horn *et al.*, 2014)		
Bias	Authors Judgement	Support for judgement
Random sequence generation (selection bias)	Low	Coin tossing, done by a nurse, not part of the study
Allocation concealment (selection bias)	Unclear	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low	No lost to follow up.
Selective reporting (reporting bias)	Unclear	Did not report all outcomes as stated on page 999
Other bias	Low	No other bias detected
Notes	Results of this study should be interpreted with caution due to unclear risk of bias.	

Risk of Bias (Vilinsky et al., 2016)		
Bias	*Authors Judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low	Coin tossing
Allocation concealment (selection bias)	Unclear	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High	participants were blinded, researcher was present in OT and not blinded

Blinding of outcome assessment (detection bias) All outcomes	High	The researcher was involved in the data collection and data analysis (not blinded).
Incomplete outcome data (attrition bias) All outcomes	Low	No participants lost in follow up
Selective reporting (reporting bias)	Low	Did not report all outcomes
Other bias	High	Room temperature differed
Result:	Results of this study should be interpreted with caution due to high risk of bias.	

Risk of Bias (Paris *et al.*, 2014)		
Bias	*Authors Judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low	Used the Research Randomizer website to generate the simple random allocation sequence.
Allocation concealment (selection bias)	High	Does not state what type of envelope the names of the treatment groups were placed into envelopes per the randomization sequence, sealed, and labelled with a sequential participant number. Does not discuss what type of envelope and who made up the envelopes given that the study nurses recruited participants and open up envelopes and provided care
Blinding of participants and personnel (performance bias) All outcomes	High	Study nurses were involved in recruitment revealed the assigned treatment provided primary care, and collected data
Blinding of outcome assessment (detection bias) All outcomes	Unclear	Not stated

Incomplete outcome data (attrition bias) All outcomes	Low	No missing data
Selective reporting (reporting bias)	Unclear	Did not report all outcomes
Other bias	Low	No other bias detected
Result:	Results of this study should be interpreted with caution due to high risk of bias.	

Appendix 3.5 GRADE evidence profile.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	active warming of pregnant women	no warming	Relative (95% CI)	Absolute (95% CI)		
neonatal hypothermia in OT												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	2/29 (6.9%)	30.0% [c]	**RR 0.14** (0.03 to 0.75)	**26 fewer per 100** (from 8 fewer to 29 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								81.0% [c]		**70 fewer per 100** (from 20 fewer to 79 fewer)		
maternal hypothermia in OT												
3	randomised trials	very serious [d]	serious [e]	not serious	serious [b]	none	66/179 (36.9%)	40.0% [f]	**RR 0.35** (0.11 to 1.17)	**26 fewer per 100** (from 7 more to 36 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								66.0% [f]		**43 fewer per 100** (from 11 more to 59 fewer)		
neonatal temperature at the end of SSC in OT (assessed with: axillar thermometer; Scale from: 35.5 to 38)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	active warming of pregnant women	no warming	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	serious [g]	not serious	serious [b]	none	29	31	-	SMD **1.03 SD higher** (1.58 lower to 3.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
maternal temperature before SSC (assessed with: tympanic thermometer; Scale from: 35.5 to 38.5)												
3	randomised trials	very serious [d]	serious [e]	not serious	serious [b]	none	179	107	-	SMD **0.01 SD lower** (0.7 higher to 0.69 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
maternal temperature during SSC (assessed with: tympanic thermometer; Scale from: 35.5 to 38.5)												
3	randomised trials	very serious [d]	not serious	not serious	serious [b]	none	179	107	-	SMD **0.75 SD higher** (0.5 higher to 1.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL
maternal temperature after SSC (assessed with: tympanic thermometer; Scale from: 35.5 to 38.5)												
3	randomised trials	very serious [d]	serious [e]	not serious	serious [b]	none	179	107	-	SMD **0.64 SD higher** (0.28 higher to 1.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
maternal hypothermia in PACU												
2	randomised trials	very serious [h]	not serious	not serious	serious [b]	none	82/160 (51.2%)	40.0% [i]	**RR 0.47** (0.09 to 2.40)	**21 fewer per 100** (from 36 fewer to 56 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	active warming of pregnant women	no warming	Relative (95% CI)	Absolute (95% CI)		
								75.0% [i]		**40 fewer per 100** (from 68 fewer to 100 more)		

Appendix 4.1. Irish Health Products Regulatory Authority (HPRA) Reply

HPRA Clinical Trials <clinicaltrials@hpra.ie> 27 Jun

to me, HPRA

Dear Aliona Vilinsky-Redmond,

I refer to your correspondence below and your subsequent follow-up e-mail sent directly to the CT unit today.
Please find the HPRA's response:
This is not considered to be an interventional CT that requires authorisation by HPRA, however Ethics committee approval may still be needed.

Kind regards,
Sinéad Murphy
Acting BPC Case Manager
Business Process Co-Ordination Unit
Health Products Regulatory Authority | An tÚdarás Rialála Táirgí Sláinte,
Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, D02 XP77.
Tel: +353 1 676 4971
Fax: +353 1 676 7836
sinead.murphy@hpra.ie
www.hpra.ie

Appendix 4.2. Adverse Event Recording Form (AERF)

The NeoHyp Trial – Serious Adverse Event Report Form

Hospital site: Theatre 1 ☐ Theatre 2 ☐ Recovery room ☐

Name of person completing this form: _____

(Use BLOCK CAPITALS please)

Date form completed: ☐☐/☐☐/☐☐☐☐

Date Serious Adverse Event occurred: ☐☐/☐☐/☐☐☐☐

Woman's Details:

(Name, Address, DOB and record Number or affix addressograph)

Woman's NeoHyp number:

Description of Serious Adverse Event

- Thermal discomfort ☐
- Postpartum Haemorrhage ☐
- Maternal hyperthermia (temperature above 37.5°C) ☐
- Neonatal hyperthermia (temperature above 37.5°C) ☐

Comments:……
……
……

Appendix 4.3. SOP Documents

SOP Number	**1**			
SOP Title	**Archiving of Essential Documents**			
	NAME	**TITLE**	**SIGNATURE**	**DATE**
Author	Aliona Vilinsky-Redmond	Lead Researcher		
Authoriser	Prof. Conan McCaul	Principal Investigator		

Effective Date:	

READ BY			
NAME	**TITLE**	**SIGNATURE**	**DATE**

Purpose

This Standard Operating Procedure (SOP) is created to describe the standard procedures to be followed when archiving essential documents related to the trial: "*Peri-operative active warming versus no peri-operative active warming during caesarean section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomized controlled trial.*"

Introduction

All contained documents in the trial master file through the duration of this study are to be retained for at least 5 years after the completion of the trial. During that period, the documents will be complete and available to the REC of Rotunda Hospital.

DEFINITIONS

1.1 ESSENTIAL DOCUMENTS

Essential documents are those documents that permit evaluation of the conduct and the quality of the produced trial. Essential documents include the Trial Master File and Adverse Event report form.

1.2 Trial Master File

The Trial Master File is a file that consists of all the essential documents which enable the evaluation of both the conduct and the quality of the RCT. Those documents show whether the researcher and the sponsor/principal investigator have complied with the principles of Good Clinical Practice. See SOP2 Trial Master Files/27th June 2017.

