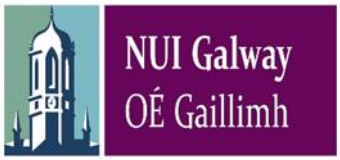

Design, synthesis, and public understanding and involvement in randomised trials

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A thesis submitted to the College of Medicine, Nursing and Health Sciences, National University of Ireland Galway, in fulfilment of the requirements for the degree of Doctor of Philosophy.

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Declaration

I, Elaine Finucane, certify that this work is submitted to fulfil the requirement of the degree of Doctor of Philosophy, at the National University of Ireland Galway. I have not obtained a degree in the National University of Ireland Galway, or elsewhere, on the basis of the work detailed in this thesis. I am the author of this thesis and the principal author of the four included papers. Contributions by others are included under 'Contributions to research'.

Signature: _____ Date: ___14/12/20_____

Abstract

Introduction

The initial aim of my PhD was to assess if amniotic membrane sweeping, a common intervention in maternity care, is a safe and effective way of preventing a formal induction of labour[1] in pregnant women at or near term[2]. However, with the arrival of a novel coronavirus (SARS-CoV-2) and the immediate and profound changes it brought to clinical practice and the conduct of clinical research, the intended pathway of my PhD research altered significantly. Therefore, my thesis comprises two sections. Section one focuses on membrane sweeping to prevent a formal induction of labour. Section two of the thesis focuses on *The People's Trial*. The aim of *The People's Trial* is to support the public understanding and knowledge of randomised trials, to understand why they matter and be better equipped to think critically about health claims by becoming involved in each step of the clinical trial process. *The People's Trial* also potentially supports researchers in learning how best to involve and engage the public in trials.

Methods

This thesis includes four papers. The first paper (Chapter 2, published), a Cochrane systematic review and meta-analysis was undertaken to assess the effects and safety of amniotic membrane sweeping for induction of labour in women at or near term. The findings of this review directly informed The MILO Study, presented in paper two (Chapter 3, published). The MILO Study is a Feasibility study protocol of a pragmatic, randomised controlled pilot trial, to evaluate the effectiveness (including optimal timing and frequency) of membrane sweeping to prevent post-term pregnancy. Paper three (Chapter 4, submitted for review), describes the process of *The People's Trial*, an online parallel group, randomised controlled trial, including aims, design, conduct and dissemination. Paper four (Chapter 5, submitted for review), reports the design, conduct and findings of the randomised controlled trial designed by the public, which we called The Reading Trial.

Results

[1]A formal induction of labour is defined 'the use of oxytocin +/- amniotomy, amniotomy only, vaginal/intracervical misoprostol, vaginal/intracervical prostaglandins or mechanical methods (including extra-amniotic Foley catheter) to stimulate uterine contractions.

[2] A pregnancy is considered to have reached full term at 37 completed weeks' gestation

The Cochrane systematic review and meta-analysis found that when comparing membrane sweeping with no treatment/sham, women randomised to membrane sweeping may be more likely to experience a spontaneous onset of labour and less likely to experience an induction of labour; however, overall, the evidence was of low certainty.

The review identified the need for further robust research to assess the optimal gestation to receive a membrane sweep and whether having more than one sweep would be beneficial. It further highlighted the need to explore women's views of membrane sweeping.

The MILO study, a feasibility study, includes a pilot randomised trial, a health economic analysis, a qualitative study and a Study Within A Trial (SWAT). The MILO study was due to commence recruitment in March 2020, with ethical approval, study documentation, site procedures, clinicians and research midwives in position to support the study conduct. The MILO Study is now due to commence recruitment in February 2021, dependent on clinical circumstances and COVID-19.

The remainder of the PhD focuses on, *The People's Trial*, a novel, online randomised trial designed by the public for the public. Over 3000 members of the public, from 72 countries, participated in *The People's Trial*, engaging in all aspects of the trial design, from choosing the trial question, to trial conduct, analysis and dissemination. We report the processes of *The People's Trial* in seven phases, mimicking the steps of a randomised trial, In December 2019, 991 participants took part in a trial designed by the public, called The Reading Trial. The trial aimed to answer a question identified and prioritised by the public '*Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed*?' The Reading Trial found that, 56/369 (42%) of people in the intervention group felt their sleep improved, compared to 112/405 (28%) of those in the control group, a difference of 14%.

Conclusion

My PhD supports the development of four papers, which individually and collectively provide an original contribution to knowledge. The outputs from this body of work include:

A multi-site feasibility study, informed by a Cochrane systematic review, which is designed and ready to commence recruitment in 2021. The findings of the MILO study, including the views of women and clinicians, will inform the optimal design of a future definitive

randomised trial to examine the effectiveness including optimal timing and frequency of membrane sweeping to prevent post-term pregnancy.

The People's Trial, a novel, online trial that has successfully involved over 3000 members of the public in the design, conduct, and dissemination of a randomised trial. This demonstrates public appetite to engage with, and learn about randomised trials, to understand why they matter, and to be better equipped to think critically about health claims.

Contributions to research

This thesis consists of four papers, one of which is published and three under peer-review.

The first paper, presented in chapter 2 is a Cochrane Systematic Review that Elaine Finucane (EF) led. This review and meta-analysis examined the current evidence to assess the effects and safety of membrane sweeping for induction of labour in women at or near term (≥ 36 weeks' gestation). EF retrieved papers found through a search conducted by the Cochrane Pregnancy & Childbirth Group search co-ordinator. EF and Declan Devane (DD) independently applied eligibility criteria. EF designed data collection forms, collected data from included studies, and assessed studies for risk of bias. Review team members (DD, Deirdre Murphy (DM), Linda Biesty (LB), Gill Gyte (GG), Amanda Cotter (AC), Ethyl Ryan (ER) & Michel Boulvain (MB)) independently collected data and assessed included studies for risk of bias. Analyse and interpretation were undertaken by EF and DD. Data were entered into the Review Manager Software by EF and independently checked by DD. The review text was drafted by EF and reviewed independently by all authors (DD, DM, LB, GG, AC, ER & MB). Post peer review, EF revised the text and after co-author approval, submitted the review for publication.

The second paper, presented in chapter 3, is a protocol for a feasibility study that includes a pilot trial, a qualitative study, a cost-effectiveness analysis, and a SWAT (Study Within A Trial). EF prepared the initial draft and edited this paper post review by co-authors (DD, LB, DM, AC, Eleanor Molloy (EM), Martin O'Donnell (MOD), Shaun Treweek (ST), Paddy Gillespie (PG), Marian Campbell (MC), John Morrison (JM), Alberto Alvarez-Iglesias (AAI) & GG). Ethical applications for the Research Ethics Committees of NUI Galway, The Coombe Women and Infants University Hospital, and University Maternity Hospital Limerick (UMHL), including all supporting documentation were prepared and submitted by EF. EF and DD attended a subsequent ethics committee meeting at UMHL to offer further information.

The MILO Study received funding of €374K from the Health Research Board (Ireland) through its Definitive Interventions and Feasibility Awards (DIFA) (2018) EF is the lead researcher on The MILO Study, with DD as Principal Investigator on the DIFA grant application. EF formulated the trial question and design, supported by DD (supervisor) and grant co-applicants (LB, DM, AC, EM, MOD, ST, PG, MC, JM, AAI, and GG). EF and DD, with the support of co-applicants, wrote and submitted the successful DIFA application.

EF designed all trial documentation, including the trial logo, Participation Information Leaflets, consent forms, clinician training materials, and data collection forms. EF and DD met with hospital management in both clinical sites to facilitate the conduct of The MILO Study. EF led, supported by DD, in recruiting, interviewing, and hiring research midwives to support the study conduct. EF led on sourcing and overseeing the design of the trial online randomisation tool.

The third paper presented in chapter 4, describes the processes of developing, conducting, and disseminating *The People's Trial*. EF is lead researcher for this study. EF prepared and applied for ethical approval to the Clinical Research Ethics Committee for NUI Galway. EF, DD, and Ann O'Brien (AOB) worked with web developers to create *The People's Trial* website, designing each component and process e.g. online consent. As the study progressed EF, DD and AOB developed the website text and graphics in tandem. Approval from the steering Group was sought at each stage of the process. Online surveys were created by EF, DD, and AOB.

EF facilitated the design and development of seven animated videos for use on *The People's Trial* website at each phase of the trial. All public communications, including those by email and social media, were scripted by EF, DD, and AOB. Questions submitted by the public for the trial to potentially address were initially assessed by EF for inclusion and independently assessed by DD and Sarah Chapman (SC). The process paper was written by EF and reviewed by DD and reviewed by co-authors (John Newell (JN), Kishor Das (KD), Paul Wicks (PW), Sandra Galvin (SG), Patricia Healy (PH), Katie Gillies (KG), Anna Noel-Storr (ANS), Heidi Gardner (HG), Mary Frances O' Reilly (MFR), ST, SC LB, & AOB). The paper was revised, to include co-author feedback by EF.

The fourth paper is a report of the randomised trial designed by the public and conducted as part of *The People's Trial*. This paper was written by EF using a plain language format. DD and ST reviewed the paper, with statistical analysis supported by JN. The paper was further reviewed by co-authors (LB, SC, MFR, SG, HG, KG, PH, ANS, PW, and AOB).

EF supported trial recruitment through diverse advertising on *The People's Trial* social media platforms during the recruitment period. EF, DD, and AOB liaised with an external company to develop, and support, public conduct of a self-randomisation tool. EF, DD, and AOB developed surveys to capture outcome data for The Reading Trial and facilitated data collection through email, social media, and website reminders. EF liaised with a graphic

designer to develop the infographic used to display the results of The Reading Trial in an accessible manner. EF and DD presented the results of The Reading Trial at the HRB-TMRN 6th annual trial methodology symposium in October 2020.

List of Publications from the Thesis

Finucane EM., Murphy DJ., Biesty LM., Gyte GML., Cotter AM., Ryan EM., Boulvain M., Devane D. (2020) Membrane sweeping for induction of labour. Cochrane Database of Systematic Reviews 2020, Issue 2. Art. No.: CD000451. DOI: 10.1002/14651858.CD000451.pub3. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000451.pub3/full?highlightAbstract=sweep%7Cmembrane%7Cmembran%7Csweeping

Finucane EM., Biesty L, Murphy DJ, Cotter AM, Molloy EJ, O'Donnell M, Treweek S, Gillespie P, Campbell M, Morrison JJ, Alvarez-Iglesias A, Gyte G, Devane D. Feasibility study protocol of a pragmatic, randomised controlled pilot trial: membrane sweeping to prevent post-term pregnancy—the MILO Study. Trials 22, 113 (2021). https://doi.org/10.1186/s13063-021-05043-9

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Under Review

Finucane E, , O'Brien A., Treweek S., Newell J., Das K., Chapman S., Wicks P., Galvin S., Healy P., Biesty L., Gillies K., Noel-Storr A., Gardner H., O'Reilly MF. & Devane D (2020) The People's Trial: supporting the public's understanding of randomised trials. Submitted to Trials Journal.

Finucane E, , O'Brien A., Treweek S., Newell J., Das K., Chapman S., Wicks P., Galvin S., Healy P., Biesty L., Gillies K., Noel-Storr A., Gardner H., O'Reilly MF. & Devane D (2020) Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed?: The People's Trial - an online, pragmatic, randomised trial. Submitted to Trials Journal.

Oral presentations

Finucane E. & Devane D., (2020) Public involvement in trial methodology research – The People's Trial. Health Research Board Trials Methodology Research Network, 6th annual trial methodology symposium 2020 (Online)

Finucane E. & Galvin S. (2019) The People's Trial – Powered by the Public. Joint MRC-HTMR - HRB-TMRN Webinar presentation: 5 November 2019

Additional publications and collaborations during PhD

Alfirevic Z., Gyte GML., Nogueira Pileggi V., Plachcinski R., Osoti AO. & Finucane EM. Home versus inpatient induction of labour for improving birth outcomes (2020). Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD007372. DOI: 10.1002/14651858.CD007372.pub4.

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Finucane E. (2020) iHealthFacts radio interview, RTE radio 1 Ray D'Arcy show

Finucane E. (2020) iHealthFacts radio interview, 98FM- Adrian Kennedy breakfast show

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Thank you so much to the University Of Limerick Hospitals Group, University Maternity Hospital Limerick and the Nursing and Midwifery Planning and Development Unit West/Midwest of the Health Service Executive, Ireland (HSE) for funding and supporting me through my PhD. A special thanks to the fantastic midwives I work with. Your support and encouragement meant so much to me.

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In addition, I would like to thank each of my co-authors on the papers included in this thesis. In particular, I would like to thank Dr Ann O' Brien for her invaluable collaboration and support during *The People's Trial.*

I would also like to thank the CHEMRES group for your encouragement and support. You are a great bunch of people to work with! To the past, present and honorary 'Room 235' crew, I'd like to say a special thanks. Your friendship, support and joy in the success of others makes room 235 a special place, thank you!

Never has the saying 'it takes a village' been truer than with this PhD. I could not have even contemplated doing this without the support of my family. You have been my '12th man' over the last four years and I could not have completed this without you…. Ok dad now I'm finished!!!

Mark, thank you so much for always believing in me. Your love and support made this a much easier journey, thank you.

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AE	adverse event;
AFI	amniotic fluid index;
CS	low segment caesarean section;
CMS	cervical membrane stripping;
CTG	cardiotocography;
GA	gestational age;
GBS	group B Streptococcus;
IV	intravenous;
NST	non stress test;
PGE2	prostaglandin E2;
PPH	postpartum haemorrhage;
PPI	present pain index;
PROM	prelabour rupture of membrane;
RCT	randomised controlled trial;
SD	standard deviation;
SEM	standard error of the mean;
TTN	transient tachypnea of the newborn;
VAS	visual analogue scale;
VBAC	vaginal birth after caesarean section;
APH	Antepartum Haemorrhage;
AR	Adverse reaction;
aRR	Average Risk ratio;
CS	Caesarean Section;
CTG	cardiotocography;
DIFA	Definitive Interventions and Feasibility Awards;
IOL	Induction of labour;
MD	Mean difference;
PG	prostaglandins;
PPH	Postpartum Haemorrhage;
PPROM	Preterm premature rupture of membranes;
PROM	Preterm premature rupture of membranes;
SMD	Standardised mean difference;
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials;

SVD	Spontaneous vaginal delivery;
SWAT	Study Within A Trial;
Tau^2	tau-squared;
TSC	Trial Steering Committee;
UMHL	University Maternity Hospital Limerick;
WHO	World Health Organization;
X^2 Chi^2/	Chi-square test.

Chapter 1: Introduction

1.1 Introduction

The research conducted and reported in this thesis coincides with the coronavirus (COVID 19) pandemic. This altered the intended pathway of my PhD research. The initial aim of my PhD was to find out if amniotic membrane sweeping is a safe and effective way of preventing a formal induction of labour in pregnant women at or near term. The MILO study, an integral component of my PhD, received funding of €374K from the Health Research Board (Ireland) through its Definitive Interventions and Feasibility Awards (2018) to support its conduct. The MILO study, a feasibility study, was due to begin recruitment in the outpatient departments of two of Ireland's largest maternity hospitals, The Coombe Women & Infants University Hospital, Dublin and The University Maternity Hospital, Limerick in March 2020. All preparatory work, including ethical approval from the participating hospital groups and NUI Galway as the trial sponsor, the preparedness of clinical sites, and identification of participating clinicians and research midwives was completed. However, due to the acute and immediate changes to clinical practice, coupled with the clinical uncertainty of a novel coronavirus, the decision was taken by clinical sites to postpone recruitment to the trial under the advisement of the participating hospital management. The MILO Study is now due to commence recruitment in February 2021, but this too is dependent on clinical circumstances and the public health guidelines associated with COVID-19.

Under these exceptional circumstances, and in light of the ongoing impact on clinical trials, the decision was taken in June 2020, in collaboration with my PhD supervisor Professor Declan Devane and Graduate Research Committee (GRC) Professor Dympna Casey, Dr Linda Biesty, and Professor Martin O'Donnell, to change the direction of my research topic. This decision reflects subsequent guidance to PhD students from Graduate Studies at NUI Galway who acknowledged that it may be necessary to '*alter your research direction so that research progress may be possible'* (Dean of Graduate Studies 18th September 2020).

Therefore, the remainder of my PhD focuses on another randomised controlled trial, *The People's Trial*. While there is an unavoidable change in focus within this thesis, the body of work collectively offers a distinct and original contribution to knowledge.

This chapter introduces the thesis and outlines the thesis structure. It discusses the context in which this research was undertaken, providing information on, and the rationale for, the research aims and objectives of this research.

1.2 The MILO Study

This section of the thesis will focus on membrane sweeping to prevent a formal induction of labour. It outlines the relevance and rationale for the research conducted as part of this thesis.

1.2.1 Overview of induction of labour

While labour and childbirth are normal physiological processes, and for most women the onset of labour is spontaneous, some women will need to have their labour induced (Calik et al., 2018). Induction of labour is not a new phenomenon; it dates back to the time of Hippocrates when he described manually dilating the cervix to induce labour (Chodankar et al., 2017). While the methods used to induce labour may, in some instances, have been refined, the basic premise remains the same, i.e., artificially stimulating contractions of the uterus to try to initiate the onset of labour (Middleton et al., 2020). In the present day, induction of labour is viewed by many as a 'common' intervention, with the World Health Organisation (WHO) estimating that approximately one in four pregnancies will end in an induction of labour (WHO 2011). Evidence further suggests that this incidence rate will continue to increase (Coates et al., 2020, Carter et al., 2020)

While induction of labour may be considered a 'common' obstetric intervention, current international guidelines advise that it should only be carried out when the risk to a mother or baby of continuing with a pregnancy is greater than the risk associated with inducing labour (World Health Organization 2011). Conversely, recent studies have found that elective induction of labour may reduce risks to both mother and baby, including the risk of caesarean section and perinatal death, when compared to waiting for labour to begin without intervening (expectant management) (Middleton et al., 2020).

While there are several clinical indications for induction of labour, including the pre-labour rupture of membranes (PPROM), fetal growth restriction, hypertensive disorders of pregnancy and intra-uterine fetal death, post-term or post-date pregnancy is the most common reason (Nippita et al., 2015, Galal et al., 2012, Society of Obstetricians and

Gynaecologists of Canada 2013). A pregnancy, which has reached 42 weeks competed gestation, is considered post-term.

1.2.2 Methods of induction of labour

There are many methods used to induce a woman's labour, including pharmacological, mechanical, and surgical methods (Vogel et al., 2017). Until the 20th century, surgical methods such as the deliberate rupture of the amniotic membranes, and mechanical methods, such as amniotic membrane sweeping, which focus on dilating and ripening the cervix, were used most commonly (Caughey et al., 2009). However, in 1954, an American biochemist, Vincent du Vigneaud, discovered the hormonal properties of oxytocin. He later synthesised it to develop a powerful drug used primarily to stimulate uterine contractions; this heralded the arrival of pharmacological methods of induction of labour (den Hertog et al., 2001). In the 1960s, the discovery of the effects of prostaglandins changed the management of induction of labour maternity care further. Prostaglandins, hormones, which are produced naturally in the body, are used to both ripen the cervix and stimulate uterine contractions (Thomas et al., 2014).

While pharmacological methods are the most recent methods of induction of labour that does not necessarily mean that they are better. Pharmacological methods of induction of labour are not suitable for all women. As an intervention that increases the risk for both the woman and her baby, they often require one-to-one care, increasing the cost and time implications for already overstretched healthcare systems (Gaudernack et al., 2018, Belghiti et al., 2011). The same is true for surgical methods of induction, which often require women to stay in hospital after receiving the intervention.

1.2.3 Description of Membrane Sweeping

Amniotic membrane sweeping is a simple intervention, performed during a vaginal exam, with consent. It potentially promotes the onset of labour by releasing localised prostaglandins, which act on the cervix, helping it to ripen, potentially initiating uterine contractions. Performing a membrane sweeping may result in an increased risk of maternal discomfort and light vaginal bleeding (WHO 2011, Boulvain et al., 2005).

1.2.4 Why this research is needed?

Chapter 1: Introduction

Worldwide the rates of induction of labour have risen exponentially, with 25% of pregnancies in the developed world ending with a formal induction of labour (Centre for Epidemiology and Evidence 2017, Sinnott et al., 2016, Humphrey & Tucker 2009). Recent systematic reviews, and other studies, have found that while many factors potentially influence the increasing rates of induction of labour, differing guidelines between hospitals, and variation in the extent to which these guidelines are adhered to by clinicians, are contributing factors (Sinnott et al., 2016, Coates et al., 2019). Membrane sweeping is currently used ad hoc in clinical practice, and this inconsistency has been further linked to a lack of confidence in the intervention (Roberts et al., 2020).

However, despite these inconsistencies, National and international guidelines, including the National Institute for Health and Care Excellence (NICE 2008), the Society of Obstetricians and Gynaecologists of Canada (Public Health Canada 2008), and the WHO (WHO 2011) state that all women should be offered the option of membrane sweeping at or near term.

Evidence based practice demands that current, robust evidence is used to inform, and guide, clinical practice (Albarqouni et al., 2018). However, questions remain on the effectiveness of membrane sweeping at or near term. When comparing membrane sweeping with expectant management, systematic reviews have found a low certainty of evidence, with significant heterogeneity between studies (Avdiyovski et al., 2019, Boulvain et al., 2005). A further systematic review in this space reported a lack of evidence to inform the review findings (Rogers 2010). All have requested further research on this intervention. In addition to understanding the overall efficacy of membrane sweeping, as with any clinical intervention, it is essential to know the optimal timing (when) and intensity (how often) of membrane sweeping needed to prevent post-term pregnancy. Evidence to support these decisions, in a meaningful way, has not been provided to date but has been requested repeatedly (National Institute for Health and Care Excellence 2008, Queensland Clinical Guidelines 2018, Royal College of Midwives 2019, Government of Western Australia North Metropolitan Health Service 2019, Society of Obstetricians and Gynaecologists of Canada 2008).

While health care practitioners often focus on the clinical indications for induction of labour, it can also have significant effects on the birth experiences of women (Roberts et al., 2020, Henderson & Redshaw 2013). Many women report that compared to a spontaneous onset of labour, induction of labour was perceived to be more painful, and negatively impacted their overall birth experience (NICE 2020, Calik et al., 2018, Hildingsson et al., 2011). A

negative birth experience can have long-term repercussions, as it may directly influence women's decision-making during future pregnancies (Redshaw et al., 2019). However, women's views and experiences of induction of labour, and membrane sweeping in particular, have been underrepresented in research and reported with a singular lens, often focusing on the physical effects of the intervention only. With this intervention, maternal satisfaction is often reported as 'pain', with little exploration of women's overall experience of membrane sweeping undertaken (Ugezu et al., 2020, Boulvain et al., 2005). To inform decisions around induction of labour for women and clinicians, further research is warranted, particularly in light of the increasing rates of the formal induction of labour (Ugezu et al., 2020, Roberts et al., 2020, Avdiyovski et al., 2019).

Membrane sweeping offers a low-risk, low-cost method to potentially prevent a formal induction of labour for post-term pregnancy, the most common reason for induction of labour. However, cost and cost-effectiveness have not been reported in the literature in any significant manner. Two small studies included in Boulvain et al (2005) provide a cost analysis for this intervention. Again, the available data is not sufficient to inform decisions. In the current economic climate, when many health decisions are informed at least in part, by cost, data on this intervention would help place it within the context of formal methods of induction of labour.

In summary, membrane sweeping, a clinical intervention, is offered routinely to pregnant women where the i) effectiveness, ii) optimal timing, and iii) frequency to prevent a formal induction of labour is unknown. Women's experience of, and satisfaction with, membrane sweeping is uncertain and the cost-effectiveness of this intervention in the context of induction of labour has not been evaluated in a meaningful way. A 2005 Cochrane Systematic Review, which fifteen years ago highlighted the need for further robust research in this space (Boulvain et al. 2005), informs the current clinical guidelines. In addition, numerous international guidelines, have repeatedly called for research to clarify these uncertainties (NICE 2008, Queensland DOH 2018). This PhD study sought to address these questions and made progress in doing so prior to COVID-19.

1.3 The People's Trial

This section of the thesis will focus on *The People's Trial*. *The People's Trial* aimed to help the public to learn about randomised trials, to understand why they matter and be better

equipped to think critically about health claims by getting them involved in clinical trial processes - from question prioritisation through to trials conduct and dissemination.

1.3.1 How does a lack of knowledge and understanding of randomised trials affect the public?

The coronavirus (COVID-19) pandemic highlighted an 'infodemic' of misinformation and disinformation, with many researchers, global organisations, and governments working to 'flatten the infodemic curve', to prevent potentially harmful, misinformation from spreading among the general public (WHO 2020). Unreliable claims cause people to make poor choices about their health, undermines public health, and potentially cause unnecessary pain and suffering (WHO 2020). With members of the public regularly discussing clinical trials for treatments and vaccinations to prevent or cure COVID -19, the pandemic has also demonstrated the importance of trustworthy, robust evidence, including randomised trials, to support informed decisions about health.

Randomised trials are used to measure the effects of health interventions such as drugs, surgical procedures, or lifestyle changes. Done well, they offer people robust, reliable evidence to support decisions about their health (Hariton & Locascio 2018). However, to make use of this evidence, it is necessary for people to understand what randomised trials are, and why they are important (Nsangi et al., 2017). Improving public knowledge about trials may help people to think critically about health claims they are faced with daily.

1.3.2 Why does public knowledge and understanding of randomised trials matter to trialists?

For trials to be successful, people need to volunteer to take part. One of the main reasons that trials are discontinued, or do not answer the questions they are designed to do, is because they cannot recruit enough participants (Gillies et al., 2019, Treweek et al., 2018). The evidence suggests that approximately half of all trials fail to recruit their sample target, leading to costly extensions (Houghton et al., 2020). A lack of public awareness and engagement with research has been suggested as a significant barrier to recruitment (Lloyd et al., 2017, Reynolds 2011). Creating public awareness, knowledge, and understanding of trials may support recruitment to, and the conduct of, clinical research (Getz 2013).

1.3.3 Why this research is needed

Chapter 1: Introduction

Involving members of the public in decisions about health and health research is important on many levels. It provides significant mutual benefit, making sure the research outputs are valued and relevant to the public as consumers, while also offering new perspectives to researchers (Involve 2020). However, distrust of research and researchers, particularly among underserved populations, has been suggested as a reason members of the public do not get involved (Sheridan et al., 2020). In a systematic review and meta-analysis of 33 studies with 6,174 people, Mills et al., (2006), and confirmed by Limkakeng et al., (2013), found that these barriers may be directly linked to a lack of knowledge and understanding of clinical research. Understanding why people take part or refuse to take part, in research is an important step in improving how we do trials (Houghton et al., 2020, Treweek et al., 2018).

Several national and international initiatives have been developed to support knowledge and understanding of clinical trials in children and young adults. A Norwegian initiative, The Informed Health Choices (IHC) program, was designed to support critical thinking about health claims in school-aged children (Austvoll-Dahlgren et al., 2015). This innovative program teaches children key concepts, or principles, that they then use to assess health claims. This initiative supports children to critically assess the robustness of the evidence behind these claims (Oxman et al., 2018). In addition, The START competition, an Irish concept developed by the HRB-Trial Methodology Research Network initiative, invites Irish schoolchildren to design and conduct their very own trials (Biesty et al., 2020). Both initiatives have successfully engaged children in learning about randomised trials in a fun, novel manner.

However, *The People's Trial* is aimed at adult learners. While adult learners benefit from active collaboration, as used in both the IHC and Start programs, they have different and distinct learning needs from children (Chan 2010). Malcolm Knowles's theory of andragogy, which focuses on supporting adult learning, a theory widely used by educators, reports that adult learning is supported by self-relevance, as adult learners interpret knowledge through their own experiences (Harper & Ross 2011). Knowles theory proposes a framework of 'learning by doing' to support adult learners. This is done by collaboratively involving adult learners in all aspects of the trial processes.

To date, there have been some educational programs aimed at supporting knowledge and understanding of randomised trials in adult members of the public. These include initiatives

such as the MT Pharmacy campaign developed by the Center for Information and Study on Clinical Research Participation (CISCRP) and the Scottish 'Get randomised' campaign (CISCRP, 2020, Mackenzie et al., 2010). While these initiatives strive to support public engagement in clinical trials, they do not offer active learning and insight into randomised trials, which initiatives like the IHC and the START competition encourage.

For any initiative to be successful, it must engage its target audience, in this case, the public. The increasing popularity of online connectivity and social media use provides an opportunity for diverse interaction, which although still unusual, is becoming more popular within the research community. In addition, a recent systematic review has also found that online recruitment to clinical trials, was more effective compared to traditional methods (Brøgger-Mikkelse et al., 2020). In addition, online recruitment was found to be significantly more cost-effective. Several programs aimed at increasing public awareness of clinical trials have successfully used this platform to engage members of the public, whilst also using its diverse reach to disseminate findings (Eli Lilly 2020, Ali et al., 2020, Pan et al., 2015). Therefore, we chose this platform to host *The People's Trial*.

In summary, the public is bombarded by health claims, through multiple mediums, every day. Supporting public knowledge and understanding of randomised trials may help people to think critically about health claims and make better-informed health decisions. One of the major challenges to the successful conduct of a trial is poor recruitment. The evidence suggests that public engagement supports recruitment to clinical trials. While knowledge and understanding of clinical trials and their processes support public engagement in, and recruitment and retention to, clinical trials there have been few initiatives to engage adult members of the public in actively learning about clinical trials. This section of the thesis will focus on the development and conduct of a novel, online initiative to support and develop public understanding of randomised trials.

1.4 Overall PhD aims

The aims of this thesis are:

Section 1:

1. To systematically review the evidence to assess the effects and safety of membrane sweeping for induction of labour in women at or near term (≥ 36 weeks' gestation) (Chapter 2).
2. To design a pilot randomised trial to assess the feasibility of conducting a definitive randomised controlled trial to examine the effectiveness, and optimal intensity (timing and frequency), of membrane sweeping to prevent post-term pregnancy (Chapter 3).
3. To design an embedded pilot SWAT (Study within a Trial) to assess if when during pregnancy a woman is invited to take part in a randomised trial (i.e., when should women be asked?) affects the number of women recruited to and retained in a trial (Chapter 3).

Section 2:

4. To support public understanding and knowledge of randomised trials by involving the public in the design, conduct, and reporting of a randomised trial (Chapters 4 & 5).

1.5 Outline of thesis

This thesis comprises six chapters, including one published peer-reviewed paper (Chapter 2) and three undergoing peer review (Chapters 3, 4 and 5) The decision was taken to present the thesis in this manner, as this supports an in-depth review of the body of work included in the PhD. The references for each paper are presented at the end of each respective chapter. Due to the independent nature of the papers included in the thesis, there is an unavoidable element of repetition.

Chapter 1 introduces the thesis and the context in which it is set. This chapter presents background information and outlines the two sections of the thesis.

Section 1

Chapter 2 presents a Cochrane systematic review and meta-analysis to assess the effects and safety of membrane sweeping for induction of labour in women at or near term (≥ 36 weeks' gestation).

Chapter 3 presents the protocol for the pilot randomised trial to evaluate the feasibility of conducting a future definitive randomised trial to evaluate the effectiveness (including optimal timing and frequency) of membrane sweeping to prevent post-term pregnancy.

Section 2

Chapter 4 presents a descriptive process paper of *The People's Trial*. Using a reflexive approach, this paper describes the processes of development, conduct, and dissemination of *The People's Trial.*

Chapter 5 presents the plain language report of The Reading Trial. A trial designed by the public for the public.

Chapter 6 presents a discussion of the two thesis sections, their components, and contribution to knowledge. It outlines the individual findings of each aspect of the work that has been undertaken. This chapter also identifies implications for practice and further research.

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Chapter 2: Cochrane systematic review

2.1 Introduction

This chapter presents paper 1, a Cochrane systematic review and meta-analysis. This review, an update of a 2005 review, was undertaken to systematically evaluate the current available evidence on membrane sweeping. To assess if membrane sweeping is an effective and safe way of inducing labour in women at or near term gestation (≥ 36 weeks' gestation). The findings of this systematic review and meta-analysis directly inform the design of a feasibility study protocol (Chapter 3).

2.2 Paper 1

Membrane sweeping for induction of labour

Finucane EM, Murphy DJ, Biesty LM, Gyte GML, Cotter AM, Ryan EM, Boulvain M, Devane D.(2020) Membrane sweeping for induction of labour. Cochrane Database of Systematic Reviews 2020, Issue 2. Art. No.: CD000451.
https://doi.org/10.1002/14651858.CD000451.pub3

2.3 Abstract

Background

Induction of labour involves stimulating uterine contractions artificially to promote the onset of labour. There are several pharmacological, surgical and mechanical methods used to induce labour. Membrane sweeping is a mechanical technique whereby a clinician inserts one or two fingers into the cervix and using a continuous circular sweeping motion detaches the inferior pole of the membranes from the lower uterine segment. This produces hormones that encourage effacement and dilatation potentially promoting labour. This review is an update to a review first published in 2005.

Objectives

To assess the effects and safety of membrane sweeping for induction of labour in women at or near term (≥ 36 weeks' gestation).

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register (25 February 2019), ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (25 February 2019), and reference lists of retrieved studies.

Selection criteria

Randomised and quasi-randomised controlled trials comparing membrane sweeping used for third trimester cervical ripening or labour induction with placebo/no treatment or other methods listed on a predefined list of labour induction methods. Cluster-randomised trials were eligible, but none were identified.

Data collection and analysis

Two review authors independently assessed studies for inclusion, risk of bias and extracted data. Data were checked for accuracy. Disagreements were resolved by discussion, or by including a third review author. The certainty of the evidence was assessed using the GRADE approach.

Main results

We included 44 studies (20 new to this update), reporting data for 6940 women and their infants. We used random-effects throughout.

Overall, the risk of bias was assessed as low or unclear risk in most domains across studies. Evidence certainty, assessed using GRADE, was found to be generally low, mainly due to study design, inconsistency and imprecision. Six studies (n = 1284) compared membrane sweeping with more than one intervention and were thus included in more than one comparison.

No trials reported on the outcomes uterine hyperstimulation with/without fetal heart rate (FHR) change, uterine rupture or neonatal encephalopathy.

Forty studies (6548 participants) compared membrane sweeping with no treatment/sham

Women randomised to membrane sweeping may be more likely to experience:

- spontaneous onset of labour (average risk ratio (aRR) 1.21, 95% confidence interval (CI) 1.08 to 1.34, 17 studies, 3170 participants, low-certainty evidence).

but less likely to experience:

- induction (aRR 0.73, 95% CI 0.56 to 0.94, 16 studies, 3224 participants, low-certainty evidence);

There may be little to no difference between groups for:

- caesareans (aRR 0.94, 95% CI 0.85 to 1.04, 32 studies, 5499 participants, moderate-certainty evidence);
- spontaneous vaginal birth (aRR 1.03, 95% CI 0.99 to 1.07, 26 studies, 4538 participants, moderate-certainty evidence);
- maternal death or serious morbidity (aRR 0.83, 95% CI 0.57 to 1.20, 17 studies, 2749 participants, low-certainty evidence);
- neonatal perinatal death or serious morbidity (aRR 0.83, 95% CI 0.59 to 1.17, 18 studies, 3696 participants, low-certainty evidence).

Four studies reported data for 480 women comparing membrane sweeping with vaginal/intracervical prostaglandins

There may be little to no difference between groups for the outcomes:

- spontaneous onset of labour (aRR, 1.24, 95% CI 0.98 to 1.57, 3 studies, 339 participants, low-certainty evidence);
- induction (aRR 0.90, 95% CI 0.56 to 1.45, 2 studies, 157 participants, low-certainty evidence);
- caesarean (aRR 0.69, 95% CI 0.44 to 1.09, 3 studies, 339 participants, low-certainty evidence);
- spontaneous vaginal birth (aRR 1.12, 95% CI 0.95 to 1.32, 2 studies, 252 participants, low-certainty evidence);
- maternal death or serious morbidity (aRR 0.93, 95% CI 0.27 to 3.21, 1 study, 87 participants, low-certainty evidence);
- neonatal perinatal death or serious morbidity (aRR 0.40, 95% CI 0.12 to 1.33, 2 studies, 269 participants, low-certainty evidence).

One study, reported data for 104 women, comparing membrane sweeping with intravenous oxytocin +/- amniotomy

There may be little to no difference between groups for:

- spontaneous onset of labour (aRR 1.32, 95% CI 88 to 1.96, 1 study, 69 participants, low-certainty evidence);
- induction (aRR 0.51, 95% CI 0.05 to 5.42, 1 study, 69 participants, low-certainty evidence);
- caesarean (aRR 0.69, 95% CI 0.12 to 3.85, 1 study, 69 participants, low-certainty evidence);
- maternal death or serious morbidity was reported on, but there were no events.

Two studies providing data for 160 women compared membrane sweeping with vaginal/oral misoprostol

There may be little to no difference between groups for:

- caesareans (RR 0.82, 95% CI 0.31 to 2.17, 1 study, 96 participants, low-certainty evidence).

One study providing data for 355 women which compared once weekly membrane sweep with twice-weekly membrane sweep and a sham procedure

There may be little to no difference between groups for:

- induction (RR 1.19, 95% CI 0.76 to 1.85, 1 study, 234 participants, low-certainty);
- caesareans (RR 0.93, 95% CI 0.60 to 1.46, 1 study, 234 participants, low-certainty evidence);
- spontaneous vaginal birth (RR 1.00, 95% CI 0.86 to 1.17, 1 study, 234 participants, moderate-certainty evidence);
- maternal death or serious maternal morbidity (RR 0.78, 95% CI 0.30 to 2.02, 1 study, 234 participants, low-certainty evidence);
- neonatal death or serious neonatal perinatal morbidity (RR 2.00, 95% CI 0.18 to 21.76, 1 study, 234 participants, low-certainty evidence);

We found no studies that compared membrane sweeping with amniotomy only or mechanical methods.

Three studies, providing data for 675 women, reported that women indicated favourably on their experience of membrane sweeping with one study reporting that 88% (n = 312) of women questioned in the postnatal period would choose membrane sweeping in the next pregnancy.

Two studies reporting data for 290 women reported that membrane sweeping is more cost-effective than using prostaglandins, although more research should be undertaken in this area.

Authors' conclusions

Membrane sweeping may be effective in achieving a spontaneous onset of labour, but the evidence for this was of low certainty. When compared to expectant management, it potentially reduces the incidence of formal induction of labour. Questions remain as to whether there is an optimal number of membrane sweeps and timings and gestation of these to facilitate induction of labour.

2.4 Plain language summary

Membrane sweeping for induction of labour

What is the question?

The aim of this Cochrane Review is to find out if membrane sweeping is a safe and effective way of inducing labour at or near term and if it is more effective than the formal methods of induction.

Why is this important?

Most commonly, formal induction of labour is offered to women when continuing with a pregnancy is considered probably more harmful for the mother or baby than the adverse effects of induction. The most common reason for formal induction of labour is post-term pregnancy (pregnancies that continue past 42 weeks' gestation).

Membrane sweeping is a relatively simple, low-cost procedure that seeks to reduce the use of formal induction of labour and it can be performed without the need for hospitalisation. It involves the clinician inserting one or two fingers into the lower part of the uterus (the cervix) and using a continuous circular sweeping motion to free the membrane from the lower uterus. Formal induction of labour involves artificially stimulating the uterus with drugs such as prostaglandins or oxytocin or by breaking the amniotic sack that holds the baby (breaking the waters).

What evidence did we find?

We searched for evidence on 25 February 2019. We included 44 randomised studies that reported findings for 6940 women from a wide range of countries including high-, middle- and low-income countries.

Studies compared membrane sweeping with no intervention or sham intervention, and also compared membrane sweeping with vaginal or intracervical prostaglandins, oral misoprostol, oxytocin and repeated membrane sweeping.

Of the seven studies that reported financial funding, two studies reported funding from pharmaceutical companies. Overall, the certainty of the evidence was found to be low.

Key results

Compared with no intervention or a sham sweep (40 studies involving 6548 women), allocated to membrane sweeping may be more likely to have spontaneous onset of labour, but we found no clear difference in unassisted vaginal births. Women may also be less likely to have formal induction of labour. We also found no clear differences between the

groups for caesarean section, instrumental vaginal births or serious illness or death of the mother or baby.

Compared with vaginal or intracervical prostaglandins (four studies involving 480 women), we found no difference in any outcomes although data were limited.

We found insufficient data to draw any conclusions in the studies comparing membrane sweep with intravenous oxytocin, with or without breaking the waters, or with vaginal/oral misoprostol. Similarly for the comparison between different frequencies of membrane sweeping.

What does this mean?

Membrane sweeping appears to be effective in promoting labour but current evidence suggests this did not, overall, follow-on to unassisted vaginal births. Membrane sweeping may reduce formal induction of labour. Only three studies reported on women's satisfaction with membrane sweeping. Women reported feeling positive about membrane sweeping. While acknowledging that it may be uncomfortable, they felt the benefits outweighed the harms and most would recommend it to other women. Further research is needed to confirm our review findings and to identify the ideal time for membrane sweep and whether having more than one sweep would be beneficial. Further information on women's views is also needed.

2.5 Summary of findings

Table 2.1 Summary of findings 1. Amniotic membranes sweeping compared to no treatment/sham for induction of labour

Summary of findings:

Amniotic membranes sweeping compared to no treatment/sham for induction of labour

Patient or population: induction of labour

Setting: Antenatal environments where amniotic membrane sweeping is likely to be used.

Intervention: Amniotic membranes sweeping

Comparison: no treatment/sham

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment/sham	**Risk with Amniotic membranes sweeping**				
Spontaneous onset of labour	598 per 1,000	**723 per 1,000** (646 to 801)	**RR 1.21** (1.08 to 1.34)	3170 (17 RCTs)	⨁⨁◯◯ LOW [a,b]	
Induction of labour	313 per 1,000	**228 per 1,000** (175 to 294)	**RR 0.73** (0.56 to 0.94)	3224 (16 RCTs)	⨁⨁◯◯ LOW [c,d]	
Caesarean section	165 per 1,000	**155 per 1,000** (140 to 171)	**RR 0.94** (0.85 to 1.04)	5499 (32 RCTs)	⨁⨁⨁◯ MODERATE [e]	
Spontaneous vaginal birth	711 per 1,000	**733 per 1,000** (704 to 761)	**RR 1.03** (0.99 to 1.07)	4538 (26 RCTs)	⨁⨁⨁◯ MODERATE [f]	
Uterine Hyperstimulation with/without fetal heart rate (FHR) changes - not reported	-	-	-	-	-	No study reported on this outcome.
Serious maternal death or morbidity	44 per 1,000	**36 per 1,000** (25 to 53)	**RR 0.83** (0.57 to 1.20)	2749 (17 RCTs)	⨁⨁◯◯ LOW [g,h]	
Serious neonatal perinatal death or morbidity	36 per 1,000	**30 per 1,000** (22 to 43)	**RR 0.83** (0.59 to 1.17)	3696 (18 RCTs)	⨁⨁◯◯ LOW [i,j]	

***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

Summary of findings:

Amniotic membranes sweeping compared to no treatment/sham for induction of labour

Patient or population: induction of labour

Setting: Antenatal environments where amniotic membrane sweeping is likely to be used.

Intervention: Amniotic membranes sweeping

Comparison: no treatment/sham

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment/sham	**Risk with Amniotic membranes sweeping**				

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

Explanations

a. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in all trials. Three trials had unclear risk of bias for randomisation. Nine trials had unclear allocation concealment and one had a high risk of bias. No trial was blinded. Twelve trials had unclear risk of bias for blinding of outcome assessment and three were high risk of bias. One trial was at high risk of selective reporting bias.

b. We downgraded (1) level for risk of serious inconsistency due to evidence of statistical heterogeneity ($Tau^2 = 0.03$; $Chi^2 = 59.79$, df = 16 ($P < 0.00001$); $I^2 = 73\%$)

c. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in all trials. Three trials had unclear risk of bias for randomisation. Ten trials had unclear allocation concealment. No trial was blinded. Ten trials had unclear risk of bias for blinding of outcome assessment and two were high risk of bias. Two trials were at high risk of attrition bias and two trials were at high risk of selective reporting bias. One trial was at high risk of selective reporting bias.

d. We downgraded (1) level for risk of serious inconsistency due to evidence of statistical heterogeneity ($Tau^2 = 0.17$; $Chi^2 = 60.72$, df = 15 ($P < 0.00001$); $I^2 = 75\%$)

e. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in all trials. Seven trials had unclear risk of bias for randomisation with one trial at a high risk of bias. Nineteen trials had unclear allocation concealment and two had a high risk of bias. No trial was blinded. Twenty two trials had unclear risk of bias for blinding of outcome assessment and five were high risk of bias. One trial was at high risk of attrition bias and two trials were at high risk of selective reporting bias.

f. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in all trials. Five trials had unclear risk of bias for randomisation with one trial at a high risk of bias. Sixteen trials had unclear allocation concealment. No trial was blinded. Nineteen trials had unclear risk of bias for blinding of outcome assessment and three were high risk of bias. Two trials were at high risk of selective reporting bias.

g. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in all trials. Two trials had unclear risk of bias for randomisation with one trial at a high risk of bias. Twelve trials had unclear allocation concealment and one trial had a high risk of bias. No trial was blinded. Eleven trials had unclear risk of bias for blinding of outcome assessment and three were high risk of bias. Two trials were at high risk of attrition bias and two trials were at high risk of selective reporting bias.

h. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 2749 being less than than the optimal information size (OIS) of 15342.

i. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in all trials. Two trials had unclear risk of bias for randomisation. Ten trials had unclear allocation concealment. No trial was blinded. Eleven trials had unclear risk of bias for blinding of outcome assessment and two were high risk of bias. Two trials had a high risk of attrition bias and two trials had a high risk of reporting bias

j. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 3696 being less than than the optimal information size (OIS) of 18716.

Table 2.2 Summary of findings 2. Amniotic membranes sweeping compared to vaginal/intracervical prostaglandins for induction of labour

Summary of findings:

Amniotic membranes sweeping compared to vaginal/intracervical prostaglandins for induction of labour

Patient or population: induction of labour

Setting: Antenatal environments where amniotic membrane sweeping is likely to be used.

Intervention: Amniotic membranes sweeping

Comparison: vaginal/intracervical prostaglandins

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with vaginal/intracervical prostaglandins	Risk with Amniotic membranes sweeping				
Spontaneous onset of labour	521 per 1,000	**647 per 1,000** (511 to 819)	**RR 1.24** (0.98 to 1.57)	339 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	
Induction of labour	319 per 1,000	**288 per 1,000** (179 to 463)	**RR 0.90** (0.56 to 1.45)	157 (2 RCTs)	⨁⨁◯◯ LOW [c,d]	
Caesarean section	221 per 1,000	**152 per 1,000** (97 to 241)	**RR 0.69** (0.44 to 1.09)	339 (3 RCTs)	⨁⨁◯◯ LOW [a,e]	
Spontaneous vaginal birth	659 per 1,000	**738 per 1,000** (626 to 870)	**RR 1.12** (0.95 to 1.32)	252 (2 RCTs)	⨁⨁◯◯ LOW [f,g]	
Uterine hyperstimulation with/without fetal heart rate(FHR) changes - not reported	-	-	-	-	-	No study reported on this outcome
Serious maternal death or morbidity	108 per 1,000	**101 per 1,000** (29 to 347)	**RR 0.93** (0.27 to 3.21)	87 (1 RCT)	⨁⨁◯◯ LOW [h,i]	

Summary of findings:

Amniotic membranes sweeping compared to vaginal/intracervical prostaglandins for induction of labour

Patient or population: induction of labour

Setting: Antenatal environments where amniotic membrane sweeping is likely to be used.

Intervention: Amniotic membranes sweeping

Comparison: vaginal/intracervical prostaglandins

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with vaginal/intracervical prostaglandins	**Risk with Amniotic membranes sweeping**				
Serious neonatal perinatal death or morbidity	70 per 1,000	**28 per 1,000** (8 to 94)	**RR 0.40** (0.12 to 1.33)	269 (2 RCTs)	⨁⨁◯◯ LOW [j,k]	

***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

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

Explanations

a. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in all trials. All trials had unclear risk of selection bias (allocation concealment) and detection bias (blinding of outcome assessment). All three trials have high risk of performance bias (blinding of participants and personnel) . One trial was at high risk of other bias.

b. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 339 being less than than the optimal information size (OIS) of 704.

c. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in all trials. All trials had unclear risk of selection bias (allocation concealment) and detection bias (blinding of outcome assessment). All trials have high risk of performance bias (blinding of participants and personnel) . One trial was at high risk of other bias.

d. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 157 being less than than the optimal information size (OIS) of 1572

e. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 339 being less than than the optimal information size (OIS) of 2568

f. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in all trials. All trials had unclear risk of selection bias (allocation concealment) and detection bias (blinding of outcome assessment). All trials have high risk of performance bias (blinding of participants and personnel) .

g. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 252 being less than than the optimal information size (OIS) of 358

h. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations. We found an unclear risk of selection bias (allocation concealment) and detection bias (blinding of outcome assessment). We found this trial to be of high risk of performance bias (blinding of participants and personnel) and other bias.

i. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 80 being less than than the optimal information size (OIS) of 5908

j. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in all trials. All trials had unclear risk of selection bias (allocation concealment) and detection bias (blinding of outcome assessment). All trials have high risk of performance bias (blinding of participants and personnel) . One trial was at high risk of other bias.

k. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 269 being less than than the optimal information size (OIS) of 9496

Table 2.3 Summary of findings 3. Amniotic membranes sweeping compared to intravenous oxytocin/amniotomy for induction of labour.

Summary of findings:

Amniotic membranes sweeping compared to intravenous oxytocin +/- amniotomy for induction of labour

Patient or population: induction of labour

Setting: Antenatal environments where amniotic membrane sweeping is likely to be used.

Intervention: Amniotic membranes sweeping

Comparison: intravenous oxytocin +/- amniotomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with intravenous oxytocin +/- amniotomy	**Risk with Amniotic membranes sweeping**				
Spontaneous onset of labour	514 per 1,000	**679 per 1,000** (453 to 1,000)	**RR 1.32** (0.88 to 1.96)	69 (1 RCT)	⨁⨁◯◯ LOW [a,b]	
Induction of labour	57 per 1,000	**29 per 1,000** (3 to 310)	**RR 0.51** (0.05 to 5.42)	69 (1 RCT)	⨁⨁◯◯ LOW [a,c]	
Caesarean section	86 per 1,000	**59 per 1,000** (10 to 330)	**RR 0.69** (0.12 to 3.85)	69 (1 RCT)	⨁⨁◯◯ LOW [a,d]	
Spontaneous vaginal birth - not reported	-	-	-	-	-	This outcome was not reported on.

Summary of findings:

Amniotic membranes sweeping compared to intravenous oxytocin +/- amniotomy for induction of labour

Patient or population: induction of labour

Setting: Antenatal environments where amniotic membrane sweeping is likely to be used.

Intervention: Amniotic membranes sweeping

Comparison: intravenous oxytocin +/- amniotomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with intravenous oxytocin +/- amniotomy	**Risk with Amniotic membranes sweeping**				
Uterine Hyperstimulation with/without fetal heart (FHR) rate changes - not reported	-	-	-	-	-	This outcome was not reported on.
Serious maternal death or morbidity	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	69 (1 RCT)	⨁⨁◯◯ LOW [a,e]	
Serious neonatal perinatal death or morbidity - not reported	-	-	-	-	-	This outcome was not reported on.

***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

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

Explanations

a. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in this trial. We found unclear risk of selection bias (Random sequence generation and allocation concealment). We found high risk of performance bias. We found unclear risk of both detection bias and reporting bias.

b. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 69 being less than than the optimal information size (OIS) of 718

c. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 69 being less than than the optimal information size (OIS) of 11212

d. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 69 being less than than the optimal information size (OIS) of 7642

e. We downgraded (1) level for risk of serious imprecision due to small sample size with no events recorded.

Table 2.4 Summary of findings 4. Amniotic membranes sweeping compared to vaginal/oral misoprostol for induction of labour. **Summary of findings:**

Amniotic membranes sweeping compared to vaginal/oral misoprostol for induction of labour

Patient or population: induction of labour

Setting: Antenatal environments where amniotic membrane sweeping is likely to be used.

Intervention: Amniotic membranes sweeping

Comparison: vaginal/oral misoprostol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with vaginal/oral misoprostol	**Risk with Amniotic membranes sweeping**				
Spontaneous onset of labour - not reported	-	-	-	-	-	This outcome was not reported.
Induction of labour - not reported	-	-	-	-	-	This outcome was not reported.
Caesarean section	160 per 1,000	**131 per 1,000** (50 to 347)	**RR 0.82** (0.31 to 2.17)	96 (1 RCT)	⨁⨁◯◯ LOW [a,b]	
Spontaneous vaginal birth - not reported	-	-	-	-	-	This outcome was not reported
Uterine hyperstimulation with/without fetal heart rate (FHR) changes - not reported	-	-	-	-	-	This outcome was not reported
Serious maternal death or morbidity - not reported	-	-	-	-	-	This outcome was not reported
Serious neonatal perinatal death or morbidity - not reported	-	-	-	-	-	This outcome was not reported

Table 2.4 Summary of findings 4. Amniotic membranes sweeping compared to vaginal/oral misoprostol for induction of labour. **Summary of findings:**

Amniotic membranes sweeping compared to vaginal/oral misoprostol for induction of labour

Patient or population: induction of labour

Setting: Antenatal environments where amniotic membrane sweeping is likely to be used.

Intervention: Amniotic membranes sweeping

Comparison: vaginal/oral misoprostol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with vaginal/oral misoprostol	**Risk with Amniotic membranes sweeping**				

***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

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

Explanations

a. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in this trial. We found high risk of performance bias and an unclear risk of both detection bias and reporting bias.

b. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 96 being less than than the optimal information size (OIS) of 3776

Table 2.5 Summary of findings 5. One frequency of amniotic membranes sweeping compared to another frequency of amniotic membrane sweeping for induction of labour

Summary of findings:

One frequency of amniotic membranes sweeping compared to another frequency of amniotic membrane sweeping for induction of labour

Patient or population: induction of labour

Setting: Antenatal environments where amniotic membrane sweeping is likely to be used.

Intervention: One frequency of amniotic membranes sweeping

Comparison: another frequency of amniotic membrane sweeping

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with another frequency of amniotic membrane sweeping	**Risk with One frequency of amniotic membranes sweeping**				
Spontaneous onset of labour - not reported	-	-	-	-	-	This outcome was not reported.
Induction of labour	231 per 1,000	**275 per 1,000** (175 to 427)	**RR 1.19** (0.76 to 1.85)	234 (1 RCT)	⨁⨁◯◯ LOW [a,b]	
Caesarean section	256 per 1,000	**238 per 1,000** (154 to 374)	**RR 0.93** (0.60 to 1.46)	234 (1 RCT)	⨁⨁◯◯ LOW [a,c]	
Spontaneous vaginal birth	735 per 1,000	**735 per 1,000** (632 to 860)	**RR 1.00** (0.86 to 1.17)	234 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	
Uterine hyperstimulation with/without fetal heart rate (FHR) changes - not reported	-	-	-	-	-	This outcome was not reported
Serious maternal death or morbidity	77 per 1,000	**60 per 1,000** (23 to 155)	**RR 0.78** (0.30 to 2.02)	234 (1 RCT)	⨁⨁◯◯ LOW [a,d]	
Serious neonatal perinatal death or morbidity	9 per 1,000	**17 per 1,000** (2 to 186)	**RR 2.00** (0.18 to 21.76)	234 (1 RCT)	⨁⨁◯◯ LOW [a,e]	

***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

Summary of findings:

One frequency of amniotic membranes sweeping compared to another frequency of amniotic membrane sweeping for induction of labour

Patient or population: induction of labour

Setting: Antenatal environments where amniotic membrane sweeping is likely to be used.

Intervention: One frequency of amniotic membranes sweeping

Comparison: another frequency of amniotic membrane sweeping

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with another frequency of amniotic membrane sweeping	**Risk with One frequency of amniotic membranes sweeping**				

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

Explanations

a. We downgraded (1) level for risk of serious bias due to evidence of methodological limitations in this trial. We found unclear risk of selection bias (allocation concealment) and we found high risk of performance bias.

b. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 350 being less than than the optimal information size (OIS) of 1414

c. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 350 being less than than the optimal information size (OIS) of 2252

d. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 350 being less than than the optimal information size (OIS) of 6182

e. We downgraded (1) level for risk of serious imprecision due to the total (cumulative) sample size of 350 being less than than the optimal information size (OIS) of 83538

2.6 Background

This systematic review is an update of a Cochrane Review 'Membrane sweeping for induction of labour' first published on 24th January 2005 (Boulvain 2005). The previous review was one of a series of systematic reviews on methods of labour induction. This cohort of systematic reviews were utilised to compare and evaluate methods of labour induction at or near term. This current (2019) update is a stand-alone review.

2.6.1 Description of the condition

Labour and childbirth are physiological processes and for the majority of women the onset of labour is spontaneous. However, some women will have an induction of labour. Induction of labour is the process of artificially stimulating uterine contractions to initiate the onset of labour. Approximately one in four pregnancies in high-middle income settings will end with an induction of labour (Bakker 2013; World Health Organization 2011). Worldwide, the incidence of induction of labour varies with 28% of women in Australia, 26.8% in England, 21.8% in Canada and 25% in Ireland having their labours induced (Australian Institute of Health and Welfare 2016; Health Canada 2008; Health Service Executive 2016; National Childbirth Trust 2017). Obstetric statistics demonstrate a significant temporal increase in these rates, a trend set to continue (Alfirevic 2016).

Current international guidelines state that induction of labour, as with any intervention, carries risks and advise it be performed only when there are clear indications that continuing with the pregnancy is of greater risk to the mother or fetus than the risk of induction of labour (ACOG 2009; Middleton 2018; World Health Organization 2011). However, recent studies have reported that elective pharmacological induction of labour for post-term pregnancy results in a lower risk of caesarean section than expectant management (Grobman 2018; Middleton 2018). Current medical indications for an induction of labour include preterm premature rupture of membrane (PPROM), intrauterine growth restriction, hypertensive disorders of pregnancy, intrauterine fetal death and post-term pregnancies (SOGC 2013). Of these, induction of labour for pregnancy considered post-term is the most common (NHS Digital 2014; Nippita 2015; Sue-A-Quan 1999).