1.3 Adverse Event Report Forms

A hardcopy is designed to record information on participant adverse event to the intervention. See SOP5 Adverse Events Report Form Completion/27th June 2017.

Responsibilities: The Researcher

The researcher on behalf of the PI is responsible for archiving all of the essential documents. The researcher will inform the sponsor/principal investigator that all of the essential documents will be archived on the researcher's password protected laptop, within the researcher's private residence.

SPECIFIC PROCEDURE

1.4 What to archive?

All essential documents need to be archived i.e. Trial Master File, adverse event forms.

1.5 When to archive?

Essential documents need to be archived once the RCT is completed. The completion of a RCT shall be determined by the PI. The date of the completion will be documented.

1.6 How long the essential documents will be archived?

All essential documents must be retained for at least 5 years after the completion of the RCT or for a longer period where so required by other applicable requirements.

1.7 How to archive?

Documents need to be stored in a way that allows access to pre-determined individuals only. The stored documents will remain complete and legible throughout the required period of retention.

All essential documents should be boxed and labelled with the study title reference number, the name of the researcher and the PI, the date they were archived, and date to be destroyed.

1.8 Where to archive?

The hardcopies of the documents will be archived in a locked cupboard within the hospital premises. All electronic documents will be saved on a password encrypted USB and will be archived in the same locked cupboard with the hardcopies. Access to either hardcopies and/or electronic copies will only permitted by authorised personnel.

SOP Number	**2**			
SOP Title	**Trial Master File**			
	NAME	**TITLE**	**SIGNATURE**	**DATE**
Author	Aliona Vilinsky-Redmond	Lead Researcher		
Authoriser	Prof. Conan McCaul	Principal Investigator		

Effective Date:		

READ BY			
NAME	**TITLE**	**SIGNATURE**	**DATE**

Purpose

This Standard Operating Procedure (SOP) is created to describe the standard procedures to be followed when preparing and maintaining a Trial Master File related to the trial: "*Peri-operative active warming versus no peri-operative active warming during*

caesarean section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomized controlled trial."

Introduction

All contained documents in the trial master file are deemed to be those which allow the evaluation and the quality of the conducted trial. Trial documents will be filed in an orderly manner.

DEFINITIONS

2.1 Trial Master File

The Trial Master File is a file that consists of all the essential documents which enable the evaluation of both the conduct and the quality of the produced clinical trial.

2.2 Essential Documents

Essential documents are those documents that permit evaluation of the conduct and the quality of the produced trial. Essential documents include the Trial Master File and Adverse Events Form.

Responsibilities: The Researcher

The researcher will prepare, maintain and have the Trial Master File available for monitoring and/or auditing by the Trial Steering Committee.

SPECIFIC PROCEDURE

2.3 Action prior commencing the trial

An electronic Trial Master File will be created at the beginning of the trial and will be organised in such a manner to allow future maintenance and review of the trial-related documents. The Trial Master File will be accessible only by the researcher, the researcher's supervisors and the Trial Steering Committee.

2.4 Trial Master File Maintenance

Essential documents will be maintained and updated in the Trial Master File, by the researcher, throughout the duration of the trial. Previous versions of the documents will be clearly labelled, in a chronological order and will be retained in the Trial Master File.

Archiving

See SOP1- Archiving or Essential Documents 27/6/2017

SOP Number	SOP03			
SOP Title	Document Control			
	NAME	TITLE	SIGNATURE	DATE
Author	Aliona Vilinsky-Redmond	Lead Researcher		
Authoriser	Prof. Conan McCaul	Principal Investigator		

Effective Date:	
Review Date:	

Revisions

No.	Section No.	Page No.	Initials/ Date

Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the standard procedures to be followed for the management of controlled documents related to the trial: "*Peri-operative active warming versus no peri-operative active warming during caesarean section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomized controlled trial.*"

Scope

The study protocol, the trial eligibility form, adverse events form, participant information sheet, informed consent form and data collection forms are some of the controlled documents in this research.

Responsibilities: Researcher

The researcher is responsible to determine which documents need to be controlled and to ensure that controlled documents of the trial are appropriately managed.

Specific procedure

3.1 Version control and naming convention

All controlled documents will be dated. Some will be named in a systematic way, especially if they belong to a series of documents e.g. SOPs.

For example:

Study protocol, participant information sheet and consent form

The first draft of the protocol will be labelled 'RCT Protocol 1' and dated. Further draft versions should be labelled 'RCT Protocol 2, 3' etc and dated.

The final original version of the protocol will be labelled 'RCT Protocol Final' and dated. This version will be submitted for the appropriate approvals (Academic supervisors, REC and TSC). Subsequent versions may be labelled 'RCT Protocol 2, 3' etc. and dated.

If the protocol is amended again during the study then the version submitted for approval of the amendment will be labelled 'RCT Protocol 4' again this will depend on last version number and so on.

Only versions and their amendments approved by TSC/REC are included in the Trial Master File.

Standard Operating Procedures

Start with the abbreviation for standard operating procedures (SOP) followed by a number starting from 1, followed by the title of the SOP e.g., Safety Reporting, followed by a version number and date.

3.2 Other considerations

Where appropriate, the following information should be on the document:

Effective date and review date if applicable;

Pagination – It is recommended that pages are numbered as "Page X of Y";

Confidential – If the document is confidential, mark "Confidential";

Approvals - Include signature and date of Author, and Authorizer e.g. for protocols. It may be more convenient to have a separate signature sheet for example SOPs. Include designation or title of signatories;

Reason for Change – If it is a revision of the control document, state reason for change and list changes.

3.3 Storage and archiving

Controlled documents should be stored in a room restricted to authorised individuals only. Any controlled documents that are deemed as essential documents, they will be part of the Trial Master File (see SOP2 Trial Master File 27/6/2017) and archived appropriately (see SOP1 Archiving of Essential Documents 27/6/2017).

Old versions of controlled documents will be archived as well.

SOP Number	**SOP4**			
SOP Title	**Safety Reporting**			
	NAME	**TITLE**	**SIGNATURE**	**DATE**
Author	Aliona Vilinsky-Redmond	Researcher		
Authoriser	Prof. Conan McCaul	Principal Investigator		

Effective Date:	
Review Date:	

Revisions

No.	Section No.	Page No.	Initials/ Date

Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures for eliciting, reporting and recording adverse events (AEs) related to the trial: "*Peri-operative active warming versus no peri-operative active warming during caesarean*

section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomized controlled trial."

Definitions

Adverse Event (AE)

An adverse event can be any inconvenient medical occurrence in a patient which does not necessarily have a causal relationship with this treatment, such as an unintended symptom, or disease temporally associated with the study intervention.

Reporting and Recording Adverse Events

4.1 When should adverse events be recorded

Any adverse event (such as hyperthermia, uncomfortable warm sensation) should be recorded after or during its occurrence. Patients and theatre staff should also be encouraged to contact the researcher at the time of any adverse event, where possible.

Adverse events will be documented in the participant's Adverse Events Report Form.