A pregnancy is considered to have reached full term at 37 completed weeks' gestation, however, up to 10% of pregnancies will continue past 42 weeks' gestation and are then considered "post-term" (Middleton 2018; Olesen 2003).

Although the reasons why some pregnancies become post-term are not understood fully, nulliparity, high body mass index and increased maternal age are all recognised risk factors (Roos 2010). Birth post 42 weeks' gestation carries increased risk for the neonate including meconium aspiration, neonatal acidaemia, low Apgar scores, macrosomia and neonatal death (0.018% at day 287 versus 0.51% at day 301+) (ACOG 2014; Heimstad 2008). The incidence of maternal complications such as severe perineal injury (third- and fourth-degree perineal lacerations) related to macrosomia (3.3% versus 2.6% at term), postpartum

haemorrhage, chorioamnionitis and endomyometritis are seen to increase post-term (Hedegaard 2014).

Labour may be induced using pharmacological, surgical and mechanical methods (Alfirevic 2016).

Pharmacological methods include the use of prostaglandins, such as dinoprostone administered either vaginally or intracervical, misoprostol administered orally, vaginally or intracervical, and oxytocin administered intravenously (Alfirevic 2014). Pharmacological methods of induction of labour are not suitable for all women (NICE 2008). Reduced levels of prostaglandins are indicated in women with a high parity and the use of prostaglandins are contraindicated in cases of women with a previous caesarean section (NICE 2008). Pharmacological induction of labour increases the risk of uterine rupture, hyperstimulation, prolonged labour and fetal and maternal compromise (World Health Organization 2011). The WHO recommend that women undergoing a pharmacological induction of labour should never be unattended, potentially increasing healthcare costs. Surgically, labour may be induced using procedures including the deliberate rupturing of the amniotic membrane known as amniotomy (Caughey 2009). Amniotomy carries the risk of umbilical cord prolapse when the presenting part of the fetus is not engaged in the pelvis. It increases the risk of infection for mother and fetus and is contraindicated in HIV positive women (Bricker 2000). Mechanical methods were among the first reported methods of induction of labour. When inducing labour, the favourability of the cervix, as assessed by the Bishops score, is the main indication of the likelihood of success (Bishop 1964). Mechanical methods of induction of labour are used to ripen and dilate the cervix encouraging the spontaneous onset of labour through manual manipulation of the cervix (de Vaan 2019). Mechanical methods include the use of an intracervical Foley catheter and membrane sweeping, also referred to as ‘stripping’ or ‘stretch and sweep’ of the membrane.

2.6.2 Description of the intervention

Membrane sweep is performed with consent during a vaginal examination. It involves the clinician inserting one or two fingers into the woman’s cervix and detaching the inferior pole of the membrane from the lower uterine segment in a circular motion (Boulvain 2008). Alternatively, the cervix may be massaged if the cervical os is closed. Membrane sweeping is a simple procedure and may be used independently or in combination with other means of induction and can be repeated multiple times.

2.6.3 How the intervention might work

Membrane sweeping is used to promote the normal physiological onset of labour by releasing localised prostaglandins F2α, phospholipase A2 and cytokines from the intrauterine tissues (Blackburn 2013). These hormones act on the cervix to augment cervical ripening potentially instigating uterine contractions. The stretching of the cervix may help to initiate the Ferguson reflex by releasing oxytocin, thereby increasing uterine activity (Blackburn 2013). The aim of this intervention is to soften and ripen the cervix, increasing cervical favourability and promoting uterine activity, to stimulate spontaneous uterine contractions potentially leading to the onset of labour and the avoidance of a formal induction of labour.

2.6.4 Why it is important to do this review

Twenty-five per cent of all pregnancies in high-middle income settings end in a formal induction of labour. Formal induction of labour is defined as the process of artificially stimulating the uterus to start labour through pharmacological or surgical methods (World Health Organization 2000). Membrane sweeping is an intervention that seeks to reduce the need for formal induction of labour. Post-term pregnancy is by far the most common reason for formal induction of labour and membrane sweeping potentially offers a low-risk, low-cost method to reduce this. Membrane sweeping is a technically simple intervention that is routinely used. It has the advantage that it may be used independently or in combination with other means of induction and can be repeated multiple times. It can be performed by obstetricians or midwives in community or clinical settings (NICE 2008; Wong 2002). Guidelines supported by bodies including the National Institute for Health and Care Excellence (NICE 2008), the Society of Obstetricians and Gynaecologists of Canada (Public Health Canada 2008), the Department of Health, South Australia (South Australia DOH 2014) and the World Health Organization (World Health Organization 2011) state that women should be offered the option of membrane sweeping at or near term. The NICE guidelines state that a membrane sweep be offered to nulliparous women at term gestation and women who have had one or more infants at 41 weeks' gestation. In addition, it recommends that women be offered further membrane sweeps during subsequent antennal visits if labour does not commence (NICE 2008).

Questions remain on aspects of this intervention including the optimal frequency of membrane sweeping for induction of labour for differing parities and gestation, women’s

satisfaction levels with this method and the use of cervical massage. Internationally, numerous guidelines have repeatedly identified the need for research to clarify these uncertainties (NICE 2008; Queensland DOH 2017). This systematic review will evaluate the available evidence to assess the effects of membrane sweeping for induction of labour in women with a live fetus at or near term (≥ 36 weeks' gestation) and address these uncertainties.

2.7 Objectives

The aim of this review is to assess the effects and safety of membrane sweeping for induction of labour in women at or near term (≥ 36 weeks' gestation).

2.8 Methods

2.8.1 Criteria for considering studies for this review

Types of studies

Randomised controlled trials and quasi-randomised trials comparing membrane sweeping for labour induction with placebo/no treatment or other methods for labour induction. This review will include randomised controlled trials which cannot be blinded due to the nature of the intervention. Randomised controlled trials and quasi-randomised trials found only as abstract trial reports were eligible for inclusion. Cluster-randomised trials were eligible for inclusion in the analyses along with individually randomised trials.

Types of participants

Pregnant women carrying a live fetus at or near term (≥ 36 weeks' gestation).

Types of interventions

Amniotic membrane sweeping.

Comparisons

Amniotic membrane sweeping versus no treatment/sham treatment – all women
Amniotic membrane sweeping versus vaginal/intracervical prostaglandins – all women
Amniotic membrane sweeping versus intravenous oxytocin +/- amniotomy – all women
Amniotic membrane sweeping versus amniotomy only - all women

Amniotic membrane sweeping versus vaginal/oral misoprostol – all women
Amniotic membrane sweeping versus mechanical methods (including extra-amniotic Foley catheter) – all women
Amniotic membrane sweep versus differing frequencies of amniotic membrane sweeping – all women
For the purpose of this review, membrane sweeping is defined as the manual detachment of the inferior pole of the amniotic membrane from the lower uterine segment. This is performed with consent by a clinician digitally through a circular motion during a vaginal examination at or near term gestation. If the cervical os is closed massage of the cervix will be accepted.

Types of outcome measures

We examined the effect of membrane sweeping had on clinical measures of maternal and infant morbidity, mortality and maternal satisfaction.

Primary outcomes

Maternal

1. Spontaneous onset of labour

2. Induction of labour (defined as the process of artificially stimulating the uterus to start labour (World Health Organization 2000)

3. Caesarean section

4. Spontaneous vaginal birth

5. Uterine hyperstimulation with/without fetal heart rate (FHR) changes. Uterine hyperstimulation defined as uterine tachysystole (more than five contractions per 10 minutes for at least 20 minutes) and uterine hypersystole/hypertonicity (a contraction lasting at least two minutes). These may or not be associated with changes in the FHR pattern (persistent decelerations, tachycardia or decreased short-term variability) (Hofmeyer 2009)

6. Maternal death or serious maternal morbidity (i.e. uterine rupture, admission to intensive care unit, septicaemia)

Neonatal

7. Neonatal death or serious neonatal perinatal morbidity (i.e. neonatal sepsis, seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood

The above seven outcomes were used in the 'Summary of findings' table.

Secondary outcomes

Maternal

8. Instrumental vaginal birth

9. Epidural analgesia

10. Postpartum haemorrhage (as defined by the trial authors)

11. Uterine rupture; all clinically significant ruptures of unscarred or scarred uteri. Trivial scar dehiscence noted incidentally at the time of surgery will be excluded (Hofmeyer 2009)

12. Augmentation of labour (defined as “the process of stimulating the uterus to increase the frequency, duration and intensity of contractions after the onset of spontaneous labour” (World Health Organization 2014)

Neonatal

13. Apgar score less than seven at five minutes

14. Neonatal encephalopathy

15. Perinatal death

Measures of satisfaction

16. Woman’s satisfaction

17. Cost

2.8.2 Search methods for identification of studies

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (25 February 2019).

The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);weekly searches of MEDLINE (Ovid);weekly searches of Embase (Ovid);monthly searches of CINAHL (EBSCO);handsearches of 30 journals and the proceedings of major conferences;weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (25 February 2019 using the search methods detailed in Appendix 1).

Searching other resources

We searched the reference lists of trial reports and reviews.

We did not apply any language or date restrictions.

2.8.3 Data collection and analysis

For methods used in the previous version of this review, see Boulvain 2005.

For this update, the following methods were used for assessing the 58 reports that were identified as a result of the updated search.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (EF and DD) extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager software (RevMan 2014) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details. Where contact was made, we have noted this in the Characteristics of included studies table (Appendix 2).

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);

- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias (where there is insufficient information to inform a judgement).

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias (where there is insufficient information to inform a judgement).

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we included missing data in the analyses we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias (where there is insufficient information to inform a judgement).

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias (where there is insufficient information to inform a judgement).

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the Handbook (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Assessment of the certainty of the evidence using the GRADE approach

For this update the certainty of the evidence was assessed using the GRADE approach as outlined in the GRADE handbook in order to assess the certainty of the body of evidence relating to the following outcomes.

Maternal

1. Spontaneous onset of labour
2. Induction of labour (World Health Organization 2000)
3. Caesarean section
4. Spontaneous vaginal birth
5. Uterine hyperstimulation with/without FHR changes. Uterine hyperstimulation defined as uterine tachysystole (more than five contractions per 10 minutes for at least 20 minutes) and uterine hypersystole/hypertonicity (a contraction lasting at least two minutes). These may or not be associated with changes in the FHR pattern (persistent decelerations, tachycardia or decreased short-term variability) (Hofmeyer 2009
6.)Maternal death or serious maternal morbidity (i.e. uterine rupture, admission to intensive care unit, septicaemia)

Neonatal

1. Neonatal perinatal death or serious neonatal perinatal morbidity (i.e. neonatal sepsis, seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood)

GRADEpro Guideline Development Tool was used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of certainty for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome. The evidence can be downgraded from 'high certainty' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

No continuous data were analysed in this review. In future updates, if appropriate, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

Cluster-randomised trials were eligible for inclusion in the analyses along with individually-randomised trials. However, we did not identify any eligible cluster-randomised studies.

Cross-over trials

Trials with cross-over designs were not eligible for inclusion.

Other unit of analysis issues

Studies with multiple arms

For studies with multiple treatment arms, we combined all relevant experimental intervention groups in the study (e.g. groups with different timings of membrane sweeping) into a single group and all comparable relevant control intervention groups into a single control group. We did not combine control groups with different types of interventions (e.g. different types of prostaglandins) in a single meta-analysis; instead we analysed these separately.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data (> 20%) in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if the I^2 was greater than 30% and either theTau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. If we identified substantial heterogeneity (above 30%), we explored it by pre-specified subgroup analysis.

Assessment of reporting biases

Where there were 10 or more studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We anticipated clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials and therefore used a random-effects meta-analysis to produce an

overall summary (we felt that an average treatment effect across trials was considered clinically meaningful). The random-effects summary is treated as the average of the range of possible treatment effects and we discuss the clinical implications of treatment effects differing between trials. Had average treatment effects not been clinically meaningful, we would not have combined trials. Results are presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

Where we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. Where the data allowed, we analysed the results by the following clinical categories of participants.

Primiparae, intact membrane versus multiparae, intact membrane. All women, intact membrane, unfavourable cervix (defined as Bishop score ≤ 6) versus all women, intact membrane, favourable cervix (defined as Bishop score ≥ 6).

Subgroup analyses was restricted to primary outcomes.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We conducted a sensitivity analysis on trial quality and on missing data. We limited sensitivity analyses to primary outcomes.

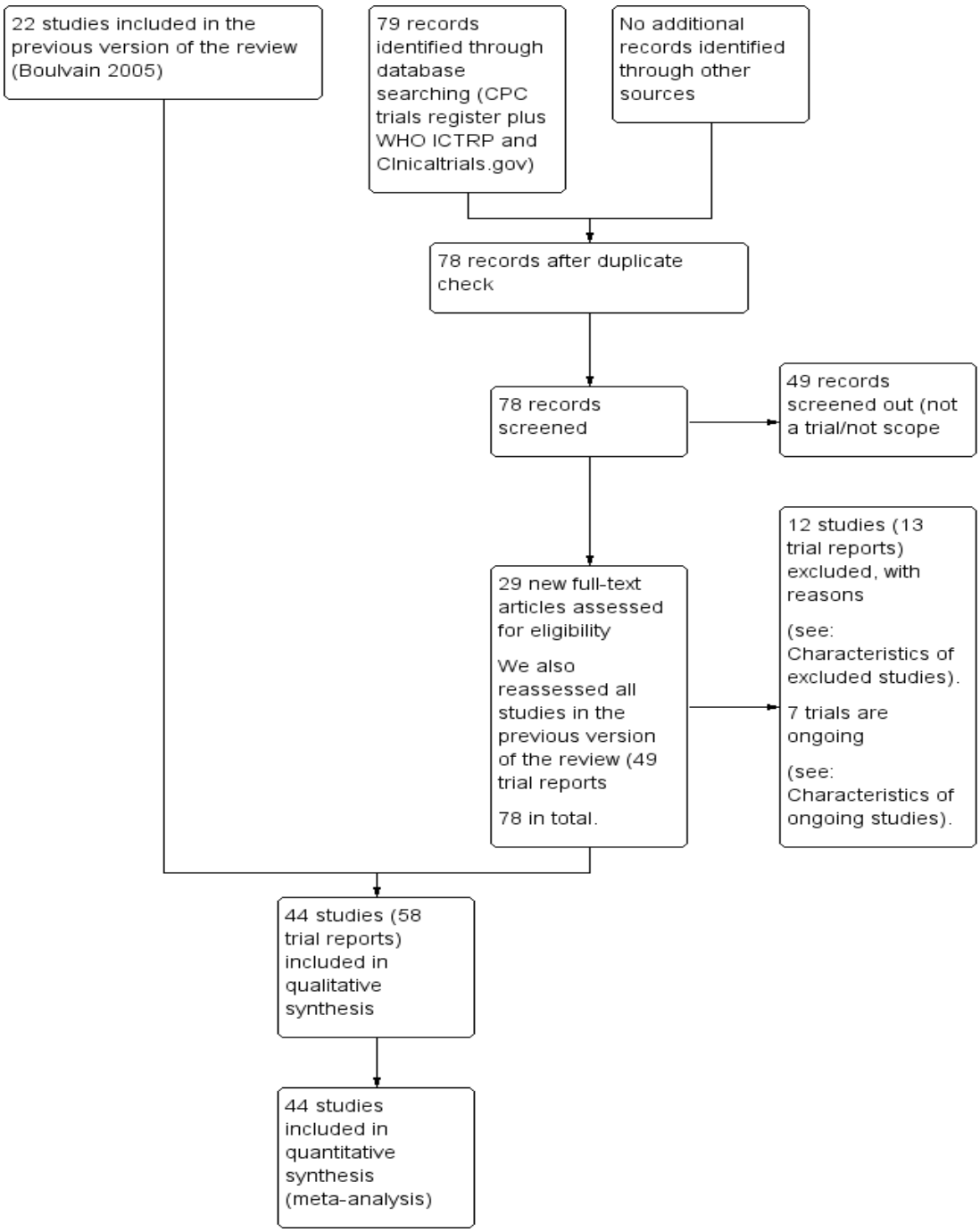
Trial quality: we excluded all studies at high or unclear risk of bias for either sequence generation and/or allocation concealment, based on growing empirical evidence that these factors are particularly important potential sources of bias (Higgins 2011).

Missing data: we excluded studies with high (> 20%) or unclear risk of attrition bias.

2.9 Results

2.9.1 Description of studies

Figure 2.1. Study flow diagram.



For this update we assessed 29 new trial reports and reassessed the 49 reports in the previous version of the review. We included 44 trials (58 trial reports) and excluded 12 (13 trial reports). Of the five trials excluded in the previous version of this review, we judged two (Gemer 2001; McColgin 1993) as suitable for inclusion. Gemer 2001 was excluded previously for a high risk of allocation concealment (selection bias) 'The study was excluded based on an inadequate method of concealment of the allocation'. McColgin 1993 was

excluded in the previous version of this review because 'No clinical outcomes reported.' Seven trials are ongoing.

Included studies

See Characteristics of included studies (Appendix 2).

Forty-four studies associated with 58 reports are included. The included studies reported data for 6940 women. Seven studies did not offer any data for outcomes included in this review (Gemer 2001; Imsuwan 1999; McColgin 1993; Salmanian 2012; Weissberg 1977; Yaddehige 2015; Yasmeen 2014).

Design

Of the 44 included studies, all were randomised at the individual level.

2.9.2 Description of intervention

Thirty-four studies (34/44) offered a detailed description of how they performed a membrane sweep (Afzal 2015; Alcoseba-Lim 1992; Allott 1993; Andersen 2013; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992; Goldenberg 1996; Gupta 1998; Hamdan 2009; Hill 2008a; Kashanian 2006; Magann 1999; McColgin 1990a; McColgin 1990b; McColgin 1993; Parlakgumus 2014; Putnam 2011; Ramya 2015; Saichandran 2015; Salamalekis 2000; Tannirandorn 1999; Ugwu 2014; Weissberg 1977; Wiriyasirivaj 1996; Wong 2002; Yasmeen 2014; Yildirim 2010; Zamzami 2014).

Ten (10/44) studies did not offer any description of how they performed a membrane sweep (Adeniji 2013; Averill 1999; Gemer 2001; Imsuwan 1999; Janakiraman 2011; Magann 1998a; Magann 1998b; Netta 2002; Salmanian 2012; Yaddehige 2015). Three studies (3/44) reported using a standardised method of membrane sweeping within the trial (Kashanian 2006; Tannirandorn 1999; Wong 2002). Fourteen studies (14/44) (n = 2808) stated they performed cervical massage if the cervix was closed and was not favourable for a membrane sweep (Andersen 2013; Cammu 1998; Crane 1997; de Miranda 2006; Doany 1997; El-Torkey 1992; Kashanian 2006; Magann 1998a; Putnam 2011; Ramya 2015; Wong 2002; Yasmeen 2014; Yildirim 2010; Zamzami 2014).

Sample sizes

Sample sizes of the included studies ranged from 50 (Gemer 2001) to 377 participants (de Miranda 2006).

Setting

The included studies were undertaken in hospital settings from a wide range of economic regions, as defined by The Word Bank 2018, including high income (25/44) (Allott 1993; Andersen 2013; Averill 1999; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; de Miranda 2006; Doany 1997; El-Torkey 1992;Gemer 2001; Goldenberg 1996; Hill 2008a; Janakiraman 2011; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990a; McColgin 1990b; McColgin 1993; Netta 2002; Putnam 2011; Salamalekis 2000; Weissberg 1977; Zamzami 2014), upper-middle income (9/44) (Hamdan 2009; Imsuwan 1999; Kashanian 2006; Parlakgumus 2014; Salmanian 2012; Tannirandorn 1999; Wiriyasirivaj 1996; Wong 2002; Yildirim 2010) and low-middle income (10/44) (Adeniji 2013; Afzal 2015; Alcoseba-Lim 1992; Dare 2002; Gupta 1998; Ramya 2015; Saichandran 2015; Ugwu 2014; Yaddehige 2015; Yasmeen 2014) countries.

Five of the studies took place in military hospitals in the USA (5/44) (Hill 2008a; Magann 1998a; Magann 1998b; Magann 1999; Putnam 2011).

Seven studies reported study funding sources (7/44) (Alcoseba-Lim 1992; Boulvain 1998; Magann 1998b; Magann 1999; McColgin 1993; Parlakgumus 2014; Wong 2002), of which two reported funding from pharmaceutical companies (2/44) (Alcoseba-Lim 1992; Boulvain 1998) (see Characteristics of included studies).

Of the 44 included trials:

1. 14 were conducted in the USA (Averill 1999; Berghella 1996; Doany 1997; Hill 2008a; Janakiraman 2011; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990a; McColgin 1990b; McColgin 1993; Netta 2002; Putnam 2011; Weissberg 1977);
2. three in India (Gupta 1998; Ramya 2015; Saichandran 2015);
3. three in Thailand (Imsuwan 1999; Tannirandorn 1999; Wiriyasirivaj 1996);
4. three in Nigeria (Adeniji 2013; Dare 2002; Ugwu 2014);
5. two in the UK (Allott 1993; El-Torkey 1992);
6. two in Canada (Boulvain 1998; Crane 1997);
7. two in Iran (Kashanian 2006; Salmanian 2012);
8. two in Turkey (Parlakgumus 2014; Yildirim 2010);

9. one in the Phillippines (Alcoseba-Lim 1992);
10. one in Denmark (Andersen 2013);
11. one in Belgium (Cammu 1998);
12. two in Israel (Gemer 2001; Goldenberg 1996);
13. one in the Netherlands (de Miranda 2006);
14. one in Malaysia (Hamdan 2009);
15. one in Greece (Salamalekis 2000);
16. one in China (Wong 2002);
17. one in Sri Lanka (Yaddehige 2015);
18. two in Pakistan (Afzal 2015; Yasmeen 2014);
19. one in Saudi Arabia (Zamzami 2014).

Participants

Three studies (n = 482) only included nulliparous women (3/44) (Cammu 1998; Gupta 1998; Salamalekis 2000). Five studies (n = 817) included multiparous women only (5/44) (Afzal 2015; Hamdan 2009; Imsuwan 1999; Ramya 2015; Yasmeen 2014). Thirty-five studies (n = 5567) included mixed parity (36/44) (Adeniji 2013; Alcoseba-Lim 1992; Allott 1993; Andersen 2013; Berghella 1996; Boulvain 1998; Crane 1997;Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992; Gemer 2001; Goldenberg 1996; Hill 2008a; Janakiraman 2011; Kashanian 2006; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990a; McColgin 1990b; McColgin 1993; Netta 2002; Parlakgumus 2014; Putnam 2011; Saichandran 2015; Salmanian 2012; Tannirandorn 1999; Ugwu 2014; Weissberg 1977; Wiriyasirivaj 1996; Wong 2002; Yaddehige 2015; Yildirim 2010; Zamzami 2014). One study (n = 74) did not report on parity (1/44) (Averill 1999).

Three studies (n = 473) included only women with a history of a caesarean section (3/44) (Afzal 2015; Hamdan 2009; Ramya 2015). Twelve studies (n = 1600) excluded women with a history of caesarean section or a uterine scare (12/44) (Adeniji 2013; Alcoseba-Lim 1992; Doany 1997; Kashanian 2006; Magann 1998a; Parlakgumus 2014; Saichandran 2015; Tannirandorn 1999; Ugwu 2014; Wiriyasirivaj 1996; Wong 2002; Yildirim 2010). Nine studies (n = 1740) included only women with an unfavourable cervix (9/44) (Adeniji 2013; Cammu 1998; Magann 1998a; Magann 1999; Putnam 2011; Ramya 2015; Salamalekis 2000; Yaddehige 2015; Yildirim 2010). Four studies (n = 574) excluded women with a closed cervix (4/44) (Allott 1993; Berghella 1996; Dare 2002; Gupta 1998).

Inclusion criteria for gestational age varied among studies. Three studies (n = 441) included women with pregnancies from 36 weeks' gestation (3/44) (Alcoseba-Lim 1992; Hamdan 2009; Netta 2002). Four (n = 398) included women with pregnancies from 37 weeks' gestation (4/44) (Afzal 2015; Averill 1999; Janakiraman 2011; Weissberg 1977). Fourteen studies (n = 2395) included women pregnancies from 38 weeks' gestation (14/44) (Berghella 1996; Boulvain 1998; Crane 1997; Dare 2002; Goldenberg 1996; Gupta 1998; Hill 2008a; McColgin 1990a; McColgin 1990b; McColgin 1993; Parlakgumus 2014; Wiriyasirivaj 1996; Yildirim 2010; Zamzami 2014). Six studies (n = 1050) included women pregnancies from 39 weeks' gestation (6/44) (Cammu 1998; Kashanian 2006; Magann 1998a; Putnam 2011; Ramya 2015; Tannirandorn 1999). Ten studies (n = 1410) included women pregnancies from 40 weeks' gestation (10/44) (Adeniji 2013; Allott 1993; de Miranda 2006; Saichandran 2015; Salamalekis 2000; Salmanian 2012; Ugwu 2014; Wong 2002; Yaddehige 2015; Yasmeen 2014). Six studies (n = 1196) included women pregnancies from 41 weeks' gestation (6/44) (Andersen 2013; Doany 1997; El-Torkey 1992; Imsuwan 1999; Magann 1998b; Magann 1999).

Two studies (n = 221) (2/44) (Janakiraman 2011; Netta 2002) examined membrane sweeping in women who were group B streptococcus positive. No additional maternal or fetal risk was noted with membrane sweeping. However, both studies were small and only abstracts were available to assess results.

The dates studies were conducted varied, with one study conducted over 40 years ago (Weissberg 1977). Twenty studies were conducted during the 1990s (Alcoseba-Lim 1992; Allott 1993; Averill 1999; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; Doany 1997; El-Torkey 1992; Goldenberg 1996; Gupta 1998; Imsuwan 1999; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990a; McColgin 1990b; McColgin 1993; Tannirandorn 1999; Wiriyasirivaj 1996) and 23 studies conducted in the 21st century (Adeniji 2013; Afzal 2015; Andersen 2013; Dare 2002; de Miranda 2006; Gemer 2001; Hamdan 2009; Hill 2008a; Janakiraman 2011; Kashanian 2006; Netta 2002; Parlakgumus 2014; Putnam 2011; Ramya 2015; Saichandran 2015; Salamalekis 2000; Salmanian 2012; Ugwu 2014; Wong 2002; Yaddehige 2015; Yasmeen 2014; Yildirim 2010; Zamzami 2014). Of these seven were conducted in the last five years (Afzal 2015; Parlakgumus 2014; Ramya 2015; Saichandran 2015; Yaddehige 2015; Yasmeen 2014; Zamzami 2014).

2.9.3 Interventions and Comparisons

Amniotic membrane sweeping versus no treatment/sham treatment

Of the 44 studies included, 40 (n = 6548) compared membrane sweeping with no treatment or sham treatment (40/44) (Afzal 2015; Alcoseba-Lim 1992; Allott 1993; Andersen 2013; Averill 1999; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992; Goldenberg 1996; Gupta 1998; Hamdan 2009; Hill 2008a; Imsuwan 1999; Janakiraman 2011; Kashanian 2006; Magann 1998a; Magann 1998b; McColgin 1990a; McColgin 1990b; McColgin 1993; Netta 2002; Parlakgumus 2014; Putnam 2011; Ramya 2015; Saichandran 2015; Salamalekis 2000; Tannirandorn 1999; Ugwu 2014; Weissberg 1977; Wiriyasirivaj 1996; Wong 2002; Yaddehige 2015; Yasmeen 2014 Yildirim 2010; Zamzami 2014).

Amniotic membrane sweeping versus vaginal/intracervical prostaglandins

Four studies (n = 480) compared membrane sweeping with vaginal/intracervical prostaglandins (4/44) (Doany 1997; Gemer 2001; Magann 1998b; Magann 1999).

Amniotic membrane sweeping versus intravenous oxytocin +/- amniotomy

One study (n = 104) compared membrane sweeping with intravenous oxytocin +/- amniotomy (1/44) (Salamalekis 2000).

Amniotic membrane sweeping versus amniotomy only

No studies compared membrane sweeping with amniotomy only.

Amniotic membrane sweeping versus vaginal/oral misoprostol

Two studies n = 160) compared membrane sweeping with vaginal/oral misoprostol (2/44) (Adeniji 2013; Salmanian 2012).

Amniotic membrane sweeping versus mechanical methods

No study compared membrane sweeping with mechanical methods.

One frequency of amniotic membrane sweeping versus another frequency of amniotic membrane sweeping

One study (n = 355) compared differing frequencies of membrane sweeping (1/44) (Putnam 2011).

Six studies (n = 1284) compared membrane sweeping with more than one intervention (6/44) (Andersen 2013; Doany 1997; Magann 1998b; Putnam 2011; Salamalekis 2000; Yaddehige 2015). Seven studies provided no data (7/44) (Gemer 2001; Imsuwan 1999; McColgin 1993; Salmanian 2012; Weissberg 1977; Yaddehige 2015; Yasmeen 2014).

2.9.4 Outcomes

Maternal primary outcomes

Spontaneous onset of labour was reported in 18 studies (Andersen 2013; Cammu 1998; Crane 1997; de Miranda 2006; Doany 1997; El-Torkey 1992; Gupta 1998; Hamdan 2009; Hill 2008a; Janakiraman 2011; Magann 1998a; Magann 1998b; Magann 1999; Ramya 2015; Saichandran 2015; Salamalekis 2000; Wong 2002; Yildirim 2010).

Induction of labour was reported in 16 studies (Allott 1993;Boulvain 1998; Cammu 1998; Crane 1997; de Miranda 2006; Doany 1997; Gupta 1998; Hamdan 2009; Hill 2008a; Janakiraman 2011; Magann 1998b; Parlakgumus 2014; Putnam 2011; Saichandran 2015; Salamalekis 2000; Wong 2002).

Caesarean section was reported in 34 studies (Adeniji 2013; Afzal 2015; Alcoseba-Lim 1992; Allott 1993; Andersen 2013; Averill 1999; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992; Goldenberg 1996; Gupta 1998; Hamdan 2009; Hill 2008a; Janakiraman 2011; Kashanian 2006; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990a; Parlakgumus 2014; Putnam 2011; Ramya 2015; Saichandran 2015; Salamalekis 2000; Tannirandorn 1999; Wiriyasirivaj 1996; Wong 2002; Yildirim 2010; Zamzami 2014).

Spontaneous vaginal birth was reported in 27 studies (Afzal 2015; Alcoseba-Lim 1992; Allott 1993; Andersen 2013; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; El-Torkey 1992; Gupta 1998; Hamdan 2009; Hill 2008a; Janakiraman 2011; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990a; Parlakgumus 2014; Putnam 2011; Ramya 2015; Saichandran 2015; Tannirandorn 1999; Wiriyasirivaj 1996; Wong 2002; Zamzami 2014).

Maternal death or serious maternal morbidity was reported in 17 studies (Alcoseba-Lim 1992; Dare 2002; Doany 1997; Goldenberg 1996; Gupta 1998; Hill 2008a; Janakiraman

2011; Kashanian 2006; McColgin 1990a; McColgin 1990b; Putnam 2011; Salamalekis 2000; Tannirandorn 1999; Ugwu 2014; Wiriyasirivaj 1996; Wong 2002; Yildirim 2010).

Uterine hyperstimulation was not reported on.

Neonatal primary outcomes

Neonatal death or serious neonatal perinatal morbidity was reported in 19 studies (Allott 1993; Andersen 2013; Boulvain 1998; Crane 1997; Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992; Gupta 1998; Hamdan 2009; Hill 2008a; Janakiraman 2011; Magann 1999; McColgin 1990b; Netta 2002; Putnam 2011; Saichandran 2015; Wong 2002; Yildirim 2010).

Maternal secondary outcomes

Instrumental vaginal birth was reported in 23 studies (Afzal 2015; Alcoseba-Lim 1992; Allott 1993; Andersen 2013; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992; Gupta 1998; Hamdan 2009; Magann 1998b; Magann 1999; McColgin 1990a; Putnam 2011; Ramya 2015; Tannirandorn 1999; Wiriyasirivaj 1996; Wong 2002, Zamzami 2014).

Epidural delivery was reported in nine studies (Allott 1993; Andersen 2013; Boulvain 1998; Cammu 1998; Crane 1997; de Miranda 2006; El-Torkey 1992; Hamdan 2009; Wong 2002).

Postpartum haemorrhage was reported in five studies (Andersen 2013; Hamdan 2009; Tannirandorn 1999; Wiriyasirivaj 1996; Zamzami 2014).

Augmentation of labour was reported in 10 studies (Adeniji 2013; Andersen 2013; Cammu 1998; de Miranda 2006; Doany 1997; Goldenberg 1996; Magann 1998a; Ramya 2015; Saichandran 2015; Wiriyasirivaj 1996).

Uterine rupture was not reported on.

Neonatal secondary outcomes

Apgar score less than seven at five minutes was reported in 12 studies (Adeniji 2013; Andersen 2013; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; Doany 1997;Goldenberg 1996; Hamdan 2009; Magann 1998b; Magann 1999; Putnam 2011).

Neonatal encephalopathy was not reported on.

Woman's satisfaction

Three studies providing data for (n = 675) women reported on maternal satisfaction (Adeniji 2013; Boulvain 1998; de Miranda 2006). One study compared membrane sweeping with oral misoprostol (Adeniji 2013). Boulvain 1998 compared membrane sweeping with a control group who underwent a vaginal examination for Bishop scoring only. de Miranda 2006 compared membrane sweeping to a control group where vaginal examination was not performed until the onset of labour

Cost

Two studies (n = 290) women reported on a cost analysis (Magann 1998b; Magann 1999). Both reported a cost per person (US dollars) and compared membrane sweeping with vaginal/intracervical prostaglandins.

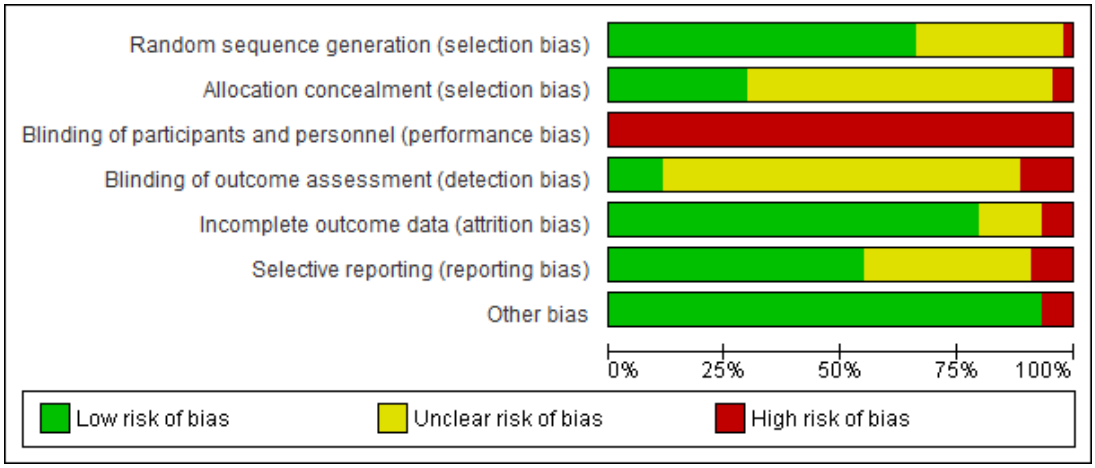
2.9.5 Excluded studies

We excluded 12 studies, see Characteristics of excluded studies (Appendix 3). Of these, 11 studies were excluded because the interventions compared did not meet our inclusion criteria (Al-Harmi 2015; Bergsjo 1989; Day 2009; Foong 2000; Ifnan 2006; Kaul 2004; Laddad 2013; Park 2013; Park 2015; Shravage 2009; Tan 2006). One study did not demonstrate an adequate method of random sequence generation or allocation concealment (Swann 1958). Of the five trials excluded in the previous version of this review, we assessed two (Gemer 2001; McColgin 1993) as suitable for inclusion. Gemer 2001 was excluded previously for a high risk of allocation concealment (selection bias) 'The study was excluded based on an inadequate method of concealment of the allocation'. McColgin 1993 was excluded in the previous version of this review because 'No clinical outcomes reported.'

2.9.6 Risk of bias in included studies

See Figure 2.2 for a summary of 'Risk of bias' assessments and Figure 2.3 for review authors' judgements about each risk of bias item across all included studies.

Figure 2.2: 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



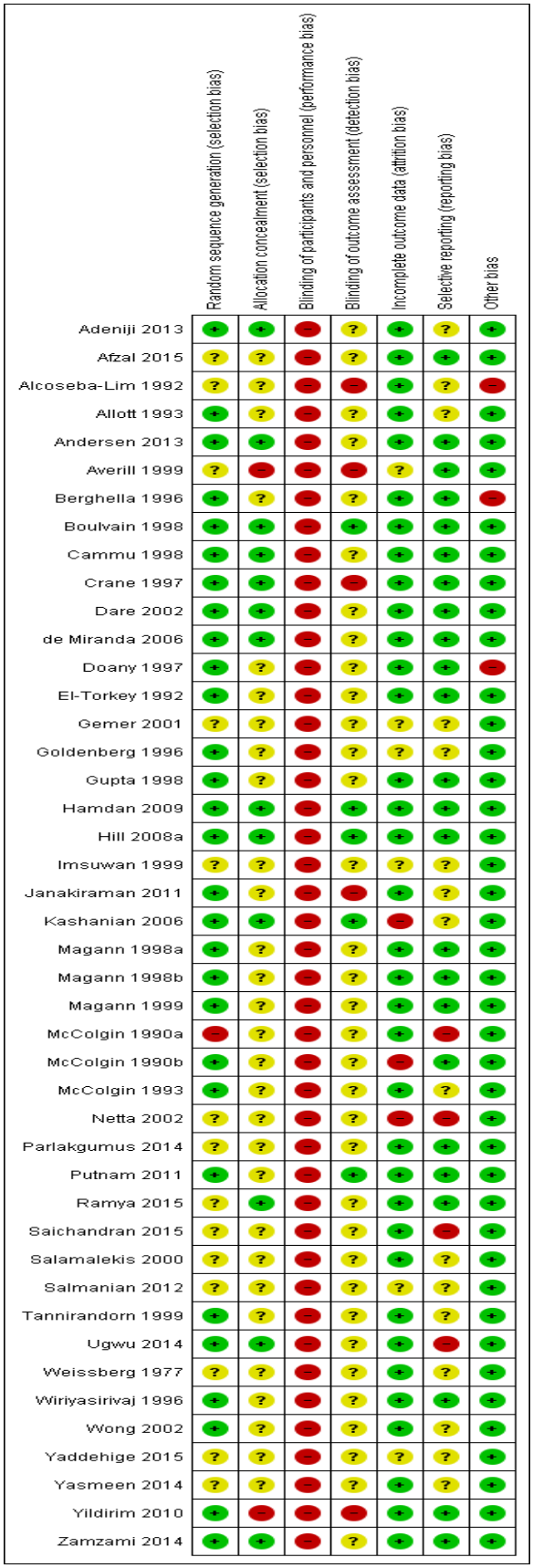


Figure 2.3: 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Allocation (selection bias)

Random sequence generation

Twenty-nine studies were judged to be at a low risk for selection bias in random sequence generation (Adeniji 2013; Allott 1993; Andersen 2013; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992;Goldenberg 1996; Gupta 1998; Hamdan 2009; Hill 2008a; Janakiraman 2011; Kashanian 2006; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990b; McColgin 1993; Putnam 2011; Tannirandorn 1999; Ugwu 2014; Wiriyasirivaj 1996; Wong 2002; Yildirim 2010; Zamzami 2014). We judged studies to be at low risk for selection bias in random sequence generation if they had stated an appropriate randomisation method clearly, e.g. Adeniji 2013 stated that 'Computer-generated random numbers were used for patient allocation'. Fourteen studies were judged to have unclear methods of random sequence generation primarily for lack of published methodological detail, e.g. Afzal 2015 states that trial participants 'were randomly allocated', with no further detail provided of the methods used given (Afzal 2015; Alcoseba-Lim 1992; Averill 1999; Gemer 2001; Imsuwan 1999; Netta 2002; Parlakgumus 2014; Ramya 2015; Saichandran 2015; Salamalekis 2000; Salmanian 2012; Weissberg 1977; Yaddehige 2015; Yasmeen 2014). McColgin 1990a was judged to be of high risk for bias as it stated that women were 'prospectively assigned' to either receive a membrane sweep group or a control group'. See Characteristics of included studies.

Allocation concealment

Thirteen studies were judged to be of low risk of bias for allocation concealment (Adeniji 2013; Andersen 2013; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; Hamdan 2009; Hill 2008a; Kashanian 2006; Ramya 2015; Ugwu 2014; Zamzami 2014). We found studies to be at low risk of bias for allocation concealment when a study reported fully the methodology used for allocation concealment, e.g. Andersen 2013 states “the allocations were contained in a series of opaque, sealed and consecutively numbered envelopes, kept in the delivery unit” “clerk opened the next envelope and informed the doctor of the woman’s allocation”. Twenty-nine were judged to be of unclear risk of bias for allocation concealment due to insufficient reporting of methodological methods, e.g. Alcoseba-Lim 1992 provided no evidence of the methods used to ensure allocation concealment (Afzal 2015; Alcoseba-Lim 1992; Allott 1993; Berghella 1996; Doany 1997; El-

Torkey 1992; Gemer 2001; Goldenberg 1996; Gupta 1998; Imsuwan 1999; Janakiraman 2011; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990a; McColgin 1990b; McColgin 1993; Netta 2002; Parlakgumus 2014; Putnam 2011; Saichandran 2015; Salamalekis 2000; Salmanian 2012; Tannirandorn 1999; Weissberg 1977; Wiriyasirivaj 1996; Wong 2002; Yaddehige 2015; Yasmeen 2014). Two studies (Averill 1999; Yildirim 2010) were judged to be high risk of bias for allocation concealment. Yildirim 2010 was found to be of high risk of bias for allocation concealment as the "investigator was not blinded to the allocation procedure" and "sealed opaque envelopes" were "withdrawn from the appropriate box and allocated to the woman" by the investigator. See Characteristics of included studies.

Blinding (performance bias and detection bias)

Performance bias

All 44 studies in our review were judged to be of high risk for performance bias. Clinicians were not blinded to the intervention in any study and it is unclear (and unlikely in our view) in most studies if study participants were blinded post allocation. For some outcomes, e.g. "induction of labour", knowledge of the allocation may have encouraged the clinician to modify the date for the procedure. See Characteristics of included studies.

Detection bias

Five studies were judged to be of low risk for detection bias (Boulvain 1998; Hamdan 2009; Hill 2008a; Kashanian 2006; Putnam 2011). We judged studies to be at low risk for detection bias if they had clearly stated an appropriate methodology to prevent detection bias, e.g. Hill 2008a states "All data were collected and all chart analysis was done by the primary author, who was also blinded to the group allocations. Unblinding did not occur until the time of data analysis." Thirty-four were judged to be of unclear risk of bias primarily due to a lack of methodological detail (Adeniji 2013; Afzal 2015; Allott 1993; Andersen 2013; Berghella 1996; Cammu 1998; Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992; Gemer 2001; Goldenberg 1996; Gupta 1998; Imsuwan 1999; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990a; McColgin 1990b; McColgin 1993; Netta 2002; Parlakgumus 2014; Ramya 2015; Saichandran 2015; Salamalekis 2000; Salmanian 2012; Tannirandorn 1999; Ugwu 2014; Weissberg 1977; Wiriyasirivaj 1996; Wong 2002;Yaddehige 2015; Yasmeen 2014; Zamzami 2014). Five studies were judged to be of high risk of bias as the outcome assessors were aware of allocation, e.g. Janakiraman

2011 states that “No blinding was attempted” in the study (Alcoseba-Lim 1992; Averill 1999; Crane 1997; Janakiraman 2011; Yildirim 2010). See Characteristics of included studies.

Incomplete outcome data (attrition bias)

Thirty-five studies were judged to be of low risk for attrition bias with minimal or no attrition noted (Adeniji 2013; Afzal 2015; Alcoseba-Lim 1992; Allott 1993; Andersen 2013; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992 Gupta 1998; Hamdan 2009; Hill 2008a; Janakiraman 2011; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990a; McColgin 1993; Parlakgumus 2014; Putnam 2011; Ramya 2015; Saichandran 2015; Salamalekis 2000; Tannirandorn 1999; Ugwu 2014; Weissberg 1977; Wiriyasirivaj 1996; Wong 2002; Yasmeen 2014; Yildirim 2010; Zamzami 2014).

Six studies were judged to be of unclear risk of bias as there was insufficient information to make an informed decision (Averill 1999; Gemer 2001; Goldenberg 1996; Imsuwan 1999; Salmanian 2012; Yaddehige 2015). Three studies were assessed as high risk of bias. Two were judged to be of high risk of bias due to high attrition rates, Netta 2002 (52%, 51/98) and Kashanian 2006 (33.5%, 51/152). McColgin 1990b was judged to be of high risk of bias as 29 of 209 women initially recruited were excluded. See Characteristics of included studies.

Selective reporting (reporting bias)

Twenty-four studies were judged as low risk for reporting bias (Afzal 2015; Andersen 2013; Averill 1999; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992; Gupta 1998; Hamdan 2009; Hill 2008a; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990b; Parlakgumus 2014; Putnam 2011; Ramya 2015; Wiriyasirivaj 1996; Yildirim 2010; Zamzami 2014). Sixteen were judged to be of unclear risk for reporting bias. Allott 1993 was judged as unclear risk of reporting bias as data were reported unclearly, with inconsistencies (see Characteristics of included studies) (Adeniji 2013; Alcoseba-Lim 1992; Allott 1993; Gemer 2001; Goldenberg 1996; Imsuwan 1999; Janakiraman 2011; Kashanian 2006; McColgin 1993; Salamalekis 2000; Salmanian 2012; Tannirandorn 1999; Weissberg 1977; Wong 2002; Yaddehige 2015; Yasmeen 2014). Four studies were judged high risk for reporting bias. Two as primary outcomes were not reported (McColgin 1990a; Saichandran 2015). One study was deemed

high risk as it only reported data on nulliparous women with a mixed parity trial (Netta 2002), and another as the study only reported outcomes for participants who did not exceed 41 + 3 weeks' gestation (Ugwu 2014). See Characteristics of included studies.

Other potential sources of bias

Forty-one studies were judged to be at low risk for other sources of bias (Adeniji 2013; Afzal 2015; Allott 1993; Andersen 2013; Averill 1999; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; El-Torkey 1992; Gemer 2001; Goldenberg 1996; Gupta 1998; Hamdan 2009; Hill 2008a; Imsuwan 1999; Janakiraman 2011; Kashanian 2006; Magann 1998a; Magann 1998b; Magann 1999; McColgin 1990a; McColgin 1990b; McColgin 1993; Netta 2002; Parlakgumus 2014; Putnam 2011; Ramya 2015; Saichandran 2015; Salamalekis 2000; Salmanian 2012; Tannirandorn 1999; Ugwu 2014; Weissberg 1977; Wiriyasirivaj 1996; Wong 2002; Yaddehige 2015; Yasmeen 2014; Yildirim 2010; Zamzami 2014). Three studies were assessed as high risk of bias, i.e. Alcoseba-Lim 1992 for imbalance within groups in baseline Bishop score, Berghella 1996 for imbalance within groups in baseline parity and Doany 1997 for unbalanced group sizes. See Characteristics of included studies.

2.9.7 Effects of interventions

See: Summary of findings table 2.1 for the main comparison: membrane sweeping compared with no treatment or a sham treatment.

Forty-four studies associated with 58 publications were included. The included studies reported data for 6940 women. Six studies did not provide data for outcomes included in this review (Gemer 2001; Imsuwan 1999; McColgin 1993; Salmanian 2012; Yaddehige 2015; Yasmeen 2014).

2.9.7.1 Comparison 1: Amniotic membrane sweeping versus no treatment/sham (Appendices 5 & 6)

Forty studies reported data for 6548 women comparing membrane sweeping with no treatment or a sham treatment (Afzal 2015; Alcoseba-Lim 1992; Allott 1993; Andersen 2013; Averill 1999; Berghella 1996; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; Doany 1997; El-Torkey 1992; Goldenberg 1996; Gupta 1998; Hamdan 2009; Hill 2008a; Imsuwan 1999; Janakiraman 2011; Kashanian 2006; Magann 1998a;

Magann 1998b; McColgin 1990a; McColgin 1990b; McColgin 1993; Netta 2002; Parlakgumus 2014; Putnam 2011; Ramya 2015; Saichandran 2015; Salamalekis 2000; Tannirandorn 1999; Ugwu 2014; Weissberg 1977; Wiriyasirivaj 1996; Wong 2002; Yaddehige 2015; Yasmeen 2014; Yildirim 2010; Zamzami 2014).

Primary outcomes

Spontaneous onset of labour

Seventeen studies reported on spontaneous onset of labour within this comparison. Women in the membrane sweeping group may, on average, be more likely to experience spontaneous onset of labour compared to women in the control group (average risk ratio (RR), 1.21 95% confidence interval (CI) 1.08 to 1.34, 17 studies, 3170 participants, low-certainty evidence Analysis 1.1). We found substantial heterogeneity (Tau^2 0.03, I^2 = 73%, P < 0.00001) between the trials contributing data. While heterogeneity remains unexplained, we note the following differences in populations. Study size varied from n = 65 (El-Torkey 1992) to n = 377 (de Miranda 2006). Three studies excluded multiparous women (Cammu 1998; Gupta 1998; Salamalekis 2000), and two excluded nulliparous women (Hamdan 2009; Ramya 2015). Five studies excluded women with a history of a uterine scar (Doany 1997; Magann 1998a; Saichandran 2015; Wong 2002; Yildirim 2010), and two studies included women with a history of a previous caesarean section or uterine scar (Hamdan 2009; Ramya 2015). Gestation at group allocation varied with a gestational difference of five weeks between Hamdan 2009 (> 36/40 weeks' gestation) and Doany 1997 (> 41/40 weeks' gestation). Five studies included only women with an unfavourable cervix (Cammu 1998; Magann 1998a; Magann 1998b; Ramya 2015; Salamalekis 2000) and one study included only women with a favourable cervix (Andersen 2013). Netta 2002 provided data for subgroup analysis of parity only. Ten of the 17 studies performed cervical massage if the cervix was closed on vaginal examination (Andersen 2013; Cammu 1998; Crane 1997; de Miranda 2006; Doany 1997; El-Torkey 1992; Magann 1998a; Ramya 2015; Wong 2002; Yildirim 2010). Ten studies did not perform cervical massage or did not report this aspect of the intervention.

As we identified substantial heterogeneity, we investigated it using a priori subgroup and sensitivity analyses.

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Three studies reported data for primiparous women. Two studies reported data for multiparous women and 12 reported data for women of unknown parity. The test for subgroup differences indicates that there is no statistically significant subgroup effect (Chi^2 5.92, P = 0.05, I^2 = 66.2%), suggesting that parity does not modify intervention effect. However, we note a smaller number of trials and participants contributed data to the multiparous and primiparous subgroups than to the unknown parity subgroup, meaning that the analysis may not be able to detect subgroup differences (Analysis 8.1).

Cervical status

No study reported data for a favourable cervix. Five studies reported data for an unfavourable cervix and 12 studies reported data for unknown cervical status. The test for subgroup differences indicates that there is no statistically significant subgroup effect (Chi^2 2.01, P = 0.16, I^2 = 50.4%), suggesting that cervical status does not modify intervention effect. However, we note a smaller number of trials and participants contributed data to the favourable and unfavourable subgroups than to the unknown cervical status subgroup, meaning that the analysis may not be able to detect subgroup differences (Analysis 13.1).

Assessment of reporting biases

As there were more than 10 studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. As asymmetry was not suggested by a visual assessment, we did not perform exploratory analyses to investigate it further (Sterne 2017).

Induction of labour

Sixteen studies reported on induction of labour. When comparing membrane sweeping with no treatment or sham, women in the membrane sweeping group may, on average, be less likely to experience an induction of labour (average RR 0.73, 95% CI 0.56 to 0.94, 16 studies, 3224 participants, low-certainty evidence; Analysis 1.2). There was substantial heterogeneity (Tau^2 0.17, I^2 = 75%, P < 0.00001) between the trials contributing data. While heterogeneity remains unexplained, we note the following differences in populations. Study size varied from n = 69 (Salamalekis 2000) to n = 742 (de Miranda 2006). The

inclusion criteria for Hamdan 2009 is multiparous women with a history of a previous caesarean section or uterine scar. Four studies did not include women with a history of uterine scar (Doany 1997; Parlakgumus 2014; Saichandran 2015; Wong 2002). Three studies excluded multiparous women (Cammu 1998; Gupta 1998; Salamalekis 2000). Twelve studies included women of mixed parity (Allott 1993; Boulvain 1998; Crane 1997; de Miranda 2006; Doany 1997; Hill 2008a; Janakiraman 2011; Magann 1998b; Parlakgumus 2014; Putnam 2011; Saichandran 2015; Wong 2002). Gestation at allocation varied, with a five-week difference noted between Hamdan 2009 (> 36/40 weeks' gestation) and Doany 1997 (> 41/40 weeks' gestation). Three studies included participants with an unfavourable cervix (Bishop score < 6) at allocation (Cammu 1998; Putnam 2011; Salamalekis 2000). Two studies included participants with a favourable cervix (Bishop score > 6) at allocation 2/16 (Allott 1993; Gupta 1998). Seven studies performed cervical massage if the cervix was closed (Boulvain 1998; Cammu 1998; Crane 1997; de Miranda 2006; Doany 1997; Putnam 2011; Wong 2002). Nine studies did not state if cervical massage was used (Allott 1993; Gupta 1998; Hamdan 2009; Hill 2008a; Janakiraman 2011; Magann 1998b; Parlakgumus 2014; Saichandran 2015; Salamalekis 2000).

As we identified substantial heterogeneity, we investigated it using a priori subgroup and sensitivity analyses.

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Five studies reported data for primiparous women. Two studies reported data for multiparous women and eleven studies reported data for women of unknown parity. The test for subgroup differences indicates that there is no statistically significant subgroup effect ($Chi^2 = 3.24$, $P = 0.20$, $I^2 = 38.3\%$), suggesting that parity does not modify intervention effect. However, we note a smaller number of trials and participants contributed data to the multiparous and primiparous subgroups than to the unknown parity subgroup, meaning that the analysis may not be able to detect subgroup differences (Analysis 8.2).

Cervical status

One study reported data for a favourable cervix. Four studies reported data for an unfavourable cervix and 13 studies reported data for unknown cervical status. The test for subgroup differences indicates that there is no statistically significant subgroup effect (Chi^2 = 3.63, P = 0.16, I^2 = 44.9%), suggesting that cervical status does not modify intervention effect. However, we note a smaller number of trials and participants contributed data to the favourable and unfavourable subgroups than to the unknown cervical status subgroup, meaning that the analysis may not be able to detect subgroup differences (Analysis 13.2).

Assessment of reporting biases

As there were more than 10 studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. As asymmetry was not suggested by a visual assessment, we did not perform exploratory analyses to investigate it further (Sterne 2017).

Caesarean section

Caesarean section was reported in 32 studies. Compared to control/sham, membrane sweeping may, on average, have little to no effect on the risk of caesarean section (average RR 0.94, 95% CI 0.85 to 1.04, 32 studies, 5499 participants, moderate-certainty evidence; Analysis 1.3). Heterogeneity was low (between the trials contributing data (Tau^2 0.00, I^2 = 1%, P = 0.45).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Four studies reported data for primiparous women. Four studies reported data for multiparous women and 25 studies reported data for women of unknown parity. The test for subgroup differences indicates that there is no statistically significant subgroup effect (Chi^2 = 0.65, P = 0.72, I^2 = 0%), suggesting that parity does not modify intervention effect. However, we note a smaller number of trials and participants contributed data to the multiparous and primiparous subgroups than to the unknown parity subgroup, meaning that the analysis may not be able to detect subgroup differences.

Cervical status

One study reported data for a favourable cervix. Seven studies reported data for an unfavourable cervix and 24 studies reported data for women of unknown cervical status. The test for subgroup differences indicates that there is no statistically significant subgroup effect ($Chi^2 = 2.87$, $P = 0.24$, $I^2 = 30.2\%$), suggesting that cervical status does not modify intervention effect. However, we note a smaller number of trials and participants contributed data to the favourable and unfavourable subgroups than to the unknown cervical status subgroup, meaning that the analysis may not be able to detect subgroup differences (Analysis 13.3).

Assessment of reporting biases

As there were more than 10 studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. As asymmetry was not suggested by a visual assessment, we did not perform exploratory analyses to investigate it further (Sterne 2017).

Spontaneous vaginal birth

Spontaneous vaginal birth was reported in 26 studies. Compared to control/sham, membrane sweeping may have, on average, little to no effect on the risk of spontaneous vaginal birth (average RR 1.03, 95% CI 0.99 to 1.07, 26 studies, 4538 participants, moderate certainty evidence; Analysis 1.4). Heterogeneity was low between the trials contributing data (Tau^2 0.00, $I^2 = 14\%$, $P = 0.26$).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Three studies reported data for primiparous women. Four studies reported data for multiparous women and 20 studies reported data for women of unknown parity. The test for subgroup differences indicates that there is no statistically significant subgroup effect ($Chi^2 = 0.62$, $P = 0.73$, $I^2 = 0\%$), suggesting that parity does not modify intervention effect. However, we note a smaller number of trials and participants contributed data to the multiparous and primiparous subgroups than to the unknown parity subgroup, meaning that the analysis may not be able to detect subgroup differences (Analysis 8.4).

Cervical status

No studies reported data for a favourable cervix. Five studies reported data for an unfavourable cervix and 21 studies reported data for women of unknown cervical status. The test for subgroup differences indicates that there is no statistically significant subgroup effect ($Chi^2 = 0.04$, $P = 0.83$, $I^2 = 0\%$), suggesting that cervical status does not modify intervention effect. However, we note a smaller number of trials and participants contributed data to the favourable and unfavourable subgroups than to the unknown cervical status subgroup, meaning that the analysis may not be able to detect subgroup differences (Analysis 13.4).

Assessment of reporting biases

As there were more than 10 studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. As asymmetry was not suggested by a visual assessment, we did not perform exploratory analyses to investigate it further (Sterne 2017).

Uterine hyperstimulation with/without fetal heart rate (FHR) changes

No studies reported on uterine hyperstimulation with/without FHR changes.

Maternal death or serious maternal morbidity

Seventeen studies reported on maternal death or serious maternal morbidity. Compared to control/sham, membrane sweeping may have, on average, little to no effect on the risk of maternal death or serious maternal morbidity (average RR 0.83, 95% CI 0.57 to 1.20, 17 studies, 2749 participants, low-certainty evidence; Analysis 1.5). Heterogeneity was low between the trials contributing data (Tau^2 0.00, $I^2 = 0\%$, $P = 0.84$).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Two studies reported data for primiparous women, but no events were reported. No studies reported data for multiparous women and 15 studies reported data for women of

unknown parity. Therefore, tests for subgroup interaction effects were not possible (Analysis 8.5).

Cervical status

No studies reported data for a favourable cervix. Four studies reported data for an unfavourable cervix and 13 studies reported data for women of unknown cervical status. The test for subgroup differences indicates that there is no statistically significant subgroup effect ($Chi^2 = 2.32$, $P = 0.13$, $I^2 = 56.9\%$), suggesting that cervical status does not modify intervention effect. However, we note no studies contributed data to the favourable subgroup and a smaller number of trials and participants contributed data to the unfavourable subgroups, meaning that the analysis may not be able to detect subgroup differences (Analysis 13.5).

Assessment of reporting biases

As there were more than 10 studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots.

We assessed funnel plot asymmetry visually. As asymmetry was not suggested by a visual assessment, we did not perform exploratory analyses to investigate it further (Sterne 2017).

Neonatal death or serious neonatal perinatal morbidity

Eighteen studies reported on neonatal death or serious neonatal perinatal morbidity. Compared to control/sham, membrane sweeping may have, on average, little to no effect on the risk of neonatal perinatal death or serious neonatal perinatal morbidity (average RR 0.83, 95% CI 0.59 to 1.17, 18 studies, 3696 participants, low-certainty evidence; Analysis 1.6). Heterogeneity was low between the trials contributing data (Tau^2 0.00, $I^2 = 0\%$, $P = 0.99$).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

One study reported data for primiparous women. No studies reported data for multiparous women and 17 studies reported data for women of unknown parity. The test for subgroup differences indicates that there is no statistically significant subgroup effect ($Chi^2 = 0.43$, P = 0.51, $I^2 = 0\%$), suggesting that parity does not modify intervention effect. However, we note no studies contributed data to the multiparous subgroup and only one contributed data to the primiparous subgroups, meaning that the analysis may not be able to detect subgroup differences (Analysis 8.6).

Cervical status

No study reported data for a favourable cervix. One study reported data for an unfavourable cervix and 17 studies reported data for women of unknown cervical status. The test for subgroup differences indicates that there is no statistically significant subgroup effect ($Chi^2 = 0.37$ P = 0.55, $I^2 = 0\%$), suggesting that cervical status does not modify intervention effect. However, we note no studies contributed data to the favourable subgroup and only one contributed data to the unfavourable subgroups, meaning that the analysis may not be able to detect subgroup differences (Analysis 13.6).

Assessment of reporting biases

As there were more than 10 studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots.

We assessed funnel plot asymmetry visually. As asymmetry was not suggested by a visual assessment, we did not perform exploratory analyses to investigate it further (Sterne 2017).

Secondary outcomes

Instrumental vaginal birth

Twenty-two studies reported on instrumental vaginal birth. Compared to control/sham, membrane sweeping may, on average, have little to no effect on the risk of an instrumental vaginal birth (average RR 1.06, 95% CI 0.91 to 1.25, 22 studies, 3888 participants, low-certainty evidence; Analysis 1.7). Heterogeneity was low between the trials contributing data (Tau^2 0.00, $I^2 = 0\%$, P = 0.67).

Assessment of reporting biases

As there were more than 10 studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots.

We assessed funnel plot asymmetry visually. As asymmetry was not suggested by a visual assessment, we did not perform exploratory analyses to investigate it further (Sterne 2017).

Epidural analgesia

Nine studies reported on epidural analgesia. Compared to control/sham, membrane sweeping may, on average, have little to no effect on the risk of epidural analgesia (average RR 1.14, 95% CI 0.97 to 1.33, 9 studies, 2162 participants, low-certainty evidence; Analysis 1.8. Heterogeneity was low between the trials contributing data (Tau^2 0.02, I^2 = 29%, P = 0.18).

Assessment of reporting biases

As there were less than 10 studies in the meta-analysis, we did not investigate reporting biases (such as publication bias) using funnel plots.

Postpartum haemorrhage

Five studies reported on postpartum haemorrhage. Compared to control/sham, membrane sweeping may, on average, have little to no effect on the risk of a postpartum haemorrhage (average RR 0.89, 95% CI 0.57 to 1.39, 5 studies, 760 participants, low-certainty evidence; Analysis 1.9). Heterogeneity was low between the trials contributing data (Tau^2 0.00, I^2 = 0%, P = 0.95).

Assessment of reporting biases

As there were less than 10 studies in the meta-analysis, we did not investigate reporting biases (such as publication bias) using funnel plots.

Uterine rupture

No studies reported on the outcome uterine rupture.

Augmentation of labour

Nine studies reported on augmentation of labour. Compared to control/sham, membrane sweeping may, on average, have little to no effect on the risk of an augmentation of labour (average RR 0.92, 95% CI 0.72 to 1.17, 9 studies, 2011 participants, low-certainty evidence; Analysis 1.10). Heterogeneity was high between the trials contributing data (Tau^2 0.09, I^2 = 69%, P = 0.001). While heterogeneity remains unexplained, we note the following differences in populations. Study size varied from n = 23 (Magann 1998a) to n = 742 (de Miranda 2006). The inclusion criteria for Ramya 2015 is multiparous women with a history of a previous caesarean section or uterine scar. Three studies did not include women with a history of uterine scar (Doany 1997; Magann 1998a; Saichandran 2015). One study excluded multiparous women (Cammu 1998). One study excluded primiparous women (Ramya 2015). Gestation at group allocation varied, with a three-week difference noted between Goldenberg 1996 (> 38/40) and Ramya 2015 (> 41/40). Three studies included participants with an unfavourable cervix (Bishop score < 6) at allocation (Cammu 1998; Magann 1998a; Ramya 2015). Six studies performed cervical massage if the cervix was closed (Andersen 2013; Cammu 1998; de Miranda 2006; Doany 1997; Magann 1998a; Ramya 2015).

Assessment of reporting biases

As there were less than 10 studies in the meta-analysis, we did not investigate reporting biases (such as publication bias) using funnel plots.

Apgar score less than seven at five minutes

Ten studies reported on Apgar score less than seven at five minutes. Compared to control/sham, membrane sweeping may, on average, have little to no effect on the risk of an Apgar score less than seven at five minutes (average RR 1.11, 95% CI 0.51 to 2.40, 10 studies, 1958 participants, low-certainty evidence; Analysis 1.11). Heterogeneity was low between the trials contributing data (Tau^2 0.00, I^2 = 0%, P = 0.74).

Assessment of reporting biases

As there were more than 10 studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots.

We assessed funnel plot asymmetry visually. As asymmetry was not suggested by a visual assessment, we did not perform exploratory analyses to investigate it further (Sterne 2017). Heterogeneity was low (I^2 = 0%) between the trials contributing data.

Neonatal encephalopathy

No studies reported on the outcome neonatal encephalopathy.

Sensitivity analyses

We conducted a sensitivity analysis excluding studies at high or unclear risk of bias for either sequence generation and/or allocation concealment, based on growing empirical evidence that these factors are particularly important potential sources of bias (Higgins 2011).We also excluded studies with high (> 20%) or unclear risk of attrition bias. Twelve of the 40 trials were judged to be of low risk of bias and included in the sensitivity analysis (Adeniji 2013; Andersen 2013; Boulvain 1998; Cammu 1998; Crane 1997; Dare 2002; de Miranda 2006; Hamdan 2009; Hill 2008a; Kashanian 2006; Ugwu 2014; Zamzami 2014). On sensitivity analyses, all pre-specified outcomes, with the exception of spontaneous onset of labour and induction of labour, were consistent with overall summary effect estimates. On sensitivity analysis, we found no difference between groups for the outcome spontaneous onset of labour (average RR 1.08, 95% CI 0.98 to 1.18, 6 studies, 1884 participants, low-certainty evidence; Analysis 20.1). Heterogeneity was moderate between the trials contributing data (Tau^2 0.00, I^2 = 37%, P = 0.16). We found no difference between groups for the outcome induction of labour (average RR 0.92, 95% CI 0.68 to 1.24, 6 studies, 1879 participants, low certainty evidence; Analysis 20.2). Heterogeneity was high between the trials contributing data (Tau^2 0.10, I^2 = 74%, P = 0.002). See: Analysis 20.1; Analysis 20.2; Analysis 20.3; Analysis 20.4; Analysis 20.5; Analysis 20.6.

2.9.7.2 Comparison 2: Amniotic membrane sweeping versus vaginal/intracervical prostaglandins (Appendices 5 & 6)

Four studies reported data for 480 women comparing membrane sweeping with vaginal/intracervical prostaglandins (Doany 1997; Gemer 2001; Magann 1998b; Magann 1999). Doany 1997 compared membrane sweeping with intravaginal PGE2 gel (4 mL at 0.5 mg/mL concentration), repeated at regular intervals until either the spontaneous onset of labour or 43 weeks and six days. Gemer 2001 compared membrane sweeping with intracervical prostaglandin E2 0.5 mg gel as a single time intervention. Magann 1998b

compared daily membrane sweeping with daily intracervical prostaglandin E2 (PGE2) gel 0.5 mg. Magann 1999 compared daily membrane sweeping with daily placement of a dinoprostone vaginal suppository (Cervidil).

Assessment of reporting biases

As there were less than 10 studies in the meta-analysis, we did not investigate reporting biases (such as publication bias) using funnel plots for any outcome.

Primary outcomes

Spontaneous onset of labour

Three studies reported on spontaneous onset of labour within this comparison (Doany 1997; Magann 1998b; Magann 1999). Compared to vaginal/intracervical prostaglandins, membrane sweeping may, on average, have little to no effect on the risk of a spontaneous onset (average RR 1.24, 95% CI 0.98 to 1.57, 3 studies, 339 participants, low-certainty evidence; Analysis 2.1). There was moderate heterogeneity between the trials contributing data (Tau^2 0.02, I^2 = 40%, P = 0.19).

While heterogeneity remains unexplained, we note the following differences in populations. Doany 1997 compared membrane sweeping with intravaginal PGE2 Gel (4 mL at 0.5 mg/mL concentration) repeated at regular intervals until either the spontaneous onset of labour or 43 weeks and six days. Magann 1998b compared daily membrane sweeping with daily intracervical prostaglandin E2 (PGE2) gel 0.5 mg. Magann 1999 compared daily membrane sweeping with daily placement of a dinoprostone vaginal suppository (Cervidil). Study size varied from n = 70 (Magann 1998b) to n = 182 (Magann 1999). Doany 1997 excluded women with a history of a previous caesarean section or uterine scar. Magann 1999 included women with an unfavourable cervix (Doany 1997; Magann 1998b) included women of mixed or unknown cervix status. Doany 1997 performed cervical massage if the cervix was closed on vaginal examination.

As we identified substantial heterogeneity, we investigated it using subgroup analyses.

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

No studies reported on subgroup analysis by parity for the outcome spontaneous onset of labour.

Cervical status

No study reported data for a favourable cervix. Two studies reported data for an unfavourable cervix and one study reported data for unknown cervical status. The test for subgroup differences indicates that there is no statistically significant subgroup effect (Chi^2 = 3.16, P = 0.08, I^2 = 68.4%), suggesting that cervical status does not modify intervention effect. However, we note no studies contributed data to the favourable subgroup and only two contributed data to the unfavourable subgroups, meaning that the analysis may not be able to detect subgroup differences (Analysis 14.1).

Induction of labour

Two studies reported on the outcome induction of labour (Doany 1997; Magann 1998b). Compared to vaginal/intracervical prostaglandins, membrane sweeping may, on average, have little to no effect on the risk of an induction of labour (average RR 0.90, 95% CI 0.56 to 1.45, 2 studies, 157 participants, low-certainty evidence; Analysis 2.2). Heterogeneity was low between the trials contributing data (Tau^2 0.00, I^2 = 0%, P = 0.79).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

No studies reported on subgroup analysis by parity for the outcome induction of labour.

Cervical status

No study reported data for a favourable cervix. One study reported data for an unfavourable cervix and one study reported data for unknown cervical status. The test for subgroup differences indicates that there is no statistically significant subgroup effect (Chi^2 = 0.07, P = 0.79, I^2 = 0%), suggesting that cervical status does not modify intervention effect. However, we note no studies contributed data to the favourable subgroup and only one contributed data to the unfavourable and unknown cervical status subgroups, meaning that the analysis may not be able to detect subgroup differences (Analysis 14.2).

Caesarean section

Three studies reported on the outcome caesarean section (Doany 1997; Magann 1998b; Magann 1999). Compared to vaginal/intracervical prostaglandins, membrane sweeping may have, on average, little to no effect on the risk of a caesarean section (average RR 0.69, 95% CI 0.44 to 1.09, 3 studies, 339 participants, low-certainty evidence; Analysis 2.3). Heterogeneity was low between the trials contributing data (Tau^2 0.0, I^2 = 0%, P = 0.87).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

No studies reported on subgroup analysis by parity for the outcome caesarean section.

Cervical status

No study reported data for a favourable cervix. Two studies reported data for an unfavourable cervix and one study reported data for unknown cervical status. The test for subgroup differences indicates that there is no statistically significant subgroup effect (Chi^2 = 0.26, P = 0.61, I^2 = 0%), suggesting that cervical status does not modify intervention effect. However, we note no studies contributed data to the favourable subgroup, two contributed data to the unfavourable and one to the unknown cervical status subgroups, meaning that the analysis may not be able to detect subgroup differences (Analysis 14.3.).

Spontaneous vaginal birth

Two studies reported on the outcome spontaneous vaginal birth (Magann 1998b; Magann 1999). Compared to vaginal/intracervical prostaglandins, membrane sweeping may have, on average, little to no effect on the risk of a spontaneous vaginal birth (average RR 1.12, 95% CI 0.95 to 1.32, 2 studies, 252 participants, low-certainty evidence; Analysis 2.4). Heterogeneity was low between the trials contributing data (Tau^2 0.0, I^2 = 0%, P = 0.79).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

No studies reported on subgroup analysis by parity for the outcome spontaneous vaginal birth.

Cervical status

No study reported data for a favourable cervix. Two studies reported data for an unfavourable cervix and no study reported data for unknown cervical status for the outcome spontaneous vaginal birth. Therefore, tests for subgroup interaction effects were not possible (Analysis 14.4).

Uterine hyperstimulation with/without FHR changes

No studies reported on the outcome uterine hyperstimulation with/without FHR changes.

Maternal death or serious maternal morbidity

One study reported on the outcome maternal death or serious maternal morbidity (Doany 1997). Compared to vaginal/intracervical prostaglandins, membrane sweeping may have, on average, little to no effect on the risk of a maternal death or serious maternal morbidity (average RR 0.93, 95% CI 0.27 to 3.21, 1 study, 87 participants, low-certainty evidence; Analysis 2.5).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

No studies reported on subgroup analysis by parity for the outcome maternal death or serious maternal morbidity.

Cervical status

No studies reported data for a un/favourable cervix for the outcome maternal death or serious maternal morbidity.

Neonatal death or serious neonatal perinatal morbidity

Two studies reported on the outcome neonatal death or serious neonatal perinatal morbidity (Doany 1997; Magann 1999). Compared to vaginal/intracervical prostaglandins,

membrane sweeping may have, on average, little to no effect on the risk of a neonatal death or serious neonatal perinatal morbidity (average RR 0.40, 95% CI 0.12 to 1.33, 2 studies, 269 participants, low-certainty of evidence; Analysis 2.6). Heterogeneity was low between the trials contributing data (Tau^2 0.0, I^2 = 0%, P = 0.43).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

No studies reported on subgroup analysis by parity for the outcome neonatal death or serious neonatal perinatal morbidity.

Cervical status

No studies reported data for a favourable cervix. One study reported data for an unfavourable cervix and one study reported data for unknown cervical status. The test for subgroup differences indicates that there is no statistically significant subgroup effect (Chi^2 = 0.61, P = 0.44, I^2 = 0%), suggesting that cervical status does not modify intervention effect. However, we note no studies contributed data to the favourable subgroup and one contributed data to both the unfavourable and the unknown cervical status subgroups, meaning that the analysis may not be able to detect subgroup differences (Analysis 14.5).

Secondary outcomes

Instrumental vaginal birth

Three studies reported on the outcome instrumental vaginal birth (Doany 1997; Magann 1998b; Magann 1999). Compared to vaginal/intracervical prostaglandins, membrane sweeping may, on average, have little to no effect on the risk of an instrumental vaginal birth (average RR 1.57, 95% CI 0.59 to 4.14, 3 studies, 339 participants, low-certainty evidence; Analysis 2.7). There was moderate heterogeneity between the trials contributing data (Tau^2 024, I^2 = 31%, P = 0.24).

Epidural analgesia

No studies reported on the outcome epidural analgesia.

Postpartum haemorrhage

No studies reported on the outcome postpartum haemorrhage.

Uterine rupture

No studies reported on the outcome uterine rupture.

Augmentation of labour

One study reported on the outcome augmentation of labour (Doany 1997). Compared to vaginal/intracervical prostaglandins, membrane sweeping may, on average, have little to no effect on the risk of an augmentation of labour (average RR 0.78, 95% CI 0.47 to 1.30, 1 study, 87 participants, low-certainty evidence; Analysis 2.8).

Apgar score less than seven at five minutes

Three studies reported on the outcome Apgar score less than seven at five minutes (Doany 1997; Magann 1998b; Magann 1999). Compared to vaginal/intracervical prostaglandins, membrane sweeping may, on average, have little to no effect on the risk of an Apgar score less than seven at five minutes (average RR 0.87, 95% CI 0.13 to 5.77, 3 studies, 339 participants, low-certainty evidence; Analysis 2.9). Heterogeneity was low between the trials contributing data (Tau^2 0.0, I^2 = 0%, P = 0.46).

Neonatal encephalopathy

No studies reported on the outcome neonatal encephalopathy.

Sensitivity analyses

All included studies for this comparison were judged to have an unclear risk for allocation concealment (selection bias) and were therefore excluded from sensitivity analysis.

2.9.7.3 Comparison 3: Amniotic membrane sweeping versus intravenous oxytocin +/- amniotomy (Appendices 5 & 6)

Only one study, with 104 participants (Salamalekis 2000) compared membrane sweeping with oxytocin.

Assessment of reporting biases

As there were less than 10 studies in the meta-analysis, we did not investigate reporting biases (such as publication bias) using funnel plots.

Primary outcomes

Spontaneous onset of labour

The one included study (Salamalekis 2000) reported on spontaneous onset of labour within this comparison. Compared to intravenous oxytocin +/- amniotomy, membrane sweeping may, on average, have little to no effect on the risk of a spontaneous onset of labour (average RR 1.32, 95% CI 88 to 1.96, 1 study, 69 participants, low-certainty evidence; Analysis 3.1).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

The one included study in this comparison (Salamalekis 2000) did not report data for multiparous women, but did report data for primiparous women for the outcome spontaneous onset of labour (Analysis 10.1).

Cervical status

Salamalekis 2000 did not report data for a favourable cervix, but reported data for an unfavourable cervix for the outcome spontaneous onset of labour (Analysis 15.1.).

Induction of labour

Salamalekis 2000 reported on Induction of labour. Compared to intravenous oxytocin +/- amniotomy, membrane sweeping may, on average, have little to no effect on the risk of an induction of labour (average RR 0.51, 95% CI 0.05 to 5.42, 1 study, 69 participants, low-certainty evidence; Analysis 3.2).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Salamalekis 2000 did not report data for multiparous women, but did report data for primiparous women for the outcome induction of labour (Analysis 10.2).

Cervical status

Salamalekis 2000 did not report data for a favourable cervix, but did report data for an unfavourable cervix for the outcome induction of labour (Analysis 15.2).

Caesarean section

Salamalekis 2000 reported on caesarean section within this comparison. Compared to intravenous oxytocin +/- amniotomy, membrane sweeping may, on average, have little to no effect on the risk of a caesarean section (average RR 0.69, 95% CI 0.12 to 3.85, 1 study, 69 participants, low certainty of evidence; Analysis 3.3).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Salamalekis 2000 did not report data for multiparous women, but did report data for primiparous women for the outcome caesarean section (Analysis 10.3).

Cervical status

Salamalekis 2000 did not report data for a favourable cervix, but did report data for an unfavourable cervix for the outcome caesarean section (Analysis 15.3.).

Spontaneous vaginal birth

Salamalekis 2000 did not report on the outcome spontaneous vaginal birth.

Uterine hyperstimulation with/without FHR changes

Salamalekis 2000 did not report on the outcome uterine hyperstimulation with/without FHR changes.

Maternal death or serious maternal morbidity

Salamalekis 2000 reported on the outcome maternal death or serious maternal morbidity; however, no event was reported for the outcome (Analysis 3.4.).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Salamalekis 2000 reported on the outcome maternal death or serious maternal morbidity; however no events were reported for the outcome (Analysis 10.4).

Cervical status

Salamalekis 2000 reported on the outcome maternal death or serious maternal morbidity; however no events were reported for the outcome (Analysis 15.4.).

Neonatal death or serious neonatal perinatal morbidity

The included study did not report on the outcome neonatal death or serious neonatal perinatal morbidity.

Secondary outcomes

Instrumental vaginal birth

The included study did not report on the outcome instrumental vaginal birth.

Epidural analgesia

The included study did not report on the outcome epidural analgesia.

Postpartum haemorrhage

The included study did not report on the outcome postpartum haemorrhage.

Uterine rupture

The included study did not report on the outcome uterine rupture.

Augmentation of labour

The included study did not report on the outcome augmentation of labour.

Apgar score less than seven at five minutes

The included study did not report on the outcome Apgar score less than seven at five minutes.

Neonatal encephalopathy

The included study did not report on the outcome neonatal encephalopathy.

Sensitivity analyses

Sensitivity analyses were not possible as only one study with an unclear risk for allocation concealment (selection bias) was included for this comparison.

2.9.7.4 Comparison 4: Amniotic membrane sweeping versus amniotomy only (Appendices 5 & 6).

We found no studies which compared membrane sweeping with amniotomy only.

2.9.7.5 Comparison 5: Amniotic membrane sweeping versus vaginal/oral misoprostol (Appendices 5 & 6).

Two studies providing data for 160 women compared membrane sweeping with vaginal/oral misoprostol (Adeniji 2013; Salmanian 2012). Adeniji 2013 compared a single membrane sweep with a single 50 µg misoprostol tablet given orally on an outpatient basis. Salmanian 2012 compared membrane sweeping with intravaginal PG E1 (misoprostol). Salmanian 2012 is a conference abstract and contributed no data. Adeniji 2013 excluded women from the study who had a history of a previous caesarean section or a uterine scar, Salmanian 2012 included multiparous and nulliparous women, no exclusion criteria were reported.

Assessment of reporting biases

As there were less than 10 studies in the meta-analysis, we did not investigate reporting biases (such as publication bias) using funnel plots.

Primary outcomes

Spontaneous onset of labour

Neither study reported on the outcome spontaneous onset of labour.

Induction of labour

Neither study reported on the outcome induction of labour.

Caesarean section

One study (Adeniji 2013) reported on caesarean section within this comparison. Compared to vaginal/oral misoprostol, membrane sweeping may, on average, have little to no effect on the risk of a caesarean section (average RR 0.82, 95% CI 0.31 to 2.17, 1 study, 96 participants, low-certainty evidence; Analysis 5.1).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Neither study reported on subgroup analysis by parity for the outcome caesarean section.

Cervical status

Neither study reported data for a favourable cervix. One study reported data for an unfavourable cervix for the outcome caesarean section (Analysis 17.1).

Spontaneous vaginal birth

Neither study reported on the outcome spontaneous vaginal birth.

Uterine hyperstimulation with/without FHR changes

Neither study reported on the outcome uterine hyperstimulation with/without FHR changes.

Maternal death or serious maternal morbidity

Neither study reported on the outcome maternal death or serious maternal morbidity.

Neonatal death or serious neonatal perinatal morbidity

Neither study reported on the outcome neonatal death or serious neonatal perinatal morbidity.

Secondary outcomes

Instrumental vaginal birth

Neither study reported on the outcome instrumental vaginal birth.

Epidural analgesia

Neither study reported on the outcome epidural analgesia.

Postpartum haemorrhage

Neither study reported on the outcome postpartum haemorrhage.

Uterine rupture

Neither study reported on the outcome uterine rupture.

Augmentation of labour

Adeniji 2013 reported on augmentation of labour within this comparison (average RR 1.81, 95% CI 1.00 to 3.28, 1 study, 96 participants, low-certainty evidence; Analysis 5.2). As the 95% CI for the RR includes the null value of 1 and given the small study size, we conclude that it is unlikely that there is, on average, a difference between groups for the outcome augmentation of labour.

Apgar score less than seven at five minutes

One study reported on Apgar score less than seven at five minutes within this comparison (Adeniji 2013); however, no events were reported (Analysis 5.3).

Neonatal encephalopathy

Neither study reported on the outcome neonatal encephalopathy.

Sensitivity analyses

We planned to exclude all studies at high or unclear risk of bias for either sequence generation and/or allocation concealment, based on growing empirical evidence that these factors are particularly important potential sources of bias (Higgins 2011). One trial (Adeniji 2013) was judged to be of low risk of bias and included in a sensitivity analysis. On sensitivity analyses, all pre-specified outcomes confirmed results in the same direction as the main analyses.

2.9.7.6 Comparison 6: Amniotic membrane sweeping versus mechanical methods (including extra-amniotic Foley catheter).

We found no studies which compared amniotic membrane sweeping with mechanical methods.

2.9.7.7 Comparison 7: One frequency of amniotic membrane sweeping versus another frequency of amniotic membrane sweeping (Appendices 5 & 6).

We found one study providing data for 355 women which compared once weekly membrane sweep with twice-weekly membrane sweep and a sham procedure (Putnam 2011).

Assessment of reporting biases

As there were less than 10 studies in the meta-analysis, we did not investigate reporting biases (such as publication bias) using funnel plots.

Primary outcomes

Spontaneous onset of labour

The one included study (Putnam 2011) did not report on this outcome.

Induction of labour

Putnam 2011 reported on Induction of labour within this comparison. There were no differences, on average, between groups for the outcome induction of labour (average RR 1.19, 95% CI 0.76 to 1.85, 1 study, 234 participants, low-certainty evidence; Analysis 7.1).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Putnam 2011 did not report on subgroup analysis by parity for the outcome induction of labour.

Cervical status

Putnam 2011 did not report data for a favourable cervix, but did report data for an unfavourable cervix for the outcome induction of labour (Analysis 18.1.).

Caesarean section

Putnam 2011 reported on caesarean section within this comparison. There were no differences, on average, between groups for the outcome caesarean section (average RR 0.93, 95% CI 0.60 to 1.46, 1 study, 234 participants, low-certainty evidence; Analysis 7.2).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Putnam 2011 did not report on subgroup analysis by parity for the outcome caesarean section.

Cervical status

Putnam 2011 did not report data for a favourable cervix, but did report data for an unfavourable cervix for the outcome caesarean section (Analysis 18.2).

Spontaneous vaginal birth

Putnam 2011 reported on spontaneous vaginal birth within this comparison. There were no differences, on average, between groups for the outcome spontaneous vaginal birth (average RR 1.00, 95% CI 0.86 to 1.17, 1 study, 234 participants, moderate-certainty evidence; Analysis 7.3).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Putnam 2011 did not report on subgroup analysis by parity for the outcome spontaneous vaginal birth.

Cervical status

Putnam 2011 did not report data for a favourable cervix, but did report data for an unfavourable cervix for the outcome spontaneous vaginal birth (Analysis 18.3).

Uterine hyperstimulation with/without FHR changes

No studies reported on the outcome uterine hyperstimulation with/without FHR changes.

Maternal death or serious maternal morbidity

Putnam 2011 reported on maternal death or serious maternal morbidity within this comparison. There were no differences, on average, between groups for the outcome maternal death or serious maternal morbidity (average RR 0.78, 95% CI 0.30 to 2.02, 1 study, 234 participants, low-certainty evidence; Analysis 7.4).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Putnam 2011 did not report on subgroup analysis by parity for the outcome maternal death or serious maternal morbidity.

Cervical status

Putnam 2011 did not report data for a favourable cervix, but did report data for an unfavourable cervix for the outcome maternal death or serious maternal morbidity (Analysis 18.4).

Neonatal death or serious neonatal perinatal morbidity

Putnam 2011 reported on neonatal death or serious neonatal perinatal morbidity within this comparison. There were no differences, on average, between groups for the outcome

neonatal death or serious neonatal perinatal morbidity (average RR 2.00, 95% CI 0.18 to 21.76, 1 study, 234 participants, low-certainty evidence; Analysis 7.5).

Subgroup analysis

The results were analysed by the clinical categories of parity and cervix favourability.

Parity

Putnam 2011 did not report subgroup analysis by parity for the outcome neonatal death or serious neonatal perinatal morbidity.

Cervical status

Putnam 2011 did not report data for a favourable cervix, but reported data for an unfavourable cervix for the outcome neonatal death or serious neonatal perinatal morbidity (Analysis 18.5).

Secondary outcomes

Instrumental vaginal birth

Putnam 2011 reported on instrumental vaginal birth within this comparison. There were no differences, on average, between groups for the outcome instrumental vaginal birth (average RR 3.00, 95% CI 0.32 to 28.42, 1 study, 234 participants, low-certainty evidence; Analysis 7.6).

Epidural analgesia

Putnam 2011 did not report on the outcome epidural analgesia.

Postpartum haemorrhage

Putnam 2011 did not report on the outcome postpartum haemorrhage.

Uterine rupture

Putnam 2011 did not report on the outcome uterine rupture.

Augmentation of labour

Putnam 2011 did not report on the outcome augmentation of labour.

Apgar score less than seven at five minutes

Putnam 2011 reported on Apgar score less than seven at five minutes within this comparison. There were no differences, on average, between groups for the outcome Apgar score less than seven at five minutes (average RR 0.20, 95% CI 0.01 to 4.12, 1 study, 234 participants, low-certainty evidence; Analysis 7.7).

Neonatal encephalopathy

Putnam 2011 did not report on the outcome neonatal encephalopathy.

Sensitivity analyses

Only one study with an unclear risk for allocation concealment (selection bias) was included for this comparison, therefore no sensitivity analyses were undertaken.

2.9.7.8 Woman's satisfaction

Three studies providing data for 675 women reported on maternal satisfaction (Adeniji 2013; Boulvain 1998; de Miranda 2006). Forty-three per cent of women (n = 26) in a study comparing membrane sweeping to oral misoprostol indicated that they felt positive about membrane sweeping (Adeniji 2013). Boulvain 1998 reported that 86.8% (n = 79) of women in the membrane sweeping group would recommend the intervention to a friend requiring induction of labour and 77.3% (n = 68) believed that the advantages of membrane sweeping outweighed the disadvantages. Few women (9.2%, n = 8) believed the procedure was not helpful for induction of labour. de Miranda 2006 reports that 88% (n = 312) of women questioned in the postnatal period would choose membrane sweeping in a next pregnancy. Women described varying degrees of discomfort while receiving a membrane sweep. It was described as 'not painful' by 31% (n = 111), 'somewhat painful' by 51% (n = 179), while 17% (n = 60) considered it 'painful' or 'very painful'. However, 88% (n = 210) of women who reported pain would choose membrane sweeping again in the next pregnancy.

2.9.7.9 Cost

Two studies reporting data for 290 women reported on a cost analysis (Magann 1998b; Magann 1999). Both studies compared membrane sweeping with vaginal/intracervical prostaglandins. Magann 1998b found that induction of labour in the prostaglandin and

control groups were significantly more expensive that the membrane sweeping group. This study reported a cost per person (US dollars) of approximately $692 in the control group, $476 per person in the membrane sweeping group and $1207 per person in the prostaglandin group. Magann 1999 compared membrane sweeping with intracervical prostaglandins. This study examined the total antenatal and intrapartum cost for membrane sweeping compared with intracervical prostaglandins. It reported that the prostaglandin group had total antenatal and intrapartum costs approximately 44% higher than the membrane sweeping group (membrane sweeping = $40,672 versus prostaglandin = $91,244). These figures show significant cost savings with membrane sweeping, however with only two relatively small studies focusing on a single comparison further research is recommended in this area.

2.10 Discussion

2.10.1 Summary of main results

We included randomised and quasi-randomised trials comparing membrane sweeping used for third trimester labour induction with placebo/no treatment or other methods listed on a predefined list of labour induction methods. We included 44 studies (20 new to this update), reporting data for 6940 participants.

Amniotic membrane sweeping versus no treatment/sham

Forty studies (6540 participants) compared membrane sweeping with no treatment or a sham treatment. We found women randomised to membrane sweeping may, on average, be more likely to experience spontaneous onset of labour (low-certainty evidence) and may, on average, be less likely to experience an induction of labour (low-certainty evidence). However, these findings should be interpreted with caution as on sensitivity analysis, we found no difference between groups for the outcomes spontaneous onset of labour and induction of labour.

There may, on average, be little to no difference between groups for the following outcomes caesarean section (moderate-certainty evidence), spontaneous vaginal birth (moderate-certainty evidence), maternal death or serious morbidity (low-certainty evidence), neonatal death or serious neonatal perinatal morbidity (low-certainty evidence), instrumental vaginal birth, postpartum haemorrhage (low-certainty evidence), augmentation of labour (low-certainty evidence) and Apgar score less than seven at five

minutes (low-certainty evidence). The outcomes uterine hyperstimulation with/without fetal heart rate (FHR) changes, uterine rupture and neonatal encephalopathy were not reported on in this comparison.

On sensitivity analyses, all pre-specified outcomes with the exception of spontaneous onset of labour and induction of labour were consistent with overall summary effect estimates.

Amniotic membrane sweeping versus vaginal/intracervical prostaglandins

Four studies (480 participants) compared membrane sweeping with vaginal/intracervical prostaglandins. Two studies included women with an unfavourable cervix only. We found, on average, little to no difference, between groups for the outcomes spontaneous onset of labour (low-certainty evidence), induction of labour (low-certainty evidence), caesarean section (low-certainty evidence), spontaneous vaginal birth(low-certainty evidence), maternal death or serious maternal morbidity (low-certainty evidence), instrumental vaginal birth (low-certainty evidence), augmentation of labour (low-certainty evidence) or Apgar score less than seven at five minutes (low-certainty evidence). No studies reported on the outcomes uterine hyperstimulation with/without FHR changes, epidural analgesia, postpartum haemorrhage, uterine rupture or neonatal encephalopathy.

Amniotic membrane sweeping versus intravenous oxytocin +/- amniotomy

One study (104) participants) compared membrane sweeping with oxytocin. We found, on average, little to no difference between the groups for the outcomes spontaneous labour (low-certainty evidence), induction of labour (low-certainty evidence) or caesarean section (low-certainty evidence).

The included study did not report on the outcomes spontaneous vaginal birth, uterine hyperstimulation with/without FHR changes, neonatal death or serious neonatal perinatal morbidity, instrumental vaginal birth, epidural analgesia, postpartum haemorrhage, uterine hyperstimulation, uterine rupture, augmentation of labour, Apgar score less than seven at five minutes or neonatal encephalopathy. The study reported on the outcome maternal death or serious morbidity but no event was recorded.

Amniotic membrane sweeping versus amniotomy only

We found no studies which compared membrane sweeping with amniotomy only.

Amniotic membrane sweeping versus vaginal/oral misoprostol

Two studies (160 women) compared membrane sweeping with vaginal/oral misoprostol (Adeniji 2013; Salmanian 2012). However, the studies used different forms of misoprostol for their analyses. One compared a single membrane sweep with a single 50 µg misoprostol tablet given orally (Adeniji 2013); the other compared membrane sweeping with intravaginal PG E1 (misoprostol) (Salmanian 2012). Salmanian 2012 contributed no data to outcomes included in this review. Adeniji 2013 compared membrane sweeping versus oral misoprostol.

We found, on average, little to no difference between groups for the outcomes caesarean section (low-certainty evidence) and Apgar score less than seven at five minutes (low-certainty evidence). Adeniji 2013 reported on the outcome augmentation of labour. As the 95% confidence interval for the relative risk included the null value of 1, we found insufficient evidence to support a difference.

Neither study reported on the outcomes spontaneous onset of labour, Induction of labour, spontaneous vaginal birth, uterine hyperstimulation with/without FHR changes, maternal death or serious maternal morbidity, neonatal death or serious neonatal perinatal morbidity, instrumental vaginal birth, epidural analgesia, postpartum haemorrhage, uterine rupture or neonatal encephalopathy.

Amniotic membrane sweeping versus mechanical methods (including extra-amniotic Foley catheter)

We found no studies which compared membrane sweeping with mechanical methods.

One frequency of amniotic membrane sweeping versus another frequency of amniotic membrane sweeping

We found one study (355 women) which compared once-weekly membrane sweep with twice-weekly membrane sweep and a sham procedure. We found on average, little to no difference, between groups for the outcomes induction of labour (low-certainty evidence), caesarean section (low-certainty evidence), spontaneous vaginal birth (moderate-certainty evidence), maternal death or serious morbidity (low-certainty evidence), neonatal perinatal death or serious morbidity (low-certainty evidence), instrumental vaginal birth (low-certainty evidence) and Apgar score less than seven at five minutes (low-certainty

evidence) between the groups. The outcomes spontaneous onset of labour epidural analgesia, postpartum haemorrhage, uterine hyperstimulation with/without FHR changes, uterine rupture, augmentation of labour and neonatal encephalopathy were not reported in this study.

Woman's satisfaction

Three studies reported on maternal satisfaction with membrane sweeping. A significant majority of women reported positively on their experiences, stating that they felt the potential advantages of the intervention outweighed the disadvantages and would in general recommend the intervention to a friend. While a cohort of women questioned in the postnatal period described membrane sweeping as painful, the majority (88%, n = 312) reported that they would choose membrane sweeping again in future pregnancies (de Miranda 2006).

Cost

Two relatively small studies reported a cost analysis for membrane sweeping (Magann 1998b; Magann 1999). Both studies were undertaken in hospital-based settings in the USA and compared amniotic membrane sweeping with vaginal/intracervical prostaglandins. These studies reported a significant cost per person difference between pharmacological induction of labour and membrane sweeping.

2.10.2 Overall completeness and applicability of evidence

This review includes 44 trials, reporting data for 6940 participants. Forty studies compared membrane sweeping with no treatment, four compared sweeping with prostaglandins, two compared sweeping with oral misoprostol, one compared sweeping with oxytocin and one compared differing frequencies of membrane sweeping. Six studies reported more than one comparison.

Of the 44 trials included in this review, 18 (18/44) reported on the outcome 'Spontaneous onset of labour', 16 (16/40) reported on the outcome 'Induction of labour', 34 (34/44) reported on the outcome 'Caesarean section', 27 (27/44) reported on the outcome 'Spontaneous vaginal delivery' and 23 (23/40) reported on the outcome 'Instrumental vaginal birth'. The assessment of these outcomes in particular are intrinsic to a comprehensive evaluation of membrane sweeping for of induction of labour and it is

surprising that so few trials reported on these, particularly as all relevant data for these outcomes are often recorded routinely in women's health care.

Four studies reported data for the comparison membrane sweeping versus vaginal/intracervical prostaglandins, one study reported data for the comparison membrane sweeping versus intravenous oxytocin +/- amniotomy, two studies reported data for the comparison membrane sweeping versus vaginal/oral misoprostol and one study reported data for the comparison of different frequencies of membrane sweeping. No studies reported on the comparison membrane sweeping versus amniotomy only or the comparison membrane sweeping versus mechanical methods. The limited data are insufficient to evaluate the efficacy of membrane sweeping for these comparisons.

Included studies comprised of women from 36 to 42 weeks' gestation with varying intensities of membrane sweeping. Questions remain as to whether there is an optimal number of membrane sweeps and the timings and gestation of these to promote spontaneous onset of labour. One study (1/44) provided data for the comparison of different frequencies of membrane sweeping. The data available are insufficient to evaluate the efficacy of this comparison.

Maternal perception of discomfort during membrane sweeping is cited routinely when discussing membrane sweeping yet only three studies (3/44) collected data on maternal satisfaction. These limited data are insufficient to meaningfully discuss women's satisfaction with membrane sweeping for induction of labour.

While membrane sweeping potentially offers a cost-effective method of preventing a formal induction of labour, there were limited data available to evaluate this. Two studies (2/44) reported a cost analysis with both comparing membrane sweeping with vaginal/intracervical prostaglandins. No cost analysis was provided for any other comparisons.

2.10.3 Quality of the evidence

This review includes 44 trials, undertaken in hospital settings from a wide range of economic and geographical regions. Overall, the risk of bias was assessed as unclear risk of bias in most domains. Thirty-one of the 44 included studies were found to have an unclear or high risk of bias for allocation concealment and 15 were found to have an unclear or high risk of bias for random sequence generation. All 44 studies in our review were judged

to be of high risk of performance bias. Clinicians were not blinded to the intervention in any study and it is unclear (and unlikely in our view) in most studies whether or not study participants were blinded post allocation. Thirty-four studies were found to have an unclear risk of detection bias primarily due to a lack of methodological detail. Nine studies were found to have an unclear or high risk of attrition bias with 20 having an unclear or high risk of bias for selective reporting.

Evidence was assessed using the GRADE approach. Evidence was downgraded for risk of serious bias when evidence of study design limitations were found. Evidence was downgraded for risk of serious inconsistency when evidence of inconsistency (statistical heterogeneity) was present and remained unexplained after exploration of a priori hypotheses that might explain heterogeneity. Evidence was assessed for imprecision by calculating the optimal information size (OIS) and using this to make judgements. Evidence was downgraded if the OIS criterion was not met.

For our comparison membrane sweeping versus no treatment/sham, our GRADE assessments in the majority were found to be of low certainty. Two outcomes were assessed to be of moderate certainty (caesarean section and spontaneous vaginal birth). We downgraded for serious bias due to evidence of study design limitations in all trials, serious inconsistency and for serious imprecision due to the total (cumulative) sample size being less than the OIS. See Summary of findings table 2.1.

For our comparison membrane sweeping versus vaginal/intracervical prostaglandins, our GRADE assessments were overall found to be of low certainty. We downgraded for serious bias due to evidence of study design limitations in all trials and for serious imprecision due to the total (cumulative) sample size being less than the OIS. See Summary of findings table 2.2.

For our comparison membrane sweeping versus intravenous oxytocin+/- amniotomy, our GRADE assessments were low certainty for all outcomes. This comparison included one trial and we downgraded for serious bias due to evidence of study design limitations in this trial. We downgraded for serious imprecision due to a small sample size with the confidence interval crossing the line of no effect. We downgraded for serious imprecision in one outcome due to a small sample size with no events recorded. See Summary of findings table 2.3.

For our comparison membrane sweeping versus vaginal/oral misoprostol, our GRADE assessments were low certainty for all outcomes. This comparison included one trial and we downgraded for serious bias due to evidence of study design limitations in this trial. We downgraded for serious imprecision due to the total (cumulative) sample size being less than the OIS. See Summary of findings table 2.4.

No study reported on the comparison membrane sweeping versus mechanical methods (including extra-amniotic Foley catheter).

For our comparison one frequency of membrane sweeping versus another frequency of membrane sweeping, our GRADE assessments were low certainty. This comparison included one trial and we downgraded for serious bias due to evidence of study design limitations in this trial. We downgraded for serious imprecision due to the total (cumulative) sample size being less than the OIS. See Summary of findings table 2.5.

2.10.4 Potential biases in the review process

A potential source of bias related to the lack of blinding within all the included trials. All 44 studies in our review were judged to be of high risk of performance bias. Clinicians were not blinded to the intervention in any study and it is unclear (and unlikely in our view) in most studies if study participants were blinded. Lack of participant blinding may also have had an effect on the reporting of maternal satisfaction with membrane sweeping.

Michel Boulvain is a principle investigator in one of the included studies (Boulvain 1998) and is the principle author of the original 2005 Cochrane Review 'Membrane sweeping for induction of labour' (Boulvain 2005). Michel's study was independently reviewed by two review authors for inclusion and risk of bias and extracted data. A third author independently reviewed the study and extracted data where any conflict was unresolved.

While review authors have differed in the course of conducting this systematic review, we have made every effort to reach consensus and endeavoured to minimise any potential bias. Two review authors independently reviewed studies for inclusion and risk of bias and extracted data. A third author independently reviewed studies and extracted data where any conflict was unresolved.

2.10.5 Agreements and disagreements with other studies or reviews

Guidelines by bodies including NICE (NICE 2008), the Society of Obstetricians and Gynaecologists of Canada (SOGC 2013), the Department of Health, South Australia (Queensland DOH 2017) and the World Health Organization (World Health Organization 2011) state that women should be offered the option of membrane sweeping at or near term. The NICE guidelines state that a membrane sweep should be offered to nulliparous women at term gestation and women who have had one or more infants at 41 weeks' gestation. In addition, it recommends that women be offered further membrane sweeps during their antenatal visits if labour does not commence (NICE 2008).

Recent studies have supported elective pharmacological induction of labour to lower the risk of caesarean section. However, these studies compared induction of labour with expectant management only, with none evaluating the potential effects of membrane sweeping on the process (Grobman 2018; Middleton 2018; Wood 2014). In addition, a 2018 Cochrane Systematic Review 'Induction of labour for improving birth outcomes for women at or beyond term' (Middleton 2018) compared induction of labour with expectant management but did not include membrane sweeping as a method of induction of labour in its analysis.

2.11 Authors' conclusions

2.11.1 Implications for practice

Membrane sweeping is probably effective in increasing the likelihood of achieving a spontaneous onset of labour. When compared to expectant management, it potentially reduces the risk of formal induction of labour. The majority of women report positive experiences and would recommend the intervention to a friend suggesting women find membrane sweeping acceptable as a method of preventing a formal induction of labour. Two small studies report that membrane sweeping potentially offers significant savings in healthcare costs.

2.11.2 Implications for research

Included studies comprised of women from 36 to 42 weeks' gestation with varying intensities of membrane sweeping. None examined the potential effect of differing gestations to commence membrane sweeping and only one reported a comparison of differing frequencies of membrane sweep. Questions remain as to the optimal gestation to commence and frequency for membrane sweeping to prevent post-term pregnancy. Future

research could address the potential impact gestation may have on the success of membrane sweeping. In addition, any potential effect the intensity of the intervention, i.e. multiple or single membrane sweeps has on this process could be evaluated.

Two small studies reported on membrane sweeping in women who were group B streptococcus positive. While no additional maternal or fetal risk was noted with membrane sweeping, further research would potentially provide data to inform health policy.

Women's perceptions and satisfaction with membrane sweeping are intrinsic to its clinical use. Our review found that few studies explored women's views of membrane sweeping. Further research is needed to assess women's overall views and acceptability of membrane sweeping. In addition, we recommend that clinician's views and acceptability of membrane sweeping, a fundamental factor to its use clinically, could also be explored.

Few studies reported on the cost-effectiveness of membrane sweeping (two relatively small studies). It would be helpful to have a cost-effectiveness analysis of the overall incurred costs, including intrapartum, postnatal and neonatal care, associated with the use of membrane sweeping to prevent post-term pregnancy. In addition, a health economic analysis of membrane sweeping relative to expectant management and other methods of induction of labour to prevent post-term pregnancy would provide valuable data to inform health policy.

2.12 Acknowledgements

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We thank Olivier Irion and Catalin Stan for their contributions to previous versions of this review.

As part of the pre-publication editorial process, this protocol/review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of Cochrane Pregnancy and Childbirth's international panel of consumers and the Group's Statistical Adviser. The authors are grateful to the following peer reviewers for their time and comments: Everett F Magann, Professor of Obstetrics and Gynecology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; Johanna Quist-Nelson, MD, Thomas Jefferson University Hospital, Philadelphia, USA.

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2.13 Contributions of authors

Elaine Finucane and Declan Devane performed inclusion/exclusion criteria to identified studies. Elaine Finucane, Declan Devane, Deirdre Murphy, Linda Biesty, Gillian Gyte, Amanda Cotter and Ethel Ryan extracted data for the included studies and completed data extraction forms. Elaine Finucane drafted the review and Declan Devane, Deirdre Murphy, Linda Biesty, Gillian Gyte, Michel Boulvain, Amanda Cotter and Ethel Ryan contributed to editing of this update.

2.14 Declarations of interest

Elaine M Finucane: This review was supported by Health Research Board, Ireland (HRB) through a HRB Cochrane Fellowship. We acknowledge gratefully the support of the University Of Limerick Hospitals Group and the Nursing and Midwifery Planning and Development Unit West/Midwest of the Health Service Executive, Ireland (HSE).

Deirdre J Murphy: none known.

Linda M Biesty: none known.

Gillian ML Gyte: I have received royalties from John Wiley & Sons in respect of 'A Cochrane Pocketbook - Pregnancy and Childbirth' Hofmeyr GJ et al. 2008.

Amanda M Cotter: none known.

Ethel M Ryan: none known.

Michel Boulvain: Michel is a principal investigator in one of the included studies (Boulvain 1998) and was the principle author of the original 2005 Cochrane Review 'Membrane sweeping for induction of labour' (Boulvain 2005). He was not involved in the data collection for this update, nor in the assessment of bias.

Declan Devane: Declan is PI for a grant from the HRB to assess the feasibility of conducting a definitive randomised trial to examine the effectiveness of membrane sweeping to prevent drug- based induction of labour in women at or near term, to explore women and clinicians acceptability of and willingness to participate in the trial and to evaluate the effects of social media study promotion on recruitment.

2.15 History

Table 2.6: Review History

Protocol first published: Issue 3, 1997 Review first published: Issue 4, 1997

Date	Event	Description
25 February 2019	New citation required and conclusions have changed	Membrane sweeping is probably effective in achieving a spontaneous onset of labour. When compared to expectant management, it potentially reduces the risk of formal induction of labour and caesarean section. However, evidence is of low certainty.
25 February 2019	New search has been performed	We searched for evidence on 25 February 2019. Twenty new studies have been added for this update. Two studies previously excluded (Gemer 2001; McColgin 1993), are now included. The review now includes a total of 44 studies reporting data for 6940 women. On reflection of peer review feedback and in consultation with the Cochrane Pregnancy and

Date	Event	Description
		Childbirth editorial team, data were analysed using the random-effects model. Within the primary outcome 'Neonatal death or serious neonatal perinatal morbidity', 'probable or definite neonatal sepsis' was specified as suitable for inclusion following peer review.
31 July 2009	Amended	Search updated. Ten new reports added to Studies awaiting classification (de Miranda 2006a; Hill 2006a; Hill 2008b; Hill 2008b; Ifnan 2006b; Imsuwan 1999a; Kashanian 2006a; Kaul 2004a; Tan 2006a; Yildirim 2008a).
18 September 2008	Amended	Converted to new review format.
9 November 2004	New search has been performed	We have added two new trials (Dare 2002; Wong 2002) , one new ongoing trial (Manidakis 1999) and a new report of Magann 1998b. We have excluded four new trials (Bergsjo 1989; Foong 2000; Gemer 2001a; McColgin 1993a).

2.16 Differences between protocol and review

2019 update of the review

We have updated the methods in line with those in the standard template used by Cochrane Pregnancy and Childbirth. We have used the GRADE approach to assess the certainty of evidence and included 'Summary of findings' tables and added in an additional

search of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).

In addition we have made the following changes.

- We have added three new primary outcomes (spontaneous onset of labour, induction of labour and spontaneous vaginal delivery).
- Prior to data extraction we removed the outcome of vaginal delivery not achieved within 24 hours.
- We reported subgroup analysis by parity (multiparous/primiparous) and cervical favourability (favourable cervix/unfavourable cervix).
- On reflection of peer review feedback and in consultation with the Cochrane Pregnancy and Childbirth editorial team, data were analysed using the random-effects model.
- Within the primary outcome 'Neonatal death or serious neonatal perinatal morbidity ', 'probable or definite neonatal sepsis' was specified as suitable for inclusion following peer review.

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2.17 Summary of key points

Chapter 2 presents a Cochrane systematic review and meta-analysis to assess if membrane sweeping is an effective and safe way of inducing labour in women at or near term gestation (≥ 36 weeks' gestation). This research was undertaken to add to the body of existing evidence on membrane sweeping, potentially informing national and international guidelines in this space and to potentially inform future research on the use of membrane sweeping to prevent formal induction of labour in women at or near term. This review, which includes 44 randomised studies and reports findings for 6940 women and their babies, substantially updates a 2005 review by Boulvain et al.

Significantly, this review and meta-analysis found that when compared with no intervention or a sham intervention, women who receive a membrane sweeping may be more likely to have a spontaneous onset of labour. In addition, these women may also be less likely to have formal induction of labour. However, we found little to no difference in unassisted vaginal births, or the risk of having a caesarean section, instrumental vaginal births or serious illness or death for women or their babies. However, as the overall certainty of the evidence informing this review was found to be low, further research is needed to confirm the review findings.

Also, we were unable to find sufficient data to support meaningful discussion on the potential effects on maternal and neonatal outcomes of differing gestations to commence membrane sweeping, or differing frequencies of membrane sweeping. The review also notes that women's perceptions and satisfaction with membrane sweeping are under-represented in research. Finally, the review found that a cost-effectiveness analysis of the overall costs associated with membrane sweeping would be helpful.

These findings informed the design of the Feasibility study reported in Chapter 3.

Chapter 3: The MILO Study

3.1 Introduction

This chapter presents the protocol for a feasibility study that includes a pilot randomised controlled trial, a qualitative study, a health economic analysis and a Study Within A Trial (SWAT). This study aims to assess the feasibility of, and inform the optimal design of, a future definitive randomised trial to evaluate the effectiveness (including optimal timing and frequency) of membrane sweeping to prevent post-term pregnancy.

The MILO study, received funding of €374K from the Health Research Board (Ireland) through its Definitive Interventions and Feasibility Awards (2018) to support its conduct. Professor Declan Devane (DD) (Principal Investigator) and Elaine Finucane (EF) (co-applicant and lead researcher) wrote the successful application for this award, supported by co-applicants.

3.2 Paper 2

Feasibility study protocol of a pragmatic, randomised controlled pilot trial: Membrane sweeping to prevent post-term pregnancy: The MILO Study

Elaine M Finucane, Linda Biesty, Deirdre Murphy, Amanda Cotter, Eleanor Molloy, Martin O'Donnell, Shaun Treweek, Paddy Gillespie, Marian Campbell, John J. Morrison, Alberto Alvarez-Iglesias, Gill Gyte, Declan Devane

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3.3 Project Abstract

Background

Post-term pregnancy is associated with an increased risk of maternal complications, respiratory distress and trauma to the neonate. Amniotic membrane sweeping has been recommended as a simple procedure to promote the spontaneous onset of labour. However, despite its widespread use, there is an absence of evidence on a) its effectiveness and b) its optimal timing and frequency. The primary aim of the MILO study is to inform the optimal design of a future definitive randomised trial to evaluate the effectiveness (including optimal timing and frequency) of membrane sweeping to prevent post-term pregnancy. We will also assess the acceptability and feasibility of the proposed trial interventions to clinicians and women (through focus group interviews).

Methods/Design

Multicentre, pragmatic, parallel group, pilot randomised controlled trial with an embedded factorial design. Pregnant women with a live, singleton fetus ≥ 38 weeks gestation, cephalic presentation, longitudinal lie, intact membranes, English speaking and ≥18 years of age will be randomised in a 2:1 ratio to:

- Membrane sweep versus no membrane sweep

Women allocated randomly to a sweep will then be randomised further (factorial component) to:

- early (from 39 weeks) versus late (from 40 weeks) sweep commencement; and
- a single verses weekly sweep

The proposed feasibility study consists of four work packages i.e., (1) a multicentre, pilot randomised trial, 2) a health economic analysis and 3) a qualitative study (4) a study within the host trial (a SWAT).

Outcomes to be collected include: recruitment and retention rates, compliance with protocol, randomisation and allocation processes, attrition rates and cost-effectiveness.

Focus groups will be held with women and clinicians to explore the acceptability and feasibility of the proposed intervention, study procedures and perceived barriers and enablers to recruitment.

Discussion

The primary aim of the MILO study is to inform the optimal design of a future definitive randomised trial to evaluate the effectiveness (including optimal timing and frequency) of membrane sweeping to prevent post-term pregnancy. Results will inform whether and how the design of the definitive trial as originally envisaged should be delivered or adapted.

Trial Registration

ClinicalTrials.gov, ID: NCT04307199. Registered 12th March 2020. https://clinicaltrials.gov/ct2/show/NCT04307199?id=NCT04307199&draw=2&rank=1

Keywords

Feasibility, pilot trial, SWAT, induction of labour, membrane sweep, post-term.

3.4 Background

Labour and childbirth are physiological processes and for the majority of women the onset of labour is spontaneous. However, some women will have an induction of labour. Induction of labour is the process of artificially stimulating uterine contractions to initiate the onset of labour. Approximately one in four pregnancies in the developed world will end with an induction of labour (Bakker et al., 2013, World Health Organisation 2011).