4.2 How Should Adverse Events and Serious Adverse Events be Recorded

When an adverse event occurs the following information should be recorded by the researcher in the participant's Adverse Events Report Form:

Nature of the adverse event in an unambiguous way using precise and specific terminology;

Record the start and stop date of the adverse events as accurately as possible;

Document the severity of the adverse event (mild, moderate, severe);

Document relationship of adverse event to study;

Document any action taken regarding the study procedures (none; discontinued permanently or discontinued temporarily);

Document if withdrawn from study due to adverse event;

Document if adverse event was expected;

Document if adverse event was serious;

Document if serious adverse event requires reporting. Serious adverse events that are expected do not require a written report, but are to be verbally reported to the sponsor;

Sponsor to review and confirm classification of serious adverse event (expected or unexpected) with the researcher.

4.3 Qi-annual Safety Reports

Safety reports should be submitted, every six months, by the researcher to the Trial Steering Committee of the study.

SOP Number	**5**			
SOP Title	**Adverse Event Report Form**			
	NAME	**TITLE**	**SIGNATURE**	**DATE**
Author	Aliona Vilinsky-Redmond	Lead Researcher		
Authoriser	Prof. Conan McCaul	Principal Investigator		

Effective Date:	

READ BY			
NAME	**TITLE**	**SIGNATURE**	**DATE**

Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the standard procedures to be followed when completing, signing and correcting Adverse Events Report Forms for the trial: "*Peri-operative active warming versus no peri-operative active warming during caesarean section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomized controlled trial."*.

Responsibilities: The Researcher

The researcher has the responsibility for completing the Adverse Events Report Forms. This was delegated to the researcher by the Sponsor.

Specific Procedure

ONLY black ballpoint pen to be used for filling the Adverse Events Report Forms.

Adverse Events Report Forms will contain only anonymised data. The patient's name and medical record number will be erased and the participant's study identification code will be added instead.

Ensure data entry is as complete as possible. If data are unavailable then the word 'missing' will be documented on the Adverse Events Report Forms. No blank spaces will be left.

ONLY information which is asked will be filled on the Adverse Events Report Forms. No additional fields will be added.

All entries must be legible.

Corrections will be made by crossing through the incorrect entry with a single line. In that way the original entry will still be readable. Correct data will be entered next to the space with initials and date added next to the correction. Correction fluid or obliterate entries should NOT be used on the Adverse Events Report Forms.

Adverse Events Report Forms s will be stored in a secure location during the course of the study and archived when the study has finished. See SOP1 Archiving of Essential Documents/27th June 2017.

When all entries and corrections are deemed to be complete, the Adverse Events Report Forms must be signed by the researcher.

A copy of the Adverse Events Report Forms will be included in the Sponsor's file.

SOP Number	**SOP06**			
SOP Title	**Informed Consent**			
	NAME	**TITLE**	**SIGNATURE**	**DATE**
Author	Aliona Vilinsky-Redmond	Researcher		

Authoriser	Prof. Conan McCaul	Sponsor		

READ BY			
NAME	**TITLE**	**SIGNATURE**	**DATE**

Purpose

This Standard Operating Procedure (SOP) is created to describe the standard procedures to be followed when obtaining Informed Consent from participants involved in the trial: "*Peri-operative active warming versus no peri-operative active warming during caesarean section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomized controlled trial."*

Definition

Informed consent is a process by which a participant is informed of all relevant aspects of the trial and voluntarily confirms her willingness to participate in that trial. Informed consent is documented by means of a written, signed and dated informed consent form.

Responsibilities: The Researcher

It is the responsibility of the researcher to ensure that written informed consent is obtained from all trial participants.

Procedure

6.1 Informing the participant

The informed consent process continues throughout the study, keeping participants informed of any new information that the investigator feels is relevant to them.

Written information in the form of a participant information leaflet, which has been approved by the Research Ethics Committee must be provided to the participant 7 days prior to obtaining written informed consent.

The most current version of the approved patient information leaflet and informed consent form will be identified by a version date in the footer.

The language used in any information about the study should be clear and concise and described in layman's terms.

Points that will be verbally discussed with the participant/family member will include:

- The focus of the study;
- Why the participant has been approached;
- The intervention of the study compared to the usual care provided;
- Local and international guideline recommendations;
- Benefit and risks of participation;
- What participants can expect if they choose to participant in the study.

The participant will be given 7 days to read the information sheet, during which time they can discuss the information with family and friends etc.

The participant should have an opportunity to discuss with questions with the researcher including the objectives, risks of the trial and the conditions under which it is to be conducted. The researcher will provide the participant with contact details allowing the participant or family members the opportunity to discuss the trial further with the researcher.

Neither the researcher nor any member of the clinical research team should influence a participant to take part or to continue to participate in the trial. It should be made clear to the participant that withdrawal from the study will not affect their care received and that they are free to withdraw from the study at any stage they wish without providing a reason.

6.2 Recording Informed Consent

The participant must sign the informed consent form prior to the randomisation process.

Three copies of the consent form should be signed and dated. One copy should be filed in the relevant section of the Trial Master File (TMF), a second copy should be given to the participant and the third copy should be filed in their medical records.

Copies of consent forms signed by participants who do not go forward to participate in the study should also be kept in the TMF and not discarded.

SOP Number	7			
SOP Title	Participant Recruitment			
	NAME	TITLE	SIGNATURE	DATE
Author	Aliona Vilinsky-Redmond	Lead Researcher		
Authoriser	Prof. Conan McCaul	Principal Investigator		

Effective Date:	

READ BY			
NAME	TITLE	SIGNATURE	DATE

Purpose

This Standard Operating Procedure (SOP) is created to describe the standard procedures to be followed when recruiting participants for the trial: "*Peri-operative active warming versus no peri-operative active warming during caesarean section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomized controlled trial."*

Definitions

Inclusion criteria

A list of requirements that an individual must meet in order to be eligible to participate in the study.

Exclusion criteria

A list of requirements that will exclude an individual from participating in the study.

Participant

An eligible individual that voluntarily consented to participate in the clinical trial.

Informed Consent

Informed consent is a process by which a participant is informed of all relevant aspects of the trial and voluntarily confirms her willingness to participate in that trial. Informed consent is documented by means of a written, signed and dated informed consent form.

Responsibilities

7.1 Researcher

The researcher on behalf of the Sponsor is responsible for creating and archiving all of the essential documents. The researcher is also responsible to train and support the admission midwife on how to recruit future participants throughout the duration of the study.

7.2 Admission Midwife

The admission midwife, after receiving clear training and support from the researcher, will approach individuals, assess their eligibility, obtain their written consent and randomly allocate them in one of the two groups (with the use of sealed opaque envelopes).

Specific Procedures

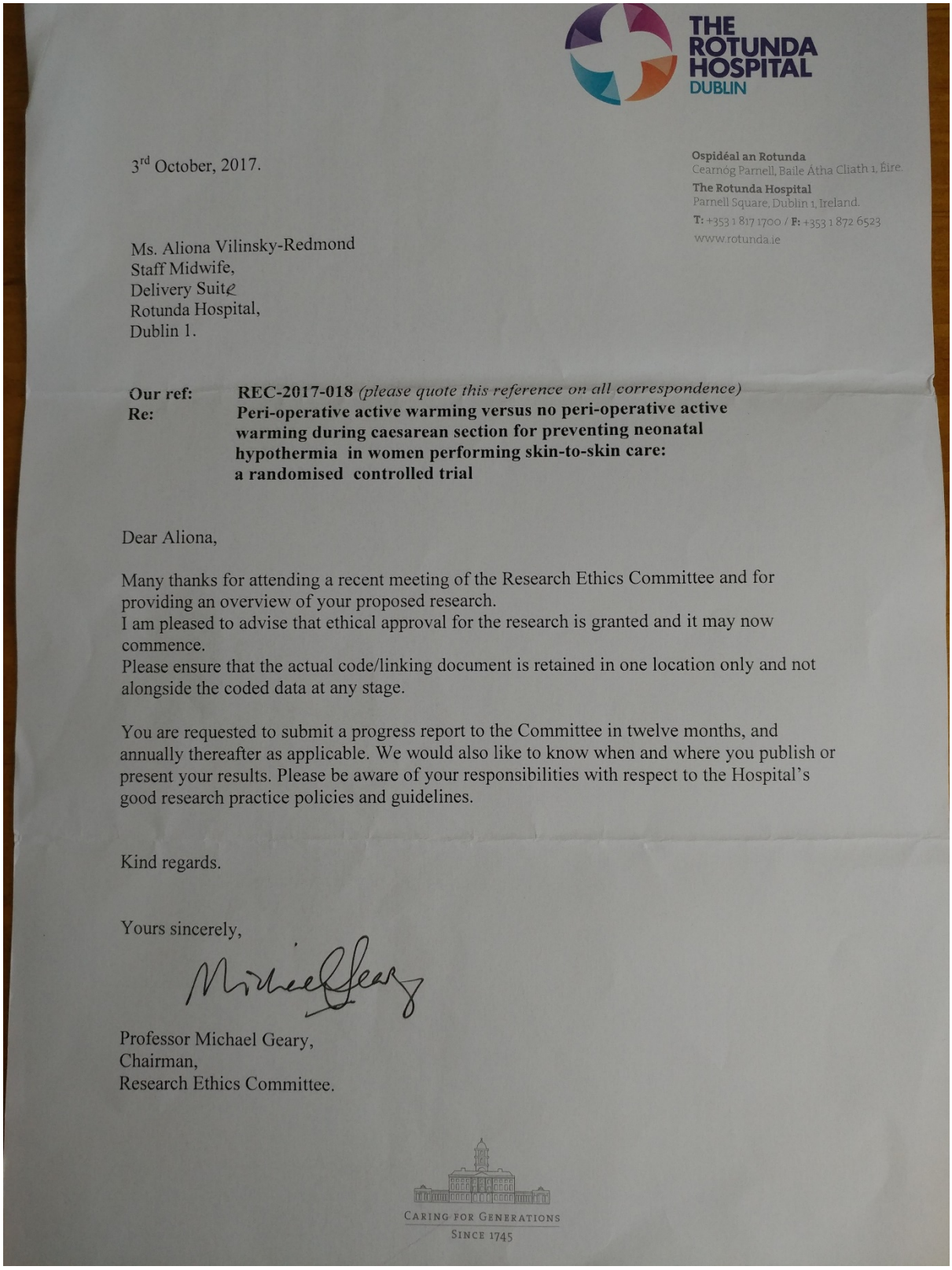
The recruitment plan as approved by the REC is;

- Patients booked for caesarean section during their antenatal visit will be offered the patient information leaflet by the antenatal clinic staff (minimum 7 days before their operation).
- On the day of their operation the admission midwife will approach each individual and assess their eligibility using the inclusion and exclusion criteria provided. The midwife will fill out the related assessment documentation.
- If the participant is eligible the admission midwife will obtain their consent form
- Three copies of the consent form should be signed and dated. One copy should be filed in the relevant section of the Trial Master File (TMF), a second copy should be given to the participant and the third copy should be filed in their medical records.

- The admission midwife will open the sequenced opaque sealed envelope to allocate the participant in one of the two trial groups.
- The outcome of the randomisation will be documented in the participant's trial register form and medical chart.
- A trial label will be applied on the front cover of the participant's medical chart.
- The consented participant will be assigned a trial participation number. The date and number of the participation will be recorded in the trial register form.
- The baseline information will then be collected.
- Eligible participants are pregnant women:
  - aged 18 years or over
  - able to provide informed consent for themselves and their babies
  - who have a singleton pregnancy between 37^{+0} and 41^{+6} weeks gestation
  - whose foetus/new-born is alive/born alive, and has no risk factors such as congenital or cardiovascular anomalies (see Appendix 1, TSRF)
  - who receive spinal or combined spinal anaesthesia for their caesarean section
  - have an elective CS
- Women will be excluded from this study if they:
  - require an emergency caesarean section
  - have pyrexia (> 37.5C on admission to ward)
  - aged <18 yrs at the time of consent
  - have a maternal medical disease (i.e. Spinal abnormalities, coagulation abnormalities, maternal serology positive)
  - have general anaesthesia
  - have a multiple pregnancy
  - have a baby born before term gestation (less than 37 weeks)
  - have a baby who has a congenital anomaly (i.e. Spina bifida, anencephaly, hydrocephaly, cardiovascular anomalies, anomalies of nervous system, defects of anterior abdominal wall)
  - have a baby who has abnormal Doppler artery velocimetry
  - have a stillbirth baby
  - have a recent USS estimating the fetal weight less than 2000g
- Recruitment will take place in a eight month period.
- An electronic file of non-eligible participants will be maintained by the researcher and will include only the number 888.

- The PI, members of the trial steering committee and members of theatre staff will be regularly updated by the researcher on the outcome of the recruitment process.
- The researcher will analyse any factors relevant to the successes and failures of the recruitment process.

Appendix 4.4. Hospital Ethics Committee approval



THE ROTUNDA HOSPITAL DUBLIN

Ospidéal an Rotunda
Cearnóg Parnell, Baile Átha Cliath 1, Éire.
The Rotunda Hospital
Parnell Square, Dublin 1, Ireland.
T: +353 1 817 1700 / F: +353 1 872 6523
www.rotunda.ie

3rd October, 2017.

Ms. Aliona Vilinsky-Redmond
Staff Midwife,
Delivery Suite
Rotunda Hospital,
Dublin 1.

Our ref: **REC-2017-018** *(please quote this reference on all correspondence)*
Re: **Peri-operative active warming versus no peri-operative active warming during caesarean section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomised controlled trial**

Dear Aliona,

Many thanks for attending a recent meeting of the Research Ethics Committee and for providing an overview of your proposed research.
I am pleased to advise that ethical approval for the research is granted and it may now commence.
Please ensure that the actual code/linking document is retained in one location only and not alongside the coded data at any stage.

You are requested to submit a progress report to the Committee in twelve months, and annually thereafter as applicable. We would also like to know when and where you publish or present your results. Please be aware of your responsibilities with respect to the Hospital's good research practice policies and guidelines.

Kind regards.

Yours sincerely,

Professor Michael Geary,
Chairman,
Research Ethics Committee.