Current international guidelines note that induction of labour, as with any intervention, carries risks and recommend it be performed only when there are clear indications that continuing with the pregnancy is of greater risk to the mother or fetus than the risk of induction of labour (American College of Obstetricians and Gynecologists 2009, World Health Organisation 2011, Gülmezoglu et al., 2006). However conversely, recent studies have reported that elective pharmacological induction of labour results in a lower risk of caesarean section than expectant management (Grobman et al., 2018, Middleton et al., 2018, Gülmezoglu et al., 2012). Medical indications for an induction of labour include preterm premature rupture of membranes (PPROM), intra uterine growth restriction, hypertensive disorders of pregnancy, intra-uterine fetal death and post-term pregnancies

(The Society of Obstetricians and Gynaecologists of Canada 2017). Of these, post-term pregnancy is the most common (Kelly et al., 2013, Nippita et al., 2015).

A pregnancy is considered to have reached full term at 37 completed week's gestation, however, approximately 10% of pregnancies will continue past 42 weeks' gestation and are then considered "post-term" (Gülmezoglu et al., 2012, Olessen et al., 2003). Birth post 42 weeks' gestation carries increased risk for the neonate including increased risk of meconium aspiration, neonatal acidaemia, low Apgar scores, macrosomia and neonatal death (American College of Obstetricians and Gynecologists 2014, Heimstad et al., 2008). The incidence of maternal complications such as severe perineal injury (third and fourth degree perineal lacerations) related to macrosomia, post-partum haemorrhage, chorioamnionitis and endomyometritis are increased post-term (Hedegaard 2014).

Labour may be induced using pharmacological, surgical and mechanical methods.

1. Pharmacological methods include the use of prostaglandins, such as dinoprostone administered either vaginally or intracervically, misoprostol administered orally, vaginally or intracervical and oxytocin administered intravenously (Alfirevic et al., 2014). Pharmacological methods of induction of labour are not suitable for all women (National Institute for Health and Care Excellence 2008). Reduced levels of prostaglandins are indicated in women with a high parity and the use of prostaglandins are contraindicated in cases of women with a previous caesarean section (National Institute for Health and Care Excellence 2008). Pharmacological induction of labour increases the risk of uterine rupture and hyperstimulation (World Health Organisation 2011).
2. Surgically, labour may be induced using procedures including the deliberate rupturing of the amniotic membranes known as amniotomy (Cuaghey et al., 2009). Amniotomy carries the risk of umbilical cord prolapse and is contraindicated when the presenting part of the fetus is not engaged in the pelvis and in women with a history of placenta praevia and vasa praevia. It also increases the risk of infection for mother and fetus and is contraindicated in HIV positive women (National Health Service Clinical guidelines 2017, Smyth et al., 2013).
3. Mechanical methods of induction of labour are used to ripen and dilate the cervix encouraging the spontaneous onset of labour through manual manipulation of the cervix (Jozwiak et al., 2012). Mechanical methods include the use of an

intracervical Foley catheter and amniotic membrane sweeping, also referred to as 'stripping' or 'stretch and sweep' of the membranes.

This study seeks to evaluate the role of membrane sweeping.

3.4.1 Description of the intervention

An amniotic membrane sweep is performed with consent during a vaginal examination. It involves the clinician inserting one or two fingers into the woman's cervix and detaching the inferior pole of the membranes from the lower uterine segment in a circular motion (Boulvain et al., 2005). Membrane sweeping is a simple procedure and may be used independently or in combination with other means of induction and can be repeated multiple times.

3.4.2 How the intervention might work

Amniotic membrane sweeping is used to promote the onset of labour by releasing localised prostaglandins F2α, phospholipase A2 and cytokines from the intrauterine tissues (Blackburn et al., 2013). These hormones act on the cervix to augment cervical ripening potentially instigating uterine contractions. The manual stretching of the cervix may help to initiate the Ferguson reflex by releasing oxytocin thereby increasing uterine activity (Blackburn et al., 2013). The aim of amniotic membrane sweeping is to soften and ripen the cervix, increasing cervical favourability and stimulate spontaneous uterine contractions potentially leading to the onset of labour and avoidance of a formal induction of labour.

3.4.3 Why is this research needed?

Post-term pregnancy is by far the most common reason for induction of labour and membrane sweeping offers a potentially low risk method to reduce this. Membrane sweeping is a technically simple intervention and may be performed by clinicians in community or clinical settings potentially providing significant reductions in cost (National Institute for Health and Care Excellence 2008, Wong et al., 2002). Recent studies have supported elective pharmacological induction of labour to lower the risk of caesarean section. However, these studies compared induction of labour to expectant management only, with none evaluating the potential effects of membrane sweeping on the process (Grobman et al., 2018, Gülmezoglu et al., 2012). Our Cochrane systematic review found, that when compared to expectant management, membrane sweeping is potentially

associated with an increased rate of spontaneous onset of labour (average RR 1.21, 95% CI 1.08 to 1.34) and a lower risk of formal induction of labour (average RR=0.73. 95% CI 0.56-0.94) when compared with expectant management (Finucane et al., 2020). It is not associated with increased rates of infection or premature rupture of membranes and has the advantage that it may be used independently or in combination with other means of induction and can be repeated multiple times.

Guidelines by bodies including NICE (National Institute for Health and Care Excellence 2008), the Society of Obstetricians and Gynaecologists of Canada (The Society of Obstetricians and Gynaecologists of Canada 2017), the Department of Health, South Australia (South Australian Maternal & Neonatal Clinical Network 2014) and the WHO (World Health Organisation 2011) state that women should be offered the option of membrane sweeping at or near term. However, the optimum gestation to perform a membrane sweep to promote cervical ripening is unknown. Further, there has been little direct comparison of the effect of multiple membrane sweeps versus a single membrane sweep to promote spontaneous labour. Internationally, guidelines have identified the need for research to clarify these uncertainties (National Institute for Health and Care Excellence 2008, Queensland Clinical Guidelines 2017). In addition, our recent Cochrane systematic review found a lack of data on the optimal timing and frequency of membrane sweeping and recommended future research in this space (Finucane et al., 2020). A cost-effectiveness analysis, including an antenatal, intrapartum, postnatal and neonatal cost analysis, comparing membrane sweeping with expectant management and other methods of labour induction has not been carried out. In a time where health care providers are weighing cost effectiveness with quality of care, this would provide invaluable data to inform health policy and is an important gap identified in our Cochrane Systematic review (Finucane et al., 2020).

Clinician's views and acceptability of membrane sweeping have been significantly under-represented in research. In addition, few studies explored women's views of membrane sweeping. Further research to explore women's and clinician's experiences and views of membrane sweeping as a method of induction of labour is needed to support the clinical application of this intervention and to inform future definitive evaluations.

3.5 Methods/Design

3.5.1 Trial aim and objective

The primary objective of the MILO study is to assess the feasibility of conducting a definitive randomised controlled trial to examine the effectiveness, and optimal intensity (timing and frequency), of membrane sweeping to prevent post-term pregnancy. The study consists of four work packages.

WP1: A pilot randomised trial assessing the feasibility of conducting a definitive trial to evaluate how often and the best time to perform a membrane sweep.

WP2: Health economic analysis assessing the feasibility of conducting a trial-based economic evaluation to examine the cost-effectiveness of membrane sweeping.

WP3: A qualitative study exploring the acceptability of the trial for women and clinicians.

WP4: A SWAT (Study within a Trial) assessing if the point at which women are invited to take part in the trial (i.e. when should women be asked?) affects the number of women recruited to and retained in the trial

Methods

The proposed feasibility study consists of four work packages:

3.6 Work package 1: Pilot randomised trial

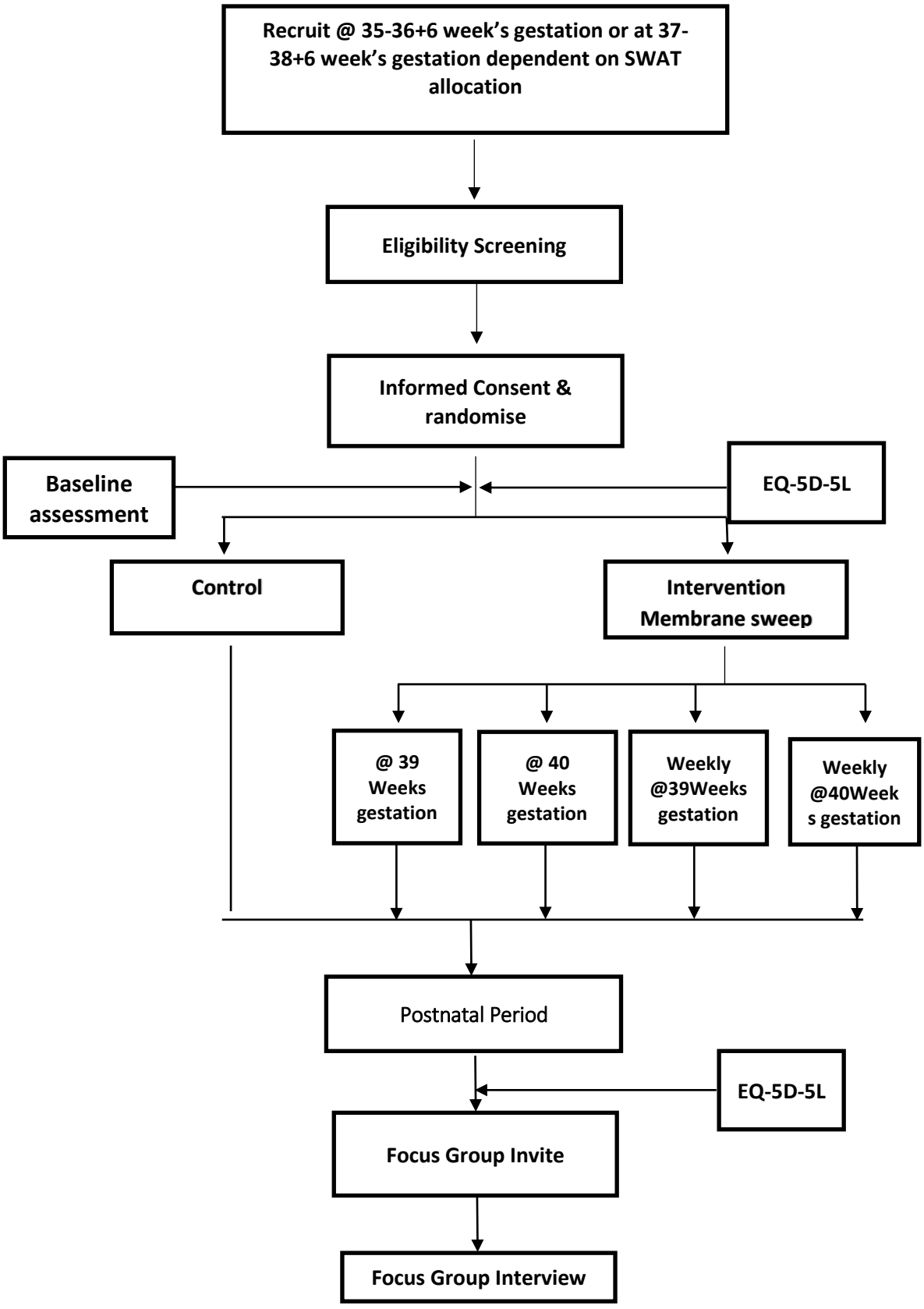
3.6.1 Methods/ Design

We will use a multicentre, pragmatic, parallel group pilot randomised controlled trial with an embedded 2x2 factorial design (Figure 1). This allows an examination of the feasibility of a staged 'gated' approach to trial analysis in a future definitive trial. For example, it allows us to evaluate the feasibility of a future trial to answer the primary question "is membrane sweeping effective in preventing post-term pregnancy" and also address the effectiveness of different timings and frequency of membrane sweeping. The advantage of using a factorial design in the MILO study is that we can assess two individual questions simultaneously in the same population.

By utilising resources dynamically, we ensure a more efficient use of resources including sample size and time (Montgomery et al., 2003). A factorial design requires a smaller sample size when compared to running two separate parallel trials resulting in reduced running and management costs and shorter time frame. The protocol has been prepared in

line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Appendix 7) (Chan et al., 2013).

Figure 3.1 MILO Study Design



3.6.2 Setting

The MILO study will be set in the antenatal outpatient Departments in two Irish maternity hospitals.

3.6.3 Participants

Inclusion and exclusion criteria

Pregnant women carrying a live singleton fetus ≥ 38 weeks completed gestation. (Gestational age will be calculated from the first day of the last menstrual period and an ultrasound examination carried out in the 2nd trimester) will be eligible. The lie must be longitudinal, presentation cephalic and amniotic membranes intact. Women must be ≥ 18 years of age on enrolment. Women will need to be able to communicate in English and give written informed consent. Women with any contraindications to a vaginal examination or vaginal birth (i.e. placenta praevia, vasa praevia, antepartum haemorrhage or undiagnosed vaginal bleeding, malpresentation i.e. transverse lie, Herpes simplex virus with active genital lesions or prodromal symptoms) will be excluded from the MILO Study.

3.6.4 Recruitment

Written trial information will be offered to women potentially eligible for participation at 35-36+6 week's gestation or at 37-38+6 week's gestation, depending on SWAT randomisation (see below), during routine antenatal appointments in each site. Clinicians and/or research midwife at participating antenatal clinics will identify women who are potentially eligible to participate in the study. Women will be given an information pack that will include a letter introducing the trial and a Participant Information Leaflet, which will inform potential participants of the background and purpose of the study, risks and benefits of participation, what participants are being asked to do, their right to withdraw and offer to answer any questions they have relating to the study. This will be followed up at the 39 week antenatal visit when the researcher will invite eligible women to participate.

3.6.5 Obtaining informed consent:

At the 39 week antenatal visit, potential for inclusion to the trial will be checked by the attending midwife and/or research midwife. The trial will be explained and questions potential participants might have will be answered. Eligible women will be asked to

participate at this time and written informed consent will be obtained from women agreeing to participate.

3.6.6 Randomisation and allocation concealment

Randomisation to intervention and control will be at the level of the individual i.e., individual randomisation, stratified by parity and centre. Randomisation is on 2:1 ratio, that is, for every two women randomised to the intervention arm (sweeping intervention), one will be randomised to the control arm (usual care). Women in the intervention group will further be randomised in a ratio of 1:1 to the factorial design. The random allocation sequence will be generated using a computer-generated random number list. Random permuted blocks of sizes 6 and 12 will be used to determine group allocation. Randomisation will be stratified by (a) parity to ensure appropriate representation of pimiparous and multiparous women to each group and (b) centre using a separate block randomisation list for each of the two centres. Block sizes will be concealed until completion of the trial.

To ensure concealment of allocation, randomisation will be done electronically using web-based random allocation based on random sequence generation detailed above. The enrolling midwife will log stratification factors with the randomisation service through a web interface after which he/she will be informed of the allocation (usual care or group allocation in the 2x2 factorial design) and the unique study ID number, which will be documented on the consent form.

3.6.7 Blinding

Clinicians performing a membrane sweep cannot be blinded and it is not feasible to genuinely blind membrane sweeping for women. Therefore, neither clinicians administering the intervention nor women will be blinded to group assignment. Data will be reviewed by two assessors blinded to group allocation

3.6.8 Intervention

Amniotic membrane sweeping is defined as the manual detachment of the inferior pole of the amniotic membranes from the lower uterine segment (Boulvain et al., 2005). This is performed with consent by a clinician digitally through a circular motion during a vaginal examination. If the cervical os is closed massage of the cervix will be accepted.

Women will initially be randomised in a 2:1 ratio to:

- Membrane sweep (2) versus no membrane sweep (1).

Those allocated to the intervention group will then be further randomised in a factorial fashion to A, B, C or D (Figure 3.2.):

A. Membrane sweep @ 39 weeks' gestation only
B. Membrane sweep @ 40 weeks' gestation only
C. Membrane sweep @ 39, 40 and 41 weeks' gestation or until onset of labour
D. Membrane sweep @ 40 and 41 weeks' gestation or until onset of labour

Figure 3.2. Group allocation using factorial design

	Sweeping @39 Weeks	Sweeping @40 Weeks
Single membrane sweeping	A	B
Weekly membrane sweeping (up to 41 weeks or until onset of labour)	C	D

Women in the intervention arm will be offered induction of labour at approximately 41 weeks' completed gestation and labour induced in most women prior to 42 weeks' gestation.

3.6.9 Control group

Women in the control arm will not receive a membrane sweep and will receive usual care (as defined by local hospital protocols and vaginal examination to determine Bishop score only). Usual care in both sites is the same and includes women attending for routine antenatal clinic appointments monthly up to week 32, fortnightly to week 38 and weekly to week 42. Women will be offered induction of labour at approximately 41 weeks' gestation and labour induced in most women prior to 42 weeks' gestation. We will identify any intricacies of usual care that might be present in each site but that might not become apparent outside of a research context as part of the study through the mapping usual care pathways. Other than randomisation to an intervention group or a control group, all

women will receive usual care as defined by local hospital protocols. Participating in this trial will not alter the intrapartum or postnatal care pathway for the woman or her infant

3.6.10 Withdrawal from trial/treatment or protocol deviation post randomisation

If a woman decides to leave the trial after randomisation, she will be withdrawn from the trial and will receive usual maternity care as defined by local hospital policy. The same strategy will be implemented for protocol violations. Randomisation will take place immediately prior to commencement of the intervention to try and mitigate these events. The Pilot trial will use intention to treat (ITT) data analysis. If a woman withdraws from the trial, we will try to obtain consent to collect data relevant to the study and/or routine follow-up data. Information and communications will be recorded in the trial database.

3.6.11 Clinician Training

All necessary midwives and obstetricians will receive the MILO training programme, which will include training on how to perform a membrane sweep per trial definition and training on the study protocol to enable them to support recruitment of women to the study, answer any questions women or their partners may have, support the taking of informed consent and randomisation of women. Recruitment will be supported by on site research midwife and training of clinicians will be dependent on the tasks they undertake. To enhance validity, reliability and generalisability of the intervention special consideration will be given to training of clinicians performing a membrane sweep to ensure treatment fidelity. We will develop a standardised intervention manual and prior to the intervention start date all clinicians who might perform a sweep will receive the manual. In addition, all relevant clinicians will receive training in the form of a tutorial video and hands on training from an experienced trainer. This training session will teach a standardised protocol for the intervention. Adherence to this protocol will be monitored throughout the trial by the research midwife and the trial project manager.

3.6.12 Outcome Measures

We will collect the following outcome data:

Primary outcomes

Outcomes relate to feasibility assessment:

1. Recruitment; Evaluation of the number and percentage of eligible women who are recruited and randomised to the study. Assessed by study-specific checklists;
2. Retention; Evaluation of the number and percentage of eligible women who are randomised, take part in and adhere to the study protocols. Data will be extracted from routinely collected data;
3. Adherence with the trial interventions; Evaluation of adherence with the trial interventions, and reasons for non-compliance assessed by study-specific checklists. Data will be extracted from routinely collected data and focus group interviews with clinicians and participants at six weeks post intervention;
4. Evaluation of the randomisation process; Evaluation of effective allocation of participants to the intervention/control group assessed by study-specific checklists and evaluation of the randomisation protocol throughout the randomisation period;
5. Evaluation of attrition rates; Evaluation of attrition rates assessed by study-specific checklists. Data will be extracted from routinely collected data;
6. Evaluation of the types of attrition; Evaluation of the types of attrition assessed by case report forms. Data will be extracted from routinely collected data;
7. Evaluation of the data collection process through study specific checklists; Evaluated, statistically and narratively, by assessing the completeness of outcome measurements at baseline and postnatal (6 weeks) through study specific checklists. Researchers will manually examine the data collected. They will assess the proportion of complete data collection forms, the quality of data collected and the applicability of this data in facilitating pilot trial outcomes;
8. Estimate the main effect of individual intervention components and their interactions; Estimates (with measures of uncertainty) of the main effect of individual intervention components and any interaction effect between the main effects of the embedded factorial design will be assessed and reported using regression analysis;
9. Evaluation of the data analysis process; as this is a feasibility study formal hypothesis testing will not be undertaken. Researchers will manually examine the data collected. Evaluation of the data analysis process will be undertaken through the assessment of gaps and limitations to the analysis process measured by study-specific checklist. Findings will be reported through descriptive statistics and graphical summaries;

10. Evaluation of the EQ5D; Assessment of the mechanism of, timing of and delivery of the EQ5D through study specific checklists;
11. Feasibility of cost analyses process through analysis of study specific documentation; Assessment of data collection tools to undertake cost effectiveness analysis through study specific documentation. Researchers will manually examine data to assess the mechanism of, timing of and delivery of the cost analysis tools;
12. Feasibility of the cost effectiveness analyses; Assessment of the mechanism and utilisation of the incremental cost-effectiveness ratio (ICER), through study specific checklists.

Clinical Outcomes

This study will also collect clinical and adverse outcome data that are likely to be collected in the future definitive trial. This is done not to evaluate the clinical effectiveness of membrane sweeping within a pilot trial but to test outcome collection processes and to help inform sample size estimates for and safety of a future definitive study. Data will be extracted from routinely collected data. These outcomes are:

<u>Primary outcome (of future definitive trial)</u>

Number of participants achieving a spontaneous onset of labour

<u>Maternal secondary outcomes:</u>

- Number of participants who underwent an induction of labour; Formal induction of labour using pharmacological or surgical methods;
- Number of participants achieving a spontaneous vaginal birth; Spontaneous vaginal birth;
- Instrumental birth; Vaginal birth which is assisted with the use of instruments;
- Caesarean section; Birth which is achieved through the surgical procedure caesarean section;
- Post-Partum Haemorrhage ≥ 500mls; Blood loss ≥ 500mls within the first 24 hours of the birth of a baby;
- Ante Partum Haemorrhage requiring hospital admission; Bleeding from the genital tract, from 24+0 weeks of pregnancy and before the birth of the baby;

- Uterine hyperstimulation with/without fetal heart rate (FHR) changes; (Uterine hyperstimulation defined as uterine tachysystole (more than five contractions per ten minutes for at least twenty minutes) and uterine hypersystole/hypertonicity (a contraction lasting at least two minutes). These may or not be associated with changes in the fetal heart rate pattern (persistent decelerations, tachycardia or decreased short term variability) (Hofmeyr et al., 2009);
- Serious maternal death or morbidity (e.g. uterine rupture, admission to intensive care unit, septicaemia);
- Epidural analgesia; Introduction of a local anaesthetic into the epidural space of the vertebral canal;
- Augmentation of established labour; The stimulation of uterine contractions using pharmacologic methods or artificial rupture of membranes to increase their frequency and/or strength following the onset of spontaneous labour or contractions following spontaneous rupture of membranes;
- Pyrexia in labour; Pyrexia that developed any time after onset of labour;
- Uterine rupture; all clinically significant ruptures of unscarred or scarred uteri. Trivial scar dehiscence noted incidentally at the time of surgery will be excluded (Hofmeyr et al., 2009);
- EQ5D-5L; EuroQol EQ5D-5L survey instrument.

<u>Neonatal secondary outcomes</u>

- Serious neonatal morbidity (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood, Proven and suspected neonatal sepsis);
- Apgar score < 7 at five minutes;
- Cord PH < 7.20; Umbilical cord blood gas test;
- Neonatal encephalopathy; (Severity of hypoxic ischaemic encephalopathy assessed using Sarnat staging; i)Stage 1 (mild): hyper-alertness, hyper-reflexia, dilated pupils, tachycardia, absence of seizures; ii)Stage 2 (moderate): lethargy, hyper-reflexia, miosis, bradycardia, seizures, hypotonia with weak suck and Moro reflexes; iii)Stage 3 (severe): stupor, flaccidity, small to mid-position

pupils which react poorly to light, decreased stretch reflexes, hypothermia and absent Moro reflex);

- Perinatal death; (the perinatal period is defined as "commences at 22 completed weeks (154 days) of gestation and ends seven completed days after birth." (World Health Organization 2019);
- Admission to neonatal intensive care unit (NICU) or equivalent.

Maternal and Neonatal Process Outcomes:

- Length of time from membrane sweep to birth of baby;
- Length of time from formal induction of labour to birth of baby;
- Overall length of maternal hospital stay;
- Length of infant stay in NICU or equivalent.

Baseline data to include age, obstetric history, parity and Bishop Score will be collected for all participants on first vaginal exam at time of randomisation.

3.6.13 Statistical methods and analysis

3.6.13.1 Sample size for pilot trial:

As this is a pilot trial and not designed to evaluate clinical effectiveness, we will not undertake a formal power analysis for sample size. We will seek to recruit 66 women per clinical site (132 women in total) over a 6-month period beginning in July 2020. This target represents 10% of that required for the definitive trial (see below) and is greater than that recommended as the minimum sample sizes for pilot studies (Connelly 2008). Data obtained from this study will inform the power analysis for a definitive trial.

3.6.13.2 Sample size for definitive trial:

The primary outcome for the definite trial will be spontaneous onset of labour. National data demonstrate a spontaneous onset of labour rate of 54% in women without routine membrane sweeping to prevent post term pregnancy. A sample size of 910 in the intervention arm and 455 in the control group (2:1 randomisation, 1,365 total) will have sufficient power (at >80%) to detect a 15% relative increase in the primary outcome

measure, that is from 54% without membrane sweeping to 62% with membrane sweeping. These calculations assume alpha of 0.05 and the test is 2-tailed.

3.6.14 Criteria for progressing to main definitive trial:

The criteria for progressing to a future definitive trial are based on the primary feasibility objectives of the pilot trial. The pilot will be deemed suitable to continue to definitive trial when the following is achieved:

(a) Recruitment

- At least 30% of eligible women agree to participate in the trial and 132 women are randomised;

(b) Completeness of outcome data

- Complete clinical outcome data that would be collected in main trial collected from at least 90% of pilot trial participants;

(c) Clinician willingness to participate

- At least 70% of participating clinicians within the two pilot sites agree that they would be happy to implement the MILO study. Clinician's views, experiences and acceptability of the MILO study will be explored within focus group interviews.

Given the primary objective of the MILO study is to assess the feasibility of conducting a definitive randomised controlled trial, we will evaluate recruitment and retention, adherence to the MILO protocol and reasons for non-compliance and clinicians and women's views, experiences and acceptability of the MILO study. In the event The MILO study does not meet the above criteria these results will inform whether and how the design of the definitive trial as originally envisaged should be delivered or adapted.

3.6.15 End of Trial- Discontinuation criteria

Individual participant

- Withdrawal of informed consent.
- Development of exclusion criteria or other safety reasons during the study.
- Incorrect enrolment or randomisation of the participant (data retained for purpose of analysis)
- Unanticipated adverse event (consideration given to whether participant should be discontinued)

Recruitment centre

- Not reaching pre-specified recruitment targets (At least 30% of eligible women agree to participate in the trial and 132 women are randomised)
- Systemic non-adherence to protocol

Trial

If IDMC requires termination of the study e.g., futility analyses show no benefit to ongoing recruitment.

For the woman, the Pilot trial is considered ended on discharge from the maternity hospital. For the infant, the pilot trial is considered ended on discharge from the maternity hospital or from the neonatal unit.

3.6.16 Co-enrolment

Women enrolled in this trial may not take part in other interventional trials during the antenatal or intrapartum period evaluating induction of labour or cervical ripening.

3.6.17 Data Collection, management and analysis

A Data Management Plan will be completed outlining the data management process prior to the collection and analysis of study data.

Data Collection Forms

Paper forms will be used in each participating site to confirm eligibility prior to randomisation and to record informed consent. Data will be collected from the participating maternity hospitals using paper-based case report forms (CRFs). Data will be collected retrospectively by the Research Midwife in each site. The participating sites will collect the woman's hospital number, and this may be used in the process of collecting missing data. With the exception of the onsite research midwife, the research team will only have access to a unique identifier for the participant for the purpose of data management. Clinical outcomes are recorded in a woman's health care records i.e. gestation, number of sweeps performed and gestation of woman at time of membrane sweep, hyperstimulation, mode of delivery, analgesia, Apgar scores, length of stay and

infant admission to NICU. This retrospective data from the clinical notes and the CRF are considered source data.

Storage of data

All identifiable information will be held on a secure, password-protected database accessible only to pre-defined personnel. Paper forms with identifiable information will be held in secure, locked filing cabinets. Personal data collected during the trial will be handled and stored in compliance with the 2018, General Data Protection Regulation (GDPR). Participants will be identified by a given code only. Data from the randomisation paper form, CRF and outcome data collected from women's notes will be entered onto a purposefully designed Excel database, within 7 days of the woman's discharge, by the research midwives. All entries to the database will be recorded and dated and each version archived to ensure good clinical practice. Entered data will later be double-checked against original forms for accuracy. All paper forms and data checking records will be securely archived after completion of trial as per requirements under the General Data Protection Regulation EU 2016/679. Direct access to source data/documents will be required for trial-related monitoring by authorised personnel only.

Data Analysis

All data will be analysed and reported in accordance with the 2010 CONSORT Extension Statement for the reporting of Pilot and Feasibility studies (Eldridge et al., 2016). As this is a feasibility study with a relatively small sample size, formal hypothesis testing is not appropriate; rather the purpose of any analyses will be to generate estimates to inform the planning of the definitive future trial. Suitable descriptive statistics and graphical summaries will be used to summarise participant characteristics. Means and standard deviations will be used for continuous variables and counts and percentages for categorical variables. Estimates of variation in main effects will be used to inform future sample size calculations. Estimates (with measures of uncertainty) of any interaction effect between the main effects of the embedded factorial design will also be undertaken. These will refine the design characteristics of the future definitive trial.

3.6.18 Reporting serious adverse events

Membrane sweeping has been found to be a low risk intervention with no increased risk of infection or premature rupture of membranes. All adverse events will be reported to the trial team and recorded on the woman's CRF. In addition, adverse events will be documented in the participant's health records. An expected adverse event is discomfort during the membrane sweeping procedure.

3.7 Work package 2: Health economic analysis

The health economic analysis will assess the feasibility of conducting a trial-based economic evaluation to examine the cost effectiveness of membrane sweeping relative to expectant management and other methods of induction of labour to prevent post-term pregnancy. The basic tasks of economic evaluation are to identify, measure, value and compare the costs and outcomes of the alternative strategies being considered. The pilot study explores the feasibility of conducting an economic evaluation in this context and will seek to inform the design of the economic evaluation to be conducted alongside the definitive RCT. Evidence collected on resource use and outcome measures alongside the pilot RCT will provide the basis for the analysis. With respect to costing, a healthcare service perspective will be adopted, and the study will seek to identify the healthcare resource items that are relevant in this case. In particular, resource use associated with the implementation of the membrane sweeping intervention and the alternative expectant management and pharmacologic control strategies will be identified, measured and costed. In addition, other resource use over the course of the pregnancy in respect of antenatal, intrapartum and postnatal care will be identified, measured and costed. Unit costs will be identified and applied to convert data on resource use to resource costs and total cost variables will be calculated. The pilot will involve the development and testing of appropriate data collection tools to undertake this process. For the pilot cost effectiveness analysis, the alternative strategies will be compared on the basis of the clinical outcome data identified in the pilot RCT. This will inform costing models for the future definitive trial. For the cost utility analysis, Quality Adjusted Life Years (QALYs) will be modelled using the EuroQol EQ5D-5L survey instrument. The pilot study will explore the feasibility, suitability and appropriate timing and delivery of the EQ5D-5L in this context. To complete the pilot study, an incremental analysis will be conducted to model mean costs and mean effects comparisons of the membrane sweeping intervention relative to the control strategies, which will inform the analysis models in the definitive trial.

Univariate and multivariate sensitivity analyses, in addition to probabilistic methods through the estimation of cost effectiveness acceptability curves, will be employed to explore uncertainty.

3.8 Work package 3: Qualitative Descriptive Study

O'Cathain et al (2015) note the contribution qualitative research can make to feasibility studies by exploring uncertainties associated, for example, with interventions, trial methodology, outcome measures, prior to the conduct of a definite trial. Drawing on the guidance O'Cathain et al., (2015) offer for such qualitative work, this feasibility study will include a qualitative descriptive study to explore the acceptability and feasibility of the MILO study. This will include the clinician and women's views of membrane sweeping, relevance and acceptance of the clinician training programme, and potential barriers and enablers to recruitment for a definitive trial.

3.8.1 Design

This work package will use a qualitative descriptive study design. Qualitative descriptive studies aim to explore and to understand the perspectives of those directly involved in certain processes or phenomenon (Sandelowski et al., 2000) and so this design lends itself well to an exploration of the views of key stakeholders participating in the MILO study.

3.8.2 Participants

Purposeful sampling will be used. Up to 10 women per clinical site (this target represents 15% of MILO participants) and all clinicians participating in the pilot trial will be invited to participate in the focus group interviews (Appendices 12, 13, 15 & 16). All potential participants will be contacted via letter when the last trial participant has been discharged from the maternity unit and invited to participate in one of two focus groups based on their geographical location. All letters will make clear the number of participants required. The experiences and views of women across the control and intervention groups will be explored in order to provide an insight into all aspects of the feasibility study.

3.8.3 Data collection

Data will be collected via focus group interviews carried out in each participating site with two focus groups for each of clinicians and women stakeholders (four focus groups in total). The sessions will be led by an experienced qualitative researcher. A topic guide, informed by the purpose of the study and by the literature, will be used to guide the focus groups.

3.8.4 Data analysis

Focus groups will be audio recorded and recordings will be transcribed verbatim and entered into Nvivo. A pseudonym will be given for each participant and will be used on all transcripts of interviews. Data will be analysed using the Framework Method, a method of analysis for qualitative data described by (Ritchie & Lewis 2003). Identified themes will inform the design of a future definitive trial.

3.9 Work package 4: Study within a trial (SWAT)

3.9.1 Background

Adequate recruitment of trial participants is essential to the success of all trials. Yet, two thirds of trials will not complete recruitment within their stated timeframe (Tooher et al., 2008). Pregnant women in particular remain underrepresented in clinical research and the recruitment of pregnant women to trials has proved challenging (Frew et al., 2014). A 2018 Cochrane systematic review examining methods to improve recruitment to randomised controlled trials found a distinct knowledge gap in evidence-based recruitment strategies (Treweek et al., 2018). A study within a trial (SWAT) provides opportunity to increase the evidence base about trial processes (e.g. recruitment and retention).

3.9.2 Aim

To evaluate the effect of the timing of the invitation to women to take part in the trial on recruitment and retention.

3.9.3 Design

Cluster randomised trial.

3.9.4 Setting

As per host pilot trial

3.9.5 Participants

As per host pilot trial

3.9.6 Intervention:

Group 1: Participant recruitment at 35 weeks - 36 weeks + 6 days gestation

Group 2: Participant recruitment at 37 weeks - 38 weeks +6 days gestation

3.9.7 Randomisation:

To minimise the impact of the embedded SWAT on the design and conduct of the definitive trial, randomisation to the different timings of recruitment will be conducted at the site level i.e., site randomisation. Each of the 2 sites will be randomised to recruit women from group 1 OR group 2.

3.9.8 Recruitment

Identifying potential participants

Clinicians at participating antenatal clinics will identify potential participants that meet the study inclusion criteria. Written trial information will be offered to women potentially eligible for participation at 35-36^{+6} week's gestation OR 37-38^{+6} week's gestation, dependent on-site randomisation in the SWAT, during routine antenatal appointments. Women will be given an information pack, which will include a letter introducing the trial and a Participant Information Leaflet, which will inform participants of the background and purpose of the study, risks and benefits of participation, what participants are being asked to do, their right to withdraw and offer to answer any questions they have relating to the study(Appendix 11). This will be followed up at the 39 week antenatal visit when the researcher will invite eligible women to participate.

3.9.9 Obtaining informed consent:

At the 39 week antenatal visit, potential for inclusion to the trial will be checked by the attending clinician and/or research staff. The attending clinician and/or research staff (we

expect this will be the researcher unless at the request of clinical staff) will be available to explain the trial and answer any questions potential participants might have. Eligible women will be asked to participate at this time and written informed consent will be obtained from women agreeing to participate (Appendix 14).

3.9.10 Outcomes:

Primary outcomes:

- evaluation of randomisation, allocation and concealment processes through focus group interviews and data extracted from routinely collected data;
- Estimate variable parameters to inform sample size for definitive trial, including standard deviation of the outcome measure.

Secondary outcomes:

- proportion of eligible women recruited; Data will be extracted from routinely collected data;
- proportion of recruited women that complete trial. Data will be extracted from routinely collected data.

3.9.11 Sample size

As per host trial

Table 3.1. outlines the schedule of enrolment, interventions, and assessments within The MILO Study

Table 3.1. Schedule of enrolment, interventions, and assessments within The MILO Study

	STUDY PERIOD					
Timepoint	**35-36^{+6} *OR* 37-38^{+6} weeks gestation** (*dependent on SWAT allocation)*	**39 weeks gestation**	**40 weeks gestation**	**41 weeks gestation**	**Postnatal period** (*after last study participant is discharged from Maternity*)	**Postnatal period** (6 *weeks after last participant has given birth*)
Eligibility screen & Written information	X					
Informed Consent		X				
Allocation		X				
INTERVENTION						
Group A		X				
Group B			X			
Group C		X	X	X		
Group D			X	X		
Qualitative study written information					X	
Focus Group Interviews						X
Qualitative study Informed Consent						X
EQ-5D-5L evaluation		X			X	

3.9.12 Ethical and safety considerations

Independent Data Monitoring Committee (IDMC)

We will establish an Independent Data Monitoring Committee (IDMC) to monitor data emerging from the MILO study. The IDMC will meet regularly (as required) to assess trial progress based on independent trial data.

Ethical approval

The MILO study will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. We have sought and obtained ethical approval from both study sites (University Maternity Hospital Limerick (Appendix 10) and The Coombe Women and Infants University Maternity Hospital (Appendix 9)).

3.10 Discussion

Conducting a feasibility study prior to a definitive trial potentially reduces the risk of research waste through evaluation of trial processes such as recruitment and retention, randomisation, intervention compliance and data management. In 2009, Chalmers and Glasziou, estimated that 85% of all health research is being avoidably wasted (Chalmers et al., 2009). Poor question choice, inappropriate trial design and inaccurate reporting of results have all contributed to research waste (Morgan et al., 2018). Worldwide, significant public funding is allocated to support biomedical and clinical research (Sampat et al., 2011). In the USA, the National Institutes of Health (NIH) invests approximately US$39.2 billion a year in medical research (National Institutes of Health 2019). In 2015/2016, the National Institute for Health Research (NIHR), invested £247 million (National Institute for Health Research 2017). Demands to improve the efficiency and effectiveness of public expenditure have increased pressure on publicly funded research budgets. For clinical trials to be sustainable, methods to reduce costs and increase productivity must be prioritised. The publication of feasibility study findings inform the design of definitive trials reducing the risk of future research waste.

3.11 Trial status

The MILO Study will begin recruiting in Feb 2021.

It is anticipated that recruitment will be completed in Oct 2021.

3.12 Protocol version

16th March 2020, version 1.1

3.13 Declarations

Ethics approval and consent to participate

Ethical approval was granted by the National University of Ireland Galway 08/08/2019 and by participating clinical sites, The University of Limerick Hospitals Group, Limerick, Ireland (29/08/2019) and The Coombe Women & Infants University Hospital, Dublin, Ireland (19/12/19). The ethical application included the Research Protocol, the patient information sheet, and informed consent forms for all work packages Written informed consent will be obtained from all participants prior to their involvement in the study (Appendices 8, 9, 10).

Consent for publication

Participant information sheets, approved by the Research Ethics Committees, advises participants that the results of The MILO Study will be submitted for publication in a scientific journal. Participants acknowledge that they have read and understood the contents of the Participant information sheets when consenting to participate in The MILO Study. Participants will not be identified in any reports or publications.

Availability of data and materials

The MILO Study has not yet begun recruiting. All data and materials will be available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Trial Funder

The Health Research Board Ireland has funded the MILO Study through the Definitive Interventions and Feasibility Awards (DIFA) 2018.

Health research Board, Grattan House 67-72 Lower Mount Street, Dublin 2, D02 H638

The funder does not have a role in the study design, data collection, analysis, and interpretation of data or in writing the manuscript.

Trial sponsor

The National University of Ireland Galway, University Road, Galway, Ireland H91 TK33

The sponsor does not have a role in the study design, data collection, analysis, and interpretation of data or in writing the manuscript.

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Not applicable

3.14 Authors' contributions

EF is a midwife and Research Associate and is responsible for study development, ethical approval, protocol preparation, protocol writing and revision. DD is the Principal Investigator of The MILO Study. DD is a midwife with formal training in biostatistics and trial methodology. DD is responsible for study development, ethical approval, protocol preparation, protocol writing and protocol revision. LB is a midwife and qualitative researcher. LB offers methodological support for the qualitative research included in our study. LB is responsible for study development, ethical approval, protocol preparation and protocol revision. DM is a consultant obstetrician. DM provides clinical guidance and support for study development, ethical approval and protocol revision. AC is a consultant obstetrician. AC provides clinical guidance and support for study development, ethical approval and protocol revision. EM is a Consultant Neonatologist & Paediatrician. EM provides clinical guidance and support for study development, ethical approval and protocol revision. ST is a health services researcher specialising in trial methodology. ST provides support for The MILO Study design, analysis, protocol preparation and protocol revision. MOD, trained in Geriatric and Stroke medicine, provides experience in multi-centred research studies. In addition, MOD offers bio-statistical and methodological support to all aspects of the MILO study. MOD is responsible for study development, statistical analysis, ethical approval and protocol revision. PG's research activity is focused on the application of the techniques of economic evaluation to inform health policy and

healthcare practice. PG offers methodological support for the economic research included in our study. PG is responsible for study development, ethical approval, protocol preparation and protocol revision. MC is a medical statistician and clinical trialist. MC is responsible for study development, statistical analysis, ethical approval, protocol preparation and protocol revision. AA-I is a clinical research biostatistician. AA-I offers bio-statistical support to all aspects of the MILO study. AA-I is responsible for study development, statistical analysis, ethical approval, protocol preparation and protocol revision. JM is a consultant obstetrician. JM provided support for study development. GG provides support in ensuring our research and study outcomes remain relevant to the consumer. GG is responsible for study development, ethical approval, protocol preparation and protocol revision.

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Section 2

The People's Trial was launched in April 2019, and as lead researcher, I was involved in all stages of the study from concept development to trial design, conduct and dissemination. With the detrimental impact of the coronavirus on the conduct of The MILO Study, a decision was taken in June 2020, to change the direction of my PhD topic. The pragmatic decision reached, in consultation with my Graduate Research Committee and PhD supervisor, was to include *The People's Trial*, a trial I had led in tandem with The MILO Study. *The People's Trial* provides a substantial and original body of work, in and of itself and offers a significant contribution to knowledge.

Chapter 4: The People's Trial

4.1 Introduction

The People's Trial aimed to support the public to learn about randomised trials, not just as participants but as trialists, involved in each step of the trial from question selection, and trial conduct to dissemination of the trial results. Secondary to this aim was the hope that *The People's Trial* would help researchers understand how best to engage with, and involve, members of the public in research processes. This chapter describes the processes involved in the development, conduct and dissemination of this novel online trial.

4.2 Paper 3

The People's Trial: supporting the public's understanding of randomised trials.

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4.3 Abstract

Background

Randomised trials are considered the gold standard in providing robust evidence on the effectiveness of interventions. However, there are relatively few initiatives to help increase public understanding of what randomised trials are and why they are important. This limits the overall acceptance of and public participation in clinical trials. *The People's Trial* aims to help the public learn about randomised trials, to understand why they matter, and to be better equipped to think critically about health claims.

Methods

Using a reflexive approach, we describe the processes of development, conduct and dissemination of *The People's Trial*.

Results:

Over 3000 members of the public, from 72 countries, participated in *The People's Trial*. Through a series of online surveys, the public chose the question *The People's Trial* would try to answer and decided the components of the trial question. In December 2019, 991 participants were recruited to a trial to answer the question identified and prioritised by the public, i.e., '*Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed?*' We called this trial The Reading Trial.

We report processes of *The People's Trial* in seven phases, paralleling the steps of a randomised trial, i.e., question identification and prioritisation, recruitment, randomisation, trial conduct, data analysis, and sharing of findings. We describe the decisions we made, the processes we used, the challenges we encountered, and the lessons we learned.

Conclusion

The People's trial engaged members of the public successfully in the design, conduct, and dissemination of a randomised trial demonstrating the potential for such initiatives to help the public learn about randomised trials, to understand why they matter, and to be better equipped to think critically about health claims.

Trial Registration

The Reading Trial was registered 4th December 2019 on ClinicalTrials.gov, ID: NCT04185818.

Keywords

Randomised trial, public engagement, online, methodology.

4.4 Background

Randomised trials are an important research design in evaluating the effects of health interventions. They have the potential to provide reliable evidence to inform health decisions. While these are exciting and challenging times for clinical trials, rising costs and regulations are making trials more expensive and complicated.

Substantial amounts of public and charitable funding are allocated to clinical research every year (Chalmers et al., 2014). There are, however, serious concerns that much of this is wasted (Glasziou & Chalmers 2018). The reasons for this waste include failure to publish completed research, inadequate reporting of research and the development of new studies without placing them in the context of previous research addressing the same question (Glasziou & Chalmers 2018, Ioannidis et al., 2014). Also, inadequate recruitment and retention of participants to trials leads to waste due to trials not being able to provide sufficient high-quality evidence to answer the question for which it was designed (Gillies at al., 2019, Treweek et al., 2018). The inability to recruit enough participants to answer a trial question is one of the main reasons trials are discontinued or request extensions, with just over 50% of trials meeting their pre-specified recruitment targets (Treweek et al., 2018, Walters et al., 2017*).*

It is important to understand why members of the public consider participating, or not participating, in a trial (Houghton et al., 2020, Treweek et al., 2018). A 2017 survey of over 12,000 members of the public, from 68 countries, including 2194 clinical trial participants, found that 84% of respondents perceived clinical research to be important, while 82% reported that they felt well informed about clinical research (Center for Information and Study on Clinical Research Participation (CISCRP) 2017). However, more detailed results demonstrate that public knowledge of clinical research may be superficial, with 51% reporting that they do not know where research is conducted and 34% of respondents reporting that they don't know what percentage of medicines must be tested in clinical research studies before being sold to the public (CISCRP 2017). Troublingly, the proportion of people 'very willing' to participate in a

clinical trial was significantly lower (31%) than a similar survey conducted by the same group four years previously (50%) (Clinical Research Participation (CISCRP 2017). Respondents who felt informed about clinical research were more willing to participate in clinical trials. When asked how the public should be educated about the clinical research process, 35% of respondents proposed learning about clinical research through educational information on the internet (CISCRP 2017).

Fear and distrust of research have been described as barriers to public involvement in research (Sheridan et al., 2020). This was found to be more common within underserved groups, such as ethnic minorities, with further systematic reviews highlighting mistrust in research as a barrier to recruitment of vulnerable populations (Bonevski et al., 2014, Rivers et al., 2013). The findings of these reviews suggest that fear and mistrust of research are linked to a lack of knowledge and understanding of clinical research or the research process. While these reviews found that knowledge had a positive impact on recruitment to clinical research, they also highlighted that confusion or a lack of understanding around specific trial processes, such as randomisation, acted as barriers to recruitment, particularly in obtaining informed consent (Houghton et al., 2020, Sheridan et al., 2020, Bonevski et al., 2014, Ford et al., 2007).

The evidence suggests a lack of understanding around what randomised trials are and why they are essential. This may negatively affect public support for, and participation in, clinical trials (Skingley et al., 2014, Kombe et al., 2019, CISCRP 2017). A poor understanding of evidence may lead to public health risks such as the under, or over use, of medicines, uninformed health choices, and unnecessary human suffering (The Academy of Medical Sciences 2017). Yet, to date, relatively few initiatives (i.e. The Informed Health Choices (Oxman et al., 2018), Just Ask 2020 (Cancer Trials Ireland 2020) have been developed to support public understanding of randomised trials.

Aim

The *People's Trial* aimed to help the public learn about randomised trials, to understand why they matter, and to be better equipped to think critically about health claims.

4.5 Study design and setting

The People's Trial was an online trial, designed by the people for the people. Using a custom-built, online platform, it sought to involve the public in all steps of a randomised trial.

4.5.1 Theoretical perspective

The People's Trial embraced the concept of 'learning by doing'. It sought to enhance understanding of randomised trials by facilitating the involvement of the public in the trial research process. Malcolm Knowles' Theory of Andragogy informed the design of *The People's Trial* (Knowles 1984). Andragogy focuses specifically on the ways adults learn. Knowles believed that adult learning should involve collaborative interactions, including the use of available resources. Knowles identified five assumptions that encourage successful adult learning (see table 4.1). These assumptions were incorporated into the design of *The People's Trial*.

Table 4.1: Malcolm Knowles' Theory of Andragogy five assumptions

Assumptions	
Self-Concept	Adult learners have an established sense of self-value and autonomy and benefit from active involvement in their learning.
Experience	Adult learners bring a lifetime of experience. To stimulate and maintain interest, participant's life experiences should be, engaged with, and connected to, during the learning process.
Readiness to learn	Readiness to learn stems from adult learners recognising and appreciating the intrinsic value of their newly acquired knowledge.
Learning orientation	Adults learn best through practical application or "learning by doing".
Motivation to learn	Adult learners are generally motivated to learn by internal factors (i.e. self-esteem and self-value) rather than external factors (for example a pay increase)

4.5.2 The team and working process

We conducted *The People's Trial* on a custom-designed, online platform (www.ThePeoplesTrial.ie). We divided the trial into seven phases, paralleling the process of a randomised trial, i.e., (i) question identification (ii) question prioritisation and selection, (iii) determining how we would answer the trial question, (iv) recruitment and randomisation, (v) trial conduct, and data analysis, (vi) developing a dissemination strategy, and (vii) dissemination of trial findings. Doing so would, we felt, opens the trial methodology process to the public. We used plain language text in all communications to maximise the accessibility of the trial to the public. We produced a series of animated whiteboard videos for each phase. These animations explained each step of the trial process as it progressed and were narrated by researchers, clinicians, and members of the public. All were designed and produced to be accessible and engaging.

During each phase of *The People's Trial,* we collected and reported website analytics, media, and social media metrics. Our hosting platform captured survey participation metrics.

We established a Steering Group of trialists, methodologists, statisticians, clinicians, research communicators and members of the public to oversee *The People's Trial.* Collectively, this group supported the methodological decisions and processes of the trial with a priority focus on ensuring public involvement in the trial processes from question identification and prioritisation to dissemination of trial findings

4.5.3 Participants

Participants in *The People's Trial* were 18 years of age or over. As we were unable to offer a translation service, participants also needed to be able to communicate in English and give written informed consent.

4.6 Procedures

4.6.1 Pre-launch

We used social media campaigns to create awareness of *The People's Trial*, highlighting the motivation behind the trial. We promoted *The People's Trial* through engaging custom-designed animations, which guided the public through the framework and objectives of the trial, highlighting the opportunity for shared learning. We also targeted national media

(radio, newspaper, and TV networks) with press releases promoting *The People's Trial.* During this time, *The People's Trial* website introduced the public and participants to members of the Steering Group and the collective expertise they brought to the project.

In preparation for the trial launch, we provided accessible, exemplar questions that trials could answer and would be familiar with a broad public audience, such as, 'Does *eating cheese cause nightmares compared to not eating cheese*?' We explained that only low risk; accessible questions would be accepted to ensure the trial was accessible to all members of the public and would be safe.

4.6.2 Baseline data

We invited members of the public to participate in each phase of *The People's Trial* independently. The public could take part in some, or all of the phases, as they wished.

We invited participants to read an information leaflet about the study and sought their consent to participate through an online form (Appendix 18 & 19). We also asked each participant to provide baseline data on whether they worked in healthcare or health research, what their understanding of randomised trials was before taking part in *The People's Trial,* and their age and gender.

4.6.3 Phase one - All good trials start with a good question

In phase one, we invited the public to submit a question they would like *The People's Trial* to tackle using a randomised trial design. We asked the public to submit their question on a QuestionPro® form embedded on *The People's Trial* website. We structured the form, and gave examples, using the framework of intervention, comparator, and outcome (figure 4.1). An animated video offered further insights into what makes a good research question and why this process is important.

Figure 4.1. Exemplar question

I would like to find out if:
Eating cheese (*the thing you'd like to test*) makes a difference to
having nightmares *(the thing you'd like to affect or change*) in comparison to
not eating cheese (*the thing you'd like to be the comparison*)

4.6.4 Phase two - A good question is one that people want to know the answer to

During phase two, we developed two surveys to investigate how little, or how much, the public liked each question submitted in phase 1.

Two steering group members reviewed all questions submitted in phase 1. A third member reviewed questions where an initial consensus on inclusion was not reached. If necessary, these questions were discussed further by the Steering Group. We excluded questions where the outcome was a health outcome requiring medical assessment and questions that targeted participants with a medical condition. We provided specific feedback on the reasons why a question was not included and posted this information on *The People's Trial* website. During this phase, we also introduced the concept of research waste and the potential cost and ethical implications associated with it.

Survey 1

Using a three-point sliding scale ((i) *No thanks, I'm not interested in us answering this question*, (ii) *I'm not sure,* and (iii) *Yes please, I'm really interested in us answering this question*) participants indicated how interested they were in answering each question. We then ranked questions based on these preferences. Using this method, the public selected the top ten most popular questions.

Survey 2

In survey 2, using a click and drop method, members of the public ranked the top ten questions in order of preference (question ranked number 1 = most favourite, and question number ten = least favourite)

Using this online iterative process, the question chosen by the public for *The People's Trial* to tackle was:

'*Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed*?'

4.6.5 Phase three - We have our question... Now it's time to think about how we'll answer this question.

In phase three, we asked the public to determine the characteristics of the intervention (reading a book in bed), the comparator (not reading a book), and the outcome (sleep). For example, we asked the public to decide if trial participants should 'Have the use of electronic entertainment or communication devices (e.g. mobile phones /tablets) in bed?', 'Go to bed and wake up at the same time as they normally would?' and 'Sleep in their own bed, in their own home, for the study duration'. We also asked the public to tell us how they felt we should measure the outcome of 'sleep'. Again, an animated video described the importance of this step in trial design.

Through this process, the public defined the intervention and comparator and decided that the primary outcome should be an evaluation of overall sleep quality, with daytime sleepiness and sleep disturbance assessed as secondary outcomes.

4.6.6 Phase four - Being a bit random– deciding who gets what in the trial?

In phase four, we invited the public to take part in *The People's Trial* randomised trial, which we called 'The Reading Trial'. We recruited members of the public, 18 years of age or older, to take part in the trial through a social media campaign. After they provided consent, participants clicked a button to self-randomise to either the intervention or the control group using a custom-built, randomisation tool, developed by Metaxis Software design ® embedded in *The People's Trial* website. An engaging, animated video explained 'randomisation', and why it is important in clinical trials.

4.6.7 Phase five - Does reading a book in bed make a difference to sleep?

During phase five, we conducted 'The Reading Trial', an online, parallel group, randomised trial, designed by the people, for the people. Participants self-randomised and were allocated in a 1:1 ratio, to the intervention group (reading a book in bed) or the control group (not reading a book in bed). We registered the 'Reading Trial' before recruitment of the first participant (registration number: NCT04185818).

4.6.8 Phase 6 - Reporting what we found

Funders and regulatory bodies require that trial results are made available to all stakeholders in a timely and accessible manner. An effective dissemination strategy leads to an increased awareness of the research being undertaken, promotes discussion, and highlights potential health benefits to stakeholders. Also, accessible and usable reporting of trial results increases the value and minimises avoidable research waste. However, most research dissemination is typically limited to academic and professional journals, which the public may not have access to or even be aware of. To ensure our trial results were accessible to the general public, our target audience, we used an online survey to ask participants of 'The Reading Trial' to rank in order of importance how and where they would like to see the results of the trial publicised.

4.6.9 Phase 7 – So what have we learnt?

During this phase, we reported the findings of 'The Reading Trial'. The dissemination strategy used, was directly informed by the results of the phase 6, online survey.

4.7 Declarations

4.7.1 Ethical approval

The People's Trial received ethical approval from the NUI Galway Research Ethics Committee (Reference Number: 19-Mar-09) (Appendix 21).

4.7.2 Role of the funding source

This research was funded by the Health Research Board in Ireland, through the Health Research Board – Trials Methodology Research Network as part of a Knowledge Exchange and Dissemination Scheme Award (grant reference KEDS-2018-012) 2018. The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or

writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit.

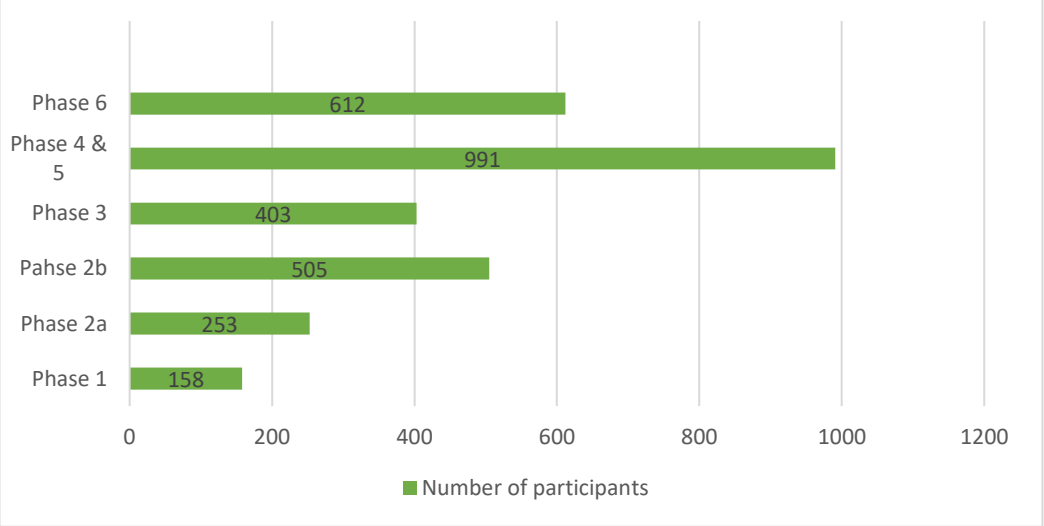
4.7.3 Trial registration

The Reading Trial was registered on 4th December 2019 with ClinicalTrials.gov, ID: NCT04185818. (https://clinicaltrials.gov/ct2/show/NCT04185818?cond=Citizen+Science%3A+The+People%27s+Trial%3A&draw=2&rank=1). The study adheres to CONSORT guidelines for randomized trials.