CARING FOR GENERATIONS
SINCE 1745

Appendix 4.5. Participant study information leaflet

Study Information for Women

The NeoHyp Trial

Full study title: Perioperative active warming versus no perioperative active warming during caesarean section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomized controlled trial.

Introduction

We would like to tell you about an important research study that we are undertaking in this hospital. This study may help to improve the health of mothers and babies who are undergoing elective (pre-planned) caesarean section. It is known as the NeoHyp trial. We want to let all women who are booked for elective caesarean section know about the detail of what we aim to examine even though some of you will not be eligible to participate in the study. Please read this information to see if you are able and would like to join this study.

What is the Neonatal Hypothermia (NeoHyp) trial?

After caesarean section, babies are placed on their mother's chest (called skin-to-skin contact) to help with the bonding process. Some babies, however, can become a little cold after they are born. This is called hypothermia and it occurs when a baby's temperature falls below normal levels. One of the suggested ways to prevent this happening might be to actively warm a woman during her caesarean section, which might, in turn, help prevent a baby getting cold as skin-to-skin is being performed. At present, all women, during their caesarean section, are given fluids through a needle in their arm or hand. This is normal practice to help keep a woman hydrated. These fluids are called intravenous (IV) fluids. In this study we wish to test if giving women intravenous (IV) fluids, during a caesarean section, that have been especially warmed before the caesarean or giving fluids that have not been especially warmed (that is, giving IV fluids that are at room temperature), makes a difference in the numbers of babies that might get cold after birth.

The full name of the study is: "Perioperative active warming versus no perioperative active warming of women, at term, for preventing neonatal hypothermia after caesarean section: a randomized controlled trial" or the 'NeoHyp study' for short.

What does the study involve?

This type of study is known as a randomised trial. Those who take part in a randomised trial are divided, randomly (by chance), into different groups. Each group is given a different treatment and the results are then compared to see if one treatment is better. The two different treatments that will be given are:

1) Room Temperature Fluids (RTF)

2) Warm Fluids (WF)

What are IV fluids and why are they used?

During a caesarean section women are given IV fluids through a plastic tubing, called a giving set, which is connected to a plastic needle in a woman's arm. This fluid (called Hartmann's solution) helps keep a woman hydrated during and after the operation, as women are asked not to drink or eat anything from the night before her operation until 4 hours after the operation. This fluid is made up of sterilised water and electrolytes (that is, nutrients that are important to the body, such as salt and calcium), and does not contain any medication in it. The same type of fluids will be used for every women taking part in the study as is normal practice in the hospital during caesarean section.

What is room temperature fluid (RTF)?

Room Temperature Fluids (RTF) are fluids given to all women who have a caesarean section in this hospital in order to keep them hydrated. These fluids are given at room temperature (that is around 25°C) without being warmed. This is the current practice of the hospital and every woman has to receive these fluids.

What is pre-warmed fluid (WF)?

Warm Fluids (WF) means that staff in the operating room will warm these fluids prior to them being given to you. The fluid is warmed to 39°C in a special warming device during your operation. This temperature is not usually associated with any side effects.

Who may join this study?

We are inviting all women who are booked for an elective (planned) caesarean section using spinal anaesthesia at the hospital AND who can say 'yes' to the following questions, to participate in this study:

- Are you over 18 years old?
- Are you at least 37 weeks pregnant at the time of your caesarean section?
- Are you expecting one baby (not twins or triplets)?
- Would you like to do skin-to-skin contact after the birth of your baby?

What happens if I join the study?

When you come into the hospital on the day of your elective caesarean section, the midwife caring for you will do a health check to make sure you are able to join the study. If you are able and wish to join the study, the midwife caring for you will ask you to sign a consent form agreeing to be part of the study. At this stage, the randomisation will take place, and you will be allocated by chance to one of the two study groups. You have an equal chance of being placed in either group.

If you are allocated to receive IV fluids at room temperature, you will receive these room temperature fluids before the anaesthetist gives you the epidural or spinal anaesthesia (the injection that numbs you from your waist down to block pain). If you are allocated to receive the warm IV fluids, you will receive warm fluids before you receive your anaesthesia.

Do I have to take part in this study?

No, taking part in this study is completely up to you. If you decide not to take part in the study, your care will not be affected in any way, and you will receive room temperature fluids, which is the normal care offered by the hospital.

What are the risks/benefits of taking part in this study?

There are no known risks to taking part in this study for your baby. However, you might feel warmer after receiving the warm fluids. If this warm sensation makes you feel uncomfortable, you can inform the midwife who is looking after you and you will stop receiving the warm fluids. The benefits of taking part in this research study are that you will have helped to answer questions that could improve the health of future generations of mothers and babies.

Can I leave the study after I have joined?

Yes, you have the right to leave the study at any time you wish. If you decide to leave the study, you must tell the midwife on duty who will contact the research midwife of the study.

Is my personal health information kept private?

The information that we will collect during this study are; your and your baby's body temperature in different times, how warm or cold are you feeling, if you had any incidence of shivering, if additional warming was needed for either you or your baby and how long the skin-to-skin contact lasted. Theatre staff will measure both your temperature and your baby's and will document them on your chart. Then the researcher will access your chart and collect the above information. All study information is kept private. You will be given a study number so that any personal information collected during the study will not be linked to your name. All study information will be kept for five years, within the hospital premises, after the study is finished and then destroyed. The results of the study may be published; however, neither your name nor any personal details about you or your baby will appear in any publications.

Who is running the study?

The study was designed and is being carried out by Aliona Vilinsky-Redmond, a Rotunda hospital midwifery staff and a midwife researcher based in Trinity College Dublin, who coordinates and is responsible for the day to day management of the trial. A Trial Steering Committee (made up of midwives/nurses and doctors) is formed to oversee and advise on the study conduct. This study has received ethical approval from the Rotunda Hospital Research Committee.

What do I do now if I wish to be in the study?

You don't need to do anything else right now. It is only when you go into hospital on the day of your caesarean section that you can 'sign up' to join the study. This is when you will have the final health check to make sure that you are able to be in the study.

Where can I get more information or ask questions about the study?

The midwives and doctors in your hospital have information about the study. Also, the research midwife, Aliona Vilinsky-Redmond, will be happy to provide you with more information. You can contact Aliona by emailing **vilinska@tcd.ie** or call at 0879906307.

THANK YOU FOR YOUR TIME AND FOR CONSIDERING TAKING PART IN THIS IMPORTANT RESEARCH STUDY

Appendix 4.6. Participant written consent form

CONSENT FORM

Research title: "Peri-operative active warming versus no peri-operative active warming of women, at term, for preventing neonatal hypothermia after caesarean section: a randomised controlled trial"

Researcher: __Aliona Vilinsky__ Tel: __0879906307_ E-mail: ___vilinska@tcd.ie_

DECLARATION by participant: Please tick (✓) and provide your initials		
1.	I have read the information leaflet for this research study and I understand the contents.	**Yes [ ] No [ ] initials [ ]**
2.	I have had the opportunity to ask questions and all my questions have been answered to my satisfaction.	**Yes [ ] No [ ] initials [ ]**
3.	I fully understand that my/my baby's participation is completely voluntary and that I am free to withdraw from the study at any time (prior to anonymization/publication) without giving a reason and that this will not affect my care/my baby's care in any way.	**Yes [ ] No [ ] initials [ ]**
4.	I understand that information from this research will be published but that I will not be identified as a participant in this research in any publication.	**Yes [ ] No [ ] initials [ ]**
5.	I understand that I/my baby will not be identified as a participant in this study (unless a legal requirement) and that the researchers may hold my personal information for '5' years after the study has been completed. After this period all data will be securely destroyed.	**Yes [ ] No [ ] initials [ ]**
6.	I understand that the researchers undertaking this research will hold in confidence and securely all collected data and other relevant information.	**Yes [ ] No [ ] initials [ ]**
7.	I freely and voluntarily consent to participating/allowing my baby to participate in this research study.	**Yes [ ] No [ ] initials [ ]**

Participant's signature: …… **Date:** ……..……..

Researcher: …… Signature: …….. Date:……

Appendix 4.7. Data collection form

Data Collection Booklet

Confidential

Woman's details

1. Woman's NeoHyp number:

2. Randomised:

WF: 1	RTF: 2

(Note: An addressograph label may be placed over questions 3 & 4 if available)

3. Woman's record number:

4. Maternal age at time of CS (date of birth):

5. Date of randomisation:

Woman's baseline characteristics

6. Gravida:

7. Parity:

8. Anaesthesia received:

Spinal	Yes: 1	No: 0
CSE	Yes: 1	No: 0

Neonatal

N1. Infant's date of birth:

N2. Apgar Scores:

At 1 minute	At 5 minute

N3. Gestation at birth:

N4. Weight in grams:

N5. Neonatal Complication:

Yes: 1	No: 0

N6. Type of Complication *(give full details; reason for admission to NICU, Treatment, Diagnosis):*

……

N7. Skin-to-skin contact:

Yes: 1	No: 0

N8. Breast-feeding:

Yes: 1	No: 0

N9. If interruption to skin-to-skin contact and/or breast feeding *(state reason and duration of interruption):*

……..

N10. Neonatal temperature (degrees Celsius):	Yes: 1	No: 0
N11. Neonatal hypothermia (T < 36.5^{0}C) before d/c from OT:	Yes: 1	No: 0
N13. Additional warming of new-born:	Yes: 1	No: 0

N14. Additional warming *(please state type, temperature setting and duration):*

……

……

<u>Maternal</u>

M1. Maternal antenatal temperature:

M2. Maternal temperature:

During CS	On PACU admission	On PACU discharge

M3. Maternal hypothermia (i.e. T < 36^{0}C) before OT discharge:	Yes: 1	No: 0
M4. Maternal hypothermia (i.e. T < 36^{0}C) before PACU discharge:	Yes: 1	No: 0

M5. Maternal thermal comfort in PACU:

Hot	warm	neutral	cool	cold
5	4	3	2	1

M6. Maternal shivering:	Yes: 1	No: 0
M7. Maternal complication:	Yes: 1	No: 0

M8. Type of Complication *(give full details; i.e. PPH, Treatment, Diagnosis):*

……

…… Yes: 1 No: 0

M9. Additional warming for the mother:

M10. Additional warming *(state type, temperature setting and duration):*

……

……

V1. Verify correct use of intervention:

Yes: 1	No: 0

V2. If the answer is no please give full details:

……
……

R1. OT ambient temperature during CS:

R2. PACU ambient temperature during admission:

R3. Total volume of IV fluids received:

R4. Estimated Blood Loss (EBL):

Appendix 5.1. Theatre staff information leaflet

NeoHyp trial information leaflet

Study title: "Perioperative active warming versus no perioperative active warming of women, at term, for preventing neonatal hypothermia after caesarean section: a randomized controlled trial".

Principal investigator: Prof Conan McCaul

Researcher: Aliona Vilinsky-Redmond

Contact details: vilinska@tcd.ie or 0879906307

Ethical Approval: Study approved by Rotunda REC (REC-2017-018)

Trial registration: clinicaltrials.gov (protocol ID: RotundaH)

Study Details

During a CS women are given IV fluids (Hartman's solution), to keep women hydrated during and after the operation, as women are asked not to drink or eat anything from the night before her operation until 4 hours after the operation. These fluids are given at room temperature (that is around 25°C) without being warmed. This is the current practice of the hospital and every woman has to receive these fluids. Many women can drop their temperature during and after the operation. And that may affect the babies' temperature after they are born while placing them on their mother's chest (called skin-to-skin contact) to help with the bonding process. This study aims to find if there is a link between mother's temperature and baby's temperature and if the temperature drop can be prevented with the use of the study intervention (IV fluids warmed to 39°C).

Type of study: two arm randomised controlled trial

Study treatments: 1) Room Temperature Fluids (RTF)

2) Pre-warmed Fluids (WF)

Participant inclusion criteria:

- Aged 18 years or over
- Able to provide informed consent for themselves and their babies
- Who have a singleton pregnancy between 37^{+0} and 41^{+6} weeks gestation
- Whose foetus/new-born is alive/born alive, and has no risk factors such as congenital or cardiovascular
- Who receive spinal or combined spinal anaesthesia for their CS
- Have an elective CS
- Who are willing and able to perform skin-to-skin contact

Study outcomes:

Primary outcome

- Neonatal hypothermia (defined as temperature < 36.50C, assessed immediately prior to transfer to PACU)

Secondary outcomes

- Maternal hypothermia (defined as temperature <360C) and assessed prior to transfer to PACU).

- Maternal tympanic temperature measured on four occasions (on admission as a baseline measure, and on 3 occasions post-intervention - see data collection method) using an adult tympanic (ear) thermometer as per current hospital practice.

0. Neonatal axillar temperatures measured on two occasions (see data collection method) using a neonatal axillar (under-arm) thermometer as per current hospital practice.
1. Maternal shivering (yes/no).
2. Maternal thermal comfort scale measurement, measured using a 1-5 scale from cold, cool, neutral, warm and hot.
3. Use of additional warming of mothers (Bair Hugger™) and the temperature setting of the device.
4. Use of additional warming of new-born (incubator) and the temperature setting of the device.
5. Occurrence of adverse events (for both new-born and mother).
6. Interruption to SSC and breastfeeding.

Sample size: 150 participants, 75 women and babies randomly allocated per group.

Data Collection: Maternal and neonatal temperatures will be measured and documented by theatre staff in the patient's charts as per usual practice. All relevant data from the participants' charts will retrospectively be collected/documented, by the researcher, on the data collection form designed specifically for the study. Data will be cross checked between the lead researcher and the theatre staff who do the measurements.

Additional information are: mother's and baby's body temperature in different times, how warm or cold a woman is feeling, any shivering incidence and how long the skin-to-skin contact lasted.

Study privacy: Data will be kept within secure hospital premises, for five years and then destroyed.

Study Risks: There are no known risks to taking part in this study for women or their baby.

Study Benefits: The benefits of this research study are that we will answer questions that could improve the health of future generations of mothers and babies.

Thank you for helping us with this study.

Appendix 5.2. NeoHyp trial poster

NeoHyp trial

Dear colleagues,

Just a gentle reminder that the NeoHyp trial (REC-2017-018) is currently running.