4.8 Results

The People's Trial was conducted, between April 2019 and November 2020. Over 3000 members of the public, from 72 countries, took part in *The People's Trial (Figure 4.2)*. Participants were invited to take part in each phase independently, meaning that individuals could participate in more than one phase, indeed this was encouraged.

Figure 4.2. *The People's Trial* participant numbers by phase



4.8.1 Phase one

During phase one, the public submitted 155 potential questions for *The People's Trial* to answer. Almost half (n=67, 43%) of participants in this phase described themselves as having 'none' or 'some' understanding of randomised trials before taking part in *The People's Trial*.

4.8.2 Phase two

In phase 2, we reviewed the 155 questions submitted by the public during phase 1. We excluded 99 questions where the outcome was a health outcome requiring medical assessment and questions that targeted participants with a medical condition. We also merged similar questions where possible. This process produced 41 questions. We prioritised the questions in two surveys.

Survey one

During survey one, 253 participants selected their top ten favourite questions from the 41 questions (see supplementary file 1). This survey found that the question *'Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed?*' was rated highly by participants, with 59% (n=117) reporting that they were 'really interested' in answering the question.

Survey two

During survey two, 505 members of the public ranked the top ten questions in order of preference (Table 4.2). The question ranked number one by the largest percentage of participants (19%, n= 97), was '*Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed?*'

This was **the** question *The People's Trial* tackled.

Table 4.2: Top ten questions chosen by the public

Rank	Percentage of votes received	question
1	19%	Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed?
2	14%	Does using a mobile phone before sleeping make a difference to sleep quality in comparison to not using mobile phone before sleeping?
3	12%	Does doing daily crosswords or puzzles make a difference to your memory in comparison to not doing daily crosswords or puzzles?
4	10%	Does exercising right after waking up make a difference to productivity at work in comparison to not exercising right after waking up?
5	10%	Does eating breakfast make a difference to concentration in the mornings in comparison to not eating breakfast?
6	9%	Does not viewing social media make a difference to short-term mood in comparison to viewing social media?
7	9%	Does going for a walk outside at lunchtime make a difference to concentration in the afternoon in comparison to not going for a walk at lunchtime?
8	6%	Does light exercise in the evening make a difference to sleep quality in comparison to no exercise in the evening?
9	6%	Does outdoor exercise make a difference to short-term mood in comparison to indoor exercise
10	5%	Does spending time outdoors make a difference to short-term mood in comparison to not spending time outdoors?

4.8.3 Phase three

During phase three, we asked the public to consider how we could answer this question. Following a broad media campaign including social media, traditional print media and national radio stations , 403 members of the public responded to our online survey to determine the characteristics of the intervention (reading a book in bed), the comparator (not reading a book in bed), and the outcome (sleep).

The public decided that participants randomised to the intervention group (reading a book in bed) should:

1. Read a book immediately before trying to go to sleep

2. Read for 15-30 minutes

3. Go to bed and wake up at the same time as they usually would

4. Not eat food or drink caffeinated drinks within 1 hour of going to bed

5. Sleep in their bed, in their own home.

This should be done for the study duration (7 nights).

Similarly, participants in the control group (not reading a book in bed) should:

1. Go to bed, and wake up at the same time as they normally would
2. Not eat food or drink caffeinated drinks within 1 hour of bed.
3. Sleep in their bed, in their own home, for the study duration (7 nights).

However, as the control group, these participants should **not** read a book immediately before trying to go to sleep.

The public also decided that participants in both groups could use electronic entertainment or communication devices (e.g., mobile phones /tablets) in bed for participants in both the intervention and control groups.

The only difference between the intervention group and the control group was reading a book in bed for the study duration (7 nights).

4.8.4 Phase four

Between 4th December 2019, and 31st December 2019, 991 people agreed to take part in The Reading Trial. Of these, 496 (50%) were allocated by chance to the 'intervention' group (reading before sleeping) and 495 (50%) control group (not reading before sleeping).

Although 564 participants were required to achieve our a priori sample size, the primary aim of *The People's Trial* was to help the public learn about randomised trials, so we continued enrolment after this sample size was achieved.

The reading trial had an attrition rate of 21.9% (n=217). Of those that didn't finish the study, 127/496 (25.6%) were in the 'intervention' group (reading a book before sleeping) and 90/495 (18.2%) in the control group (i.e. not reading a book before sleeping).

However, 774 people (369 (47.7%) people in the intervention group and 405(52.3%) in the control group) from 43 countries reported outcomes.

The two groups were, on average, similar in baseline characteristics. Also, participants in both groups reported similar sleep quality at the beginning of the trial (Table 4.3).

Table 4.3. Summary statistics for participant characteristics at the start of 'The Reading Trial'

People who took part in The Reading Trial	Reading Group (n=369) n(%)	Not Reading Group (n=405) n(%)
Age:		
• 18 - 24 years	21 (6%)	28 (7%)
• 25 - 44 years	193 (52%)	209 (51%)
• 45 - 64 years	123 (33%)	145 (36%)
• 65 years and over	32 (9%)	23 (6%)
Gender:		
• Female	289 (78%)	325 (80%)
• Male	75 (20%)	78 (19%)
• Prefer not to say/ self-describe	5 (1%)	2 (0.5%)
Understanding of randomised trials:		
• Good understanding	251 (68%)	278 (69%)
• Some understanding	101 (27%)	105 (26%)
• No understanding	17 (5%)	22 (5%)
Healthcare background:		
• Healthcare	238 (65%)	269 (66%)
• Not healthcare	131 (34%)	136 (34%)
Sleep Quality at the start of the trial:		
• Terrible	7 (2%)	6 (1%)
• Poor	51 (14%)	51 (13%)
• Fair	175 (47%)	181 (45%)
• Good	115 (31%)	152 (37%)
• Excellent	21 (6%)	15 (4%)

Data are numbers of people (%)

4.8.5 Phase five

The reading trial found that reading a book in bed before going to sleep improved sleep compared to not reading a book in bed before going to sleep. In the intervention group, 156 (42%) people reported an improvement to their sleep quality compared to 112(28%) people in the control group, a difference of 14% favouring the intervention group. Considering the uncertainty in this estimate, we calculated that the difference in the population is likely to be between 8% and 22%, favouring those on the intervention. The full results of The Reading Trial are reported separately as a plain language trial report.

4.8.6 Phase six

During phase 6, 612 participants, from 47 countries, told us where and how they would like the results of The Reading Trial publicised. Most people chose to have the trial results displayed visually or published as a plain-language summary. The public indicated they would like to see the results displayed on *The People's Trial* website and publicised through social media campaigns. The findings of this online survey informed *The People's Trial* dissemination strategy, which includes a plain-language report, the publication of all trial results on *The People's Trial* website visually, through graphs, an animated short video, and an audio blog. Access to individual predictive results using a custom-designed nomogram, embedded on *The People's Trial* website is in development and will also be available to all on the website. (Figures 4.3 & 4.4).

Figure 4.3: Where the public want the results disseminated

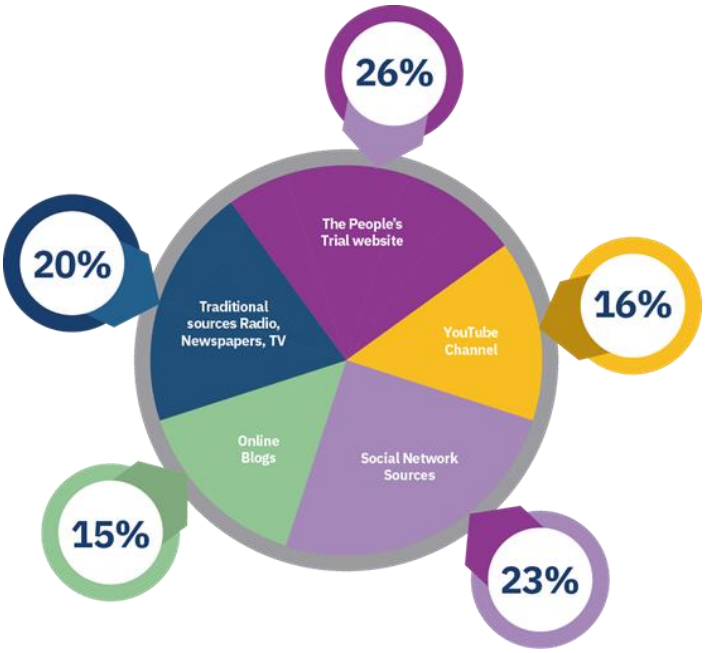
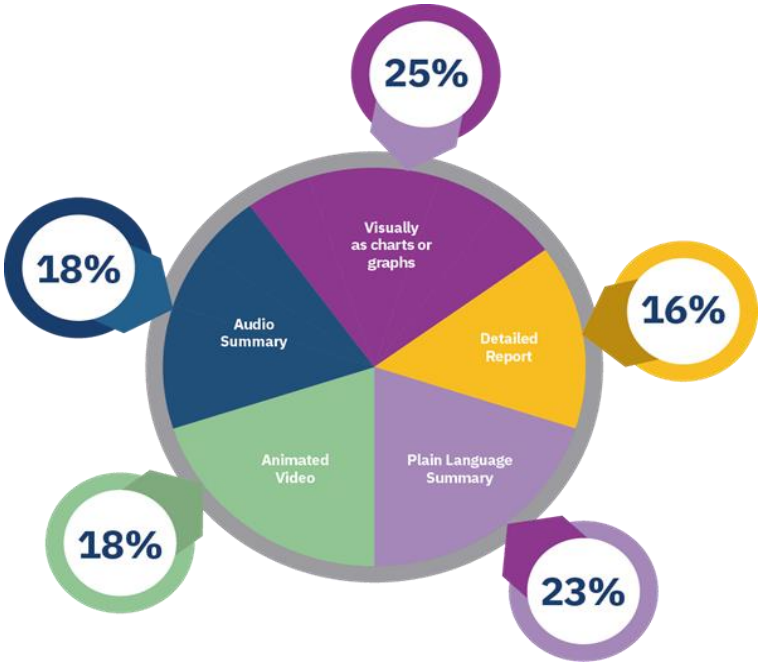


Figure 4.4: How the public want the results disseminated



The People's Trial website (www.thepeoplestrial.ie) has recorded 9,552 unique users, with 15,258 sessions and 25,382 page views to date.

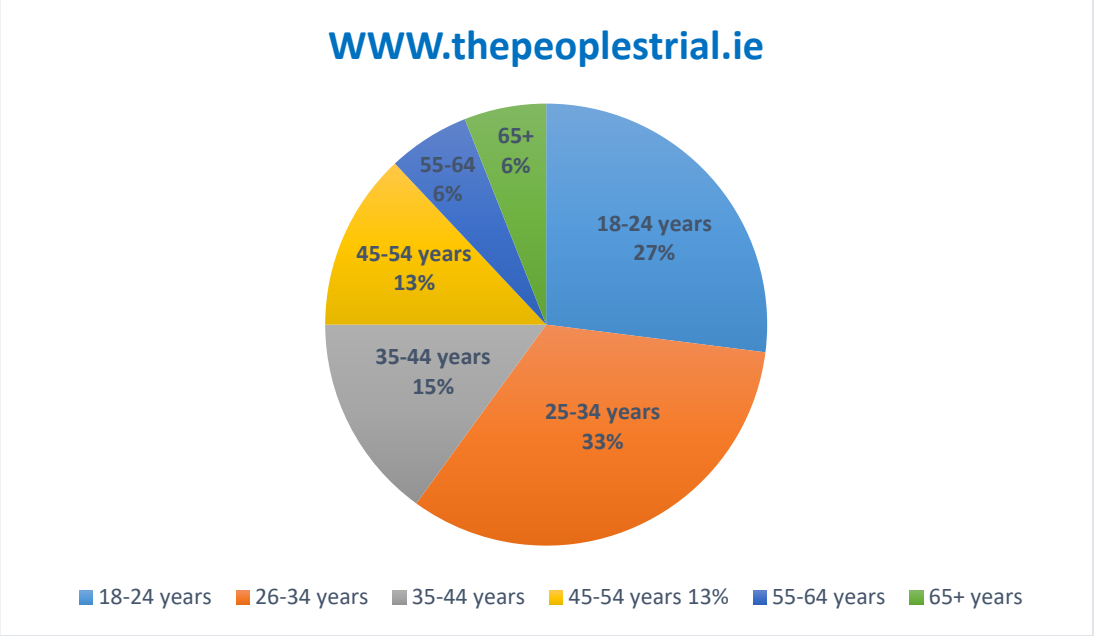
Visitors to the site were predominantly from Ireland (35%) and the UK (35%), see Table 4.4. Overall, 46% of site users were female, and 54% male.

Table 4.4. *The People's Trial* website demographics

Country	Number of unique visitors to www.Thepeoplestrial.ie
Ireland	3205 (35%)
United Kingdom	3198 (35%)
United States of America	376 (4%)
France	308 (3%)
Australia	246 (3%)
Germany	232 (3%)
Canada	231 (3%)
Russia	101 (1%)
India	79 (0.86%)
Spain	78 (0.85%)

While *The People's Trial* website attracted users from all age groups, 61% were between 18 and 34 years, with just 6% of users age 65 or older (figure 4.5).

Figure 4.5. Age profile of website users



Social media was the principal method of advertising for *The People's Trial*, with 39% of new users accessing *The People's Trial* website directly from social media platforms. During the recruitment phase of The Reading Trial (December 2019), *The People's Trial* Twitter account achieved 197k Twitter impressions, with 3029 profile visits and 275 mentions. Traditional media sources were also utilised to promote the trial, incorporating press releases, blogs, and interviews with members of the steering group on national radio stations.

4.9 Continued Accessibility

The People's Trial website (www.ThePeoplesTrial.ie) is maintained as a live site with unrestricted, public access to review all steps of the trial. All educational tools, such as the animated explanatory videos, are maintained on this site and *The People's Trial* YouTube channel, and are free to use.

4.10 Discussion

While clinical trials are not unusual, and there have been initiatives which aim to educate members of the public about randomised trials, such as the 'Understanding Clinical Trials' programme funded by CISCRP, or the 'Wellcome Monitor', funded by the Wellcome Trust, we believe *The People's Trial* is unique in its active involvement of the public in creating the steps of the trial process from identifying and prioritising the trial question to trial conduct

and dissemination (The Wellcome Trust 2020, CISCRP 2020). *The People's Trial* offered members of the public the opportunity to take part in and learn about randomised trials in an accessible, online environment. The trial supported a shared learning experience for participants and researchers, where members of the public were supported to learn about randomised trials through active participation in all trial processes and researchers learned how public participation could inform and improve trial processes. This project demonstrates a public willingness to access and engage with learning and knowledge on trial methodology. *The People's Trial* also highlights the role of social media in promoting clinical trials and their processes within the broader public arena. While an online trial supports accessibility and inclusion, it was not without its challenges, primarily because of the nature of *The People's Trial*. *The People's Trial* began as a concept, which required the active participation of members of the public to develop. When designing *The People's Trial* website, the steering group did not know the trial question, and therefore the intervention, comparator, outcome, sample size, etc. were all unknown. The team, including our web development team, had to respond organically, and promptly, to the trial needs as it progressed. To minimise the risk of project slippage, we engaged experienced web designers and volunteer testers to ensure all aspects of the online trial were fully functional before releasing each phase to the public. To further promote inclusion, the website design was optimised specifically for members of the public participating on mobile phones.

Due to budget constraints, a significant limitation of the trial was the exclusion of individuals not competent in the English language. While we would like to see this limitation addressed in future trials, all members of the Steering Group worked to ensure the language used throughout *The People's Trial* was accessible, appropriate, and relevant, albeit in English only.

A significant unforeseen challenge to *The People's Trial* was the current COVID-19 pandemic. Although the trial conduct and data collection were completed before the onset of the pandemic, the publication of the results of 'The Reading Trial', and the invitation to participate in the evaluation survey was delayed. The delay was primarily due to the re-assignment of the research team to research projects focused on the coronavirus pandemic.

4.11 Conclusion

To be effective, clinical trials need participants, but recruitment and retention continues to be challenging with almost half of all trials not meeting their target sample size (Walters et

al., 2017). The evidence suggests that knowledge of trials and why they are important has a positive impact on recruitment to clinical research (Brandberg et al., 2016). While confusion and a lack of understanding of clinical trials has been shown to have the opposite effect (Houghton et al., 2020, Sheridan et al., 2020). This paper describes the process of developing and conducting a novel, online initiative to potentially address these challenges.

In a time where the public is actively seeking information on trials and research methodology through online platforms, *The People's Trial* offered the possibility of opening trial processes to a broader audience. The public's views on trial design and the acceptability of trial processes have been underrepresented in research to date.

With over 3000 members of the public participating, from 72 different countries, *The People's Trial* demonstrates the potential for public participation to inform and improve randomised trial processes, while also providing an opportunity for shared learning. *The People's Trial* offers important insights for researchers on public involvement in designing trial processes. Using innovative, novel methods, it successfully engaged the broader public in planning, designing, conducting, and reporting a randomised trial.

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Chapter 5: The Reading Trial

5.1 Introduction

This chapter presents a plain language report of an online, randomised trial called The Reading Trial. The design of The Reading Trial was directly informed by *The People's Trial*, described in chapter 4. The plain language format used in this report was the method of dissemination chosen by participants of *The People's Trial*. The question The Reading trial would try to answer was suggested and prioritised by the public. The question chosen by the public was:

'*Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed?*'

This paper reports that trial.

5.2 Paper 4

***Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed? The People's Trial*- an online, pragmatic, randomised, controlled trial**

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5.3 Project Abstract

Background

The best way of comparing healthcare treatments is through a randomised trial. In a randomised trial, the treatment (intervention) being tested is compared to something else, often another treatment. Who gets what is decided at random i.e., everyone has an equal chance of getting any of the treatments. It allows any differences found to be put down to the treatment received rather than other things, such as where people live, or health conditions they might have.

The People's Trial aimed to support public understanding of randomised trials by involving them in every step of the trial process. The question chosen by the public for *The People's Trial* was:

'*Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed?*'

This paper describes that trial, called 'The Reading Trial'.

Methods

The Reading Trial was an online, randomised trial. Members of the public were invited to take part through social media campaigns. People were asked to either read a book in bed before going to sleep (intervention group) or not read a book in bed before going to sleep (control group). We asked everyone to do this for seven days, after which they measured their sleep quality.

Results

During December 2019, a total of 991 people took part in The Reading Trial, half (496 (50%)) in the intervention group and half (495 (50%)) in the control group. Not everyone finished the trial: 127 (25.6%) people in the intervention group and 90 (18.18%) people in the control group.

Of those providing data, 156/369 (42%) people in the intervention group felt their sleep improved, compared to 112/405 (28%) of those in the control group, a difference of 14%. When we consider how certain we are of this finding, we estimate that in the Reading Trial

sleep improved for between 8% and 22% more people in the intervention group compared to the control group.

Conclusions

Reading a book in bed before going to sleep improved sleep quality compared to not reading a book in bed.

Trial Registration

Registered 4th December 2019 on ClinicalTrials.gov, ID: NCT04185818.

Keywords

Randomised trial, public engagement, online, methodology, research co-production, sleep.

This report is written using a plain language format. This is done in direct response to how people told us they wanted the results of The Reading Trial to be shared (phase vii of The People's Trial).

5.4 Background

The COVID-19 pandemic has highlighted the importance of reliable evidence, including randomised trials,[3] in supporting people to make decisions about their health Clinical trials for treatments and vaccinations are regularly discussed and reported by mainstream and social media. Trials are now a part of the public consciousness. Still, one of the main reasons trials are discontinued, causing research waste, is because not enough people take part in trials (Gillies et al., 2019, Treweek et al., 2018), and those that do take part may not stay in the trial to the end (Treweek 2018). A study looking at recruitment to trials found that during 2011, over 48,000 people took part in trials that could not meaningfully answer the question they were designed to answer because the trials did not recruit enough people (Carlisle et al. 2015). Similarly, a recent systematic review of 151 publicly funded randomised trials also found that 44% of trials did not recruit enough people to meet their target sample size (Walters et al., 2017). This has serious ethical and cost implications (Macleod et al., 2014).

3 Randomised trials are a type of research study that compares groups of people receiving different interventions and looks at which of these improves health outcomes the most. An intervention is anything that aims to make a change to someone's health such as drugs, surgical procedures, or lifestyle changes. In a randomised trial the decision about which group a person joins in a trial is made randomly, which means that people have an equal chance of being placed into any group.

Programmes and initiatives that explore ways to improve the likelihood of people taking part in, and staying in, clinical trials would help reduce waste of resources and money (Kadam at al., 2016).

Research tells us that if people have some knowledge and understanding of clinical trials, this is helpful when inviting them to take part (CISCRP 2017, Brandberg et al., 2015). When people are confused about trials and their processes, it has the opposite effect (Sheridan et al., 2020, Bonevski et al., 2014, Ford et al., 2007). Distrust and fear of research and researchers stop people from becoming involved in research projects, particularly in underserved groups such as minority ethnic and socioeconomically disadvantaged groups (Sheridan et al. 2020, Bonevski et al. 2014, Rivers et al., 2013).

The People's Trial was an online initiative to support and develop people's understanding of randomised trials, in a novel, accessible way, by involving them in the trial research process from beginning to end.

The People's Trial was conducted in seven phases and followed the steps of a randomised trial (i) proposing questions the trial would try to answer, (ii) prioritising and selecting these questions, (iii) determining how we would answer the trial question, (iv) inviting people to take part in and self-randomise to the intervention (reading a book in bed) or the control (not reading a book in bed) group, (v) carrying out the trial requirements (reading or not reading a book in bed before sleep) and examining the information collected during the trial, (vi) deciding how the findings of the trial would be communicated, and (vii) communicating the trial's results. Members of the public drove all seven phases and were the ones making key design decisions. Details on the processes underpinning *The People's Trial* are reported separately.

The question chosen by the public for *The People's Trial* was:

'*Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed?*'

While we did not ask people who took part in The People's trial why they chose this question, recent studies suggest that problems with sleep are increasing and are a public health concern, with one in four people reporting that they don't sleep well (Ford et al., 2015 Watson et al., 2015). The extent of poor sleep quality may be greater as people are thought

to under-report sleep problems to health care providers (Filip et al. 2017). Research has shown that many factors including gender, marital status and socioeconomic status impact on the quality of sleep (Grandner et al., 2010).

The most common type of sleep problems reported are difficulty trying to get to sleep, and not being able to stay asleep; these problems are often referred to as insomnia (Montgomery & Denis 2002). Tiredness and irritability felt by those experiencing insomnia can negatively affect everyday life (Kleinman 2009, Leger 2008, Chattu 2019). Evidence also suggests a strong relationship between prolonged insomnia and mood disorders, such as depression and anxiety. Insomnia has also been linked to medical conditions such as high blood pressure (Calhoun 2017).

Reading in bed before sleeping is a low cost, accessible intervention that may potentially improve sleep quality. The Reading Trial aimed to find out if reading a book in bed before sleep makes a difference to sleep quality, compared to not reading a book in bed.

5.5 Methods

5.5.1 Trial design and setting

The Reading Trial was an online, randomised trial with two groups. It took place on a purpose-built website (www.thepeoplestrial.ie), with no face-to-face interaction. The Reading Trial was pragmatic, in that the intervention (reading a book in bed before going to sleep) and the comparator (not reading a book in bed) happened in 'real-life' conditions, for example in peoples' own homes.

5.5.2 Participants – who took part?

People who took part in The Reading Trial (the participants) were 18 years of age or over. As we couldn't offer a translation service, people who took part in the study also needed to be able to read about the trial and report their experiences in English.

5.5.3 Participants – how we asked people to take part?

We invited people to take part in the trial using social media campaigns on Facebook, Twitter, Instagram, and YouTube. We asked people to go to *The People's Trial* website, where an animated video described the aim of *The People's Trial* and the steps involved in taking part

in a randomised trial. We also included a Participant Information Leaflet on the website, which was available to read and download (Appendix 20). This gave detailed information on the purpose of the trial, what people could expect to happen if they took part in the trial, and potential risks and benefits to taking part in the trial.

After reading the Participant Information Leaflet, people who wanted to take part in The Reading Trial showed their agreement (consent) using an online form. Altogether, 991 people agreed to take part in The Reading Trial.

People taking part in the study gave us some information about themselves. This included their age group, gender, email address (so we could contact them with trial-related information), whether or not they worked in healthcare or health research, and what they felt their level of understanding of randomised trials was. People also told us about their sleep quality in the seven days before taking part in The Reading Trial.

5.5.4 Randomisation of participants

A researcher that was not part of *The People's Trial* team created an online program which placed (or allocated) people into the intervention group (reading a book in bed), or the control group (not reading a book in bed). Who got what was decided randomly, which meant that everyone had an equal chance of being in the intervention group or the control group; we call this process randomisation. We did this using a 1:1 ratio. This meant that for every person placed in the intervention group (reading a book in bed), one other person was placed in the control group (not reading a book in bed). This was done to make sure The Reading Trial was a fair comparison between the two groups.

Neither the researchers nor people taking part in the trial knew in advance which group a person would be put into. Because the trial relied on people doing or not doing something, it was impossible to hide, or blind, people to the group they were placed into (reading or not reading a book) in this trial. This meant that people taking part in The Reading Trial were aware of the group that they were allocated to. The researchers running the trial day-to-day did not know who was in each group.

5.5.5 Interventions

As part of *The People's Trial*, people told us what they meant by the trial question. Through an online survey they defined the characteristics of the intervention (reading a book in bed),

the comparator (not reading a book in bed), and the outcome (sleep quality). They also told us how the trial would measure the outcome.

Intervention Group

People in the intervention group:

1. Read a book for 15-30 minutes immediately before trying to go to sleep for seven nights in a row
2. Went to bed and woke up at the same time as they usually would
3. Did not eat food or drink caffeinated drinks within 1 hour of going to bed
4. Slept in their bed, in their own home, for the study duration
5. Could use electronic entertainment or communication devices (e.g. mobile phones/tablets) in bed for the seven nights of The Reading Trial.

Control Group

People in the control group did the same as those in the intervention group, except they did NOT read a book immediately before trying to go to sleep.

This meant that people in the control group:

1. Did not read a book immediately before trying to go to sleep for seven nights in a row
2. Went to bed and woke up at the same time as they usually would
3. Did not eat food or drink caffeinated drinks within 1 hour of going to bed
4. Slept in their bed, in their own home, for the study duration.
5. Could use electronic entertainment or communication devices (e.g. mobile phones/tablets) in bed for the seven nights of The Reading Trial.

There were no other rules. This meant that the only difference between the intervention group and the control group was reading a book in bed, or not, for the seven nights of the study.

5.5.6 Outcomes

The primary outcome of The Reading Trial was overall sleep quality. This was measured using a scale (or questionnaire) called the 'single item sleep quality scale (SQS)' (Snyder et al. 2018); this was developed to measure sleep quality using a simple format. When compared to longer more complex questionnaires, this simple scale produced similar results (Snyder et al. 2018). After completing The Reading Trial, people rated their overall sleep quality using this visual scale, which is numbered from 0 to 10, with numbers increasing in units of one, (0 = terrible, 1–3 = poor, 4–6 = fair, 7–9 = good, and 10 = excellent).

The other outcomes we measured were sleep disturbance and daytime sleepiness. We measured Sleep disturbance using the PROMIS (Patient-Reported Outcomes Measurement Information System) Short Form Sleep Disturbance Scale (eight items each on a 5-point scale with a difference of one unit between each point on the scale). Developed by The National Institutes of Health (NIH 2020, Cella et al., 2007), The PROMIS scale measured how often people had problems connected to not having enough sleep. People's experience of 'daytime sleepiness' was measured using a 10-point scale, again the points on the scale increase in units of one. Previous studies have found this simple scale to be accurate in measuring daytime sleepiness when compared to more complex scales (Riegel et al., 2013)

For all outcomes, the time we were interested in was the seven days during which a person took part in The Reading Trial.

5.5.7 Sample size - How many people did we need to get reliable results?

We wanted to be sure that we had enough people (in other words, a large enough 'sample size') taking part in The Reading Trial to be confident that the results were reliable. To inform our sample size, we searched the literature to see how common sleep disorders were reported across different countries and in different groups of people (e.g., students, older adults). We also looked at how sleep quality was reported, e.g. sleep disturbance (sleep broken by wakening) or sleep latency (the amount of time it takes you to go from being fully awake to sleeping) and sleep duration (how long you sleep). One study of 2089 people estimated that 57% of people aged 18-70 years have enough sleep (Kerkhof 2017). This gave us some information on the number of people reporting poor quality sleep in general and, based on this information, we felt that an improvement of at least 10% would be considered meaningful.

We calculated how many people we would need to take part in the trial for us to have enough information to ensure a high chance (80%), of being able to detect a real difference in sleep quality in the two groups, and a low chance (5%), of seeing a difference that was not real or one that happened just by chance. Using this information, we estimated that we would need at least 564 people in The Reading Trial, of which 282 would be in the intervention group (reading a book in bed) and 282 in the control group (not reading a book in bed).

If a person left the trial after being placed in one of the groups, but before the trial had started, we didn't use their information. To try to lessen the possibility of this happening, people were placed in their groups on the same day as they started the trial. We tried to include everyone who began the trial in our calculations. If someone left the trial, we asked that person if we could still collect information important to the study even though they were no longer taking part in the trial. We recorded all information and communication with people taking part in the trial on a database that was only accessible to the research team. We analysed the data by looking at the outcomes for people in each group who completed the outcome assessments at Day 7. We also used a method of data analysis called intention to treat which analysed the information of everybody randomised in The Reading Trial based on the groups to which they were allocated and whether they completed the trial or not.

As The Reading Trial took place over a short time frame (7 days) and was a low-risk study, the Steering Group, a group of people that provided overall supervision of the trial, decided that a Data Management Committee would not be necessary for this study. The ethics committee, a committee whose role is to protect people taking part in research (World Health Organisation 2009), were happy with this decision.

5.5.8 Analysing information

In this section, we will describe the different analyses we carried out in to check if reading a book at night is likely to improve quality of sleep.

We analysed the data collected on everybody who completed The Reading Trial based on which of the two groups they were randomly allocated to. Not everyone completed the outcome assessments at Day 7, in fact 217 (21.9%) people did not. This can create problems when analysing trial data, so we repeated the analysis just described, but this time filled in gaps in the data using a statistical technique called *imputation*. This uses the data we do have from participants to estimate what the missing data might have been and allowed us

to see how sensitive our results were to missing data. We found that reading a book before going to sleep still improved sleep quality.

5.5.8.1 Main Outcome

We calculated our sample size to detect a difference in the amount of people with improved sleep quality. We measured sleep quality on a visual scale that went from 0 to 10. This allowed us to consider whether people had improved quality of sleep, no change, or a worse quality of sleep from the start to the finish of the trial. We then compared this information for people in the intervention group (reading a book in bed) with people in the comparator group (not reading a book in bed). We looked at the data to see how certain we could be of our findings. We checked the data by creating graphs and summaries that would help us identify unusual values that needed further checking.

Once we were happy that the data were correct, we created graphs to help us check visually whether the two groups were similar at the start of the trial (i.e. that randomisation worked). We also checked if our findings weren't simply a result of other differences between the groups. We did this by working out the 'typical', or most likely value for each measurement and then looking at how these were different from person to person and between the intervention (reading a book in bed) and the control group (not reading a book in bed). This information is not only useful to this trial but to help design future trials that also wish to compare sleep quality.

We compared the overall sleep quality between people in the intervention group and people in the control group. We used a statistical model, called a Proportional Odds Model, that take into account that sleep quality in The Reading Trial was measured using categories (i.e. 'terrible' being the worst sleep quality through to 'excellent' being the best sleep quality) as well as the influence of:

- initial sleep quality
- gender
- age
- knowledge of clinical trials
- whether they worked in healthcare or not.

As part of the main analyses, we looked at whether a person's quality of sleep improved from the start to the finish of the trial. We compared this information for people in the

intervention group with people in the control group to see if the proportion of people with improved sleep was likely to be different in general.

5.5.8.2 Secondary outcomes

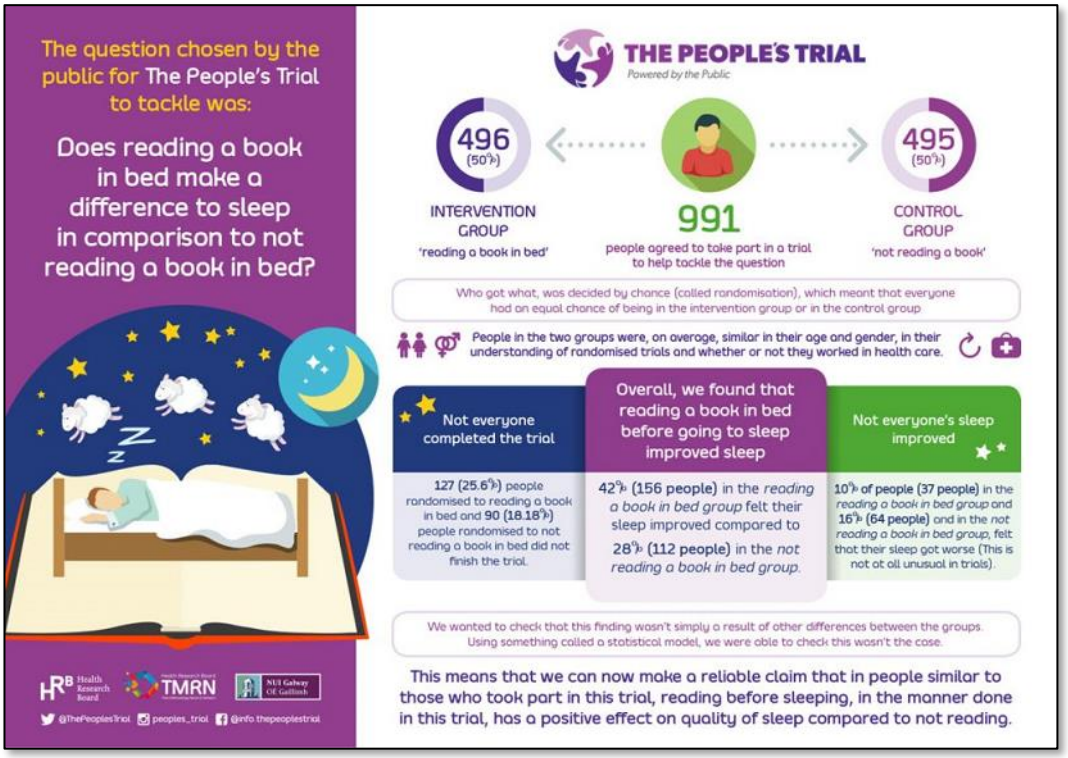
We looked at changes in sleep disturbance and daytime sleepiness between the intervention and control groups. This time we used a statistical model, called a Linear Model, which took into account that sleep disturbance and daytime sleepiness are measured as a score (i.e. sleep Disturbance was measured on a 5-point scale, daytime sleepiness was measured using a single 10-point scale). Once again, we took into account the influence of people's initial sleep quality, gender, age, knowledge of clinical trials and whether a participant worked in healthcare or not.

To make sure our findings were not simply a result of chance, we decided, before we did any analyses, what level of certainty we would need to see in order to claim that reading a book in bed is beneficial to people similar to those who took part in The Reading Trial. The value generally used in clinical trials to represent this level is 0.05, meaning that there is a 1 in 20 chance of falsely claiming that the intervention (reading a book in bed) worked and this is the value we used for The Reading Trial.

5.6 Results

An infographic showing the key results of The Reading Trial is shown in Figure 5.1.

Figure 5.1: The Reading Trial results



Between 4th December 2019 and 30th December 2019, a total of 991 people took part in The Reading Trial. These 991 people were placed into one of two groups: 496 (50%) in the 'reading a book in bed' group (called the intervention group) and 495 (50%) in 'not reading a book' group (called the control group). Although The Reading Trial needed 564 people to reach its target sample size, *The People's Trial* aimed to help the public learn about randomised trials, so people continued to join the trial after this number was reached.

Not everyone completed the trial. This sometimes happens in trials, even though it is something researchers would like to avoid. In this trial, 127 (25.6%) people randomised to reading a book in bed (the intervention group) and 90 (18.18%) people randomised to not reading a book in bed (the control group) did not finish the trial. People who didn't complete the trial were mainly younger (158/217 (73%) were aged 44 years or younger) or told us they didn't have good sleep quality to start with (146/217 (67%) of people who didn't finish the trial told us they had fair, poor or terrible sleep to begin with).

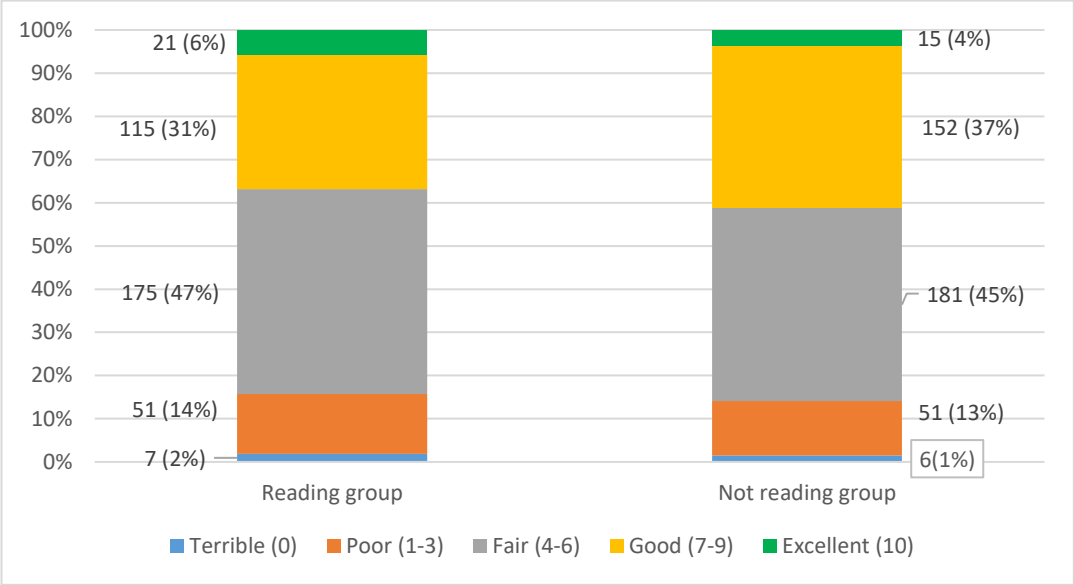
In the end, 774 people from 43 countries; 369 (47.67%) people in the intervention group and 405 (52.33%) in the control group, stayed in The Reading Trial to the end. The characteristics of these 774 people are presented in Table 5.1.

Table 5.1: How similar were people in the two groups (reading a book in bed and not reading a book in bed) at the start of the trial? Data are numbers of people (%)

People who took part in The Reading Trial	Reading Group (n=369) n (%)	Not Reading Group (n=405) n (%)
Age:		
• 18 - 24 years	21 (6%)	28 (7%)
• 25 - 44 years	193 (52%)	209 (51%)
• 45 - 64 years	123 (33%)	145 (36%)
• 65 years and over	32 (9%)	23 (6%)
Gender:		
• Female	289 (78.3%)	325 (80.2%)
• Male	75 (20.3%)	78 (19.2%)
• Prefer not to say/ self-describe	5 (1.3%)	2 (0.5%)
Understanding of randomised trials:		
• Good understanding	251 (68%)	278 (69%)
• Some understanding	101 (27%)	105 (26%)
• No understanding	17 (5%)	22 (5%)
Healthcare background:		
• Healthcare	238 (64.5%)	269 (66%)
• Not healthcare	131 (35.5%)	136 (34%)

The characteristics of people in the two groups were, on average, similar at the start of the trial (See table 5.1). Also, people in both groups told us they had similar sleep quality at the beginning of the trial (see Figure 5.2). Randomisation worked to make the two groups as similar as possible at the time people joined the trial. There were some small differences. We look at what impact these might have had later in this analysis.

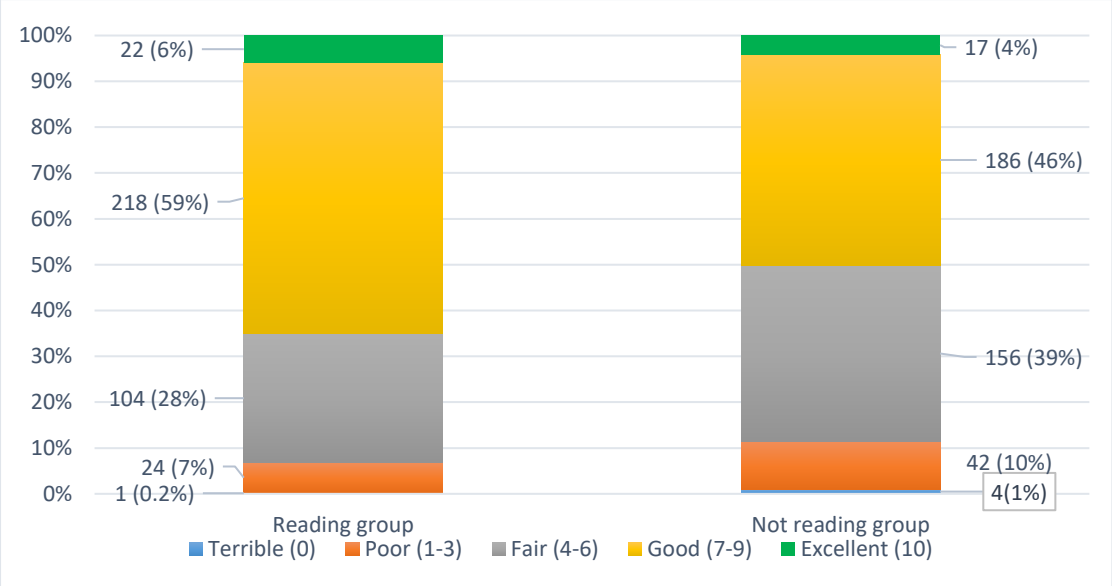
Figure 5.2: Sleep quality at the start of The Reading Trial People rated their overall sleep quality at the start of the trial using a visual scale (from 0 to 10), which increased in units of one (0 = terrible, 1–3 = poor, 4–6 = fair, 7–9 = good, and 10 = excellent).



When we looked at the sleep quality at the end of the trial those in the reading group tended to have better overall sleep quality (Figure 5.3).

Figure 5.3: Sleep quality at the end of The Reading Trial

People rated their overall sleep quality at the end of the trial using a visual scale (from 0 to 10), which increased in units of one (0 = terrible, 1–3 = poor, 4–6 = fair, 7–9 = good, and 10 = excellent).



We also found that people in the intervention group (reading a book in bed) had lower sleep disturbance, on average, compared to those in the control group (not reading a book in bed) (see Table 5.2). However, we did find a very slight increase in the average daytime sleepiness in the reading group.

Table 5.2: What did sleep quality look like in the two groups (reading a book in bed and not reading a book in bed) at the end of the trial?

Sleep quality at the end of the trial	Reading Group (n=369) n (%)	Not Reading Group (n=405) n (%)
• Terrible	1 (0.27%)	4 (0.99%)
• Poor	24 (6.50%)	42 (10.4%)
• Fair	104 (28.2%)	156 (38.5%)
• Good	218 (59.1%)	186 (45.9%)
• Excellent	22 (5.9%)	17 (4.25)
Sleep Disturbance[7] Mean[4] (sd)[5] Median (min, max)~	46.7 (7.97) 45.5 [28.9, 70.8]	49.9 (7.94) 50.1 [28.9, 73.0]
Daytime Sleepiness[8] Mean (sd) Median[6] (min, max)	6.86 (1.93) 7 [0, 10]	6.15 (2.05) 7 [0, 10]

When we looked at each participant to see how many told us they had improved, had no change, or had a worse quality of sleep from the start to the finish of the trial, we found:

- Overall, **reading a book in bed before going to sleep improved sleep quality**. In the intervention group (reading a book in bed), 42% (156 people) felt their sleep quality improved compared to 28% (112 people) in the comparator group (*not reading* a book in bed), a difference of 14% favouring the intervention group.
- When we take into account how certain we are of this finding, we estimate that the difference is likely to be between 8% and 22%.

4 Mean tells us the average sleep disturbance score indicated by people who took part in The Reading Trial.

5 The standard deviation (sd) tells us the amount of variability we found in the individual scores people reported for sleep disturbance compared to the mean score.

6 The median tell us what the "middle" score was in the list of scores indicated by people when we asked them to score their daytime sleepiness after taking part in The Reading Trial.

7 We measured Sleep disturbance using the PROMIS (Patient-Reported Outcomes Measurement Information System) Short Form Sleep Disturbance Scale (eight items each on a 5-point scale with a difference of one unit between each point on the scale).

8 Daytime sleepiness' was measured using a 10-point scale. The points on the scale increase in units of one.

- Although reading improved sleep quality overall, not everyone's sleep improved. 10% of people (37 people) in the reading group and 16% (64 people) in the not reading group felt that their sleep got worse (Figure 5.3).

It is highly unlikely, a probability of less than 0.001 (much less than 1 in 20 (0.05)), that we would have seen this improvement in sleep quality in people due to chance alone. This probability is called a 'p-value' and is typically reported in the results of a trial. As it is much less than our threshold of 0.05, there was convincing evidence that people in the intervention group (reading a book in bed) were more likely to have better overall sleep quality than those in the control group (not reading a book in bed).

Not surprisingly, a person's sleep quality at the start of the trial influenced their sleep quality at the end of the trial.

There was little evidence that a person's gender, age, knowledge of clinical trials, or whether they worked in healthcare, played an important role in sleep quality at the end of the trial.

We also found evidence that people in the intervention group (reading a book in bed) experienced less sleep disturbance compared to people in the control group (not reading a book in bed). We found that sleep disturbance is likely to be lower, on average, by between 2 and 4 units when reading a book in bed before sleeping. As sleep disturbance is recorded on a scale from 1 to 100 this is the same as saying that sleep disturbance is likely to be lower by 2% to 4% in those that read a book before sleeping.

We found that daytime sleepiness is likely to be higher, on average, by between 0.5 and 1 unit for people in the intervention group (reading a book in bed). As daytime sleepiness is recorded on a scale from 1 to 10 this is the same as saying that daytime sleepiness is likely to be higher by 5% to 10% in those that read a book before sleeping.

Even though sleep disturbance was lower in the intervention group (reading a book in bed), the decrease is small and likely to have little impact practically. Similarly, although daytime sleepiness was higher in the intervention group, again the increase was very small and likely to have little impact.

5.7 Serious adverse events

The question The Reading Trial explored included a familiar, accessible, low-risk intervention (reading a book in bed) and comparator (not reading a book in bed). Using an 'every day'

intervention lessened the risk of people experiencing any harm from the intervention. Using a common intervention also made the question relevant for a wider group of people. No adverse events were reported during The Reading Trial or in the follow-up period.

5.8 Discussion

Sleep problems are relatively common with one in four people reporting that they don't sleep well. This causes different issues for different people; for some, its difficulty getting to sleep and for others, it is staying asleep. However, despite being a common problem that can severely affect a person's quality of life, it is often under-diagnosed and under-reported to health care providers (Filip et al. 2017, Blunden et al. 2004). When it is reported, the most common treatment for insomnia is medication (Montgomery 2002). It is estimated that approximately one-third of adults age 50 and older in the United States take sleep medication (McLeod et al. 2018). While non-drug sleeping aids are available, such as cogitative behaviour therapy (CBT), these often require significant time and commitment (MacLeod et al., 2018). They can also be costly.

The Reading Trial evaluated a low cost, accessible intervention that potentially affects sleep quality. The Reading Trial demonstrated that in a group of people similar to those who took part in the trial, reading a book in bed before sleeping improves sleep quality compared to not reading a book in bed. We found that reading in bed before sleep not only potentially improves overall sleep quality but also people in the reading group experienced fewer problems staying asleep. While we did find a higher rate of daytime sleepiness in people allocated to reading a book in bed, the difference we found was very small and likely to have little impact on a person's daytime sleepiness in practice.

Recent studies highlight the positive effects of public and patient involvement in clinical trials, including increased health literacy and knowledge of trial processes (Mann et al., 2018, Price et al., 2018), People who took part in The Reading Trial experienced the process of randomisation first-hand and discovered through a lived experience, why this is important. They learnt what makes a 'good' trial question and thought about how we might conduct the trial, identify and measure outcomes and how we might best share the trial results.

The Reading Trial had a number of strengths. It included a large, diverse sample of participants that provided a more accurate measure of the effect of reading a book in bed on overall sleep quality in the general public. We used a randomised trial design, which is

considered the gold standard when measuring the effect of an intervention. The public showed, through an online survey, their preference for how we should measure the outcome 'sleep'. We prioritised the outcomes (overall sleep quality, sleep disturbance and daytime sleepiness) based on this response, leading us to choose 'overall quality of sleep' as the primary outcome. We also used an online format to invite people to take part in the trial and ran the trial online, which enabled the involvement of members of the public in clinical research.

As with any study, The Reading Trial had some limitations. We assessed the effect of reading a book in bed on sleep quality for seven nights. We do not know if continuing to read in bed before sleep in the manner suggested in the Reading Trial, would increase, decrease, or maintain the effect we found on overall sleep quality. People who took part in The Reading Trial told us the effect, if any, the intervention (reading a book in bed) made to their sleep using an online questionnaire. When people self-report the effects of an intervention in this way, it may lead to an over or under-estimation, of the true effect of the intervention. This is known as response bias, and it occurs when the person completing a questionnaire, mistakenly tries to make themselves or the intervention appear 'better', even when the survey is anonymous (Spitzer 2019, Rosenman et al. 2011).

While online trials are becoming more common, we believe that The Reading Trial was special. It was a trial designed *by the people, for the people*. The Reading Trial needed people to get involved and create each step of the trial process. It would only be successful if people embraced the trial they had created. While *The People's Trial* offered people an opportunity to learn about randomised trials, its little sister, The Reading Trial, offered almost one-thousand people the experience of actually taking part in a trial, in a low risk, accessible environment.

Moreover, we believe the results. The Reading Trial was a real trial following standards those who work professionally in trials would recognise. Involving the public directly in design decisions does not compromise rigour, but it does increase relevance.

5.9 Conclusion

Overall, we found that reading a book in bed before sleeping, in the manner done in this trial, improves the quality of sleep compared to not reading a book in bed before sleeping. Getting people to take part in randomised trials can be difficult. Supporting public knowledge and

understanding of the reasons why we do randomised trials and why they are important, has a positive impact on public engagement. Involving the public directly in design decisions as done in *The People's Trial*, helps not only public understanding but improves our trials.

5.10 Declarations

5.10.1 Ethical approval

The People's Trial, which includes The Reading Trial, received ethical approval from the NUI Galway Research Ethics Committee.

5.10.2 Role of the funding source

This research was funded by the Health Research Board in Ireland, through the Health Research Board – Trials Methodology Research Network as part of a Knowledge Exchange and Dissemination Scheme Award 2018 (grant reference KEDS-2018-012).

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit.

5.10.3 Trial registration

Registered on 4th December 2019 with ClinicalTrials.gov, ID: NCT04185818. (https://clinicaltrials.gov/ct2/show/NCT04185818?cond=Citizen+Science%3A+The+People%27s+Trial%3A&draw=2&rank=1). The study adheres to CONSORT guidelines for randomized trials.

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Chapter 6: Discussion

Here I provide an overview of the work undertaken and discuss the overall body of work. I outline the concept behind each project and the key findings of each, identifying the gaps in knowledge addressed. I discuss implications for practice and policy if any, and the suggestions for future research in this space.

6.1 Outline of thesis

This thesis is made up of four papers, all offer new insight and evidence contributing to knowledge and learning.

Section 1:

I undertook a Cochrane Systematic review and meta-analysis to assess the current evidence on membrane sweeping to prevent a formal induction of labour, a common obstetric intervention (chapter 2). The findings of this review informed the design and methodology of my 2nd paper, a feasibility study protocol, to assess the feasibility of, and inform the optimal design of a future proposed definitive randomised trial to examine the effectiveness (including optimal timing and frequency) of membrane sweeping to prevent post-term pregnancy (chapter 3).

As discussed previously, the next step in this journey should have been to conduct The MILO Study. However, with the onset of the coronavirus pandemic the direction of my PhD changed to focus on another randomised trial, *The People's Trial*.

Section 2:

The People's Trial focused on supporting members of the public to critically assess health claims they see, hear, and read about through multiple mediums. We did this by inviting members of the public to get involved in all stages of a clinical trial. *The People's Trial* process paper (Chapter 4) describes this journey. My final paper, (chapter 5) reports on a trial directly informed by *The People's Trial*. It is reported using a plain language format, as directed by the findings of *The People's Trial*.

6.2 Key findings

6.2.1 Membrane sweeping for induction of labour - Cochrane systematic review and meta-analysis

This Cochrane systematic review and meta-analysis assessed the effects and safety of membrane sweeping for induction of labour in women at or near term (≥ 36 weeks' gestation). It included 44 trials reporting data for 6940 women.

A key finding was that membrane sweeping may promote spontaneous labour. However, overall, the certainty of the evidence was low. This indicated a clear need for further robust evidence to inform the use of this intervention clinically. Also, we found a lack of evidence to inform the optimal time (gestation) and frequency to perform a membrane sweep. Maternal experience of, and satisfaction with this intervention are intrinsic to its clinical use and the findings of our review indicate that further evidence is needed to meaningfully explore this aspect of the intervention and therefore inform decision-making. Similarly, membrane sweeping offers a potentially low-cost alternative to a formal induction of labour; however, we found limited data addressed this. The results of this review, and meta-analysis, add to the body of existing evidence on membrane sweeping, potentially informing national and international guidelines in this space.

6.2.2 Membrane sweeping for induction of labour: The MILO Study

This study was informed directly by the findings of the Cochrane systematic review. The paper presents a methodologically robust, protocol to conduct a multi-site, randomised controlled, feasibility study. Although, due to the coronavirus pandemic, recruitment did not commence in time for inclusion of the trial results in this thesis, The MILO study presents an important opportunity to inform a future clinical trial on the effectiveness of membrane sweeping to prevent post-term pregnancy.

6.2.3 The People's Trial: supporting the public's understanding of randomised trials.

The People's Trial successfully engaged the public in an online learning initiative. Over 3000 members of the public, from 72 countries, participated in *The People's Trial*. Each phase of the trial offered methodological learning opportunities for participants. While directed primarily towards supporting public understanding and knowledge of randomised trials, *The People's Trial* offered unique insights to researchers, highlighting a public appetite to collaborate in all aspects of trial design and insight into how trial results might be better

disseminated to trial participants and the public. The custom-built website hosting the trial, including all education videos developed during the trial; remain active with all phases available for review providing continuous learning opportunities.

6.2.4 *Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed? The People's Trial- an online, pragmatic, randomised, controlled trial*

During December 2019, 991 people took part in The Reading Trial, 496(50%) in the intervention group, and 495(50%) in the control group. The results of The Reading Trial were reported using a plain language format, as requested by the public. The results indicate that reading a book in bed, before going to sleep, improved sleep quality. The findings further suggest that reading a book in bed before sleeping, in the manner done in this trial, results in slightly less sleep disturbance. Although the decrease in sleep disturbance was very small and likely to have little practical impact. We also found a slight increase in daytime sleepiness in the intervention group. However, again the increase was very small and likely to have little impact. The Reading Trial also highlighted the role of social media in recruiting participants and the potential for online trials to support inclusion and accessibility.

6.3 Discussion

6.3.1 Cochrane systematic review & meta-analysis

Evidence-based practice uses the most reliable and robust evidence, people's values and preferences, and clinical expertise, to inform clinical decisions (Sackett et al., 1996). To support clinicians, patients, and members of the public in their decision-making, the most current evidence must be available (Sackett et al., 1996). A systematic review identifies and evaluates all the evidence available to answer a research question. Combining this evidence, systematically, is more likely to provide reliable, robust evidence on which to inform healthcare decisions (Cochrane 2020).

To that end, I undertook a Cochrane systematic review to evaluate all current evidence on the effectiveness of membrane sweeping in preventing a formal induction of labour. This Cochrane systematic review is an update of a 2005 review of the same title**.** It includes 44 studies, 20 new to this update, and reported data for 6940 women and their infants. The original review included 22 trials, reported data for 2797 women and was last updated in 2009. Ten studies were added to the 'studies awaiting classification' at that time. The

decision was taken to update the review, rather than start afresh, as updating systematic reviews with new evidence is considered a more efficient method (Garner et al. 2016)

Although this was an update to an existing review, it is different from Boulvain et al. (2005), in several important ways. I made significant changes, including the addition of new comparisons and outcomes, and the use of updated methodology, including an updated risk of bias assessment, which was applied to all studies including those in the original review. The 2005 review by Boulvain et al. incorporated a standardised protocol, which was used to frame this review (Hofmeyr et al., 2000). However, the protocol was updated with the agreement of the Cochrane Pregnancy and Childbirth editorial team.

6.3.1.1 Agreements and disagreements with the previous version of this review

Finucane et al., (2020) concluded that membrane sweeping may be effective in achieving a spontaneous onset of labour. It reported that membrane sweeping potentially reduces the incidence of a formal induction of labour. The overall finding of our review differs from the conclusion reached by Boulvain et al., (2005), which found that the '*routine use of sweeping of membranes from 38 weeks of pregnancy onwards does not seem to produce clinically important benefits*' and that its use in reducing the necessity for a formal induction of labour should be *'balanced against women's discomfort and other adverse effects*' (Boulvain et al., 2005).

Our findings, on the effectiveness of membrane sweeping, differ for several reasons, including the addition of new studies (data from twenty new studies were added to this update) and updated review methods. These differences are discussed below:

Within Boulvain et al., (2005), the risk of bias was assessed for random sequence generation and allocation concealment only. The current review assessed the risk of bias through dual independent assessment of all included studies, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). Bias can affect the results of studies causing inaccuracies including false positive or false negative results (National Health and Medical Research Council 2019). Assessing risk of bias supports the interpretation of findings in the context of our review. Due to potential clinical heterogeneity (differing methods for performing the sweep e.g. 10/44 studies did not describe how they performed the sweep, differing gestations, differing obstetric history) we used a random-effects model to perform a meta-analysis. This model assumes that there are differences in

the effects measured by each of the included studies (Higgins et al., 2019). Therefore, our reported effects are an estimate of the mean of the distribution of effects in the included studies. This is in contrast to Boulvain et al. 2005, where a fixed-effects model was used to undertake the analysis.