For the anaesthetic team, please when you identify a study participant, remember to:

- Use the IV giving set for the Hotline for administering IV fluids.
- Measure the maternal temperature after the baby is born and while the woman is still operating.
- Document the maternal temperature in the anaesthetic chart among the rest vital signs.

For the midwifery team, please remember to:

- Measure neonatal temperature after the first skin-to-skin contact in OT is finished.
- Measure neonatal temperature after the second skin-to-skin contact in PACU is finished.
- Document the neonatal temperature in the neonatal chart as per usual practice.

For the PACU team, please remember to document in the maternal chart the following information:

- Maternal temperature on admission to PACU and prior PACU discharge.
- How warm or cold a woman is feeling during her admission in PACU.
- Any incidence of maternal shivering
- How long the skin-to-skin contact lasted in PACU.

If you have any queries about the trial, please don't hesitate to contact me either in person or in my email vilinska@tcd.ie.

Thank you for all your help and support.

Aliona Vilinsky-Redmond

NeoHyp trial

Midwifery researcher

Appendix 5.3. Trial Screening and Register Form (TSRF)

This form MUST be fully completed on admission for <u>all</u> women who are admitted for an elective caesarean section at term.

Date: ☐☐/☐☐/☐☐☐☐

Study information received prior to Admission for caesarean section: Yes ❒ No ❒

Eligibility (See criteria on the back of this form)

Eligible for NeoHyp Trial: Yes ❒ No ❒

If no, <u>DO NOT PROCEED</u> and document primary reason for ineligibility:

Consent – Check consent Booklet *(this will be N/A where a woman is ineligible for NeoHyp)*

NeoHyp Trial Consent form signed and witnessed:

Yes ❒ NeoHyp trial number: ☐☐☐☐☐

No ❒

If no, <u>DO NOT PROCEED</u> to randomisation

Randomisation – Please open sealed opaque envelope for group allocation

Group allocation: Warm Fluids ❒

Room Temperature Fluids ❒

Envelope number: ☐☐☐

Signature <u>and</u> printed name of midwife/doctor completing this form:

Printed Name: Signature:

NeoHyp Trial Screening and Register Form – Eligibility Criteria

Please tick as appropriate for EACH risk factor. If 'YES' is ticked for any risk factor the woman is ineligible and should not be considered further for the NeoHyp trial

Risk Factor	Yes	No
Prematurity *(<37 + 0)*		
Antepartum Haemorrhage *(single episode at >24 weeks)*		
Pyrexia *(> 37.5C on admission to ward)*		
Caesarean section under general anaesthesia		
Maternal age <18 yrs at time of consent		
Maternal medical Disease: - Spinal abnormalities - Coagulation abnormalities - Maternal serology positive - Severe renal functional impairment		
Stillbirth		
The most recent USS estimated foetal weight less than 2000g		
Abnormal Doppler artery velocimetry		
Foetal congenital abnormality in this pregnancy • Spina bifida/meningomyelocele • Anencephaly • Hydrocephaly • Cardiovascular anomalies • Anomalies of Nervous system • Defects of anterior abdominal wall		
Multiple pregnancy		

Confirmed following review by the NeoHyp Trial Steering Committee and DSB members

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

THE ROTUNDA HOSPITAL DUBLIN

Trial Steering Committee Terms of Reference

REC-2017-018

Neohyp Trial

Title of Trial: Perioperative active warming versus no perioperative active warming during caesarean section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomized controlled trial.

This is a parallel two group, randomised controlled trial.

Terms of Reference

The Trial Steering Committee (TSC) provides an independent review body for the clinical trial data and will review the report made by the Data Monitoring Board on the safety of trial participants and the study progress and adherence to the protocol. The TSC comprises six experts, independent from the trial research team and the researcher and her academic supervisors, which are non-independent members of the trial but are considered ex officio.

The responsibilities of the TSC are to:

- Review/approve the protocol and trial documentation in a timely manner.
- Concentrate on patient safety, progress of the trial and adherence to the protocol.
- Provide advice to the researcher on all appropriate aspects of the trial. Specifically, the TSC will:
    - Approve any amendments to the protocol.
    - Approve and comment on the statistical analysis plan.
    - Monitor recruitment rates.
    - Monitor completion of data sheets.
    - Monitor follow-up rates.
    - Oversee the timely reporting of trial results.

- Approve and comment on any abstracts and presentations of any results *during* the running of the trial.
- Receive reports from the DMB.
- The TSC will make decisions as to the future continuation (or otherwise) of the trial.

Membership

The members of the TSC have expertise in the following areas: clinical trials, statistical analysis, study methodology, nursing/midwifery, neonatology, obstetrics and anaesthesia.

Mrs Aliona Vilinsky-Redmond (researcher)

Staff Midwife, Rotunda Hospital, Dublin, PhD student, Trinity College Dublin

Dr Margaret McCann (non-independent member)

Assistant Professor in Nursing, Head of Nursing department, Trinity College Dublin.

Dr Maria Brenner (non-independent member)

Associate Professor in Children's Nursing, Trinity College Dublin.

Professor Conan McCaul (independent member)

Consultant Anaesthetist, Rotunda Hospital, Dublin.

Dr Mark Hehir (independent member)

Assistant Master, Obstetrician, Rotunda Hospital, Dublin.

Ms. Jane Hickey (chair)

Midwifery Manager, Theatre Department, Rotunda Hospital, Dublin.

Ms. Derval Dickson (independent member)

Nursing Manager, Theatre Department, Rotunda Hospital, Dublin.

Ms. Christine McDermott (independent member)

Advanced Nurse Practitioner, NICU, Rotunda Hospital, Dublin.

Competing Interests

No member of the TSC has financial, proprietary, professional, or other interests that may affect decision-making. At the beginning of each TSC meeting the members present will confirm that no competing interests exist. Competing interests should be disclosed to the TSC prior to any discussion, and the TSC will determine how to handle such potential conflicts (i.e. a member with a potential conflict does not vote or take part in the relevant discussion).

Meetings

The TSC will meet twice during the trial, unless they decide that there is a need for additional meetings. Responsibility for calling and organising the TSC meetings lies with the researcher. All meetings will take place within Rotunda Hospital at a time/date that suits all TSC members. The researcher will prepare a report and circulate it to the TSC before each meeting. At the end of the meeting the TSC members will decide in a written format whether or not the trial should continue. The chair of the TSC will inform the researcher if an additional meeting is needed. Further communication will take place vie e-mail and/or telephone.

First Meeting

The first meeting will take place in late September 2017, when members will:

- Review/familiarise themselves with the study protocol.
- Review and provide feedback on these draft Terms of Reference (TOR)
- Agree the schedule and format for future meeting (for example, face to face or conference call)

Second/Final Meeting

The second meeting will focus on the safety, rights and well-being of trial participants. This meeting will take place after the trial has commenced. In this meeting members will monitor the recruitment rates, the follow-up rates, the data sheets and every relevant aspect of their role as described above. Finally, the TSC will revise the DMB review for allowing the trial to continue or otherwise. The TSC will provide evidence to support any requests for extensions, including that all practicable steps have been taken to achieve targets.

Confidentiality

All materials, discussions, and proceedings of the DMB are strictly confidential.

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Data Monitoring Board Terms of Reference

REC-2017-018

Neohyp Trial

Title of Trial: Perioperative active warming versus no perioperative active warming during caesarean section for preventing neonatal hypothermia in women performing skin-to-skin care: a randomized controlled trial.
This is a parallel two group, randomised controlled trial.

Terms of Reference

The Data Safety Monitoring Board (DSMB) provides an independent review body for the clinical trial data and will advise the Trial Steering Committee on the safety of trial participants and the validity and scientific merit of the trial during recruitment, treatment and follow-up. The DSMB comprises three experts, independent from the trial research team.

The primary responsibilities of the DSMB are to:

- Review the study protocol in order to familiarise themselves with the approved process
- Review and advise on unblinded interim analysis of outcome data and adverse event reports
- Submit confidential written reports to the Trial Steering Committee concerning the continuation of the trial and whether there are any ethical or safety reasons why the trial should not continue, without revealing the unblinded interim results unless they deem it necessary to do so
- Maintain confidentiality on its internal discussions and activities.

Membership

The members of the DSMB have expertise in the following areas: clinical trials, statistical analysis, study methodology, nursing/midwifery, neonatology and anaesthesia.

Professor Jonathan Drennan,

Nursing & Midwifery
University College Cork
Cork
Ireland

T: +353-21-490-3000
E: jonathan.drennan@ucc.ie

Professor Eugene Dempsey

Consultant Neonatologist, Lecturer in Paediatrics and Child health

University College Cork
Cork
Ireland

T: +353-21-490-3000
E: G.Dempsey@ucc.ie

Doctor Terence Tan

Consultant Anaesthetist
Coombe Women & Infants University Hospital
Cork Street
Dublin 8
ttan@coombe.ie

Competing Interests

No member of the DSMB is directly involved in the conduct of the study. Furthermore, no member has financial, proprietary, professional, or other interests that may affect independent decision-making by the DSMB. At the beginning of each DSMB meeting, the members present will confirm that no competing interests exist. Competing interests should be disclosed to the DSMB prior to any discussion and the DSMB will determine how to handle such potential conflicts (i.e. a member with a potential conflict does not vote or take part in the relevant discussion). If they wish, the DSMB will seek guidance from the Trial Steering Committee if they are uncertain about a potential competing interest.

Meetings

The DSMB will meet three times during the trial, unless they decide that there is a need for additional meetings (for example, to review additional analyses).

First Meeting

The first meeting will take place in early October 2017, when members will:

- Review/familiarise themselves with the study protocol.
- Review and provide feedback on these draft Terms of Reference (TOR)
- Agree the schedule and format for future meetings (for example, face to face or conference call)
- Agree the format and the timing of the interim reports.

Second Meeting

The second meeting will discuss unblinded interim results, with a particular focus on the safety, rights and wellbeing of trial participants. This meeting will take place after the trial has commenced. Data for the interim analysis will include accrual and dropout rates, baseline data, data relating to compliance with interventions and outcome data comparing the effects in the intervention groups. This information will be supplied by the researcher (Aliona Vilinsky-Redmond).

Final Meeting

The final meeting will discuss the findings of the trial and will take place at the end of the trial. This is expected to be September 2019.

Format and Scheduling of Meetings

Face to face meetings are preferable but conference calls are also acceptable, if this is agreed by all members of the DSMB and the researcher. The location of the meetings will be decided between the DSMB members and the researcher, via e-mail, before the first official meeting. If the meeting is to be conducted by conference call the researcher will co-ordinate these calls.

Meetings will be either open or closed and this will be determined by the DSMB. The DSMB can interact with the researcher to clarify issues in relation to the conduct of the trial or any other issues as they arise.

Meetings with be organised by the researcher in consultation with the DSMB and dates/times for meetings will be agreed in advance. The researcher will prepare a report and circulate it to the DSMB before each meeting. After each meeting at which unblended interim analyses are reviewed (currently, the second meeting only), the DSMB chairperson will submit a written report to the researcher on whether or not the trial should continue.

Outcome of Meetings

All significant communication between the DSMB and the researcher should be in writing. The DSMB will send the researcher a confidential written report within 2 week of the relevant meeting providing their opinion on whether the Trial Steering Committee should:

- continue the study without changes
- continue the study with changes
- terminate the study

The recommendation should be based on unanimity or formal majority voting and justified in the report.

Confidentiality

All materials, discussions, and proceedings of the DSMB are strictly confidential.

Appendix 5.6. DSMB report on the interim results

18th March 2018

Dear Aliona,

We had a quick look at your data. There is no difference between warming or no warming in Baby T1, T2, Maternal T1, T2, T3, or T4. There is also no difference in shivering between both groups. There is also no difference in thermal comfort between the groups with a median score of 3 for both groups. In terms of normality tests, Baby T1, T2, and Maternal T1 does not meet normality test, and is therefore not normally distributed. You will probably have to complete the study before you can make any conclusions.

The interim analysis does not reveal any significant findings. Please continue with the study.

Yours Sincerely,

Terry Tan

Appendix 5.7. DSMB report on the final results

Dear Aliona,

We had a look at your data and found the following. There is no difference maternal age, infant weight, IV fluid volume, estimated blood loss and SSC duration. There is a statistical difference in gestation age (p= 0.034).

There is no statistical difference between warming and no warming in Baby T2, Maternal T1 and T4. But there is a statistical difference in Baby T1 (p=0.021), Maternal T2 (p<0.001) and T3 (p<0.001). Overall, Baby T2 correlated positively with Baby T1 and negatively with PACU temp. Baby T1 correlated positively with IV fluid volume and EBL.

No serious adverse events occurred during the trial. Please continue with the data analysis.

Yours Sincerely,

Terry Tan

Appendix 6.1 Multicollinearity table

Multicollinearity prior to Logistic Regression Analysis (Binary)					
	Standard Deviation (SD)	**Standard Error (SE)**	**df**	**Overall Standard Error (OSE)**	**VIF**
Maternal temperature (during SSC in OT)	0.35	0.009	148	0.30	0.05
Maternal Hypothermia (during SSC in OT)	0.31	0.08	148	0.31	3.21
Maternal temperature (PACU admission)	5.72	0.06	148	0.30	37.09*
Maternal temperature (before PACU discharge)	0.87	0.07	148	0.30	8.76*
OT ambient temperature	0.29	0.008	148	0.32	0.03
PACU ambient temperature	0.24	0.002	148	0.32	0.002
SSC duration	0.24	0.002	148	0.32	0.002
Gestational age	0.29	0.008	148	0.32	0.03
Weight	0.00	514.14	148	0.23	0.002
IV fluid volume	0.00	503.88	148	0.23	0.002
Type of feeding	0.004	0.49	148	0.23	2.15
EBL	0.00	222.31	148	0.23	0.006
Additional maternal warming	0.48	0.04	148	0.23	3.14
Additional neonatal warming	0.42	0.04	148	0.23	2.64

*** Indicates high multicollinearity therefore these variables will be excluded from the regression analysis as they violate one of the regression assumptions.**