Our review incorporated the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework to grade the quality of the evidence presented within the systematic review. Although it can be argued that GRADE methodology can produce subjective findings, it offers a transparent method for grading evidence (Siemieniuk & Guyatt 2020). We also included Summary of Findings tables to present a summary of the main results for each comparison supporting accessibility (Schünemann et al., 2020).

Our review included a significant addition to the comparisons evaluated in the review. We included a comparison of amniotic membrane sweeping versus differing frequencies of amniotic membrane sweeping. This was in response to a request for evidence from international guidelines (NICE 2008). This comparison highlighted the dearth of evidence to support how this intervention should be administered, a crucial factor to inform clinical practice. We found just one study (n=355 women) comparing once-weekly with twice-weekly membrane sweep and a sham procedure.

Another significant difference between this update and the earlier version of the review is the inclusion of new outcome measures. Boulvain et al., (2005) did not include 'spontaneous onset of labour' as an outcome measure. They did, however, conduct analysis on outcomes that were not pre-specified e.g., 'not in labour or not delivered within 48 hours and 'not delivered within one week', and discussed the spontaneous onset of labour within this context, stating that membrane sweeping '*generally reduces the delay between randomisation and spontaneous onset of labour*'. This statement agrees with the finding of our review, where we found that in comparison to expectant management, or doing nothing, women who received a membrane sweep were, on average, 21% more likely to experience a spontaneous onset of labour (average risk ratio (RR), 1.21 95% confidence interval (CI) 1.08 to 1.34).

While Boulvain et al., (2005) included vaginal delivery as an outcome measure; it was restricted to vaginal birth within 24 hours. However as noted by Boulvain et al., (2005), '*Because sweeping of membranes is not generally aiming at inducing labour in the short-term and is usually performed as an outpatient procedure, primary outcomes as 'vaginal delivery*

not achieved in 24 hours'…was not reported by the investigators'(Boulvain 2005). Taking this into consideration, and to include as much evidence as possible to inform our review findings, the decision was taken to remove the constrictions imposed by this time limit. Therefore, for the comparison 'amniotic membrane sweeping versus no treatment/sham', our review reported data from 26 studies for the outcome 'spontaneous vaginal birth'.

In addition, we included 'Induction of labour' as an outcome for our review. Membrane sweeping is often used as a precursor to, or in conjunction with, formal methods of induction of labour. Therefore, it was important to include these data in the review to inform clinical guidelines and practice. Notably, our review found that when comparing membrane sweeping with no treatment or sham, women receiving a membrane sweep were, on average, less likely to experience an induction of labour (average RR 0.73, 95% CI 0.56 to 0.94). While this is a significant outcome to inform clinical practice, it should be noted that the certainty of the evidence was low.

Women's satisfaction, in the previous version of this review, was based on the findings of two studies (Boulvain et al., 1998; Wong et al., 2002), which reported data for this outcome. In agreement with Srivastava et al., (2015), we believe maternal satisfaction is more complex and faceted than simply measuring pain, as in the previous version of this review, and we therefore adopted a broader outcome of maternal satisfaction. We found, that although women describe experiencing pain and discomfort when receiving a membrane sweep, most women also reported they would choose this intervention in subsequent pregnancies. In addition, when asked about satisfaction, a significant majority described a positive experience, reporting that the potential advantages of the intervention outweighed the disadvantages (de Miranda et al., 2006). This finding has implications for the narrative surrounding membrane sweeping in the clinical context.

In the current climate, cost-effectiveness, or cost savings, are often a driver of health decisions (Toffoli et al., 2018). This coupled with the economic implications of increasing rates of induction of labour is of concern to overstretched healthcare services. Therefore, we included 'cost' as an outcome of the review. However, we found just two small studies (n = 290 women) reporting a cost analysis (Magann et al., 1998b; Magann et al., 1999). While these studies reported significant cost savings associated with membrane sweeping, we suggest that further research, with larger sample sizes, is warranted in this space.

6.3.1.2 Agreements and disagreements with other studies or reviews

The results of our review differ from a review conducted in 2010 (Rogers 2010). Rogers found '*no statistically significant difference in the length of the gestation of pregnancy when women who had received a single cervical sweep were compared with those who had not*'. This review, which included three randomised trials and reported data for 419 women, noted that the inclusion of few studies, with a small sample size, was a significant limitation (Rogers 2010).

Our Cochrane review and a 2019 review by Avdiyovski et al., (2019) both find evidence for the effectiveness of membrane sweeping for the promotion of spontaneous onset of labour. Our Cochrane review contains all studies included in the review by Avdiyovski et al., (2019) However, there are significant methodological differences between our review and Avdiyovski et al., (2019) (including the use of different models for meta-analysis and the use of GRADE).

While Avdiyovski er al., (2019) reports an increase in the risk of premature rupture of membranes in women receiving a membrane sweep (RR 1.23 95% CI: 0.957–1.582), the confidence interval crosses the line of no effect, implying there is little to no difference between the groups. This finding agrees with Boulvain et al., (2005). In addition, Avdiyovski et al. (2019) report findings for subgroup analysis of 'single versus multiple membrane sweeping'. However, this is a subgroup analysis with significant statistical heterogeneity (I^2=69%, p=.039). Also, subgroup analysis of the 'effectiveness of membrane sweeping by gestation' was broadly assessed by Avdiyovski et al. (2019) as membrane sweeping pre-and post-40 weeks' gestation. While both gestations were found to 'be favourable in promoting spontaneous labour', Avdiyovski et al. (2019) appear to compare the effect of treatment on the outcome separately within each subgroup. This approach potentially leads to multiple testing errors because instead of using only one calculation to test subgroup interaction effects, two different calculations are required for each subgroup analysis.

These findings highlight an absence of high-quality evidence on the optimal gestation and frequency of membrane sweeping during pregnancy, demonstrating the need for continued research in this area. Further, in agreement with our conclusions, Avdiyovski et al., (2019) recommend further research to explore women's experiences of membrane sweeping

6.3.1.3 Significance of the results

Our review found that overall membrane sweeping appears to be effective in promoting the spontaneous onset of labour in women at or near term (> 36 weeks' gestation). Significantly, it also found that it potentially reduces the risk of a woman undergoing a formal induction of labour. The results from this systematic review and meta-analysis add to the body of existing evidence around membrane sweeping, offering new evidence to support national and international guidelines.

6.3.1.4 Strengths and limitations of the review

Our review includes a large sample size, 44 studies, 22 to this update, reporting data for 6940 women and their infants. We performed a methodologically robust systematic review and meta-analysis using reproducible methods. Our review team included people with extensive experience in conducting systematic reviews and meta-analysis, and people with topic expertise. We assessed the certainty of the evidence using GRADE and reported findings in this context. The evidence was found to be generally low quality, mainly due to study design, inconsistency, and imprecision. Therefore, results must be interpreted with caution. Although we included uterine hyperstimulation with/without fetal heart rate (FHR) change, uterine rupture and neonatal encephalopathy as outcome measures, none of our included studies reported on these outcomes. In addition, we found no studies that compared membrane sweeping with amniotomy only or mechanical methods. In 2018, after completion of our data extraction, a core outcome set (COS) was developed to standardise reporting of trials on induction of labour (Dos Santos et al., 2018). Although our systematic review reports many of the outcomes in that COS, we did not include all the suggested outcomes (i.e., postnatal depression and time from induction of labour to delivery). This COS should be the guiding framework for all future reviews in this space.

6.3.1.5 Implications for practice

Current national and international, guidelines state that all women at or near term should be offered a membrane sweep (NICE 2008). However, maternity hospitals and clinicians working within the maternity services adopt these guidelines ad hoc (Kenyon et al., 2017). This has been linked to a lack of confidence in the effectiveness and safety of membrane sweeping (Roberts et al., 2020). The current guidelines are informed by an outdated systematic review and international bodies (NICE 2008) have requested an update to the previous version of this review. Our review offers evidence to inform and update this guidance.

6.3.1.6 Implications for research

Although our review reports the current evidence on membrane sweeping, the certainty of this evidence overall was found to be low, therefore we recommend further robust randomised controlled trials be undertaken to evaluate the efficacy of membrane sweeping in preventing a formal induction of labour.

We do not know if having a membrane sweep at 36 weeks completed gestation, has the same effect as having a sweep at 41 weeks' gestation. None of the studies included in this review reported on the potential effect differing gestations may have on membrane sweeping. Similarly, we do not know the potential effect differing intensities of membrane sweeps (i.e., number and timings of sweeps) may produce. However, these research questions have been posed by international guidelines for several years (NICE 2008).

As with any intervention, it is crucial to understand the perception and experience of all involved. With this intervention, the views and experiences of women have been under-represented (Roberts et al., 2020). While previous research has focused on 'pain', often simply assessing pain scores, the results of this review, demonstrate that maternal satisfaction is more complex. Further research on women's experiences and views of membrane sweeping is needed to inform the clinical narrative of this intervention.

As discussed, cost-effectiveness is an increasing focus for our health services. Membrane sweeping potentially offers a low-risk, low-cost method to prevent a formal induction of labour. However, there is a lack of data to ensure a meaningful discussion in this space. Few studies have assessed the cost implications of this intervention, particularly in the Irish and European context. Further studies should be undertaken to address this knowledge gap.

6.3.2 Membrane sweeping for induction of labour: The MILO Study

The design of this feasibility study protocol was directly informed by the above recommendations (section 6.3.1.6).

The MILO Study protocol was developed to inform the optimal design of a future definitive randomised trial to examine the effectiveness (including optimal timing and frequency) of membrane sweeping to prevent post-term pregnancy (Finucane et al., 2020). Conducting a feasibility study before a definitive trial ensures all methodology and process components of the trial have been tested in 'real world' scenarios, thereby reducing the risk that public

money and resources will be committed to a trial that does not work or is fundamentally flawed (Morgan et al., 2018, De Meulemeester et al., 2018). The design of the feasibility study was informed by current reporting guidelines (Eldridge et al., 2016).

Clinical equipoise exists when the clinical community disagrees with or is unsure of the effect of an intervention (Cook & Sheets 2011). As membrane sweeping is an intervention used ad hoc in Irish maternity hospitals, we conducted an informal telephone survey (Dec 2018), on current policy and practice regarding membrane sweeping in the six largest national maternity hospitals (The National Maternity Hospital, The Coombe, Women's and Infants University Hospital, The Rotunda Hospital, University Hospital Galway (UHG), University Maternity Hospital Limerick (UMHL) and Cork University Maternity Hospital (CUMH)).Using informal, descriptive conversations, we requested information on the practice of membrane sweeping to prevent a formal induction of labour within each site. The publicised gudelines on induction of labour within each hospital were also reviewed for this purpose. We found that two of the six hospitals, UHG and The Coombe, Women's and Infants University Hospital, refer to the use of membrane sweeping in the information provided to women on the induction of labour. The other four maternity hospitals do not have a policy on membrane sweeping. All hospitals surveyed report the use of membrane sweeping as '*sporadic*', '*not routinely offered'*, '*dependent on individual clinicians views*', and not an intervention '*that is bedded into practice*'. In addition, data were collected on national induction of labour methods and rates using the Irish Maternity Indicator System, a national instrument reporting monthly and annual data from Irish maternity hospitals that supports comparison across maternity hospitals. Data were transcribed and themes noted from these sources using a systematic approach. This provided an overall view of the current policy and practice regarding membrane sweeping within the Irish maternity healthcare system.As the MILO Study is assessing the effectiveness and optimal timing and frequency of a membrane sweep to prevent a formal induction of labour, we embedded a 2x2 factorial design within a two-arm parallel-group design to answer these questions. This allows us to evaluate efficiently the feasibility of a future trial to answer the primary question "is membrane sweeping effective in preventing post-term pregnancy" while also addressing the effectiveness of different timings and frequency of membrane sweeping. The main advantages of using a factorial design are sample size efficiency and cost-effectiveness. Using a factorial design, we will assess two separate questions simultaneously in the same population. Offering a more efficient and effective use of available resources when compared to running two separate parallel trials (Torgerson & Torgerson 2008, Pandis et al., 2014).

The MILO Study will be conducted in the antenatal outpatient departments of two Irish maternity hospitals, Limerick University Maternity Hospital and The Coombe, Women's and Infants University Hospital. We chose these hospitals are they have a combined annual birth rate of more than 13,000 and provide a tertiary level service to women from diverse socioeconomic, ethnic, and cultural backgrounds.

Cognisant of conducting a randomised trial in an already overstretched area, we developed The MILO Study to minimise its impact on the clinical area. We aligned the MILO Study intervention and comparator to the standardised schedule for antenatal visits, as outlined in the Health Service Executive, Maternity and Infant Care Scheme (HSE 2020). We did this for two reasons 1) to minimise disruption to clinic practice and the workload of participating clinicians and clinics and 2) to maximise the potential population from which we would recruit. Recruitment to clinical trials is often challenging with many trials unable to complete recruitment within their pre-specified timeframe (Treweek et al., 2018). This can be particularly true with the recruitment and retention of pregnant women who are often under-represented in clinical trials (Frew et al., 2014). Assessment of recruitment processes will be a vital part of the feasibility study to inform a future definitive trial. To consolidate this strategy, I met with Midwifery and Clinical managers in both sites, to introduce the MILO Study, discuss logistics, and agree on our intervention schedule. The MILO Study includes four work packages, including a health economic analysis, a qualitative study, and a Study Within A Trial (SWAT). All were designed to align with and complement the MILO Study question and mitigate disruption to clinical practice.

I advertised shortlisted and interviewed, midwives for the role of Research Midwife within the MILO Study. I liaised with Human Resources to issue contracts to the successful midwives, both of whom are current employees within the clinical sites. Providing dedicated research midwives, supports continuity of care, a concept highlighted by Bedson et al., (2014) as a facilitator to successful recruitment. Also, in the current climate, this recruitment strategy is advantageous, as women will not be exposed to additional personnel at each visit, reducing their risk of infection.

To promote intervention fidelity, I will facilitate scheduled training events, which all clinicians will attend. Training documentation to accompany these events are designed to support clinician learning. To support the online randomisation of participants, I liaised with Sealed Envelope©, an online software company specialising in randomisation, and developed

inclusion and exclusion parameters for this program and tested the randomisation program to produce a working randomisation tool for The MILO Study.

6.3.2.1 Challenges

In March 2020, The World Health Organization declared a global pandemic (World Health Organization 2020). It presented unforeseen and unique challenges to the conduct of clinical trials (Mitchell 2020). As with all other aspects of life, it caused significant clinical disruption, causing health services to make drastic and immediate changes to their usual practice. National screening initiatives were halted, and elective clinical procedures were postponed (Health Service Executive 2020). Similarly, COVID-19 had an immediate effect on the conduct of clinical trials, particularly trials at the recruitment stage (van Dorn, 2020).

The MILO Study was due to commence recruitment in March 2020, with ethical approval, study documentation, site arrangements, clinicians, and research midwives in position to support the study conduct. However, with the arrival of the COVID-19 pandemic, it was not feasible to commence study recruitment at that time.

The MILO Study will now commence recruitment in February 2021. Like many other trials, the MILO Study has adapted its design to incorporate new clinical guidelines. The current national guidelines, which advise keeping a distance of 2 meters between people, will change our approach to participant recruitment (HSE 2020). Initially, we planned to offer written trial information to women potentially eligible for participation during routine antenatal appointments. We planned to offer women an information pack, which included a letter introducing the trial and a Participant Information Leaflet and offer to answer any questions women have relating to the study. However, due to current pandemic guidelines, we will be unable to offer a room to support private discussion at the time of recruitment. Therefore, in addition to offering contact details for the research team, we will offer women, through a letter contained in the information pack, the option to provide their contact details (telephone number and/or email) for scheduled calls with the research team. The contact details will only be used for this purpose during the recruitment phase, and with the express consent of women, and will be destroyed in line with GDPR guidelines. Women will not be asked to provide consent at this time; this platform is to offer further information on The MILO Study if requested. All conversations will be followed up at the 39-week antenatal visit when the researcher will invite eligible women to participate as previously noted.

In addition, within our qualitative work package, all focus group meetings with clinicians and women will now be conducted online, as either a group or one to one meeting.

6.3.2.2 Strengths and Limitations of the protocol

Although due to the coronavirus pandemic we were unable to conduct the MILO Study to date, it is due to commence in February 2021. We have produced a robust, protocol, undergoing peer review, to conduct this study and inform the design of a future trial. The MILO Study was directly informed by a substantial systematic review and meta-analysis that ensured the trial questions were relevant and unanswered to date (Jones et al., 2013). The results from this study will add to the body of existing evidence around feasibility studies and complex intervention designs.

Employing a factorial design potentially results in lower running costs over a shorter conduct time. We are aware, however, of the complexity of this design. As highlighted by Hardy et al., (2013), who successfully delivered a robust randomised trial using this methodology, an innovative team is required (Hardy et. al., 2013). To this end, The MILO Study team includes collaborators with significant methodological experience in factorial trial design and conduct.

6.3.2.3 Implications for research

The MILO Study presents an important opportunity to directly influence a future clinical trial on the effectiveness of membrane sweeping to prevent post-term pregnancy. Also, the findings of the pilot SWAT will inform a future definitive SWAT assessing recruitment of an underrepresented population (pregnant women) to a clinical trial.

6.3.3 The People's Trial: supporting the public's understanding of randomised trials.

The evidence suggests that public knowledge and understanding of randomised trials is limited and directly affects people's ability to make fully informed decisions about their health (Center for Information and Study on Clinical Research Participation 2017).

Clinical trials and members of the public have a symbiotic relationship. Clinical trials are instrumental in providing reliable evidence on the effects of interventions that potentially improve public health. However, to use this evidence to inform healthcare decisions, people must understand it. In addition, while randomised trials are viewed by many as the gold standard method to provide robust evidence on the effects of health care interventions, they

need members of the public to engage with them as participants to be successful (Crockett et al., 2019, Hariton & Locascio 2018).

Under-recruitment to clinical trials is one of the main reasons trials stop or go over their predicted time, increasing costs, and research waste (Gillies et al., 2019). Trials that are unable to recruit sufficient participants run the risk of being underpowered; causing them to not answer the question they were designed to do (Treweek et al., 2018)

The evidence suggests that a lack of public engagement may have a significant impact on recruitment to trials (Lloyd et al., 2017). Further, fear and distrust of research are shown to be barriers to engagement in research. Significantly, it has been noted that improving education and awareness of clinical trials in members of the public has a positive effect on engagement with research findings and recruitment to trials (Holzer et al., 2015, Getz 2013, Caldwell et al., 2010).

6.3.3.1 Agreements and disagreements with other studies or reviews

The concept for *The People's Trial* was informed by two educational initiatives aimed at children. The Informed Health Choices (IHC) program, a Norwegian initiative, was designed to support critical thinking about health claims in children age 10 to 12 years of age (Austvoll-Dahlgren et al., 2015). This initiative aimed to support children to recognise health claims and assess the reliability of the evidence supporting these claims (Oxman et al., 2018). In the IHC initiative, children were taught key concepts, or principals needed to assess health claims using relatable stories and scenarios in a classroom-based program (Nsangi et al., 2015). Further studies demonstrate that knowledge was retained a year after participation in the program (Nsangi et al., 2020, Semakila et al. 2020). *The People's Trial* also builds on a Health Research Board - Trial Methodology Research Network (HRB TMRN) initiative called The START Competition, with which I am involved. This initiative invites Irish schoolchildren in 5th and 6th class (age 10 to 12 years) to design and conduct a randomised trial, a concept based on learning by doing (Biesty, et al., 2020). Both The START Competition and the IHC initiative focus on supporting children to critically assess the robustness and reliability of the evidence used to support health claims.

However, in contrast to the IHC and START initiatives, *The People's Trial* was aimed at adult learners, 18 years of age and older. To support this demographic, we developed an initiative focused on the concept of 'learning by doing', which incorporates Malcolm Knowles' theory

of andragogy, a theory that focuses on the needs of adult learners. For the most part children's learning within educational systems is based on external motivation, such as pleasing parents or teachers. However, adults as autonomous learners choose to learn, and this choice is often motivated by the value placed on the acquired knowledge. Knowles suggests actively involving adults in a learning initiative, which resonates and engages with learners. To support this, we designed *The People's Trial* to engage participants in all decisions surrounding the trial design, conduct, and dissemination. Participants suggested, and ultimately chose, the trial question; a process that connected and invested participants in *The People's Trial*. In addition, participant autonomy was valued and maintained throughout the trial, with participant choices instrumental in the design process. Throughout *The People's trial*, the use of plain language communications and animated videos highlighted the relevance of each phase of the trial to participants. 'Learning by doing' is not a new concept, but rather one used innately when learning from experience. This framework is one also used as a pedagogical approach by educators to support hands-on teaching methods, promoting active learning and engagement (Odongo & Talbert-Slagle2019, Nairn 2020). This method of learning has been applied successfully in many different settings including clinical education (Linganna 2020, DeCelle 2016).

I sought ethical approval before commencing *The People's Trial*. This application was unusual, in that, at the time of submission we did not know the basic components of the proposed trial. We did not know the intervention, the comparator, or the outcomes to be measured. What we did know were the processes we would use, and the parameters we would set to ensure the final question would be inclusive and pose a negligible risk. We also knew the process we would employ to obtain the trial question. In the ethical application, I outlined the process of each step of the trial and received full ethical approval from the NUI Galway Research Ethics Committee.

Involving people in a truly collaborative initiative has been shown to support engagement (Horowitz et al., 2019). Almost 4.57 billion people, 59% of the world's population, are active on the internet, with one in two EU citizens (not including the UK) searching online for health information (Statista 2020, European Commission 2020). To this end, we chose an online platform to support accessibility and inclusion to host our educational initiative.

Online interaction, particularly through social media provides a low-cost, partially inclusive method of engaging the public. Several initiatives to improve public awareness on clinical

trials have used online platforms in this manner (Ali et al., 2020, Pan et al., 2015, Widjaja et al., 2014, Mackenzie et al., 2010). *The People's Trial* successfully engaged the public using a broad social media campaign, run on various applications (Twitter, Facebook, and Instagram). Each of these applications appeals to different demographics, promoting diverse engagement. *The People's Trial* website has had over 9.5K unique visitors to the site, from 117 different countries, using 90 different languages, with over 25K page views. In addition, the learning support and results of each phase of *The People's Trial* were publicised on our social media channels. Therefore, this project potentially supported the learning of many people who did not engage with *The People's Trial* website, supporting additional, but unmeasured learning outputs from this initiative.

The website was designed to visually support inclusivity, depicting individuals of different ages, races, gender, disabilities, and culture in all graphics and optimised for use on mobile phones. Plain language was used throughout the website and in all communications with the public. As *The People's Trial* evolved organically throughout the trial process, so too did the website. This necessitated rapid content development, with ongoing Steering Group consultation and website design. In addition, all surveys were purposefully created and embedded within the website. All were written in plain language and were designed to take on average four minutes to complete. This timeframe was based on market surveys in this space, supporting public participation (Vidyard 2019). We also created custom-designed, animated videos, using plain language scripts, and voice-overs from a diverse group of volunteers, using colloquial accents. The animations included diverse ethnicities and demographics, again aimed at supporting inclusivity. The optimal video length was another consideration, with marketing research predicting that viewer engagement peaks at two minutes and drops off significantly after three minutes. Therefore, we kept all video timelines within three minutes, with the majority averaging two minutes in duration (Fishman 2016)

Engaging the public with research, and clinical trials, in particular, can be challenging (Houghton et al., 2020). However, *The People's Trial* successfully recruited over 3000 members of the public, from 72 countries, with approximately 40% of participants telling us that they had some, or no understanding of randomised Trials before taking part in *The People's Trial*. Further, public participation increased with each phase of the trial.

Communication with participants did not, and should not, finish when the trial concluded (National Institutes of Health 2016). Members of the public, clearly indicated that they would

like to be informed of the trial results using formats that support accessibility and inclusion, including plain language reports, videos, and visual graphs. This supports findings of several other reviews and individual studies where research participants strongly indicate that they would like to be informed of trial results (Raza et al., 2020, Shalowitz & Miller, 2008, Long et al., 2016).

The potential benefits of communicating trial results to participants are clear, including positive impacts on future health and supporting a positive experience on the overall research experience (Melvin et al., 2020, MacNeil & Fernandez 2006). However, optimal methods of disseminating results to participants are under-reported in the literature. A recent audit of 1404 trials, reported that although the majority of trial investigators intended to report trial results to participants, reporting of feedback methods was lacking (Raza 2020). Although the majority of funders require the wide dissemination of study results, the majority of results are published in peer-reviewed and academic journals, which participants and members of the public may not have access to and may not be aware of.

6.3.3.2 Strengths and Limitations

In collaboration with the public, *The People's Trial* designed a robust, methodologically sound protocol for a randomised controlled trial. The trial conformed to the 2013 Spirit Statement and the Consort Statement 2010 (Chan et al., 2013, Eldridge et al., 2016) (Appendix 7). Within *The People's Trial*, learning was unobtrusive. We incorporated information about complex methodologies simply into the trial.

Similar to the findings of many trials, recruitment of older adults to *The People's Trial* proved challenging (Chatters et al., 2018, Piantadosi et al., 2015, McHenry et al., 2015). This may be due to a lack of familiarity with online engagement and non-participation in the social media platforms we chose (van Middelaar et al., 2017, Price-Haywood et al., 2017, Hill et al., 2008). In future trials, we would try to address this limitation by supplementing our recruitment strategy with additional recruitment initiatives aimed specifically at this population including, radio, newspaper, and health care practices (GP and public health centres).

A significant limitation of *The People's Trial* was the exclusion of individuals not competent in the English language. This was simply a result of budget constraints. Although we endeavoured to use plain language in all communications, we will address this limitation in

future trials. In addition, *The People's Trial* excluded children and young adults under 18 years of age. This limitation is one we also plan to address in future trials.

An unforeseen challenge to *The People's Trial* was the coronavirus (COVID-19) pandemic. Although we had completed the trial conduct and data collection, the publication of the results of 'The Reading Trial', and an invitation to participate in an evaluation survey were delayed. This delay may have affected the overall experience and learning of participants.

6.3.3.3 Implications for practice

The success of *The People's Trial* suggests that online trials support public engagement, recruitment, and retention to clinical trials. This has significant practical implications for trials, particularly in the current environment (coronavirus pandemic). The level of public engagement in *The Peoples Trial* highlights a public appetite for collaborative initiatives on the design and conduct of randomised trial designs.

Finally, *The People's Trial* demonstrates the value of social media in engaging and communicating with a wide demographic, supporting recruitment and retention to clinical trials, and the dissemination of trial results.

6.3.3.4 Implications for research

Members of the public have strongly indicated that the results of trials in which they participate should be made available to them in accessible formats. Participants in *The People's Trial* strongly support the use of plain language papers to support accessible dissemination of trial results. This should be considered when developing future dissemination strategies for research studies.

A significant limitation of *The People's Trial* was the exclusion of individuals not competent in the English language. We would like to see this limitation addressed in future trials to assess what, if any, removal of this limitation has on inclusion and recruitment and retention rates.

It would be helpful to know if the reported learning of participants in *The People's Trial* was maintained over a longer period. A follow-up survey at one-year post participation would provide supplementary data on the efficacy of the initiative and should be considered in any

future research in this space. A trial of *The People's Trial* would assess its effect and should be considered.

6.3.4 Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed? The People's Trial- an online, pragmatic, randomised, controlled trial.

The question chosen by the public for *The People's Trial* to answer was:

'Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed?'

Sleep is a normal physiological process that is essential in maintaining good overall health (Watson 2015). The incidence of sleep disorders continues to rise and is associated with significant economic and public health implications (Reynolds et al., 2017, Jaiswal et al., 2017, Ford et al., 2015, Hillman & Lack 2013). Before commencing The Reading Trial, we undertook a literature review to find out if this question had been answered previously. Although we noted 334 citations, we were unable to find any high-quality literature that assessed this question, in the population we were studying. A lack of relevant research highlights a significant gap in the evidence to address a growing public health issue (Filip et al., 2017).

As described above, the protocol for The Reading Trial was informed directly by participants of *The People's trial*. The question was submitted and prioritised by the public, and the methodology was agreed upon by all participants. This process supports relevance and inclusivity. The Reading Trial was an online, parallel-group, randomised trial. It took place on a purpose-built website (www.thepeoplestrial.ie), with no face-to-face interaction.

In response to a mandate from the public, The Reading Trial report was written in plain language. While some trials include plain language summaries within-trial reports, and the European Union Clinical Trials Regulation ((EU CTR) 536/2014) requires the inclusion of lay summaries, it is still not the norm to see lay summaries of results reported (Barnes & Patrick, 2019, European Commission 2014). In *The People's Trial,* the public went one-step further and indicated that they would like plain language text to be extended to the full trial report.

6.3.4.1 Agreements and disagreements with other studies or reviews

The protocol for The Reading Trial was designed by the people, for the people, as part of an education initiative. However, the study adheres to CONSORT and SPIRIT guidelines for designing and conducting randomized trials (Chan et al., 2013, Eldridge et al., 2016). The Reading Trial, observed the same methodological standards as any clinical trial, producing robust evidence.

Throughout the literature, most randomised trials assessing the effect of an intervention on sleep quality, as in The Reading trial, targeted specific population groups such as cancer patients (Zachariae et al., 2018), older adults (Hmwe et al., 2020), or those with a history of mental health diagnosis (Harb et al., 2019). In comparison, The Reading Trial is an outlier, as it includes a broad, diverse sample base reflective of the general population and offers an analysis of an intervention to potentially improve sleep quality across this population.

The Reading Trial experienced an overall attrition rate of 21.9% (127 (25.6%) people randomised to the intervention group and 90 (18.18%) people randomised to the control group). Failure to recruit enough participants to answer the trial question is a constant challenge for clinical trials, with the evidence suggesting that approximately 50% of clinical trials do not reach their target sample size (Applequist et al., 2020, Treweek et al., 2018). However, in contrast to the challenge faced by a significant majority of clinical trials, The Reading Trial exceeded, by almost double, the a priori estimated sample size of 564 people, within 27 days of commencing recruitment.

Randomisation is used to reduce bias by creating balanced groups without systematic differences. Attrition can introduce bias as it may affect the balance between the intervention and the control groups achieved through randomisation. To explore attrition effects (21.9% (127 (25.6%)) had on the primary outcome (overall sleep quality) of The Reading Trial we performed a sensitivity analysis using intention to treat analysis (ITT) (McCoy 2017). We analysed data from all randomised participants in The Reading Trial, whether or not they completed the trial, or provided outcome data. To do this, we used a method called regression imputation. We calculated a probable value by estimating all available information. We then imputed the missing outcome data with this value. This has the advantage of preserving data, however, no new data is added (Kang 2013). Using ITT analysis, we found that reading a book in bed before going to sleep still improved sleep quality.

Similar to a 2018 systematic review and meta-analysis, which found that patient and public involvement increases recruitment to clinical trials, recruitment in The Reading Trial may potentially be attributed to the success of *The People's Trial* in engaging with the public as collaborators (Crocker et al., 2018). The Reading Trial continued to recruit participants after it had reached its a priori sample size, as this trial, as part of *The People's Trial*, was not just focused on answering the trial question, but also on supporting public education and engagement through participation.

The Reading Trial utilised social media to create a sense of community supporting recruitment to The Reading Trial. Although this is a novel approach, as a cost-effective alternative to traditional recruitment methods, social media is becoming a more popular recruitment tool (Khatri et al., 2015). Studies that compare the recruitment of trial participants using social media with traditional means, such as print; have reported similar success, as noted in a recent systematic review exploring the use of Facebook to recruit participants for health research purposes (Whitaker et al., 2017).

The results of The Reading Trial were disseminated, as stipulated by participants, using a plain language format, visual graphs, and a custom-designed infographic posted on *The People's Trial* website. Also, all results were publicised through social media channels. We launched *The People's Trial* results during the HRB-TMRN online symposium, in October 2020. Similar to Luc et al., (2019), we found that using social media to advertise the publication of our trial results, positively impacted interest in our study results. Using this method, we noted a 75% increase in visitor traffic to *The People's Trial* website when we launched the trial results.

6.3.4.2 Strengths and Limitations

The protocol for The Reading Trial was informed directly by *The People's Trial*. The Reading trial, successfully evaluated a low cost, low-risk intervention, within a diverse population. Sleep problems are a rising public health concern (Filip et al., 2017). The findings of the trial suggest that reading a book in bed before sleep, in the manner outlined in The Reading Trial, potentially affects sleep quality.

Participation in The Reading Trial offered members of the public hands-on experience of participating in a clinical trial, in a fun, low risk, and collaborative environment supporting learning and development.

The Reading Trial highlights that online recruitment appeals to a wide demographic of participants. In addition, using an online platform supported retention and broad dissemination of trial results in The Reading Trial.

The Reading Trial took place over a short timeframe (7 nights). It would be helpful to know if the effects of reading in bed on overall sleep quality were maintained, increased, or decreased over a longer period.

The Reading Trial took place online with no face-to-face contact. Therefore, self-reported surveys were used to collect data for *The People's Trial*. This method is open to reporting bias, potentially influencing trial results (Spitzer & Weber 2019).

To evaluate intervention fidelity, we asked participants to assess their compliance with the study protocol through a self-reported survey. This survey asked participants to indicate how often, over the 7 days of the Reading Trial, they read before sleeping, slept in their bed, went to bed and woke up at the same time as they usually would and ate food or drank caffeinated drinks within 1 hour of bed. As previously discussed, a limitation of this method of data collection is the potential for reporting bias. In addition, if participants did not return outcome surveys, despite receiving email reminders, we were unable to collect outcome data for those participants.

6.3.4.3 Implications for practice

The findings of this study add to the body of existing evidence on sleep disorders, offering robust evidence to inform a public health issue. In addition, The Reading Trial offers insight on how participants of trials want to have trial results disseminated.

6.3.4.4 Implications for research

The public has indicated how they would like the results of trials they have participated in communicated. The Reading Trial was disseminated, in part, using a plain language paper. To fully engage members of the public in research, this dissemination strategy should be considered for all future research.

In addition, the results were disseminated through *The People's Trial* website using a custom-designed infographic. This infographic was also widely shared on social media channels. Similar to all communications with the public during *The People's Trial*, a plain-language

overview of the trial results were available for the public on the project website. Further qualitative and quantitative research on the potential benefits of these methods of dissemination should be undertaken to support public inclusion and engagement in research.

The Reading Trial offered members of the public the opportunity to participate in a randomised trial, experiencing all trial processes. Due to budget constraints, we were only able to offer this experience to members of the public with a working knowledge of English. Further research should address this challenge to support diverse learning opportunities.

6.3.5 Conclusion

This PhD was undertaken during a pandemic. Although the coronavirus forced a change in direction to the research included in this thesis, the work presented here offers a significant contribution to the evidence underpinning clinical practice and trial methodology.

This thesis presents four papers that report on a body of work completed on two separate trials.

Section 1

1. The Cochrane Systematic review and meta-analysis informs national and international guidelines with robust current evidence.
2. The MILO Study protocol, informed by a significant systematic review and meta-analysis, will commence recruitment in February 2021. This body of work adds to the existing evidence on membrane sweeping to prevent a formal induction of labour. The feasibility study will inform a future definitive trial on the effectiveness of membrane sweeping to prevent post-term pregnancy.

Section 2

3. *The People's Trial* demonstrates that public collaboration in all aspects of trial design, conduct, and dissemination is mutually beneficial, providing a unique opportunity for shared learning. In addition, this study found that supporting public knowledge and understanding of randomised trials and why they are important, has a positive impact on public engagement.
4. Participants in *The People's Trial* designed a robust, methodologically sound protocol for a randomised controlled trial that was relevant to the public. The Reading Trial found that reading a book in bed before sleeping, in the manner done in this trial,

improves the quality of sleep compared to not reading a book in bed before sleeping. These findings add to the body of existing evidence in this space.

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Appendices

Appendix 1.

Paper 1: Search terms for ClinicalTrials.gov and the WHO ICTRP

membrane(s) AND sweep(ing)

membrane(s) AND strip(ping)

Appendix 2.

Paper 1: Characteristics of included Studies

Adeniji 2013

Methods	Prospective randomised controlled trial
Participants	**Setting:** antenatal clinic, Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Nigeria. **Duration of study:** 3 years (between April 2007 and March 2010) **Inclusion criteria:** "singleton live fetus, post-term pregnancy from 40 weeks and 1 day to 40 weeks and 9 days, intact fetal membranes, Bishops score ≤ 5 and cephalic presentation". Page 5. **Exclusion criteria:** "post-term pregnancies of > 40 weeks and 10 days, multiple pregnancies, grand multiparity, cephalopelvic disproportion, previous caesarean section or a uterine scar, fetal malpresentation, fetal distress, placenta praevia, antepartum haemorrhage, premature rupture of the membranes and medical disorders." Page 5. **Parity**: mixed, both nulliparous and multiparous included in the study. Page 5. **Bishop score:** not recorded
Interventions	**Oral misoprostol group (OM) (N = 50):** "a single 50 ug misoprostol tablet orally on an outpatient basis." Page 5. **Membrane stripping group (MS) (N = 46):** "had MS once only at the antenatal clinic. Patients with unyielding cervices preventing access into the cervical canal were termed 'failed MS'." Page 5. "All patients in both groups who did not go into spontaneous labour after 48 hours were categorised as 'failed labour induction' and together with the women with post-term pregnancies of > 40 weeks and 10 days managed according to our departmental protocol of cervical ripening and labour induction (transcervical Foley catheter or intravaginal misoprostol) to ensure delivery before 42 weeks' gestation." Page 5.
Outcomes	Spontaneous labour Vaginal delivery Caesarean section Apgar score < 7 at 5 minutes Women's satisfaction Oxytocin augmentation
Notes	**Funding:** none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:** yes; "were recruited after giving informed consent". Page 5. **Ethical approval**: "The institutional ethical review committee approved the study". Page 5. Email sent to author 28 August 2017 requesting study data and subgroup data Re-sent 20 September 2017, no reply to date.
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random numbers were used for patient allocation", page 5.
Allocation concealment (selection bias)	Low risk	"sealed opaque envelopes containing papers marked OM or MS (50 each) were placed in a box, thoroughly mixed and then numerically labelled.", " were allocated sequential numbers in order of recruitment…and the correspondingly numbered envelope was opened", page 5.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants: not discussed. Blinding of personnel: partial blinding. "attending obstetricians in the labour ward were blinded to the labour-inducing agents used in the study groups." (Page 5). Unclear if all other personnel involved were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	n = 4 (8%) patients in nulliparous group could not have MS owing to inability to gain access to the cervical canal and were removed from analysis
Selective reporting (reporting bias)	Unclear risk	Rates for hospital admission not reported explicitly
Other bias	Low risk	No other bias indicated.

Afzal 2015

Methods	Randomised controlled trial	
Participants	**Setting:** Department of Obstetrics & Gynaecology, Benazir Bhutto hospital, Rawalpindi, Pakistan. **Duration of study:** Jan 2008 to Dec 2008. **Inclusion criteria:** "Singleton second pregnancy with previous one lower segment transverse cesarean section, having longitudinal lie and cephalic presentation at 37 weeks of gestation confirmed by ultrasonography were included in the study. There was no absolute indication of cesarean section in present pregnancy." page 386. **Exclusion criteria:** "Patients with any contraindication for vaginal delivery like cephalopelvic disproportion, breech and placenta previa, maternal medical disorders necessitating urgent delivery like severe pre-eclampsia were excluded from the study." page 386. **Parity:** not recorded **Bishop score:** not recorded	
Interventions	**Membrane stripping (n = 55):** "Membrane sweeping was started a 37 weeks and was done every 3rd day till she went into the labor or she reached 41 weeks. Even at 41 weeks of gestation if she did not go into labor, induction with prostaglandin or elective lower segment cesarean section was done depending upon the bishop score." Page 386. **Control group (N = 55):** women "were not subjected to such membrane sweeping and spontaneous onset of labor was awaited till 41 weeks. After 41 weeks induction with prostaglandin or elective lower segment cesarean section was done depending upon the bishop score." Page 386.	
Outcomes	Normal vaginal delivery Caesarean section Assisted vaginal delivery Spontaneous onset of labour before 41 weeks	
Notes	**Funding:** none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:** yes; "Informed consent was taken from each patient" page 386. **Ethical approval:** not stated Email sent to author 28 July 2017 requesting further information Resent 20 September 2017. No reply to date.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	"were randomly allocated to Group-A (sweeping of membrane) and Group-B (no intervention)" page 386. Insufficient information given to inform a judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information given to inform a judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported. Personnel: not reported, but unlikely that clinicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias
Selective reporting (reporting bias)	Low risk	No selective reporting bias noted. Protocol not available.
Other bias	Low risk	No other bias noted. Protocol not available.

Alcoseba-Lim 1992

Methods	Prospective randomised controlled trial.
Participants	**Setting:** Chong Hua Hospital, Cebu City, Philippines. **Duration of study:** 6 months (1 August 1991 to 31 October 1992) **Inclusion criteria:** women of 38 weeks' gestation based on "declared last menstrual period and the fundal height at each prenatal visit." The "result of the ultrasound done before 26 weeks age of gestation was used to confirm age of gestation". Page 139. **Exclusion criteria:** "Uncertain dates for gestational age (with size dates discrepancy not confirmed by ultrasound < 26 weeks). Abnormal fetal presentations. History of vaginal spotting during the course of current pregnancy (suspects of low-lying placenta, placenta previa)." Patients who had a history of a "previous caesarean section who did not want to try vaginal birth". Page 140. **Parity:** mixed. Both nulliparous and multiparous women included (% presented in Table 2 of manuscript page 140). 28/65 (43.1%) nulliparous women in membrane sweeping group versus 24/65

	(36.9%) nulliparous women in control group. 37/65 (56.9%) multiparous women in membrane sweeping group versus 41/65 (63.1%) multiparous women in the control group. **Bishop score:** (% presented in Table 2 of manuscript page 140) **Bishop score at initial visit: Stripped Non stripped** </= 4 61 40 > 4 4 25	
Interventions	**Membrane stripping(n = 65):** patients "undergo membrane stripping once every week until delivery." "Accomplished by digital separation of the chorionic membrane from the lower uterine segment with one or two circumferential passes." "In patients with long and closed cervices, the cervix was digitally stretched until stripping could be accomplished" Page 139 **Control group (n = 65):** weekly "pelvic examination and bishop scoring was done". Page 139 All the patients were examined by the same examiner. Page 139	
Outcomes	Spontaneous vaginal delivery Low forceps delivery Caesarean section Chorioamnionitis Meconium staining	
Notes	**Funding:** Nestle Phils, Medichem Pharmaceuticals Inc, Pfeizer **Trial authors' declaration of interest:** none stated **Informed consent obtained:** not stated Email sent 28 August 2017 requesting further information. Resent 20 September 2017. No reply to date.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not method reported " the subjects were then randomly assigned to a group". Page 139
Allocation concealment (selection bias)	Unclear risk	No evidence of allocation concealment given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No evidence of blinding of participants or personnel demonstrated. Participants: no reported. Personnel: not reported.

Blinding of outcome assessment (detection bias) All outcomes	High risk	No evidence of blinding of outcome assessment demonstrated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias
Selective reporting (reporting bias)	Unclear risk	It is noted that page 141 of study states "Vaginal spotting was observed in 20(30.7%)". However table 5, page 141 reports: spotting n = 17 (26.2%)
Other bias	High risk	Imbalanced groups for initial Bishop score, page 141.

Allott 1993

Methods	Prospective randomised controlled trial
Participants	**Setting:** antenatal clinic of district general hospital, UK. Page 898 **Duration of study:** 18 months. Page 898 **Inclusion criteria:** "Beyond 40 weeks gestation as determined by mid-trimester ultrasound scanning." "Pregnancies in which no risk factors such as intra-uterine growth restriction or hypertension had been detected". Page 898 **Exclusion criteria:** "Those presenting with a closed cervix were not included in the trial as the cervix has to be potentially sweepable" Page 898 **Parity:** mixed. Both nulliparous and multiparous women included (% presented in Table 1 of manuscript page 899). 43/99 (43.4%) nulliparous women in membrane sweeping group versus 44/96 (45.8%) nulliparous women in control group. 56/99 (56.6%) multiparous women in membrane sweeping group versus 52/96 (54.2%) multiparous women in the control group. **Bishop score:** Score ≤ 6 and Score ≥ 7 recorded
Interventions	**Membrane stripping (n = 99):** a vaginal examination was performed to assess the Bishop score. "The sweep was performed by inserting the examiners index finger as far through the internal cervical os as possible and rotating twice through 360 degrees". Page 898 **Control group (n = 96):** "A vaginal examination was performed to assess the Bishop score". Page 898 "After the initial intervention there were no further differences in management" between the groups". "All were assessed by the same person to minimise subjective differences". All women were given a deadline date for labour induction in the absence of a

	spontaneous onset. A minimum gap of 4 days was planned between the examination and the induction in all cases. Sweeping of membranes or Bishop's score performed by the principal investigator. Page 899
Outcomes	Spontaneous vaginal delivery Induction of labour Caesarean section operative vaginal birth Apgar score < 6 at 5 minutes serious neonatal infection Serious neonatal outcomes Epidual in labour Maternal pyrexia?? *number of women starting spontaneous labour reported for every day between day 1 to day 7 after randomisation.*
Notes	**Funding:** none declared **Trial authors' declaration of interest:** Dr. D. Elbourne, Oxford perinatal epidemiology unit advised in study design. Mr. A. Smith helped in preparation of manuscript. **Informed consent obtained:** "all gave informed consent" **Ethical approval:** unclear; "after reading an explanatory document as stipulated by the district ethical committee" Email for further information sent 28 August 2017. Resent 20 September 2017. No reply to date

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Using a computer generated list of random numbers, women were randomised to a membrane sweep or no further procedure. A sealed envelope was opened for each woman after entry into the trial". Page 898.
Allocation concealment (selection bias)	Unclear risk	"A sealed envelope was opened for each woman after entry into the trial" It is not reported if envelope was opaque, sequential or numbered.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants: not discussed Binding of personnel: "All were assessed by the same person (H.A.) to minimise subjective differences in evaluation". Page 898.
Blinding of outcome	Unclear risk	Not reported.

assessment (detection bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Unclear risk	Insufficient information given to make informed judgement.However it is noted that caesarean section data unclear. Table 3, page 901 figures differ from written report.
Other bias	Low risk	No other bias noted.

Andersen 2013

Methods	Randomised controlled trial
Participants	**Setting:** delivery wards at Hvidovre University Hospital, Odense University Hospital & Roskilde University Hospital, Denmark. **Duration of study:** 1 January 2007 – 31 November 2009 **Inclusion criteria:** "Healthy women with an uncomplicated spontaneous singleton pregnancy, a cephalic presentation, intact fetal membranes and with Danish spoken" "pregnancy week 41+2-41+4". "whenever an acupuncture certified midwife was available" "Gestational ages were estimated using fetometric ultrasound parameters obtained before 22 weeks of gestation". Page 556 **Exclusion criteria:** "Women treated with any kind of acupuncture and women treated with sweeping of the fetal membranes within the last 2 weeks before the study were excluded". Page 556 **Parity:** mixed, both primiparous and multiparous women included in this study **Bishop score:** median/mean Bishop score recorded
Interventions	"Women in the active groups were treated twice during 41+3-41+5 weeks of pregnancy or on the nearest working day". "The women in the control group received the usual control with CTG during week 41+3" "certified acupuncturists performed the acupuncture. Experienced midwives performed the sweeping of the fetal membranes" Page 556 **Acupuncture (n = 104):** acupuncture needles placed bi-laterally at points LI4 (Augmentation of uterus contractions), ST 36 (Improves strength of the body, immune system and nutrient uptake), LR 3 (calming, reduces pain), BL 60 (augmentation of contractions), BL 31, BL 32, GV 20 (mental calming), SP 6. Electrical stimulation performed at points BL31(has impact on gynaecologic organs), BL 32 (has impact on gynaecologic organs) and SP6 (induction of

	labour, augmentation of contractions, and has an effect on difficult births combined with LI 4 and LR 3. Needles were left in place for at least 30 minutes. Stimulation was performed at a frequency of 8 0 Hz medium. Page 556 **Sweeping (n = 103):** "performed by circulating the investigating fingers three times between the lower membranes and their attachment to the cervix, separating membranes and the cervix as much as possible. If membrane sweeping was not possible because of a closed cervix, cervical massage was performed by moving the cervix in relation to the pregnancy" Page 556 **Acupuncture and sweeping (n = 100):** "treated twice during 41+3-41+5 weeks of pregnancy or on the nearest working day". Page 556 **Control (n = 100):** "Usual control with CTG during week 41+3" "In women not delivered by week 42+0, a midwife blinded regarding which group the woman was allocated to induced labour on the nearest working day" page 556	
Outcomes	Spontaneous onset of labour Caesarean section Instrumental vaginal delivery Epidural analgesia PPH (as defined by the trial authors) Apgar score less than 7 at 5 minutes Augmentation pH < 7.05	
Notes	**Trial authors' declaration of interest:** none declared **Funding:** not reported **Consent:** "written consent" given. page 556 **Ethical approval:** "Danish Scientific Ethical Committee approved the research" Page 556 Email with request for further information sent 28 July 2017. Resent 20 September 2017. No reply to date.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-randomization system accessible through a telephone line (voice response)" Page 556 "two women were not randomised because of difficulties with the telephone connection to the computer randomisation system" Page 556
Allocation concealment (selection bias)	Low risk	"computer-randomization system accessible through a telephone line (voice response)" Page 556

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: "Randomization was performed just before (the same day) the treatment was initiated" "Treatment could not be hidden from the pregnant women" Page 556 Personnel: allocation only blinded to midwife performing induction of labour if woman not in spontaneous labour at 42+0 weeks' gestation. "However women "occasionally might have told the midwife" their allocated group. Page 556.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias. 10 women were excluded post randomisation. "4 women declined further participation when informed of group" N = 4 women discontinued (n = 3) or did not receive (n = 1) intervention because of staff shortages, page 556. < 20%
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias. No protocol available.
Other bias	Low risk	No protocol available.N = 4 women discontinued (n = 3) or did not receive (n = 1) intervention because of staff shortages, page 556.

Averill 1999

Methods	Randomised controlled trial
Participants	**Setting:** not reported **Duration of study:** 1 year **Inclusion criteria:** "patients with reliable GA and a candidate for vaginal delivery." page 47S **Exclusion criteria:** none stated **Parity:** not recorded **Bishop score:** not recorded
Interventions	**Membrane stripping group (N = 38):** weekly membrane stripping, page 47S **Control group (N = 36):** weekly cervical exam "Patients were randomized to WMS or a weekly cervical exam" page 47S
Outcomes	Caesarean section

Notes	**Funding:** none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:** "signed the consent" page 47S **Ethical approval:** none declared Email sent to Dr. Averill requesting full study 10 April 2017. Resent 30 July 2017. No response to date	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized" page 47S
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported. Personnel: not reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No evidence of attrition bias."4 were lost to follow up" unknown whether pre or post randomisation. Page 47S.
Selective reporting (reporting bias)	Low risk	Maternal age, mean GA, Bishop score < 7 recorded as outcome but not reported. Page 47S.
Other bias	Low risk	Abstract only available. However, no other bias noted.

Berghella 1996

Methods	Randomised controlled trial.
Participants	**Setting:** Chinatown Health Clinic affiliated with New York Downtown Hospital. New York, USA. Page 927 **Duration of study:** 1 July 1991 to 30 October 1991, when the first author was the sole obstetrical provider for the clinic, and from 1 July 1993 to 30 October 1993, when the second author was the sole obstetrical provider for the clinic. Page 927

	Inclusion criteria: 38 weeks' gestation "all patients included in the study were low risk. Exact gestational age was verified either by a pelvic examination during the first 12 menstrual weeks to confirm size appropriate for dates, by an ultrasound examination before the 20th week, or both". Page 927 **Exclusion criteria:** "Patients who presented after 20 weeks", "multiple pregnancy, placenta previa, low-lying placenta, non vertex presentation, fetal growth restriction, and any medical complication of pregnancy, such as hypertension and insulin-dependent diabetes." "Patients with long, closed cervices that did not allow stripping". Page 927 **Parity:** mixed, both nulliparous and multiparous women included. (Table 1 Page 928) **Bishop score:** "Bishop scores were recorded for all patients." (Table 1 Page 928)
Interventions	**Duration of study:** 1 July 1991 to 30 October 1991, when the first author was the sole obstetrical provider for the clinic, and from 1 July 1993 to 30 October 1993, when the second author was the sole obstetrical provider for the clinic. Page 927 **Setting:** Chinatown Health Clinic affiliated with New York Downtown Hospital. New York, USA. Page 927 **Membrane stripping: n** = **73** weekly stripping of membranes starting at 38 weeks' gestational age. "Stripping of membranes was performed uniformly by both authors by separating an approximately 2 cm to 3 cm section of the lower membranes from its cervical attachment with at least two circumferential passes of the index finger." Stripping was repeated weekly according to randomisation until delivery occurred. Page 928 **Control group:n** = **69** "Weekly gentle cervical examinations" "gentle cervical examinations were repeated weekly according to randomisation until delivery occurred."Page 928 Bishop scores were recorded for all patients. Page 928
Outcomes	Spontaneous vaginal delivery: Vacuum Low forceps Primary caesarean section
Notes	**Funding:** none declared. **Trial authors' declaration of interest:** none declared. **Informed consent obtained:** "signed informed Internal Review Board consent forms and were randomized" Page 927 **Ethical approval:** not stated Email sent to Dr Vincenzo Berghella requesting information for subgroup analysis. Sent 10 August 2017 and 28 August 2017 No reply to date.
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized using computer generated numbers from opaque, sealed envelopes." Page 927
Allocation concealment (selection bias)	Unclear risk	Allocation concealment with "opaque, sealed envelopes." Page 927. Not stated if numbered or sequential.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: blinding of patients not reported. Personnel: clinicians not blinded "These time frames were chosen so that only one investigator would perform all the examinations in a given period." Page 927
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding details given in study. "After all the patients had delivered, the data were analyzed for statistical differences using the two-sample t test, the Mann-Whitney test, the generalized Fisher exact test, or x2, as appropriate." Page 928
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.It is noted that 7 patients "initially included in the study were excluded because of long closed cervices not amenable to stripping" page 928
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias.
Other bias	High risk	There is disparity in the study numbers as shown in table 1 page 928: Control group (n = 69): Primiparous n = 43 multiparous n = 26 Sweep group (n = 73): Primiparous n = 35 multiparous n = 38 Also as stated in the study "the original Bishop scores of the two groups were not recorded and compared, so this small study could have been biased by dissimilar patient characteristics in the two groups." Page 929

Boulvain 1998

Methods	Randomised controlled clinical trial
Participants	**Setting:** 3 tertiary care hospitals of the province of Quebec, Canada. Page 35 **Duration of study:** 17 months**(**1 April 1995 to 1 October 1996). Page 35 **Inclusion criteria:** included if eligible for a "non-urgent medical indication for induction of labour and a single fetus in cephalic presentation. Non-urgent medical indication for induction included: post-term pregnancy, hypertension, diabetes, fetal growth retardation without signs of fetal distress, or other medical complications of pregnancy. Post-term pregnancy was defined as gestational age > 287 days when formal induction of labour was scheduled". 'Only women at term (≥ 266 days) were included in the trial'. Written informed consent must have been obtained. Gestational age was calculated from the last menstrual period and an ultrasound examination carried out in the middle trimester. Induction date between 3 and 7 days after randomisation. A date for formal induction of labour was given prior to randomisation, at least 3 days and not later than 1 week after inclusion. Page 35 **Exclusion criteria:** "Women presenting with placenta praevia, abnormal cervical discharge, or contraindications to vaginal delivery were excluded." Page 35 **Parity:** mixed, both nulliparous and multiparous women included. Page 36 (Table 1) **Bishop score:** recorded (not available for 2 women, 1 in each group) Page 36 (Table 1)
Interventions	**Membrane stripping (n = 99):** "examination began with assessment of the Bishop score, followed by the intervention. Physicians were requested to report the characteristics of the cervix (dilatation 0-3 points effacement 0-3, station 0-3, consistency 0-2, position 0-2) before performing the intervention'˜. Sweeping of the membranes consisted in circular movements of the examining finger between the lower segment of the uterus and the fetal membranes. When the membranes could not be reached, physicians were requested to attempt to gently dilate the cervix. If this manoeuvre was successful, sweeping was performed. If the cervix acted as a barrier to the examining finger, cervical massage was performed" Page 35 **Control group (n = 99):** women in the control group had only a vaginal examination for Bishop scoring. Page 35
Outcomes	Epidural Spontaneous vaginal delivery Forceps/vacuum delivery Caesarean section Apgar ≤ 7 at 5 minutes

	Neonaltal infection Neonatal convulsions Formal induction of labour **Evaluation of pain during examination:** VAS (n = 87-87) PPI (n = 94-92) labour agentry scale (n = 90-85)	
Notes	**Funding:** study was supported by grant number 6605-4645- 401 of NHRDP, Health Canada. Dr Boulvain received salary support from Astra Pharma. Dr Fraser receives salary support from the Medical Research Council of Canada. Dr Marcoux holds a Health Research Scholarship from Health Canada. Page 39 **Trial authors' declaration of interest:** none stated. **Informed consent obtained:** yes Page 35 **Ethical approval:** not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated list of random numbers, with randomly permuted blocks of six and eight, stratified by hospital" Page 35.
Allocation concealment (selection bias)	Low risk	"the allocations were contained in a series of opaque, sealed and consecutively numbered envelopes, kept in the delivery unit" "clerk opened the next envelope and informed the doctor of the woman's allocation" Page 35
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: unclear if women blinded. Personnel: clinician not blinded Page 35
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Obstetric data were abstracted from the hospital charts by a research assistant who was unaware of the treatment allocation". Page 36.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The analysis was based on "Intention to treat". However it was noted that "Two women in the control group were excluded after randomisation: one withdrew her consent and the other failed to meet the main inclusion criteria in that she was not scheduled for induction of labour" Page 36

Selective reporting (reporting bias)	Low risk	No selective reporting bias noted.
Other bias	Low risk	No other bias noted.

Cammu 1998

Methods	Randomised controlled trial
Participants	**Setting:** antenatal clinic of a university teaching hospital, Belgium. **Duration of study:** not stated. **Inclusion criteria**: "nulliparous with a singleton fetus in cephalic presentation and having no detected risk factors, such as hypertensive disorders, diabetes mellitus or intrauterine growth retardation. The women were recruited at 39 completed weeks of gestation. Gestational age had been determined in all the women by ultrasound. Third trimester ultrasound examination had been performed to exclude placenta praevia, abnormal fetal presentation and fetal growth retardation" Page 42 **Exclusion criteria:** limited to nulliparous women because they are at greater risk of failed induction and dystocia and their pregnancies and labour are not influenced by previous birth experience. Third trimester ultrasound examination had been performed to exclude placenta praevia, abnormal fetal presentation and fetal growth retardation. Page 42 **Parity:** only nulliparous women included **Bishop score:** Initial Bishop Score: Mean Bishop score on admission to labour ward
Interventions	**Membrane sweeping: (n = 140)** "sweeping of the membranes" on a weekly basis. This involved "digital separation of 2-3 cm of the membranes from the lower uterine segment" was "performed at every visit, rotating the finger at least twice through 360 degrees. A closed cervix was stretched digitally until membrane sweeping could be carried out. A closed cervix that would not admit a finger was vigorously massaged." Page 42 **Control group: (n = 138)** "normal digital examination on a weekly basis." "The study was carried out by two certified gynaecologists with more than ten years of experience and by an assistant in training**.** Induction of labour was planned from 41 completed weeks onwards. If labour had to be induced for medical reasons before 41 weeks, the woman was not excluded from the study group to which she had been assigned. Page 42
Outcomes	Spontaneous labour Augmented labour Induced labour Epidural analgesia

	Instrumental delivery Caesarean section Apgar < 7 at 5 minutes Atrerial cord blood < 7.1
Notes	**Funding**: none stated **Trial authors' declaration of interest**: none stated **Informed consent obtained**: not stated **Ethical approval:** the protocol was approved by the university medical ethics committee Email sent 30 August 2017 Reply 30 August 2017 "At 39 completed weeks of gestation women were asked to participate in a RCT. A list of random numbers was generated by a computer. Numbered sealed envelopes containing the treatment allocations were kept by the attending nurse of the antenatal clinic and were opened after entry to the trial." "The trial was conducted in a University Hospital and none of the patients was private. Patients followed a standardized labour induction protocol and women were delivered by residents under supervision. Delivery room midwives and attending physicians (obstetricians) were unaware of the treatment allocations after randomisation." "Only primiparous women were included in the study." "Mean Bishop score at randomisation in the sweeping group was 3.35 (SD 1.8) and in the control group 3.39 (SD 1.6). Mean Bishop score on admission to the labour ward was 7.7 (SD 1.9) in the sweeping group and 7.2 (SD 2)"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A list of random numbers was generated by a computer." Page 42
Allocation concealment (selection bias)	Low risk	"Numbered sealed envelopes containing the treatment allocations were kept by the attending nurse of the antenatal clinic and were opened after entry to the trial". Page 42. Not reported if opaque.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: blinding of participants not discussed. Personnel: during labour "Midwives and obstetricians were unaware of the treatment allocations after randomisation". Page 42

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Labour was managed by nurse midwives. The women were delivered by residents who were supervised by certified obstetricians. Midwives and obstetricians were unaware of the treatment allocations after randomisation". Page 42
Incomplete outcome data (attrition bias) All outcomes	Low risk	N = 287-9 = 278 "An additional nine women were excluded after randomisation for various reasons: multipara (n = 4), spontaneous rupture of the membranes before randomisation (n = 2), vaginismus (n = 2) and unexpected non vertex presentation (n = l)" < 20% Page 42
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting, however no trial protocol available.
Other bias	Low risk	No other bias noted.

Crane 1997

Methods	Randomised controlled trial
Participants	**Setting:** Grace General Hospital, Newfoundland, Canada. **Duration of study:** 18 months **Inclusion criteria:** "low risk (as defined by the Newfoundland antenatal form), at 38-40 completed weeks 'gestation based on firm dates (last menstrual period) or early ultrasound (at or before 18 weeks' gestation)." Written informed consent. Page 586 **Exclusion criteria:** exclusion criteria included important medical diseases, pregnancy complications (including bleeding, hypertension, or preterm labour), evidence of fetal growth restriction, history of perinatal mortality or low birthweight infant, uncertain dating, premature rupture of membranes (PROM), abnormal presentation, placenta previa, scheduled caesarean delivery, or any other contraindication to vaginal delivery. Page 586 **Parity:** mixed, both nulliparous and multiparous women included (% presented in Table 1 of manuscript page 587). **Bishop Score:** Bishop scores were recorded for all patients (% presented in Figure 1 of manuscript page 587).

Interventions	"The groups were stratified based on the status of the cervix at pelvic examination (opened versus closed), with randomization within the strata." Page 586 **Membrane stripping (n = 76):** "after the status of the cervix was determined (i.e. whether it admitted a fingertip through the internal OS). Those assigned to the sweeping-membranes group underwent sweeping, whereby as much membrane as possible was separated from the lower uterine segment by sweeping the examiner's index finger twice in a circumferential manner. If the examiner was unable to pass a fingertip through the cervix, vigorous cervical massage was performed, defined as firmly rubbing the external OS in a circular manner with the examining index finger."Page 587 **Control group (n = 74): "**the control group had an internal examination only." Page 587
Outcomes	Spontaneous onset labour Induction **Mode of birth** Spontaneous Forceps/vacuum Caesarean **Analgesia in labour:** Epidural Apgar score < 7 at 5 minutes Neonatal infection
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:** "consent for enrolment was sought. Written informed consent was obtained from all subjects" **Ethical approval:** "the study was approved by the Human Investigation Committee of Memorial University of Newfoundland as well as the hospital." Email sent requesting further information: Email received 8 September 2017 "With regards to our study, participants and personnel were not blinded. Outcome assessment was not blinded.

	We no longer have the original data file for this study. At the time the study was completed and published (1997) out ethics board required retention of research data for 10 years. We have since moved to a new site and in this move some research files older than 10 years were destroyed."	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random-number tables by blocks of six, using opaque, sealed, sequentially numbered envelopes. The groups were stratified based on the status of the cervix at pelvic examination (opened versus closed), with randomization within the strata.". Page 586
Allocation concealment (selection bias)	Low risk	"random-number tables by blocks of six, using opaque, sealed, sequentially numbered envelopes." "The envelope was opened by the attending nurse during the internal examination by an investigator, after the status of the cervix was determined". Page 586
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel: not blinded. "The envelope was opened by the attending nurse during the internal examination by an investigator, after the status of the cervix was determined" But clinicians aware of group allocation prior to intervention/no intervention. Page 586 Participants: not blinded. This bias was confirmed by Dr. Crane on 8 September 2017 in an email stating, "participants and personnel were not blinded. Outcome assessment was not blinded."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment was not blinded "Medical records were reviewed after delivery to record these variables." This bias was confirmed by Dr. Crane on 8 September 2017 in an email stating, "participants and personnel were not blinded. Outcome assessment was not blinded."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.

Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias noted.
Other bias	Low risk	No evidence of other bias. Protocol not available

Dare 2002

Methods	Randomised controlled trial
Participants	**Setting:** Owolowo University teaching hospitals, Ile-lfe, Nigeria **Duration of study:** 18 months (1 January 1998 to 31 May 2000) **Inclusion criteria:** "Singleton gestation in the cephalic presentation at 38 weeks gestation, early confirmation of pregnancy by ultrasonography and no contraindications to vaginal delivery" Page 283 **Exclusion criteria:** "closed cervix not amenable to stripping at 38 weeks gestation, placenta praevia, medical complications of pregnancy such as insulin dependent diabetes mellitus, rupture of fetal membranes, unexplained vaginal bleeding, intrauterine growth restriction or a prior uterine incision" Page 283 **Parity:** mixed. both nulliparous and multiparous women included (% presented in Table 1 of manuscript page 284). **Bishop score:** recorded (% presented in Table 1 of manuscript page 284).
Interventions	**Membrane sweep (n = 69):** "membrane stripping" "Stripping of the membranes was performed by separating approximately 2-3cm of chorionic membranes from the lower uterine segment using two circumferential passes of the examining finger" Page 283 **Control group (n = 68):** "gentle cervical examination" Page 283 "All patients were examined by the same person to minimise subjective differences in evaluation. Bishop scores were recorded for all patients" Membranes stripping or gentle cervical examination, performed by 1 clinician.
Outcomes	Spontaneous vaginal delivery Assisted delivery Caesarean section Chorioamnionitis Apgar score < 7 at 5 minutes Neonatal death (congenital heart defects)
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:**"all candidates gave signed informed consent before randomization"

	Ethical approval: yes; "This study was approved by the hospital ethical committee on human investigation" Email sent 30 August 2017, 26 October 2017. No reply to date	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated random schedule". Page 283
Allocation concealment (selection bias)	Low risk	"The allocation of assignment was concealed by placement in a numbered, opaque sealed envelope which was drawn in consecutive order". Page 283
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not discussed Personnel: "examined by the same person to minimise subjective differences in evaluation" Page 283
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias."One hundred and sixty-nine women were eligible for the study of whom 11 (6%) declined to participate. Of the 158 who signed the consent, nine were lost to follow-up and 12 were excluded because of long, closed cervices not amenable to stripping" < 20%". Page 284
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias.
Other bias	Low risk	No evidence of other bias.

de Miranda 2006

Methods	Randomised controlled trial
Participants	**Setting:** midwifery practices, the Netherlands. **Duration of study:** June 2000 to March 2003. **Inclusion criteria:** "low risk (single fetus in cephalic presentation, no pregnancy complications or risk factors and no

	contraindications to normal vaginal delivery), with a reliable gestational age of 41 weeks (range 40+6to41+3)" Page 403. **Exclusion criteria:** "history of blood loss after the first trimester or suspicion of loss of amniotic fluid during pregnancy."Page 403 **Parity:** mixed,**b**oth nulliparous and multiparous women included (Table 1 page 404). **Bishop score**: not recorded.
Interventions	**Membrane stripping (N = 375)** "Women allocated to the control group received routine monitoring. To prevent prostaglandin release, vaginal examination was not performed in the control group until the onset of labour. In addition, we asked the midwives to refrain from advice regarding sexual intercourse as a way of stimulating labour onset, regardless of the allocation." Page 403 **Control group (N = 367)** "Women allocated to sweeping received routine monitoring as well, followed by a vaginal examination for assessment of the cervical ripeness (Bishop score (BS) and immediate sweeping. Sweeping was performed by separating the lower membranes as much as possible from their cervical attachment, with 3 circumferential passes of the examining fingers. When sweeping was not possible because the cervix was closed, cervical massage was performed. Massage of the cervical surface was performed with circular pushing and massaging movements of the fore finger and middle finger for approximately 15 seconds. Sweeping was repeated every 48 hours, with a maximum of 3 times, until labour commenced or 42 weeks of gestation was reached. The midwives explained to the women who had been swept that blood-stained mucus or painful contractions could occur." Page 403
Outcomes	Spontaneous onset of labour < 42 weeks Spontaneous onset of labour ≥ 42 weeks labour induction total Epidural Spontaneous vaginal delivery Forceps delivery Vacuum delivery Caesarean section Augmentation of labour Adverse neonatal outcomes Perinatal death Women's perception of sweep
Notes	**Funding**: none declared **Trial authors' declaration of interest**: none declared **Informed consent obtained:** "A written informed consent was obtained at the antenatal visit of 41 weeks" Page 403 **Ethical approval:**"The ethics committee of the Academic Medical Center of Amsterdam approved the trial" Page 403

	Email sent 30 August 2017 requesting data for subgroup analysis. Reply received 31 August 2017...follow-up email sent 20 September 2017 Subgroup data received 26 October 2017	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"blocked randomisation using 30 blocks of 25,26 with a variable allocation ratio of 12:13 or 13:12" Page 403
Allocation concealment (selection bias)	Low risk	"The allocations were placed within consecutively numbered, opaque, sealed envelopes. A box containing the agreed number of randomisations (variable for each centre) was then sent to the midwifery practices where they were kept." Page 403
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel: "The participating midwives were unaware of the randomisation method." Does not reference blinding for intervention. Page 403 Participants: not discussed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	After every randomisation, the numbered envelope containing the allocation card was posted to the trial coordinator together with a randomisation form containing the date of randomisation, the allocation group and the subject characteristics." Page 403 "Data concerning prenatal care, obstetric intervention, delivery and infant condition were recorded on a case report form (CRF)." "The midwives asked all women to complete the questionnaires." Page 403
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias. "Primary analysis was by intention to treat, i.e. three women allocated to sweeping, who did not receive the intervention, and 19 women randomised to the control group, who were nevertheless swept, were analysed according to the allocated group." < 20% (375 in the sweeping group and 367 in the control group). Page 404

Selective reporting (reporting bias)	Low risk	No selective reporting bias noted.
Other bias	Low risk	No other bias noted.

Doany 1997

Methods	Double-blinded placebo-controlled study
Participants	**Setting:** UCLA Medical Center, California, USA **Duration of study**: not stated **Inclusion criteria:** "Singleton pregnancy in the cephalic presentation who were referred for fetal surveillance at 287 days of gestation or more". "Reactive nonstress test, amniotic fluid index (AFI) between 5 cm and 25 cm. Fetal weight between 2500 g and 4500 g and uterine contractions less frequent than every 5 mins" Page 72 **Exclusion criteria:** "No prenatal care, previous uterine surgery, acute or chronic medical or psychiatric illness or drug use" Page 72 **Bishop score:** Bishop score ≤ 6 recorded.
Interventions	Women were randomised to 1 of 4 treatment groups The treatments were administered at 287 days (41 weeks) and 294 days (42 weeks) of gestation, then every 3–4 days until 307 days (43 weeks and 6 days) of gestation. The assigned treatment was given at each visit after a reactive NST, a normal AFI and a Bishop score. Page 72 **Group 1: n** = **28** no membrane stripping and placebo gel **Group 2: n** = **37** no membrane stripping and 4 mL (0.5 mg/mL PGE2 gel) **Group 3: n** = **50** membrane stripping or cervical massage and placebo gel **Group 4: n** = **28** membrane stripping or cervical massage and 4 mL (0.5 mg/mL PGE2 gel) "The examining finger was introduced into the cervical canal and a total of three circumferential sweeps were made between the lower uterine segment and the chorionic membranes." "When the cervical canal was not accessible, the cervical canal was pulled anteriorly and massaged." "This was followed by placing 4 mL of an unlabeled gel, containing either a placebo or 2mg of PGE2, via syringe, in the posterior vaginal fornix" "both patients and staff were blinded to the type of gel administered" "After treatment patients underwent continuous external fetal and uterine monitoring….for 1 hour" If there was no sign of fetal distress the patients were allowed to go home. Page 72 "Management of study patients in labour and delivery was not controlled and thus was physician dependent. Physicians managing labour were blinded to the study group assignment." Patients were admitted to labour ward when they had "clear changes in both effacement and dilatation of the cervix or if they are in the active

	phase of labour defined by cervical effacement > 80% & cervical dilatation ≥4cm." Page 72	
Outcomes	Spontaneous labour Induction of labour Caesarean section Operative vaginal delivery 5-minute Apgar < 7 Amnionitis Hemorrhage Probable sepsis (neonate) Oxytocin augmentation Pre-eclampsia	
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained**: not stated **Ethical approval:** "approval from our institutional Human Subject for Research Committee" Emailed for further information 28 August 2017; 8 January 2018. No reply to date	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomized, by table of random numbers, into one of four treatment groups". Page 72
Allocation concealment (selection bias)	Unclear risk	No information given on concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: unclear risk of bias. "Both patients and staff were blinded to the type of gel administered." Unclear if blinded to membrane sweep. Personnel: high risk of bias. "Physicians managing labor were blinded to the study group assignment." Page 72. Personnel blinded to gel administered, however clinician not blinded to membrane sweep. "The mixture, with a final PGE2concentra-tion of 0.5 mg/mL, was placed in syringes of 4-mL allocations. The placebo gel consisted of hydroxyethyl cellulose gel mixed with an inert emulsion (Fattibase, Paddock Labs, Inc., Minneapolis, MN) to produce a gel indistinguishable from the PGE2mix, and was

		similarly placed in syringes of 4-mL allocations. All gel samples were stored in a freezer at 25to07C, and were updated weekly. The gel samples were thawed at room temperature for 10 min prior to administration" Page 72
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information given to inform judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No selective reporting bias noted. The following discrepancy was noted "the only complication which was statistically more prevalent was preeclampsia, which occurred in 7/64(11%) of PGE2-gel-receiving subjects, groups II and IV" n = 65 in these groups not 64 as stated (10.7% v's 10.9%). Page 73. However we judged this discrepancy as unlikely to make a clinically important difference
Other bias	High risk	Group sizes are imbalanced: group I = 28 group II = 37 group III = 50 group IV = 28 Unequal number of women in the 4 groups, reasons for imbalance not explained in the methods section. Author contacted, no reply received to date.

El-Torkey 1992

Methods	Randomised controlled trial
Participants	**Setting:** Antenatal clinic, district maternity hospital, UK **Duration of study:** June 1990 to March 1991 **Inclusion criteria:** pregnant women between 41 and 42 weeks' gestation. "women who opted for induction of labour were randomly allocated to undergo sweeping of the membranes or to act as controls". Deadline date for labour induction given after randomisation. Page 456 **Exclusion criteria:** none stated **Parity:** mixed. Both nulliparous and multiparous women included. **Bishop score:** cervix > 4 cm at first exam
Interventions	**Membrane stripping (n = 33):** "As much of the membranes as possible was separated from the lower segment" "If cervix would not admit a finger it was massaged vigorously to encourage prostaglandin release". "Sweeping of the membranes was

	performed by one of the authors (M.E-T.).” “After allocation the subjects were given a date for formal induction of labour”Page 456 **Control group (n = 32):** no vaginal examination. Page 456
Outcomes	Spontaneous onset of labour: Epidural **Mode of birth** Caesarean section Forceps Spontaneous **Neonatal outcomes** Apgar < 6 at 5 minutes Serious neonatal infection Neonatal perinatal death
Notes	**Funding**: none declared **Trial authors’ declaration of interest:** none declared **Informed consent obtained**: no, only women in sweeping group were "informed of the purpose of the trial". page 456 **Ethical approval**: no,”formal ethical approval of the study was not sought” Unable to contact either author. Unable to locate current place of work or email address. Hospital trial was set in now closed.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by “random permuted blocks”. Page 456.
Allocation concealment (selection bias)	Unclear risk	The randomisation codes were placed in opaque sealed envelopes which “were kept in the antenatal clinic”. Page 456. However not noted if envelopes were sequential or sealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: "Those who were randomized to sweeping were informed of the purpose of the trial and the procedure". "The women randomized to the control group were not aware that they were taking part". Page 456. Personnel: not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias. “Because of this marked difference in the proportions of subjects achieving spontaneous labour the trial was stopped before 110 women were recruited. The decision to stop the trial was made by the authors themselves, the decision being based on the statistical stopping rule for randomized trials (Pocock,1983)”
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias noted.
Other bias	Low risk	No evidence of other bias noted.

Gemer 2001

Methods	Randomised controlled trial	
Participants	**Setting:** Israel **Duration of study**: not reported "fifty patients" **Inclusion criteria**: not reported **Exclusion criteria**: not reported **Parity**: not reported	
Interventions	N = 50 2 groups **Group 1:** membrane sweep **Group 2:** intracervical PGE2 0.5 mg gel	
Outcomes	Change in Bishop score Active labour with 24 hours Birth within 24 hours	
Notes	M Boulvain excluded this study based on inadequate method of concealment	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to inform judgement "50 women were randomised".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: while not reported, highly likely that it is not possible to blind.

		Personnel: partially blinded, "A Bishop score was assigned by a blinded examiner prior to and 24 hours following the procedure"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to inform judgement.
Other bias	Low risk	No other sources of bias noted

Goldenberg 1996

Methods	Randomised controlled trial.
Participants	**Setting:** antenatal Unit, Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center**,** Israel. Page 130 **Duration of study:** 17 months (1 January 1992 to 30 June 1993). Page 130 **Inclusion criteria:** all term patients who arrived at the unit and had a history of regular periods. This “unit accepts low-risk pregnant women and routinely does follow-up by means of a non-stress test and ultrasonographic evaluation at ≥ 38 weeks to decrease mortality and morbidity of the fetus. The gestational age was ascertained by using the last-known menstrual period, ultrasound examination before 10 weeks’ gestation, and no size/date discrepancy by uterine size assessment.” “A non-stress test, blood pressure and urine analysis are routinely carried out on all the patients of the antenatal unit. Only low-risk pregnant patients who fulfilled the above criteria underwent stretching of the cervix and Stripping of the fetal membranes.” Page 130 **Exclusion criteria:** "None refused inclusion" Page 130 **Parity:** mixed. Both nulliparous and multiparous women included (table 1 page 130 of study). **Bishop score:** Baseline Bishop score recorded (Table 1 page 130). Bishop score at 38-40 weeks recorded (Table 3 page 133). Bishop score at 41-43 weeks recorded (Table 3 page 133).
Interventions	**Membrane stripping: n** = **152. "**The procedure was performed once at term by 2 of the authors (M.G. and D.B.) using clean examination gloves and an obstetric cream. Stretching of the cervix and vagina was accomplished as described by Ferguson (3), and stripping of the membranes was accomplished by digital separation of the

	membranes from the lower uterine segment with 1 or 2 circumferential rotations." Page 130 **Control group: n** = **141 "**A pelvic examination was performed by palpating the cervix for Bishop's scoring". "The interval from the procedure to spontaneous labor was recorded, defining spontaneous labor as labor on self-admission of the patients to the delivery room due to painful regular contractions occurring twice every 10 min, or more frequently. A cervical dilatation of 2-3 cm on entry to the labor ward was considered arbitrary, to indicate the active phase of labor in women who were admitted, or rupture of the fetal membrane at term with contractions." Page 130	
Outcomes	Augmentation Amnionitis Caesarean section Maternal febrile morbidity Apgar score < 7 at 5 minutes	
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:** "Informed consent was obtained from all the patients". Page 130 **Ethical approval:** not stated.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"All patients were assigned by computer randomization to a stretching/stripping group or to a non-stretching/stripping group" page 130
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel: "The procedure was performed once at term by two of the authors (M.G. and D.B.)" Page 130 Participants: blinding of participants not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	302 participants enrolled. 9 lost to follow-up when they requested "to halt the procedure" page 130. 293 participants randomised. Intervention group n = 152, Control group n = (150-9) 141. It is noted that "An additional nine patients from the stretching/stripping group were excluded because of difficulty in performing the procedure." page 130.
Selective reporting (reporting bias)	Unclear risk	Mode of delivery is a stated outcome, however only caesarean section is reported on, Page 130. Fetal outcome post delivery only reported as "postpartum complications…not statistically different", no detailed data given, Page 130.
Other bias	Low risk	No evidence of other bias

Gupta 1998

Methods	Randomised controlled trial.
Participants	**Setting:** Antenatal clinic of the Department of Obstetrics and Gynaecology, PGIMER, Chandigarh, India. **Duration of study:** not stated **Inclusion criteria:** women with "confirmed gestational age, early confirmation of pregnancy, cephalic presentation and with no contraindication for vaginal delivery" "at 38 weeks gestation" and "informed consent" received. Ultrasound was done to assess the fetal growth parameters, biophysical profile and placental localization (Page 116). **Exclusion criteria:** "Women with closed cervix at 38 weeks gestation; known medical disease or medical complications of pregnancy; multiple pregnancy; hydramnios; premature rupture of membranes PROM; vaginal or cervical infection; low lying placenta; intrauterine fetal death; malpresentation; patients in labor; and major degree of cephalopelvic disproportion." Ultrasound was done to assess the fetal growth parameters, biophysical profile and placental localization (Page 116). **Parity:** only primigravida included in the study. **Bishop score:** (Table I, Page 117). Bishop score < 6 Bishop score ≥ 6
Interventions	**Membrane stripping: n** = **50** "stripping of membranes was done by digital separation of 2/3 cm of chorionic membranes from lower uterine segment using two circumferential passes of the examining fingers. Thereafter, all patients were followed weekly till delivery or scheduled induction. At onset of labor repeat cervical swabs were taken and placental membranes sent for bacterial culture studies" (Page 116). **Control group: n** = **50** "Only pelvic examination" (Page 116).

	Under aseptic precautions all patients were examined by the same person to minimise subjective difference in evaluation	
Outcomes	Spontaneous onset of labour Vaginal delivery total Spontaneous vaginal birth Assisted vaginal delivery Caesarean section Acute fetal distress Still birth Meconium aspiration TTN Chorioamnionitis Neonatal infection	
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:** "informed consent was taken" **Ethical approval**: not stated Email sent requesting further information. Reply 31 August 2017 stating author retired. No contact details available	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was done using a computer generated list of random numbers", page 116.
Allocation concealment (selection bias)	Unclear risk	"a sealed envelope was opened for each women after entry into the trial.", page 116. Does not report if the envelope was sequential, opaque or numbered.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported Personnel: not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data	Low risk	No evidence of attrition bias.

(attrition bias) All outcomes		
Selective reporting (reporting bias)	Low risk	All outcomes reported. No evidence of reporting bias.
Other bias	Low risk	No evidence of other bias.

Hamdan 2009

Methods	Randomised controlled trial
Participants	**Setting:** Outpatient clinic, University hospital, Kuala Lumpur, Malaysia. **Duration of study:** 3.5 year period. 2002 to 2005 **Inclusion criteria:** "Women with one transverse lower segment cesarean scar, a singleton pregnancy, cephalic presentation, intact membranes, and gestational age more than 36 weeks who were agreeable to VBAC and passed specialist assessment for VBAC". Page 746 **Exclusion criteria:** "obstetric contraindications to VBAC (e.g. placenta previa, suspected macrosomia, suspected cephalopelvic disproportion, abnormal fetal lie, and obstructive pelvic masses)." Page 746 **Parity:** only multiparous women included. **Bishop score:** Bishop score at each session recorded (session 1 to 5).
Interventions	**Membrane stripping (N = 108):** "Immediately after randomization, women assigned to "sweep" had their cervix stretched and membranes stripped from the lower uterine segment in the manner as previously described." Page 746 **Control group (N = 105):** "Women assigned to "no sweep" had a gentle vaginal examination for their Bishop score. Page 746 "Weekly follow-up sessions based at the antenatal clinic with the investigators were arranged to repeat membrane sweeping or vaginal examination until delivery. The Bishop score was recorded at each session In our center, induction of labor for prolonged pregnancy is typically offered at 41 weeks of gestation.19 Induction of labor for diabetes that required drug treatment is offered at 38 weeks and for gestational diabetes adequately controlled by diet, induction of labor is offered at 40 weeks.20 Upon prelabor rupture of membranes, women were offered either immediate uterine stimulation, typically with oxytocin, or expectant inpatient management for up to 24 hours.21 All women with a previous cesarean delivery who were offered formal induction of labor were counselled about a higher risk of scar rupture and of unplanned cesarean delivery and the option of a planned repeat cesarean delivery was given." Page 746

Outcomes	Spontaneous onset of labour Induction of labour Caesarean section Spontaneous vaginal delivery Augmentation of labour Instrumental delivery Caesarean delivery PPH Epidural analgesia Umbilical cord artery PH < 7.1 Apgar score 6 or less at 5 minutes	
Notes	**Funding:** none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:** "All participants provided written informed consent." **Ethical approval:** ethical approval for the trial was obtained from the Medical Ethics Committee of the University of Malaya Medical Center, page 746 Emailed 30 August 2017 requesting further information sent.Resent 20 September 2027. No reply to date.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"prepared by an author (M.H.) in blocks of 50 using a computer-generated randomization sequence (available online at http://www.random.org/)." Page 746
Allocation concealment (selection bias)	Low risk	"sequential opening of numbered sealed opaque envelopes indicating "Sweep" or "No Sweep." Only investigators aware of allocation. Page 746
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: "Blinding of participants and delivery providers was effected by a policy of not revealing allocated treatment to them unless requested for an important clinical need. There was no request to unblind during the trial. Page 746 Personnel: Only investigators aware of allocation. However it appears investigators preformed membrane sweep. All participants received standard management by delivery providers." Page 746
Blinding of outcome assessment	Low risk	Collected by authors who are noted to be blind until data analysis

(detection bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported. "Analysis by intention to treat". Page 747
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias noted. Protocol not available
Other bias	Low risk	No evidence of other bias noted. Protocol not available

Hill 2008a

Methods	Randomised controlled trial
Participants	**Setting:** Tripler Army Medical Center, Honolulu, Hawaii, USA. **Duration of study:** March 2006 to May 2007 **Inclusion criteria:** "All patients had confirmation of gestational age by first-trimester crown rump length or mid second trimester biometry assessment. Singleton pregnancy, cephalic presentation, and anticipated vaginal delivery." Page 1314 **Exclusion criteria:** "Three categories: indications for labor induction, indications for cesarean delivery, and contraindications to membrane sweeping. Included multiple gestation, placenta previa, placental abruption, pregestational or gestational diabetes, chronic or gestational hypertension, preeclampsia, any pregnancy with an indication for induction other than impending postmaturity, any pregnancy for which a cesarean delivery was planned, history of preterm delivery, history of vasa previa, active cervical infection, third-trimester vaginal bleeding, mullerian anomalies, severe fetal anomalies, and active genital herpes infection." Page 1314 **Parity:** mixed. Both nulliparous and multiparous women included. **Bishop score:** only cervical dilatation recorded
Interventions	**Membrane stripping (N = 162):** "she received a cervix examination at every visit from 38 weeks of gestation until delivery. If the cervix was dilated, the provider swept a finger in a 360-degree fashion inside the cervix, thereby separating the lower uterine segment from the amniotic sac. If the cervix was closed, it was massaged as described by prior authors." Page 1314 **Control group (N = 138):** "a weekly cervix examination was performed from 38 weeks of gestation until delivery. Special effort was made on this examination not to stretch or manipulate the cervix." Page 1314
Outcomes	Vaginal delivery

	Caesarean delivery Chorioamnionitis Endomyometritis Labour induction Spontaneous labour Neonatal infection	
Notes	**Funding:** none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:**"written informed consent" **Ethical approval:** not stated Email sent requesting information on subgroup analysis 30 August 2017. Limited reply received.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"a computer-generated randomizer program" Page 1314. "Participants were randomly assigned to receive either weekly membrane sweeping or no membrane sweeping for the duration of the pregnancy after 38 0/7 weeks gestational age" Page 1314
Allocation concealment (selection bias)	Low risk	Method of allocation concealment not reported."Participants were not informed as to the group allocation." Page 1314 "Each patient was identified by a computer-generated sequential number that was placed in her chart" Page 1314
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel: not blinded. "Each patient was identified by a computer-generated sequential number that was placed in her chart. Upon seeing a patient who was enrolled in the trial during a routine prenatal appointment, the clinician would enter the participant number into a Web-based program that would tell the provider whether to sweep or not to sweep the membranes. These data were not included in the patient chart. A computer log was kept of all access through the program to the patient identifier to ensure no one but the clinician seeing the patient for routine obstetric appointments accessed her group assignment. Providers who admitted the patient to the labor and delivery unit were also blinded to the patient's group allocation." Page 1314 Participants: "Participants were not informed as to the group allocation." It was understood that many

		patient would realize which intervention they were receiving, but we felt that not informing the patients of their group allocation would increase the quality of the blinding process…" data were not included in the patient chart" Page 1314
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded: "The same restrictions were placed on the authors of this article until the end of the trial and the completion of all data collection. All data were collected and all chart analysis was done by the primary author, who was also blinded to the group allocations. Unblinding did not occur until the time of data analysis." Page 1314
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias noted. All outcomes reported for "Intent to treat basis".
Other bias	Low risk	No evidence of other bias noted.

Imsuwan 1999

Methods	Randomised controlled trial
Participants	**Setting:** Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok. Thailand **Duration of study**: not stated **Participants randomised:** N = 284 **Inclusion criteria:** "Gestational age of 38 weeks who attended antenatal clinic at Phramongkutklao Hospital." page 267 **Exclusion criteria**: not reported **Parity:** "Only gravida women included in this study". No further details reported. Page 267 **Bishop score**: not reported
Interventions	**Group 1:** "first group had pelvic examination alone". Page 267 **Group 2:**" pelvic examination with membrane stripping beginning at 38 weeks gestation and continuing weekly till the onset of labor or reaching 42 complete weeks" Page 267
Outcomes	Delivery post 41 complete weeks' gestation. Page 267
Notes	**Funding**: not stated **Trial authors' declaration of interest**: not stated **Informed consent obtained**: not stated

	Ethical approval: not stated Email sent 25 May 2017 Reply 8 June 2017 Dr. Tanapat "Thank you for your interest in this article, I do not have a copy of the reprint with me however I will contact Dr. Imsuvan who is a staff at the Department of Obstetrics and Gynecology, Phramongkutklao Hospital and the RTCOG for you to see if they have a copy of the article. You can also go to web site of The Royal Thai College of Obstetricians and Gynecologists (RTCOG) to search their journal or as their staff to find the article for you." Further email sent 14 June 2017. RTCOG replied 2 August 2017 with copy of abstract. Full study never published per RTCOG	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Eligible gravidas were randomized" page 267
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported. Personnel: not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not discussed.
Selective reporting (reporting bias)	Unclear risk	Maternal and fetal complications stated as trial outcomes but data not supplied. Page 267. Protocol not available.
Other bias	Low risk	No evidence of other bias

Janakiraman 2011

Methods	Randomised controlled trial	
Participants	**Setting:** Outpatients obstetric clinic, USA **Duration of study:** not stated **Participants randomised:** N = 123 **Inclusion criteria:** "All women who presented to an outpatient obstetrics clinic who were >/= 37 weeks, were candidates for vaginal delivery and qualified for GBS prophylaxis were offered enrolment." (Page S41). **Parity:** mixed. Both nulliparous and multiparous women included (Page S41). **Bishop score**: not stated	
Interventions	**Membrane stripping (N = 61):** in the intervention group sweeping was attempted at each visit (Page S41). **Control group (N = 62):** no membrane sweeping was attempted. Standard CDC protocol antibiotic prophylaxis was given (Page S41).	
Outcomes	Vaginal delivery LTCS labour induction Chorioamnionitis Composite neonatal outcome	
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained**: not stated **Ethical approval**: not stated Email requesting further information sent 11 April 2017 Reply 26 April 2017 "The women in the membrane sweep group that were not swept were mostly because they had a closed cervix (they were randomized before a cervix exam was done) The women that were in the no sweep group that were swept usually had their membrane swept because of provider or patient preference." Further information requested. Reply received 8 September 2017	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomized using random number generation and block randomization"

Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not blinded. Personnel: not blinded. "No blinding was attempted"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"No blinding was attempted"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Abstract of conference proceeding. "7 women withdrew from the study or were lost to follow-up" (4/61 women from the intervention group, 3/62 women from the control group) < 20%.
Selective reporting (reporting bias)	Unclear risk	Abstract of conference proceeding. Full trial not available per author. 3 (4.9%) women in the control group received 1 membrane sweep (table). 19 (31.7%) of women in membrane sweep group received no sweep.
Other bias	Low risk	Abstract of conference proceeding. Full trial not available per author. However, no other bias noted.

Kashanian 2006

Methods	Randomised controlled trial
Participants	**Setting:** Akbarabadi Teaching Hospital in Tehran, Iran **Duration of study:** not reported **Participants randomised:** N = 122 **Inclusion criteria:** "gestational age of 39 weeks (with dates determined on the basis of the last menstrual periods and ultrasound performed during the 1st trimester), singleton gestation, vertex presentations, and intact membranes"." (Page 42) **Exclusion criteria:** "clinically significant vaginal bleeding, placenta previa, severe cervicitis, evidence of spontaneous labor (more than three painful contractions in 10 min), a known contraindication to labor induction (e.g., prior vertical uterine incision, acute fetal compromise, active herpes), systemic disorder, decreased fetal movements, any sign of fetal distress and any high-risk pregnancy, or inability to give informed consent." (Page 42)

	Parity: mixed. Both nulliparous and multiparous women included (Page 42). **Bishop score:** baseline Bishop score mean +/-SD recorded	
Interventions	**Membrane stripping (N = 50):** "Sweeping was performed by one of the investigators. Sweeping was performed based on a standard method. As much of the membranes as possible was separated from the lower segment. If the cervix did not allow a finger, it was massaged for 2 min to stimulate prostaglandin release. The women were observed for a few hours after the procedure and were discharged, if they were well. The patients were instructed to admit to the labor ward, if they had leaking, labor pain, or excessive vaginal bleeding" (Page 42). **Control group (N = 51):** "only vaginal examination for determining Bishop score. Vaginal examination was performed by the same investigator for both groups. " "Women were admitted to the labor ward whenever they had labor pain. In others, pregnancies were followed till 41 weeks, in case of lack of labor pain, induction was started to terminate labor." (Page 42).	
Outcomes	Puerperal fever Caesarean section	
Notes	**Funding**: not stated **Trial authors' declaration of interest**: not stated **Informed consent obtained:** "written informed consent" **Ethical approval:** "approval from the Hospital Ethics Committee" Unable to contact author.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"four parts, block random using sealed, sequentially distributed envelopes to which the letters A, B, C, and D had been allocated", page 42.
Allocation concealment (selection bias)	Low risk	"sealed, sequentially distributed envelopes to which the letters A, B, C, and D had been allocated: the letters A and C to the sweeping group and the letters B and D to the control group; the patients chose the envelopes which were opened by the investigator, and according to the letters, the group of patients was determined", Page 42.
Blinding of participants and personnel (performance	High risk	Participants: unclear if participants blinded once allocated to groups. "the patients choose the envelopes, which were opened by the investigator" Page 42

bias) All outcomes		Personnel: not blinded. "the patients chose the envelopes which were opened by the investigator, and according to the letters, the group of patients was determined", Page 42. "Sweeping was performed by one of the investigators, and vaginal examination also was performed by the same investigator for the control group." "Follow-up of the patients was performed by another investigator who was blinded to the groups of patients; therefore, at this stage, neither the investigator nor the patients knew which was the study group." Page 42.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Follow-up of the patients was performed by another investigator who was blinded to the groups of patients; therefore, at this stage, neither the investigator nor the patients knew which was the study group." page 42.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Twenty-one women who did not give birth in our hospital were excluded from the study", < 20%. N = 122 Intervention group = 50 (60-10) Control group = 51 (62-11) Page 42.
Selective reporting (reporting bias)	Unclear risk	"Data regarding premature rupture of membranes, abnormal bleeding during hospitalization, Bishop score, timing of delivery, mode of delivery, and birth weight were collected." For mode of delivery only data given for caesarean section
Other bias	Low risk	No evidence of other bias

Magann 1998a

Methods	Randomised controlled trial
Participants	**Setting:** Obstetric clinics at the Naval Medical Center in San Diego, California, and the University of Mississippi Medical Center in Jackson Mississippi,USA (page 891). **Duration of study**: not stated **Participants randomised:** N = 65 (79 women met the Bishop score inclusion criteria. 14 of these women were excluded for a positive fetal fibronectin test result). **Inclusion criteria:** "uncomplicated singleton pregnancies and were candidates for a vaginal delivery at 39 weeks' gestation". All women who had "Vertex presentation, no placenta previa, or other contraindications to a vaginal delivery" were invited to participate. Gestational age was determined on the basis of the patients last menstrual period, initial examination, first auscultation of fetal heart tones with an ultrasound stethoscope (Medason, Newark, Calif), ultrasonography, or both performed before 20 weeks'

	gestation. Negative fetal fibronectin test result and a Bishop score ≤ 4 (page 891). **Exclusion criteria:** women whose "estimated date of confinement was uncertain was not included in this study". History of previous caesarean section (page 891). **Parity:** mixed. Both nulliparous and multiparous women included (Table 1, page 891). **Bishop score:** both baseline Bishop score and Bishop score at delivery (mean +/-SD) recorded
Interventions	**Membrane stripping (n = 33):** "Examination every 3 days with membrane sweeping and Bishop score determination". "Membrane sweeping was performed by placing a finger through the cervix and performing 2 circumferential sweeps with the examining finger. If the cervix would not admit a finger, the examining finger was placed into the cervix every 3 days until the sweeping could be performed." (page 891). **Control group (n = 32):** "Gentle vaginal examination only every 3 days with a Bishop score assigned." "Examinations were continued every 3 days until spontaneous labor, rupture of the membranes, or the patient completed 41 weeks' gestation at which time all remaining patients were admitted to labor and delivery for labor induction." (page 891). .
Outcomes	Spontaneous labour Induction at 42 weeks Augmentation of labour **Mode of birth** Vaginal delivery Caesarean section
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:** yes: "After signing an informed consent form before the 39-week pelvic examination" **Ethical approval:** "This study was approved by the Investigational Review Board at the Naval Medical Center in San Diego and the University of Mississippi Medical Center in Jackson, Mississippi." page 891. Unable to source contact details for Dr Magann

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"These cards had been obtained from a random number table and placed the patients in one of two groups." Page 891.

Allocation concealment (selection bias)	Unclear risk	"a card was drawn from a consecutive series of sealed opaque envelopes." Page 891.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not blinded. Personnel: not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting bias.
Other bias	Low risk	Author has treated induction of labour and augmentation in labour as mutually exclusive events, e.g. if a woman has a pharmacological induction of labour with further interventions to augment contractions this still included in the data for induction of labour. Control group n = 32, 18 women had IOL at 42 weeks. A further 7/14 women had augmentation.

Magann 1998b

Methods	Randomised controlled trial.
Participants	**Setting:** Naval Medical Center, San Diego, California, USA (Page 1279). **Duration of study:** 6 months (March 1996 to September 1996) (Page 1279). **Participants randomised:** n = 105 **Inclusion criteria**: no contraindication to a vaginal delivery. Bishop score ≤ 4. Uncomplicated pregnancy. ≥ 41 weeks' gestation. Informed consent signed (Page 1279). **Exclusion criteria:** contraindication to a pelvic examination, i.e. placenta praevia, rupture of membranes (Page 1279). **Parity:** mixed. Both nulliparous and multiparous women included (Page 1280, Table II).

	Bishop score: Bishop score at entry (mean +/-SD) recorded	
Interventions	**Membrane sweeping group: n** = **35** "daily membrane stripping performed" (Page 1280). **Prostaglandin group: n** = **35** "0.5mg of prostaglandin E2 (PGE2) gel placed into the cervix on a daily basis as an outpatient." (Page 1280). **Control group: n** = **35** "gentle daily cervical examination" "All patients were examined to determine Bishop scoring by one of the two examiners who were blinded to group assessment." "If the Bishop score totaled ≥8 or the patient reached the forty second week of pregnancy the patient was admitted for induction of labour." All patients received a modified biophysical profile (NST and amniotic fluid index) every 3 days except for those women in the prostaglandin group who had daily biophysical profiling after the insertion of the intracervical prostaglandin (Page 1280).	
Outcomes	Spontaneous onset of labour Formal induction of labour Induction at 42 weeks Spontaneous vaginal delivery Caesarean section delivery Forceps delivery Apgar < 7 at 5 minutes Cost analysis	
Notes	**Funding:** "Departments of Obstetrics and Gynecology, Naval Medical Center and University of Mississippi Medical Center. Supported in part by the Vicksburg Hospital Medical Foundation." page 1279. **Trial authors' declaration of interest:** none declared **Informed consent obtained:** yes **Ethical approval:** "study was approved by the Institutional Review Board" page 1280. Unable to source contact details for Dr Magann	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"patients were randomly assigned to one of the groups by drawing the next in a series of opaque sealed envelopes that had been generated from a random number table", page 1280.
Allocation concealment (selection bias)	Unclear risk	"by drawing next in series of opaque sealed envelopes" page 1280.

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported Personnel: "All patients were examined to determine Bishop scoring by one of the two examiners who were blinded to group assessment." Further blinding of personnel not discussed, page 1280.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias.
Other bias	Low risk	No evidence of other bias.

Magann 1999

Methods	Randomised control trial.
Participants	**Setting:** antenatal diagnostic unit, USA. **Duration of study:** 18 months (January 1995 until June of 1996) (Page 88). **Participants randomised:** N = 182. **Inclusion criteria:** > 41 weeks, "a singleton pregnancy, vertex presentation, intact membranes, reassuring antenatal assessment, no contraindication to a vaginal delivery, and a Bishop score of ≤ 4." (Page 88). **Exclusion criteria:**"patients whose gestational age was uncertain" and "women not desiring to participate." (Page 89). **Parity:** mixed. Both nulliparous and multiparous women included (% presented in Table 2 of manuscript page 89). **Bishop score:** Bishop score at trial entry and admission to labour ward (mean +/-SD) recorded.
Interventions	**Membrane sweeping (n = 91):** "daily membrane sweeping." "The technique for membrane sweeping involved the separation of the membranes from the lower uterine segment with two circumferential sweeps of the examining finger. If the cervix did not permit entrance of the examining finger, the cervix was stretched by the examining finger daily until membrane stripping could be accomplished." (Page 89). **Dinoprostone group (n = 91):** "daily placement of a dinoprostone(prostaglandin E2) vaginal suppository

	(Cervidil)."(releasing 0.3 mg/hour over 12 hours)."Women in the dinoprostone group had daily nonstress tests and amniotic fluid evaluation following placement of the prostaglandin. Patients were discharged from the hospital after a reassuring assessment and if any contractions were present after the contractions had begun to decrease in intensity and frequency. All patients were instructed to return to labor and delivery for regular contractions, rupture of membranes, fever, or decreased fetal movement." (page 89). "All patients were examined by one of two examiners, blinded to group assignment to determine the daily Bishop score. Following the examination, the membranes were either stripped or the vaginal suppository was placed. Patients were examined on a daily basis until spontaneous labor, rupture of membranes, a Bishop score of $8 occurred (at which time patients were admitted for labor induction), or 42 weeks was attained, at which time all remaining patients were admitted for labor induction." (Page 89).	
Outcomes	Labour Induction at 42 weeks Postpartum endometritis Cost **Mode of birth** Spontaneous vaginal Caesarean section Forceps **Neonatal outcome** Apgar score < 7 at 5 minutes NBICU admission	
Notes	**Funding:** "Supported in part by the Vicksburg Hospital Medical Foundation" **Trial authors' declaration of interest:** none declared **Informed consent obtained:** "all participants signed an informed consent before entrance into the study" page 89. **Ethical approval:** yes,"This study was approved by the Institutional Review Board." page 89. Unable to source contact details for Dr Magann	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly assigned to one of two groups by drawing a card, generated from a table of random numbers", page 89.
Allocation concealment (selection bias)	Unclear risk	"sealed in an opaque envelope", page 89. Not stated if numbered or sequential.

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: blinding of patients not discussed. Personnel: "All patients were examined by one of two examiners, blinded to group assignment to determine the daily Bishop score" (Page 89). Blinding of clinicians post initial assessment not discussed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of clinicians post initial assessment not discussed. Not stated if person collecting the data was blinded to the interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias.
Other bias	Low risk	No evidence of other bias.

McColgin 1990a

Methods	A prospective randomised controlled trial.
Participants	**Setting:** USA **Duration of study**: not stated. **Participants randomised:** N = 103. **Inclusion criteria:** women at term (38 to 42 weeks' gestation) with gestational age ascertained by menstrual dates, early examination, and sonography before 20 weeks. Women with closed cervix were included (Page 811). **Exclusion criteria:** uncertain dates, abnormal fetal presentations, known medical complications of pregnancy, low lying placenta, placenta praevia, scheduled repeat caesarean section, or no desire to participate (Page 811). **Parity:** mixed. Both nulliparous and multiparous women included. No further data given. **Bishop Score:** unfavourable Bishop score (≤ 5) recorded.
Interventions	**Membrane stripping (n = 51):** weekly stripping of the membranes "digital separation from the lower uterine segment with 1 or 2 circumferential passes. Normally 1-2cm of the membranes was separated from the lower uterine segment." "In patients with long closed cervices"… "the cervix was digitally "stretched" until membrane stripping could be accomplished" (Page 811). **Control group (n = 48):** "weekly pelvic examination without membrane stripping" to assess cervix for Bishop scoring.

	All patients were examined every week in the same manner until admitted to labour/delivery ward or advanced beyond 42 weeks completed gestation. Two of the authors (SWM and JCU) performed almost all the membrane stripping and assignment of Bishops score (> 98%) (Page 811).	
Outcomes	Caesarean section Forceps of vacuum Spontaneous vaginal delivery Chorioamnionitis Augmentation Oxytocin post SROM (induction of labour) Delivery within 1 week	
Notes	**Funding**: none declared **Trial authors' declaration of interest:** Department of Obstetrics and Gynaecology, United States Airforce Hospital, Tyndall Air Force base, Florida, USA. Department of Obstetrics and Gynaecology, University of Mississippi Medical Center, Jackson, Mississippi, USA (page 811). **Informed consent obtained:** yes "and obtaining informed consent" (page 811) **Ethical approval**: not stated. Unable to contact Dr McColgin	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"we prospectively assigned patients at term (38-42 weeks' gestation)", page 811. Unable to contact authors.
Allocation concealment (selection bias)	Unclear risk	Not reported. Method of randomisation not described Not stated if sealed, opaque envelopes used/or other method of allocation concealment. Unable to contact author.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Paticipants: not reported. Unable to contact author. Personnel: not blinded. "two authors (SWM and JCM performed almost all the membrane striping and assignment of Bishop's score (> 98%).", page 812.
Blinding of outcome assessment	Unclear risk	Not reported if person collecting the data was blinded to the interventions. Unable to contact author.

(detection bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias. 4 exclusions (2 patients in non-stripped arm received stripping, 1 with pre-eclampsia and 1 with breech presentation). N = 99 (103-4) < 20%.
Selective reporting (reporting bias)	High risk	Data for age, parity, Bishop scores and gestational age were recorded but are not reported in study, page 812. Maternal and neonatal complications stated as trial outcomes but not reported in data.
Other bias	Low risk	No evidence of other bias

McColgin 1990b

Methods	Randomised controlled trial.
Participants	**Setting:** University of Mississippi Medical Center**,** Jackson, Mississippi, USA. **Duration of study:** enrolment = March 1998 to June 1999 (Page 679). **Participants randomised:** N = 209. **Inclusion criteria:** 38 weeks' gestation. "Gestational age was ascertained by uterine size and by ultrasound before 20 weeks' gestation with no size dates discrepancy." (Page 678). **Exclusion criteria:** uncertain gestational dating criteria, nonvertex presentation, a known medical complication of pregnancy, vaginal or cervical infection. Placenta praevia, low lying placenta (Page 678). Exclusions after randomisation (29 women). Past history of caesarean section (17) in both groups. In the stripping group, 5 women were excluded for various reasons (abnormal presentation (2), dates unclear (1), pain (1), breast cancer (1)). In the control group, 7 women were excluded for various reasons (labour induction for maternal fetal indications (3), non vertex (1), dates (1), inadvertent stripping (1), renal disease (1)) (Page 679). **Parity:** mixed. Both nulliparous and multiparous women included (Table 1 page 679). **Bishop score:** initial Bishop score recorded (Mean ± SEM). Weekly Bishop scores collected in study but data not provided.
Interventions	**Membrane stripping (n = 90):** "Stripping of the membranes was accomplished by digital separation of 2-3cm of the membranes from the lower uterine segment using 2 circumferential passes of the examining finger. In patients with long and closed cervices, the cervix was "stretched" digitally until membrane stripping could be accomplished." (Page 678).

	Control group (n = 90): "Pelvic examination was performed by atraumatic assessment of the cervix for Bishop scoring" (Page 678). Bishop score was recorded for all patients (Page 678). All patients were examined every week in the same manner until delivery/scheduled induction or advanced beyond 42 weeks completed gestation (≥ 294 days).	
Outcomes	Maternal Infection Fetal death (double nuchal cord) Mode of delivery: data not reported	
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained:** "Informed consent was obtained" **Ethical approval**: not stated. Unable to contact Dr McColgin	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"assigned by computer randomisation", page 678.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not stated. Personnel: "two authors (S.W.M. and J.C.M. performed almost all the membrane striping and assignment of Bishop's score (>98%)." No further information on blinding of personnel given, page 679.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated if person collecting the data was blinded to the interventions, therefore, insufficient information to inform judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 209 women initially recruited, 29 were excluded in total (< 20%). Although VBAC (vaginal birth after caesarean section) or history of a caesarean section were not listed in the exclusion criteria, 17 women with a history of caesarean section wanting a VBAC were excluded "when it became apparent that caesarean deliveries and post

		term pregnancies were unfairly biased against the control group in this select population" page 679
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias
Other bias	Low risk	No evidence of other bias.

McColgin 1993

Methods	Randomised controlled trial	
Participants	**Setting:** University of Mississippi Medical Center**,** Jackson, Mississippi, USA. **Duration of study:** 6 months (Page 72). **Participants randomised:** N = 30. **Inclusion criteria:** > 38 weeks' gestation (gestational age was ascertained from known last menstrual period, early assessment by ultrasonography before 20 weeks' gestation, and no size-dates discrepancy.) (Page 72). **Exclusion criteria:** uncertain gestational dating criteria, known medical complications of pregnancy, findings of cervical or vaginal infection, low-lying placenta (or placenta previa), or non-vertex presentation (Page 72). **Parity:** mixed.	
Interventions	**Three arms** **Membrane sweep (n = 10)** **Control with Bishop evaluation (n = 10)** **Control without cervical evaluation (n = 10)**	
Outcomes	No clinical outcomes reported	
Notes	Study reported on uterine contractile activity; change in phospholipase A2 activity and prostaglandin F2α	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (seection bias)	Low risk	"Thirty patients were randomly divided" "by means of a computer generated list of envelopes" page 72
Allocation concealment (selection bias)	Unclear risk	Sequentially assigned "list of envelopes" page 72 not reported if opaque or numbered

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: while not reported, highly likely that it is not possible to blind. Personnel: not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data reported for all randomised participants
Selective reporting (reporting bias)	Unclear risk	No protocol. Outcomes stated in methods reported in results
Other bias	Low risk	No evidence of other bias

Netta 2002

Methods	Randomised prospective controlled trial
Participants	**Setting:** New York, USA **Duration of study**: not reported **Participants randomised:** N = 98 **Inclusion criteria:** "36 weeks gestation with uncomplicated pregnancy" Ultrasound confirmation of gestational age (Page S221). **Exclusion criteria:** with"no evidence of placenta previa" (Page S221). **Parity:** mixed. Both nulliparous and multiparous women included (Page S221). **Bishop score**: not stated
Interventions	**Membrane stripping (n = 44):** "weekly CMS beginning at 38 weeks" (cervical membrane stripping)(Page S221). **Control group (n = 54):** "cervical exams deferred until labour" (Page S221). "All patients underwent vaginal-rectal cultures for GBS at the time of recruitment" (Page S221)
Outcomes	Nulliparous induction Neonatal infections
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained**: not stated **Ethical approval**: not stated

	Email sent requesting further information 8 August 2017. Resent 18 August 2017. No reply to date.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported "a randomised prospective study was performed".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported. Personnel: clinicians not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	98 women "Completed the protocol", 44 = membrane stripping 54 = control group. Attrition not reported. Authors only reported data on the primiparous women, so the denominators are 20 and 27, respectively. Data not provided for 51 of 98 women = 52%. Author contacted no reply to date.
Selective reporting (reporting bias)	High risk	Data collected for gestational age at delivery, mode of delivery, PROM, labour induction, maternal carriage rate of GBS and neonatal outcomes. Overall rates of gestational age at delivery, mode of delivery and PROM not provided. IOL rates only reported for nulliparous women.
Other bias	Low risk	Conference abstract only. No protocol available. Author contacted. No reply to date. However, no other bias noted.

Parlakgumus 2014

Methods	Randomised controlled trial
Participants	**Setting:** Baskent University, Adana, Turkey

	Duration of study: February 2011 to March 2011. **Participants randomised:** N = 165. **Inclusion criteria:** "Low risk women at 38+0 - 39+0 weeks of gestation." "Gestational age was confirmed with dating ultrasound" (Page 683). **Exclusion criteria:** "History of uterine surgery including caesarean section, presentations other than cephalic, multiple pregnancy and contraindications to membrane sweeping which included placenta praevia, placental abruption, rupture of the membranes, active bleeding and labour." (Page 683). **Parity:** mixed. Both nulliparous and multiparous women were included (Table 1 page 685). **Bishop score:** Bishop score < 5 recorded
Interventions	**Membrane stripping (N = 69)** "Swept the membranes in the sweeping group, by separating the lower membranes as much as possible from their cervical attachment, with a 360 degree pass of the examining fingers" (Page 684). **Control group (N = 71)** "Cervical length was measured **(cervix1)** in both groups by examiner 1 and the Bishop Score was determined in the control group and sweeping was performed in the sweeping group by examiner 2. Two days later the patients had another cervical length measurement **(cervix 2)** by examiner 1, blinded to the group and results of the examiner 2" (Page 684).
Outcomes	Spontaneous vaginal delivery Caesarean section Induction of labour
Notes	**Funding:** Baskent University Foundation Huriye Ayse Parlakgumus **Trial authors' declaration of interest**: not stated **Informed consent obtained:** yes "written informed consent" (Page 683). **Ethical approval:** yes "The study protocol was approved by the local ethics committee" "Helsinki declaration" (page 683).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"sealed envelopes which included treatment allocations were prepared", page 683.
Allocation concealment (selection bias)	Unclear risk	"sealed envelopes which included treatment allocations were prepared"

		"women in both groups selected an envelope", page 683. Study does not state if envelopes were opaque or sequential.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants:"the patients were also blinded to the group they were allocated to. However because of discomfort women felt during sweeping, total blinding was not possible", page 684. Personnel: incomplete blinding. "Examiner 1 …assessed the bishop score in the control group and swept the membranes in the sweeping group", page 684.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Examiner 1**: cervical length was measured (cervix1) in both groups by examiner 1 before women opened the envelopes that gave allocation. "examiner 1, blinded to the groups which the patients were allocated to", page 681. **Examiner 2:** "opened the envelopes, assessed the Bishop score in the control group and swept the membranes in the sweeping group", page 682. **Examiner 1:** 2 days later the patients had another cervical length measurement (cervix 2) by" examiner 1 blinded to the groups which the patients were allocated to", page 682 "Data on delivery were retrieved from patient files and in cases of missing data, the women were contacted by the phone and other hospital records were searched", page 685.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting Authors reported they "may have performed the second cervical scan too early."…"if measured at "later time, we could have found more significant results", page 687.
Other bias	Low risk	No evidence of other bias

Putnam 2011

Methods	Randomised controlled trial
Participants	**Setting:** Obstetrics/gynecology clinic, Naval Medical Center, USA. **Duration of study:** January 2005 to June 2008. **Participants randomised:** N = 389

	Inclusion criteria: "Women at 39 weeks ± 2 days gestation with an unfavorable cervix, a singleton pregnancy, ≥18 years of age, reliable pregnancy dating that included a first trimester ultrasound, ultrasound confirming that the placenta was clear of the cervix, and who had no contraindication to a vaginal delivery" (Page 288). **Exclusion criteria:** Bishop's score was ≥ 4, contraindication to a vaginal delivery (Page 288). **Parity:** mixed. Both nulliparous and multiparous women were included (Table 1 page 290). **Bishop score:** Bishop score at recruitment (Table I, Page 290) and admission to labour ward (Table II, Page 291) recorded.
Interventions	**Control group (n = 117): group I** "cervix examined weekly but did not have their membranes swept" (Page 288). **Membrane stripping 1 x/week (n = 119): Group II:** "weekly membrane sweeping" (Page 288). **Membrane stripping 2 x/week (n = 119): Group III:** "twice-weekly membrane sweeping." (Page 288). "The technique of membrane sweeping was defined as separating the fetal membranes from the lower uterine segment with two circumferential sweeps by the examining finger. If the cervix did not permit entrance of the finger on examination, the finger was placed into the cervix and two circumferential sweeps were done. This was done serially depending on the frequency of the group assignment until entrance of the examining finger could be accomplished. Women in the control group had their cervix examined and the Bishops' score recorded every 7 days. Group I women had their membranes swept every 7 days and Group II women had their membranes swept every 3–4 days. Membrane sweeping was continued according to the assigned frequency until 41 weeks of gestation. At 41 weeks, all remaining women were admitted to the hospital for labor induction." (Page 288).
Outcomes	Induction of labour Vaginal delivery Caesarean delivery Chorioamnionitis Instrumental vaginal delivery Apgar score < 7 at 5 minutes
Notes	**Funding**: not stated **Trial authors' declaration of interest**: not stated **Informed consent obtained**: not stated. **Ethical approval:** yes,"study was approved by the Chief of Navy Bureau of Medicine and Surgery, Washington, DC, through the local Clinical Investigation Program (International Review Board)" (Page 288).
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The method of randomization and group assignment was determined by drawing a card from a sealed opaque envelope", page 288.
Allocation concealment (selection bias)	Unclear risk	"The method of randomization and group assignment was determined by drawing a card from a sealed opaque envelope that would assign the participants to Group I (control), Group II (once-weekly sweeping), or Group III (twice-weekly sweeping). The cards were prepared in blocks of 30 envelopes", page 288. Not reported if envelopes were sequential or numbered.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported. Personnel: partially blinded. "this study could not be blinded to the membrane sweeping investigator but was blinded to all other providers and to the investigator collecting data on each participant", page 288.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"this study could not be blinded to the membrane sweeping investigator but was blinded to all other providers and to the investigator collecting data on each participant", page 288
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Ramya 2015

Methods	Randomised controlled trial
Participants	**Setting:**"antenatal outpatient department of Mahatma Gandhi Medical College and Research Institute", India (Page 1). **Duration of study:** January 2011 to June 2012 **Participants randomised:** N = 150 **Inclusion criteria:** "women with one previous caesarean section with non-recurrent indications, singleton pregnancy and cephalic

	presentation, gestational age of 39 weeks, intact membrane and candidates willing for VBAC." (Page 1). **Exclusion criteria:** "multiple gestations, malpresentations, placenta praevia, abruptioplacentae, suspected cephalo-pelvic disproportion, gestational diabetes, chronic or gestational hypertension, pre eclampsia, gestational age less than 39 weeks, H/O premature ruptures of membranes, vasa praevia, congenital anomalies, any previous abortions, More than one transverse lower segment caesarean scar, Previous classical caesarean scar, any other uterine surgeries related to gynaecology." (Page 1). **Parity**: multiparous women were included with history of a previous caesarean section (Table 1 page 2). **Bishop score:** "pre swiping Bishop score recorded" (Table 1 page 2).	
Interventions	**Membrane stripping (N = 75):** "During vaginal examination, if cervix admitted one finger, the foetal membranes were separated from the cervix and the lower uterine segment as far as possible by sweeping a finger through 360 degrees. When the cervix was closed attempts to stretch the cervix open or cervical massage was performed. Sweeping was done at 39 and 40 weeks." (Page 1). **Control group (N = 75):** "gentle vaginal examination was done once at 39 weeks for Bishop scoring and no further examination was done till the onset of labour (Page 2). All the cases were monitored by daily Non Stress Test, amniotic fluid index was measured once in every three days till onset of labour or 41 weeks. Any condition requiring immediate delivery was excluded from the study and was managed according to the institutional protocol (Page 2).	
Outcomes	Spontaneous onset of labour Vaginal birth after caesarean section Caesarean section Oxytocin augmentation Instrumental vaginal delivery	
Notes	23/75 in control group and 21/75 in Membrane sweeping group had caesarean section on maternal request. **Funding**: not stated **Trial authors' declaration of interest**: not stated **Informed consent obtained:** yes, "informed written consent". **Ethical approval:** yes,"Ethical committee clearance".	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation not reported "were randomly assigned" page 1 (abstract).

Allocation concealment (selection bias)	Low risk	"reassigned into two groups by the sequential opening of numbered sealed opaque envelopes indicating a "sweep" or "No Sweep", page 1
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported. Personnel: not reported. Unlikely that clinicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting noted.
Other bias	Low risk	No evidence of other bias.

Saichandran 2015

Methods	Randomised controlled trial
Participants	**Setting:** Hospital setting, India. **Duration of study:** not reported. **Participants randomised:** N = 100 **Inclusion criteria:** "**a)** uncomplicated singleton pregnancies with cephalic presentation and intact membranes, **b)** candidates for vaginal delivery, **c)** gestational age 40 + 0 weeks and **d)** primigravida/primipara." (Page 1883). **Exclusion criteria:** "scarred uterus or speculum findings suggestive of vaginal infection" (Page 1883). **Parity:** mixed. Both nulliparous and multiparous women were included (Table I, Page 1883). **Bishop Score:** < 5, > 5 recorded. Data given in hours from last sweep to spontaneous labour and delivery (Table 4, Page 1884)
Interventions	**Membrane stripping (n = 48):** "In the study group vaginal examination was performed for pelvic assessment and Bishop Score. During examination if the cervix is admitting a finger the fetal membranes are separated from the cervix and lower uterine segment as far as possible by sweeping a finger through 360 degrees. When the cervix is closed, attempts to stretch the cervix open or cervical massage was performed. Similar procedure was

	repeated every 48 hours till 41 ± 0 weeks (i.e. 40 ± 0, 40±3, and 40 ± 5) or until labor commenced." (Page 1883). **Control group (n = 50):** "no pelvic examination was performed till the onset of labour or time of induction i.e. 41 ± 0 weeks. This is to avoid stimulation with cervical examination which can also raise the prostaglandin concentration causing ripening of the cervix." Both the groups were monitored by NST (daily) and AFI (once in every 3 days). Any conditions warranting immediate delivery were excluded from the study and were managed according to the institute protocol (Page 1883).	
Outcomes	Spontaneous onset of labour Induction of labour Vaginal delivery LSCS Augmentation Perinatal death	
Notes	"Out of the fifty in the study group, 2 were excluded due to requirement of immediate induction of labor after the first sweeping were excluded from the final analysis" (Page 1883). This data were included in over all study number and induction of labour outcome. **Funding**: not stated **Trial authors' declaration of interest**: not stated **Informed consent obtained:** yes, "informed consent was obtained" (Page 1883). **Ethical approval:** yes,"The ethical committee of our medical college approved the study" (Page 1883).	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported, "The participants of the study were allocated randomly by", page 1883.
Allocation concealment (selection bias)	Unclear risk	"The participants of the study were allocated randomly by the use of sealed opaque envelops for study and control groups.", page 1883. No comment regarding sequentially numbered.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported. Personnel: not reported.

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	N = 100. Intervention group = 48 (50-2) Control = 50. "Two among the study group, who required immediate induction of labor after the first sweeping were excluded from the final analysis", Page 1883.
Selective reporting (reporting bias)	High risk	Primary outcome measure of " ….. any maternal or fetal complication" not reported, page 1883. All other outcomes appear to have been reported.
Other bias	Low risk	No evidence of other bias.

Salamalekis 2000

Methods	Randomised controlled trial.
Participants	**Setting:** University of Athens "Areteion" hospital, Athens, Greece. **Duration of study**: not reported. **Participants randomised:** N = 104 **Inclusion criteria:** nulliparous, gestational age between 40 -41 weeks (281 to 287 days), singleton pregnancy and cephalic presentation. Bishop score ≤ 5. Uneventful pregnancy with gestational age determined clinically and by ultrasound during their 1st trimester (Page 241). **Exclusion criteria**: no maternal complications (hypertension, diabetes) or the fetus (congenital anomalies, growth retardation) (Page 241). **Parity:** primiparous women only included. **Bishop score:** initial Bishop score (Table I, Page 241) and Bishop score on admission to labour ward (Table II, page 242) recorded.
Interventions	**Membrane stripping (N = 34):** "Sweeping of the membrane with a bishop score ≤ 5. During the procedure the examiners fingers were inserted as far as possible through the internal os, separating the membranes from the lower uterine segment and rotating 360◦." (Page 241). **Oxytocin uterine stimulation (n = 35): "**Uterine stimulation with very low doses of Oxytocin for 6 hours. A diluted oxytocin infusion of 10 IU per 1000 mL of Ringers lactate solution was prepared and I.V. infusing was initiated with 0.5mU/min which was doubled hourly, reaching a maximum of 4mU/min. All these patients had continuous cardiotocographic monitoring throughout the 6 hour infusing period." (Page 241). **Control group (N = 35):** "Gentle vaginal examination." (Page 241).

	All patients were "followed up for 4 days after the vaginal examination or sweeping of the membranes and were filed in a fetal movement chart.". "When signs of labour were noted they were transferred to the labour ward" (Page 241).	
Outcomes	Spontaneous onset of labour Chorioamnionitis Caesarean section Induction of labour	
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained**: not stated **Ethical approval**: not stated Email sent 28/08/17, 2 November 2017 requesting further information. No reply to date	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Type of randomisation not reported. "our randomly selected study" page 241
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported. Personnel: not reported. It was not possible to blind the clinician who gave the intervention. It is unclear if the same clinician was there at the birth or made the decisions that might affect outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make informed decision. Trial protocol not available.

Other bias	Low risk	No evidence of other bias.

Salmanian 2012

Methods	Randomised controlled trial	
Participants	**Setting:** Islamic Republic of Iran. **Duration of study:** not reported. **Participants randomised:** N = 60 **Inclusion criteria:** "pregnant women (gestational age >40w), primigravida and gravida 2" other inclusion criteria not reported (Page S811). **Exclusion criteria:** not reported. **Parity:** mixed. Both nulliparous and multiparous women included (primigravida and gravida 2), however no data provided (Page S811). **Bishop Score:** mean of Bishop score change recorded only. Baseline and final Bishop scores not recorded (Page S811).	
Interventions	**Group A (N = not reported):** membrane stripping **Group B (N = not reported):** PGE2	
Outcomes	Data supports subgroup analysis only	
Notes	**Funding**: none declared **Trial authors' declaration of interest:** none declared **Informed consent obtained**: not stated **Ethical approval**: not stated Email sent 5 June 2017 requesting further data. Email sent 28 September 2017 requesting further details. No reply to date.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not blinded. Personnel: unclear.
Blinding of outcome assessment (detection	Unclear risk	Not reported.

bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not reported.
Selective reporting (reporting bias)	Unclear risk	No protocol available. Conference abstract only.
Other bias	Low risk	No protocol available, conference abstract only. However, no other bias noted.

Tannirandorn 1999

Methods	Randomised controlled trial.
Participants	**Duration of study**: November 1994 to March 1995 (patients were enrolled). **Setting:** Antenatal clinic, Department of Obstetrics and Gynaecology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. **Participants randomised:** N = 96. **Inclusion criteria:** gestation between 39 and 40 weeks verified by known last normal menstrual period, early confirmation through size and ultrasound prior to 20 weeks' gestation and no size/date discrepancy during antenatal visits (Page 230). **Exclusion criteria:** uncertain dates, abnormal fetal presentations, unengaged fetal head, known medical complications of pregnancy, placenta praevia known lower genital tract infections, history of a previous caesarean section or no desire to participate in the study (Page 230). **Parity:** mixed. Both nulliparous and multiparous women included (Page 230).
Interventions	**Membrane stripping (n = 41):** in the membrane stripping group: "Stripping of the membranes was done by digital separation of 2-3cm of the membranes from the lower uterine segment using two circumferential passes of the examining finger under aseptic technique. In those patients with long closed cervices randomised to the stripping group the cervix was stretched digitally until membrane stripping could be accepted" This intervention was performed weekly along with a gentle pelvic examination for Bishop scoring (Page 230). **Control group (n = 39):** in the control group: a weekly "gentle pelvic examination for Bishop scoring was given." "The authors performed all membrane stripping and assignment of Bishop scores after standardisation of the technique." If gestational age reached > 42 completed weeks (> 294 days) without spontaneous onset of labour, the patients were admitted

	into the hospital for fetal monitoring and induction was performed with either Prostin E2 vaginal tablet or IV oxytocin (Page 230).	
Outcomes	Spontaneous vaginal delivery Caesarean section Forceps delivery Puerperal morbidity PPH Chorioamnionitis	
Notes	**Funding**: none declared. **Trial authors' declaration of interest:** none declared. **Informed consent obtained:** yes "obtaining informed consent" (Page 230). **Ethical approval:** yes "the protocol was approved by the ethical committee of the faculty of medicine Chulalongkorn Hospital" (Page 230). Email sent 17 August 2017 and 28 August 2017 requesting further information. No reply to date	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"assigned to one of two groups according to a table of random numbers", page 230.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: blinding of participants not reported. Personnel: "Only the authors performed all membrane stripping and assignment of Bishop scores after standardization of the technique.", page 230.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	N = 80 (96 were recruited, 16 were excluded. Of those excluded 7 had lower genital tract infections, 4 delivered at another hospital, 3 could not perform membrane sweeping and 2 did not participate in the study) < 20%. Page 230.

Selective reporting (reporting bias)	Unclear risk	Insufficient information to make informed decision.
Other bias	Low risk	No evidence of other bias.

Ugwu 2014

Methods	Randomised controlled trial
Participants	**Setting:** Nigeria Teaching Hospital (UNTH), Enugu, Nigeria **Duration of study:** February 2012 – November 2012 **Participants randomised:** N = 134 **Inclusion criteria:** "All uncomplicated singleton pregnancies at a gestational age of 40–41 weeks, without uterine contractions" (Page 30). **Exclusion criteria:** "unsure of date, pre-conception irregular menstrual cycle, evidence of any contraindication to vaginal delivery, medical diseases in pregnancy, and term premature rupture of membranes." (Page 30). **Parity:** mixed. Both nulliparous and multiparous women were included in this study. **Bishop score:** Pre-recruitment Bishops score was recorded (Table I, Page 32).
Interventions	**Membrane stripping (n = 67):** "membranes stripped under aseptic procedure in the antenatal clinic of the hospital without hospital admission. With the woman in dorsal position, initial cervical assessment for the Bishop score was carried out. Thereafter, the investigator's examining finger was introduced into the cervical os. Then, the fetal membranes were digitally separated from the lower uterine segment by two circular movements of the introduced finger. Where the membranes could not be reached, digital stretching of the cervix was attempted, followed by membrane sweeping, when successful. In cases of failed digital cervical stretching or unfavorable cervix (low bishop score), cervical massaging in the vaginal fornices was performed for 10 s. Each participant in the membrane sweeping group was observed for 1 h in the clinic after the procedure. Prophylactic antibiotics were not administered after the stripping of membranes." (Page 30). **Control group (N = 67):** "vaginal examination only to assess the initial Bishop score." (Page 30).
Outcomes	Spontaneous vaginal delivery Assisted vaginal delivery Caesarean section Apgar < 7 at 5 minutes Chorioamnionitis Spontaneous labour within 72 hours of intervention Formal induction of labour
Notes	**Funding**: none declared.

	Trial authors' declaration of interest: none declared. **Informed consent obtained:** yes "written informed consent" (Page 30). **Ethical approval:** yes."obtained from the Institutional Review Board of the UNTH, Enugu." (Page 30). Author contacted 8 August 2017 to clarify trial data Further email sent 28 September 2017. Author reply as follows: (1.) Question: Can you please clarify why there were 2 sets of random numbers (1 to 134) and how these were used to conceal allocation? Ans: First, by 2 sets of random numbers we meant...a set of 67 random numbers for intervention group (labelled A) and another set of 67 random numbers for control group (labelled B), making a total of 134. Each envelop containing a 5 x 5 cm white paper labelled either ''A'' for intervention group or ''B'' for control group, was opaque and sealed. They were kept by a third party (neither the researchers nor the patients) who did not know about the research objectives. (2.) Question: The data for the following outcomes are reported for only the women who did not go post-term (> 41+3). Is it possible for you to provide the outcome data on all women so it may be included in our review? Spontaneous vaginal birth Caesarean section Instrumental vaginal delivery Augmentation of labour Apgar score less than 7 at 5 minutes Answer: "Unfortunately our study was not designed to include intention to treat analysis. So, we limited our data collection and analysis to women who delivered before "post-term" (41+3)."
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	*"*…computer-based random sequence generator…" also "…two sets of random numbers (1 to 134) corresponding to the intervention and control groups…" Email sent to author to clarify: Question: Can you please clarify why there were 2 sets of random numbers (1 to 134) and how these were used to conceal allocation? Answer 17 August 2017: "First, by 2 sets of random numbers we meant...a set of 67 random numbers for intervention group (labelled A) and another set of 67 random numbers for control group (labelled B), making a total of 134."

Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes were labelled sequentially from 1 to 134 by the statistician; each numbered envelope contained a 5 9 5 cm white paper labelled either ‘‘A’’ for intervention group or ‘‘B’’ for control group, corresponding to appropriate number set described above. The envelopes were kept by a medical intern (third party), blinded to the study’s objectives. Furthermore, serial numbers 1–134 were consecutively assigned to each recruited woman following an informed consent. Page 30. Email sent to author to clarify. Answer 17 August 2017: ”Each envelop containing a 5 x 5 cm white paper labelled either ‘‘A’’ for intervention group or ‘‘B’’ for control group, **was opaque and sealed**. They were kept by a third party (**neither the researchers nor the patients**) who did not know about the research objectives.”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants: not reported Blinding of personnel: not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Eleven participants delivered outside the study centre and were lost to follow-up" < 20%. Author reports 17/08/2017: "Unfortunately our study was not designed to include intention to treat analysis".
Selective reporting (reporting bias)	High risk	Reported data did not include women (membranes sweeping n = 10, and control n = 24) whose pregnancies progressed to post-term pregnancy. Author contacted for clarity: Reply 17/08/2017: "Unfortunately our study was not designed to include intention to treat analysis. So, we limited our data collection and analysis to women who delivered before "post-term" (41+3)."
Other bias	Low risk	No evidence of other bias

Weissberg 1977

Methods	Randomised controlled trial	
Participants	**Setting:** Jackson Memorial Hospital, Miami Florida, USA **Duration of study**: not reported **Participants randomised:** n = 91 **Inclusion criteria:** ≥ 37 weeks' gestation (Judged from the date of the last menstrual period and uterine size) (Page 125). **Exclusion criteria:** none stated **Parity:** mixed. Both nulliparous and multiparous women were included in this study. **Bishop score:** baseline Bishop score was recorded at randomisation (Table II, Page 126)	
Interventions	**Membrane stripping (n = 46):** "Digital separation of the membranes from the lower uterine segment as far as possible with the examining finger." (Page 125). **Control group (n = 45):** "Finger inserted into the vagina to palpate the cervix for Bishop scoring without any stripping of the membranes away from the uterus" (Page 125). All women were examined by the same examiner and evaluated as to the length of gestation, estimated fetal size and status of the cervix utilising the Bishop scoring system." The procedure was considered to have failed if they did not go into labour within 48 hours of their pelvic examinations (Page 125).	
Outcomes	spontaneous labour within 48 hours	
Notes	**Funding**: not stated **Trial authors' declaration of interest**: not stated **Informed consent obtained**: not stated **Ethical approval**: not stated Unable to locate contact details for author	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"forty-six randomly selected patients underwent digital stripping of membranes", page 125. No further detail reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel	High risk	Participants: not reported. Personnel: not reported.

(performance bias) All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"all the hospital charts were reviewed after delivery and the clinical data were extracted and placed on punch cards and appropriately analysed with the aid of a computer", Page 125.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Unclear risk	Stated outcome postpartum morbidity not reported. No protocol available. Insufficient information to make informed decision.
Other bias	Low risk	No evidence of other bias. No protocol available

Wiriyasirivaj 1996

Methods	Randomised controlled trial
Participants	**Setting:** Antenatal clinic, Maharaj Nakorn Chiang Mai University Hospital, Thailand. **Duration of study:** 4 October 1994 to 4 November 1994. **Participants randomised:** N = 120 **Inclusion criteria:** 38 weeks' gestation with, "certain dates assessed by known last menstrual period, early assessment by uterine size, or examination by ultrasound before 28weeks' gestation. Vertex presentation, ability to attend follow-up visits. Intention to deliver at the Maharaj Nakorn Chiang Mai University hospital." Page 767 **Exclusion criteria:**"previous caesarean section, known medical, surgical or obstetric complications of pregnancy that would preclude vaginal delivery." Size-date discrepancy during antenatal visits. Placenta praevia or low lying placenta as assessed by ultrasound." Page 767 **Parity:** mixed. Both nulliparous and multiparous women included. **Bishop score:** initial Bishop score recorded.
Interventions	"gentle pelvic examinations were done in both groups to assess the status of the cervix by Bishop scoring."Page 767"only one obstetrician performed membrane stripping and Bishop scoring in all patients" Page 768 **Membrane stripping (N = 61):** "Membranes were stripped by digital separation from the lower uterine segment as far as possible, using a gloved examining finger". "Unfavourable cervices were stretched digitally as much as possible, or until membrane stripping could be accommodated" Page 767

	Control group (N = 59): "gentle pelvic examination for Bishop scoring" Page 768 "Gentle pelvic examinations for Bishop scoring was continued weekly in both groups, whereas the study group also had the membranes stripped weekly until the onset of labour. If gestational age reached 42 completed weeks without spontaneous onset of labour, formal induction was scheduled with either prostaglandin vaginal suppository or intravenous oxytocin drip." Page 768	
Outcomes	Intrapartum fever Oxytocin **Method of delivery** Spontaneous Forceps Vacuum Caesarean Postpartum fever PPH Chorioamnionitis	
Notes	**Funding**: not stated **Trial authors' declaration of interest:** not stated **Informed consent obtained:** yes, "After giving informed consent, subjects were assigned to one of two groups" **Ethical approval:** yes, "The study was approved by the ethical committee of the Faculty of Medicine, Chiang Mai University" Email requesting further data sent 30 August 2017. Resent 20 September 2017. No reply to date.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"subjects were assigned to one of two groups according to a table of random numbers. A simple randomization scheme was prepared by a research nurse before the trial began" Page 767
Allocation concealment (selection bias)	Unclear risk	"the code for each patient was kept in a sealed, black opaque envelope". Not reported if envelopes were sequential or numbered. Page 767
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported. Personnel: not reported.

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Protocol not available
Other bias	Low risk	No evidence of other bias. Protocol not available

Wong 2002

Methods	Prospective randomised controlled trial
Participants	**Setting:** The Princess Margaret hospital, A regional obstetric unit in Hong Kong. Page 632 **Duration of study:** 18 months (1 July 1998 to 31 December 1999). Page 632 **Participants randomised:** N = 120 (133 eligible, 13 refused to participate) **Inclusion criteria:** "All pregnant women beyond 40 weeks of gestation, with dates determined by last menstrual periods and ultrasound performed before 26 weeks**.**" Page 632 **Exclusion criteria:** "Women with previous uterine scar, uncertain gestational age, women who refused to participate, or those who have other indications requiring early induction of labour were excluded" Page 632 **Parity:** mixed. Both nulliparous and multiparous women included.**"**Patients were stratified into two groups, namely, nulliparous and multiparous, before randomisation."(Table 1 of manuscript page 634). However results not reported according to parity. **Bishop score**: not recorded
Interventions	**Membrane stripping: n** = **60** "Sweeping was performed by four obstetricians using a standardised method" `"As much of the membranes as possible were separated from the lower segment. If the cervix would not admit a finger it was massaged for two minutes to encourage prostaglandin release" Page 633 **Control group: n** = **60 "** "Women allocated into the control group did not have any form of vaginal examination"(Page 633). One woman in the control group had sweeping of membranes instead of no intervention.
Outcomes	Spontaneous onset of labour:

	Induction of labour Epidural Caesarean section Forceps delivery Vacuum delivery Spontaneous vaginal delivery Serious neonatal infection Neonatal perinatal death.	
Notes	**Funding:** funded by the Hong Kong Society of Obstetricians and Gynaecologists (Page 635). **Trial authors' declaration of interest:** none stated **Informed consent obtained:** not stated **Ethical approval:** yes, "study was approved by the Hospital Ethical Committee" (Page 632). Email sent 30/08/18 and 28 September 2017 requesting further information. No reply to date.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Six different blocks of 20 randomisation codes generated by computer" Page 633.
Allocation concealment (selection bias)	Unclear risk	Page 633 "..were placed in opaque sealed envelopes. Three separate blocks of randomisation codes were kept for the nulliparous and the other three blocks for multiparous pregnant women. Envelope was opened after a date for formal induction was given". Not reported if envelopes were sequential or numbered.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported Personnel: clinicians not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.

Selective reporting (reporting bias)	Unclear risk	"Sweeping was unintentionally performed in one woman randomised to the control group", page 633. Although women were stratified by parity and subgroup analysis completed no results were reported according to parity. Author contacted for further data, no reply to date.
Other bias	Low risk	No evidence of other bias.

Yaddehige 2015

Methods	Randomised controlled trial
Participants	**Setting:** hospital setting, Sri Lanka. **Duration of study:** not reported. **Participants randomised:** N = 160 **Inclusion criteria**: not discussed **Exclusion criteria**: not discussed **Parity:** mixed. Both nulliparous and multiparous women were included **Bishop score:** Bishop score measured at commencement of the study and at 48 hours post intervention. Only data for mean Bishop score post intervention recorded, page 5.
Interventions	**Group 1:** cervical massage group. Page 5 **Group 2:** membrane sweeping group. Page 5 **Group 3:** control group (no intervention). Page 5
Outcomes	No data reported for outcomes. Subgroup analysis only.
Notes	**Funding**: not stated **Trial authors' declaration of interest:** not stated **Informed consent obtained**: not stated **Ethical approval**: not stated Emailed Dr Yaddehige for further data 10 April 2017, 12 April 2017 and 6 June 2017. Email resent 20 September 2017. No reply to date.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No method of randomisation described…"Participants were randomly assigned to " Page 5
Allocation concealment (selection bias)	Unclear risk	Not reported

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported Personnel: not reported. Unlikely clinicians blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only. No data given on attrition provided.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make informed decision. No data on mean Bishop score 48 hours post intervention given. No baseline Bishop score reported and no specific data given on all other outcomes
Other bias	Low risk	Abstract only. Did not provide methodological reasoning to satisfy any of the other risk of bias domains. However, no other bias noted.

Yasmeen 2014

Methods	Randomised controlled trial
Participants	**Setting:** "Labour room Gyne unit", department of obstetrics and gynecology, BVH, Bahawalpur, Pakistan. **Duration of study:** February, 2013 to August, 2013. **Participants randomised:** N = 60 **Inclusion criteria:** "Patients of para 2 and para 5 with age from 25 to 35 years, Uncomplicated single cephalic term pregnancy, Candidates for vaginal delivery and patients with 40-41 weeks estimated gestational age (by early pregnancy scan)". Page 876 **Exclusion criteria:** "primigravidae, grand multipara, high risk pregnancy and patients presentation other than cephalic". Page 876 **Parity:** only multiparous women included. **Bishop score**: not recorded
Interventions	**Membrane stripping (N = 30):** "sweeping membrane was done." "digital separation of 2-3cm of the membranes from lower uterine segment by rotating the finger at least twice through 360 degrees was done. A closed cervix was stretched digitally until membrane sweeping could be carried out. A closed cervix that would not admit a finger was vigorously massaged. Women who underwent

	sweeping was told that spotting or blood stained cervical mucus may appear." Page 876 **Control group (N = 30):** "no sweeping was done." Page 876
Outcomes	Spontaneous labour within 48 hours
Notes	**Funding**: not stated **Trial authors' declaration of interest:** not stated **Informed consent obtained:** yes, "after informed consent" Page 879. **Ethical approval**: not stated Email sent to clarify data on 12 April 2017. Email re-sent 30 August 2017 to request further information. No reply to date.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not reported…"patients were randomized" Page 876
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not discussed. Personnel: not discussed. Unlikely clinicians have been blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make informed decision.Main stated outcome was proportion of women achieving spontaneous labour within 48 hours. This is not clearly reported. Email sent to author to clarify on 12 April 2017. No reply to date.

Other bias	Low risk	No information given on first 4 domains. However, no evidence of other bias.

Yildirim 2010

Methods	Randomised controlled trial
Participants	**Setting:** Bakirkoy Maternity and Pediatric Diseases Training and Research Hospital, Istanbul, Turkey **Duration of study:** October 2006 and July 2007. **Participants randomised:** N = 351 **Inclusion criteria:** "a single live fetus in cephalic presentation, gestational age between 38 and 40 weeks as determined by the last menstrual period or by a first- or second-trimester ultrasound scan, no previous cesarean section or any uterine surgery, a Bishop score < 4 in the presence of a closed cervix and no contraindication to vaginal birth". Page 682 **Exclusion criteria:** "previous cesarean delivery and uterine surgery, intrauterine fetal death, twin pregnancies, estimated fetal weight 44500g, known gross fetal anomalies or breech presentation". Page 682. **Parity:** mixed. Both nulliparous and multiparous women included. Women who agreed to participate were first stratified into nulliparous and multiparous groups. Bishop score: cervical status and Bishop score (median, IR) recorded.
Interventions	"Pelvic examinations were performed to assess the status of the cervix by Bishop scoring. Transvaginal ultrasonographic measurement of cervical length was performed with the standard longitudinal view of the cervix while the patient's bladder was empty. The probe was placed in the vagina approximately 3 cm proximal to the cervix to avoid distortion of its position or shape and a sagittal view of the cervix, with the echogenic endocervical mucosa along the length of the canal, was obtained. Three measurements were obtained using a Voluson 730 Expert ultrasound machine (GE Medical Systems Kretztechnik, Zipf, Austria) equipped with a 4–11 MHz probe. The shortest measurement was recorded" Page 682 Membrane stripping (N = 179): "Sweeping was performed by separating the lower membrane as much as possible from its cervical attachment, with three circumferential passes of the examining fingers. When sweeping was not possible because the cervix was closed, cervical massage was performed. Massage of the cervical surface was performed with circular pushing and massaging movements of the forefinger and middle finger for approximately 30 s. Sweeping was performed by only one of the investigators, and vaginal examination also was performed by the same investigator for the control group." Page 682 "The women were observed for a few hours after membrane sweeping and, if they were well, they were discharged. The women

	were warned to expect a 'show' and were allowed to go home with a fetal movement chart. They were instructed to go to the labor ward if they experienced decreased fetal movement, rupture of the membranes or excessive vaginal bleeding or suspected the onset of labor." Page 682 Control group (N = 167): vaginal examination. After the initial intervention, there were no further differences in management between the sweeping group and control group. All women were given a deadline date for labour to be induced in the absence of spontaneous onset. Thereafter, all patients were followed weekly until delivery or scheduled induction, and sweeping was not repeated. Page 682	
Outcomes	Spontaneous onset of labour Vaginal delivery Caesarean section Maternal infection Maternal discomfort Neonatal mortality	
Notes	Funding: not stated Trial authors' declaration of interest: not stated Informed consent obtained: yes "Written informed consent to participate in the study was obtained from all women who entered the study" Ethical approval: the hospital ethics committee approved the study. Email requesting further information sent 30 August 2017. Resent 20 September 2017. No reply to date.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"First stratified into nulliparous and multiparous groups". "Randomisation was carried out by using sealed opaque envelopes with a piece of paper inside marked 'Sweep' or 'No Sweep'. Envelopes were prepared in blocks of 20 (10 sweep and 10 no sweep) for each stratified group. Envelopes were then shuffled and placed in boxes marked 'nulliparous' and 'multiparous'. Boxes were refilled as required with blocks of 20 envelopes." Page 682
Allocation concealment (selection bias)	High risk	"The investigator was not blinded to the allocation procedure." "using sealed opaque envelopes with a piece of paper inside marked 'Sweep' or 'No Sweep'." "For random assignment to treatment groups, an envelope was withdrawn from the

		appropriate box and allocated to the woman. Once allocated, an envelope was discarded if a woman chose to withdraw, or there was an error in recruitment" Page 682.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personnel: not blinded "The allocated envelope was opened by the clinician performing the initial vaginal examination just prior to that examination." page 682 Participants: Study states "therefore, at this stage, neither the investigator nor the patients knew the identity of the study group". However it also states that "The procedure allocation was recorded in the woman's chart." Page 682
Blinding of outcome assessment (detection bias) All outcomes	High risk	A sticker bearing the identification of the randomised woman was affixed to the paper marked 'Sweep' or 'No Sweep', and the paper was placed in a sealed drop box until unblinding at the end of the study. "Follow-up of the patients was performed by another investigator who was blinded to which group the patients were in; therefore, at this stage, neither the investigator nor the patients knew the identity of the study group. However "The procedure allocation was recorded in the woman's chart." Page 682
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias."Data were analysed on an intent-to-treat basis" Page 682
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias.
Other bias	Low risk	No evidence of other bias.

Zamzami 2014

Methods	Randomised controlled trial
Participants	**Setting:** Antenatal clinic, King Abdulaziz University Hospital, Jeddah, Saudi Arabia. **Duration of study: 1** January 2011 to 1 January 1 2012 **Participants randomised:** N = 160 **Inclusion criteria:** "singleton pregnancy, cephalic presentation, and anticipated vaginal delivery (Page 30).

	Exclusion criteria: "indications for induction of labor, indications for cesarean section, and contraindications to membrane sweeping, such as multiple gestation, placenta previa, placental abruption, history of preterm delivery, vasa previa, active cervical infection, Mullerian anomalies, severe fetal anomalies and active herpes infection." (Page 30). **Parity:** mixed. Both nulliparous and multiparous women included (Table II, Page 32). **Bishop score:** Bishop score (Initial), mean SD (Table II, Page 32). Bishop score on admission to LW, mean SD	
Interventions	**Membrane stripping (N = 80): "**All membrane sweeping group was performed by one clinician investigator and women allocated to control group received routine monitoring; in each case, the cervix was dilated and the health provider swept a finger in a 360° manner inside the cervix, thereby separating the lower uterine segment from the amniotic sac. If the cervix was closed, it was massaged digitally." Modified Bishop scoring were determine as the following; cervical dilatation, effacement and fetal station" (Page 31). **Control group (N = 80)**: no sweep (Page 31). All pregnant women "both groups" who did not enter spontaneous labor or remaining undelivered at 41 weeks' gestation were being admitted and underwent for induction of labour.	
Outcomes	Induction (at 41 weeks) Spontaneous labour (< 41 weeks) SVD Vacuum delivery Caesarean section Apgar score < 7 PPH	
Notes	**Funding**: not stated **Trial authors' declaration of interest:** not stated **Informed consent obtained:** yes, "provided written informed consent from all participants." (Page 31). **Ethical approval:** yes "approved by the Biomedical Ethics Research Committee and Human Investigation "according to principles of Helsinki Declaration" at King Abdulaziz University" (Page 30). Email sent 28 August 2017 requesting information. Resent 10 September 2017.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Women were assigned randomly at 38 weeks" "using computer-generated numbers", page 31.

Allocation concealment (selection bias)	Low risk	“allocation concealed in opaque sealed envelopes that were drawn in order.”, page 31.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not reported Personnel: not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias. 80 women excluded pre randomisation (60 declined to participate, 20 did not meet inclusion criteria). All outcomes reported on “intention to treat” analysis, page 31.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting noted. All outcomes reported in methods reported in results, page 33.
Other bias	Low risk	No evidence of other bias

Appendix 3.
Paper 1: Characteristics of excluded studies

Study	Reason for exclusion
Al-Harmi 2015	Sweeping of membranes was evaluated as an addition to induction of labour with oxytocin, amniotomy or prostaglandins. Quote: "Women were assigned to having their membranes "swept" or "not swept" at the initiation of labor induction"
Bergsjo 1989	Randomised comparison of sweeping of membranes and oxytocin (94 women) versus expectant management with surveillance (94 women) in women with post-term pregnancy (at or beyond 42 weeks of gestation).
Day 2009	Quote: "A prospective, randomized controlled trial was performed" "who were undergoing labor induction after 34 weeks were screened. Eligible women were randomly assigned to membrane sweeping at the time of labor induction (case) or no sweeping with the first vaginal exam (control)." Intervention commenced at 34 weeks' gestation. Confirmed with author through email 18 April 2017.
Foong 2000	Sweeping of membranes was evaluated as an addition to oxytocin, amniotomy or prostaglandins. Method of concealment of the allocation is unclear. The results of this study suggested that sweeping of membranes during the induction of labour process reduces the risk of caesarean section (8/124 versus 17/124, P = 0.06). This effect was more apparent in nulliparous women who had cervical ripening with prostaglandins (unfavourable cervix) (3/48 versus 12/55, P = 0.01).
Ifnan 2006	Quote: "women admitted for normal delivery requiring induction of labour with singleton live pregnancy" "randomized into two groups for cervical ripening by Foley's catheter ballooning method (group-A) and by hydrostatic membrane sweeping (group-B)". Our review defines membrane sweeping as the clinician inserting 1 or 2 fingers into the cervix and detaching the inferior pole of the membranes from the lower uterine segment in a circular motion (Boulvain 2005)
Kaul 2004	This study was excluded as the gestational age of participants was outside the parameters of our review PICO. Quote: "Sixty women with singleton pregnancy and ascertained gestational age between 34 and 38 weeks,Bishop score -6 were randomized either to membrane stripping or cerviprime gel instillation."
Laddad 2013	This study was excluded as it uses a mechanical device, intra-cervical Foley catheter, rather than a digital sweep by a clinician, as defined in the review protocol to facilitate membrane sweeping. Quote: "A randomized, prospective study" "patients at term with a Bishop's score < 3 with various indications for induction were randomly allocated to receive (200 pts) intra-cervical Foley's catheter or PGE2 gel (200 pts)"
Park 2013	The study examines the effect of concurrent membrane sweeping with dinoprostone. This combination does not satisfy the review protocol.

Study	Reason for exclusion
Park 2015	The study examines the effect of concurrent oxytocin with membrane sweeping. This combination does not satisfy the review protocol.
Shravage 2009	This study contains 2 groups Group 1: membrane sweep + cerviprime Group 2: no sweep + cerviprime The study only examines the effect of membrane sweeping when combined with cerviprime. This combination does not satisfy the review protocol.
Swann 1958	Method of allocation: women had to be allocated to 1 of the following groups: (1) stripping; (2) insertion of the finger in the cervix; (3) vaginal examination. 1 in every 3 women had to be allocated in turn to each group. Despite this schedule (not concealed to the resident in charge) that would have produced balanced groups, 147 women were allocated to membrane stripping, 29 to 'finger control' and 45 to 'Bishop score only'. This major imbalance, together with the inadequate method of randomisation, raises the suspicion of a selection bias. In addition, outcome measures were poorly defined and results difficult to interpret.
Tan 2006	The study examines the effect of membrane sweeping when combined with either dinoprostone pessary or amniotomy, quote: "randomly assigned to receive membrane sweeping or no membrane sweeping at initiation of formal labor induction with either dinoprostone pessary or amniotomy.". This combination does not satisfy the review protocol.

Appendix 4.
Paper 1: Characteristics of ongoing studies

Leong 2017

Trial name or title	Membrane sweeping versus transcervical Foley catheter for induction of labour in women with previous caesarean delivery
Methods	Randomised controlled trial
Participants	**Inclusion criteria** Pregnant women with 1 previous caesarean section who are admitted to Sibu Hospital for induction of labour (IOL) will be recruited. The inclusion criteria are age at least 18 years old, gestational age ≥ 37 weeks, singleton pregnancy, reassuring fetal status and modified Bishop score ≤ 6. **Exclusion criteria** Ruptured membranes, intrauterine death, polyhydramnios, severe fetal anomalies, and multiple pregnancy. Contraindications for IOL, e.g. placenta previa, suspected macrosomia, suspected cephalopelvic disproportion, non-cephalic presentation, and obstructive pelvic masses.
Interventions	**Two groups** **Group 1:** membrane sweeping Membrane sweeping involves the insertion of a digit past the internal cervical os followed by 3 circumferential passes of the digit causing separation of the membranes from the lower uterine segment. When the cervix is closed, a massage of the cervical surface for 15 to 30 seconds will be performed instead. Membrane sweeping will be undertaken twice a day at 8 to 10 hours apart. **Group 2:** transcervical Foley catheter for induction of labour in women with previous caesarean delivery Transcervical Foley catheter No. 18 F will be inserted under aseptic technique into the endocervical canal surpassed beyond the internal os. The balloon will be inflated with 60 mL of sterile water and the catheter is plastered to patient's thigh with gentle traction. The catheter will be checked for its position and the traction at 6-hour intervals. If it were expelled spontaneously, it would not be re-inserted. Otherwise, the catheter will be removed after 24 hours.
Outcomes	**Primary outcome measures** Achievement of favourable cervix (Bishop score of 8 or more) within 48 hours of induction of labour (time frame: from the time of commencing induction until the time whereby the cervix becomes favourable (Bishop score of 8 or more), assessed up to 48 hours). The number of women who achieve Bishop score of 8 or more within 48 hours of induction of labour **Secondary outcome measures** Induction outcomes: improvement of modified Bishop score at interval of 24 hours after induction (time frame: from the time of commencing induction until 4 hours after induction). The difference of modified Bishop score between pre-induction and 24 hours post-induction. The score is assessed based on the station of the presentation, os dilation, and effacement (or length), position and consistency of the cervix. Score ranges from 0 to 12. A score of 8 or more generally indicates that the cervix is ripe/favourable. Induction outcomes: improvement of modified Bishop score at interval of 48 hours after induction (time frame: from the time of commencing induction till 48

	hours after induction). The difference of modified Bishop score between pre-induction and 48 hours post-induction. The score is assessed based on the station of the presentation, os dilation, and effacement (or length), position and consistency of the cervix. Score ranges from 0 to 12. A score of 8 or more generally indicates that the cervix is ripe/favourable. Delivery outcomes: mode of delivery (time frame: at time of delivery). Final mode of delivery, i.e. vaginal delivery and caesarean section. Delivery outcomes: duration of oxytocin augmentation (time frame: from the time of administrating oxytocin augmentation until the time of delivery, assessed up to 16 hours). Duration of oxytocin augmentation during intrapartum period. Delivery outcomes: induction to vaginal delivery interval (time frame: from the time of induction of labour until the time of vaginal delivery, assessed up to 72 hours). Duration between the time of induction of labour and vaginal delivery Delivery outcomes: amniotomy to vaginal delivery interval (time frame: from the time of amniotomy till the time of vaginal delivery, assessed up to 16 hours). Duration between the time of amniotomy and vaginal delivery. Maternal outcomes: uterine hyperstimulation (time frame: from the time of induction until the time of delivery, assessed up to 72 hours). The occurrence of uterine hyperstimulation (> 5 contractions per 10 minutes for at least 20 minutes or a contraction lasting at least 2 minutes with/without abnormal fetal heart rate) during labour process. Maternal outcomes: uterine rupture (time frame: from the time of induction until the time of delivery, assessed up to 72 hours). The occurrence of uterine rupture during labour process. Maternal outcomes: postpartum haemorrhage (time frame: from the time of delivery until the time of discharge, assessed up to 48 hours). The occurrence of postpartum haemorrhage (estimated blood loss ≥ 500 mL) after delivery. Maternal outcomes: maternal pyrexia (time frame: from the time of induction until the time of delivery, assessed up to 72 hours). The occurrence of maternal fever (temperature > 38.0 °C once, or 37.5 °C on 2 occasions 2 hours apart) during labour process. Maternal outcomes: duration of hospitalisation (time frame: from the time of induction until the time of discharge home following delivery, assessed up to 120 hours). To measure the duration of hospitalisation required. Neonatal outcomes: 5-minute Apgar score (time frame: upon the baby is delivered, assessed up to 5 minutes of life). To measure the Apgar score of the newborn at 5 minutes of life, scores range between 0 to 10, score < 7 is considered abnormal. Neonatal outcomes: cord pH (time frame: upon baby is delivered, assessed immediately). To obtain umbilical cord blood of the newborn for pH measurement upon birth, normal levels are 7.25 and above, pH < 7.25 is abnormal and < 7.0 is considered pathological acidosis due to perinatal asphyxia.
Starting date	31 October 2017
Contact information	Yong Soon Leong, Ministry of Health, Malaysia Email: yongsoonleong@moh.gov.my
Notes	Trial completed. Email sent 26/06/2019 requesting trial data. Reply received 26/06/19 from Dr Leong stated:

	"I regret to inform you that it is not feasible for us, at the moment, to provide you the information and findings about the trial"

Manidakis 1999

Trial name or title	Prostaglandins versus stripping of membranes in management of pregnancy beyond 40-41 weeks
Methods	
Participants	Women beyond 40 weeks of gestation with an unfavourable cervix
Interventions	**Three groups** **Group 1:** daily prostin-E2 1.5 to 3 mg at 41 weeks for 3 days **Group 2:** twice-weekly 2 to 3 minute 'non vigorous' membrane stripping at 40 weeks **Group 3:** quote: "expectant management with twice weekly cervical examination"
Outcomes	Induction of labour with other methods.
Starting date	Reported as a pilot study during a meeting in 1999.
Contact information	Unknown
Notes	Unable to contact authors

Pathiraja 2014

Trial name or title	Induction of multiparous women at term using different methods: prostaglandin E2 (dinopristone) vaginal gel, intracervical Foley catheter insertion and sweeping of membrane: an open-label, randomised controlled trial.
Methods	Randomised controlled trial
Participants	**Inclusion criteria** Multiparous women undergoing induction of labour at the study setting. Gestation more than 40 + 4 weeks Singleton pregnancy with cephalic presentation Unruptured membrane Modified Bishop Score (MBS) less than 8 **Exclusion criteria** Primiparity Malpresentation and unstable lie. Favourable cervix (MBS of 8 or above)

	Any contraindication to vaginal birth, with previous uterine surgery (including caesarean section, placenta previa and other placental anomalies) Age less than 18 years Lethal fetal congenital anomaly Known allergy to any of the interventional products
Interventions	**Four arms** Arm 1 (prostaglandin group): dinoprostone gel 2 mg will be inserted following initial cervical assessment. If the cervix is unfavourable after 6 hours a second dose of prostaglandin (2 mg) will inserted. Fetal well-being will be monitored by CTG at 3 hours and 5 hours after insertion of prostaglandin. Arm 2 (Foley catheter group): the Foley catheter balloon will inserted through the cervical canal and the catheter bulb dilated with 60 mL of normal saline done. Sufficient cervical dilatation will result in the catheter dropping out. The Foley catheter will be kept for a maximum of 48 hours. Fetal well-being will be monitored by CTG and daily Doppler assessment. Arm 3 (membrane sweeping group): the sweeping of membrane will done once daily till 41 weeks. Fetal well-being will be monitored by CTG at 3 hours after membrane sweeping and daily Doppler assessment. Arm 4 (control group): spontaneous onset of labour will be awaited with fetal monitoring done daily by 20 minutes CTG and daily Doppler assessment.
Outcomes	**Primary outcomes** Time interval between induction of labour to vaginal delivery Rates of failed induction (needing caesarean section or second induction method) **Secondary outcomes** Requirement for oxytocin augmentation Incidence of uterine hyperstimulation Incidence of intrapartum fetal blood sampling Mode of delivery Blood loss at delivery Incidence of maternal pyrexia (> 37.3°C) Perineal lacerations require suturing Apgar score at 1 minute and 5 minutes Need for admission to a neonatal intensive care unit (NICU).
Starting date	Anticipated start date 15 October 2014
Contact information	Dr. P.D.M. Pathiraja Registrar in Obstetrics and Gynaecology New unit for Obstetrics and Gynaecology Teaching Hospital, Peradeniya 0812388261 0772532828 madushan_pathi@yahoo.com

Notes	Email requesting trial information sent. No reply to date.

Sharma 2012

Trial name or title	Induction of labour in women with previous one caesarean section. Prosprctive double blind randomised control trial comparing the effect of mifepristone with sweeping stretching and trans-cervical Folley's catheterization.
Methods	Randomised controlled trial
Participants	Pregnant females, age 18 to 40 years of age with a singleton pregnancy, previous 1 low segment caesarean section, no other uterine scar or previous rupture. Gestation beyond 40 weeks and cephalic presentation.
Interventions	Group 1: no details reported in trial report. Group 2: women in this group will have initial assessment of Bishop score by senior consultant and receive 400 mg of mifepristone at 40 weeks 5 days gestation and will be re-assessed at 24 hours and 48 hours later by senior consultant (blinded to the group of patient). If patient goes into labour this will be accounted for. Any time if Bishop score is more than 6, amniotomy will be performed followed by oxytocin infusion. If Bishop score is still less than 6 after 48 hours they will be induced with oxytocin. Group 3: women in this group will be inserted with trans-cervical catheter after initial cervical assessment (Foley catheter number 16 filled with 30 mL of normal saline) at 40 weeks 5 days gestation and will be advised to pull the catheter every 20 minutes for 1 minute each. Foleys catheter will be removed after 6 hours, if it does not come out on its own. These women will be re-assessed vaginally after 24 hours or earlier if catheter comes out, if Bishop score is more than 6, amniotomy will be performed followed by oxytocin infusion otherwise re-assessed at 48 hours and induced with oxytocin.
Outcomes	To compare the proportion of women entering labour after use of mifepristone alone as compared to sweeping stretching of cervix or use of trans-cervical Foley’s catheter. Proportion of women vaginally delivered in each group Proportion of women with caesarean section in each group Duration of labour in women in each group Need and amount of oxytocin required in each group Proportion of women with scar dehiscence/rupture in each group Neonatal outcomes
Starting date	States "open to recruitment" 11 April 2017
Contact information	DR RPGMC KANGRA Aat TANDA (HP) Proff and Head, OBG, DR RPGMC KANGRA AT TANDA (HP) Kangra HIMACHAL PRADESH

	176001 India Tel: 91-9218925471 Email: sureshsverma@gmail.com
Notes	Emailed trial authors for further information on membrane sweeping intervention. No reply to date.

Sheffield 2018

Trial name or title	Membrane sweeping in early labour and delivery outcomes.
Methods	Randomised controlled trial
Participants	**Inclusion criteria** 1. Singleton pregnancy at or after 39 weeks' gestation, intact membranes, cephalic presentation, nulliparous, Bishop score < 7, English or Spanish speaking **Exclusion criteria** 1. Prior uterine surgery precluding vaginal delivery, maternal condition precluding vaginal delivery, fetal anomaly, prior membrane stripping
Interventions	**Two groups** **Group 1** Mmbrane sweeping Participants assigned to membrane sweeping will have an additional exam during their initial evaluation in which the membrane will be separated from the cervix and lower part of the uterus with a finger inserted into the cervical os. This would be done with at least 1 rotation counterclockwise and 1 rotation clockwise. **Group 2** Control. Routine vaginal examination
Outcomes	**Primary outcome measure** 1. Decrease in caesarean delivery rate (time frame: up to 3 weeks). **Secondary outcome measures** 1. Time to delivery (time frame: up to 3 weeks). Length of labour from randomisation to delivery 2. Operative vaginal delivery rate (time frame: up to 3 weeks). Assess a decrease in operative vaginal delivery 3. Labour augmentation rate reduction (time frame: up to 3 weeks). Assess the reduction in the rate of labour augmentation (via the use of oxytocin and/or amniotomy)
Starting date	May 20,2018
Contact information	Principal Investigator: Jeanne S Sheffield, MD Johns Hopkins University

Notes	Trial not completed. Recruitment phase due to finish 1 June 2019.

Shipman 2000

Trial name or title	The SNS trial: Sweeping vs no sweeping of membranes in uncomplicated post-date pregnancies
Methods	Unknown
Participants	Unknown
Interventions	**Two Groups:** **Group one:** Membrane sweeping **Group two:** No membrane sweep
Outcomes	Unknown
Starting date	Unknown
Contact information	Mrs Marion Shipman, Senior Clinical Audit Facilitator, Clinical Audit Department, Watford General Hospital, Vicarage Road, Watford, WD1 8HB, UK.
Notes	Unable to contact author

Turgay 2018

Trial name or title	The effect of membrane sweeping on the delivery time and the need of induction in term pregnancy.
Methods	Randomised controlled trial
Participants	**Inclusion criteria** 1. Age 18-35 years 2. Vertex presentation 3. No contraindication for vaginal delivery 4. No contraindication for labour induction **Exclusion criteria** 1. Active vaginal infection 2. Previous uterine surgery 3. Systemic disease 4. Multiple pregnancy 5. Fetal anomaly and suspicious fetal health status
Interventions	**Two groups** **Group 1** Membrane sweeping **Group 2** Control. No intervention
Outcomes	**Primary outcome measures**

	1. Need of labour induction (time frame: during pregnancy. 40 weeks and 6 days for gestational age). Patient need induction for delivery or not. If the patient reach 40 weeks 6 days for gestational age and spontaneous delivery does not begin spontaneously, labour induction is needed. 2. Duration of delivery (time frame: during delivery). The time of the latent and active stage of delivery
Starting date	May 2018
Contact information	Batuhan Turgay, MD. Principal Investigator, Ankara University
Notes	Trial not completed, currently in recruitment phase. CTG: cardiotocography PG: prostaglandins

Appendix 5
Paper 1: Data and analyses Comparisons

Amniotic membranes sweeping versus no treatment/sham

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spontaneous onset of labour	17	3170	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.08, 1.34]
2 Induction of labour	16	3224	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.56, 0.94]
3 Caesarean section	32	5499	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.85, 1.04]
4 Spontaneous vaginal birth	26	4538	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.99, 1.07]
5 Maternal death or serious morbidity	17	2749	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.57, 1.20]
6 Neonatal death or serious neonatal perinatal morbidity	18	3696	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.59, 1.17]
7 Instrumental vaginal birth	22	3888	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.91, 1.25]
8 Epidural analgesia	9	2162	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.97, 1.33]
9 Postpartum haemorrhage	5	760	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.57, 1.39]
10 Augmentation of labour	9	2011	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.17]
11 Apgar score less than seven at five minutes	10	1958	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.51, 2.40]

Amniotic membranes sweeping versus vaginal/intracervical prostaglandins

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spontaneous onset of labour	3	339	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.98, 1.57]
2 Induction of labour	2	157	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.56, 1.45]
3 Caesarean section	3	339	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.44, 1.09]
4 Spontaneous vaginal birth	2	252	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.95, 1.32]
5 Maternal death or serious morbidity	1	87	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.27, 3.21]
6 Neonatal death or serious neonatal perinatal morbidity	2	269	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.12, 1.33]
7 Instrumental vaginal birth	3	339	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.59, 4.14]
8 Augmentation of labour	1	87	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.30]
9 Apgar score less than seven at five minutes	3	339	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.13, 5.77]

Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spontaneous onset of labour	1	69	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.88, 1.96]
2 Induction of labour	1	69	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	69	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.12, 3.85]
4 Maternal death or serious morbidity	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Amniotic membranes sweeping versus vaginal/oral misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Augmentation of labour	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Apgar score less than seven at five minutes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction of labour	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Caesarean section	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Spontaneous vaginal birth	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Maternal death or serious morbidity	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Neonatal death or serious neonatal perinatal morbidity	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Instrumental vaginal birth	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Apgar score less than seven at five minutes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Amniotic membranes sweeping versus no treatment/sham (Primiparae/Multiparae)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spontaneous onset of labour	17	3170	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.08, 1.34]
1.1 Parity - Multiparae	2	361	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.92, 1.20]
1.2 Parity - Primiparae	3	447	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.15, 1.72]
1.3 Parity - unknown	12	2362	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.05, 1.38]
2 Induction of labour	17	3271	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.92]
2.1 Parity - Primiparae	5	600	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.14, 0.85]
2.2 Parity - Multiparae	2	303	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.52, 1.47]
2.3 Parity - unknown	11	2368	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.58, 1.06]
3 Caesarean section	32	5499	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.83, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Primiparae	4	493	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.41, 2.21]
3.2 Multiparae	4	585	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.48, 1.19]
3.3 Parity - unknown	25	4421	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.79, 1.07]
4 Spontaneous vaginal birth	26	4538	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.99, 1.07]
4.1 Primiparae	3	424	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.18]
4.2 Multiparae	4	585	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.82, 1.75]
4.3 Parity - unknown	20	3529	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.99, 1.07]
5 Maternal death or serious morbidity	17	2749	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.57, 1.20]
5.1 Parity - Primiparae	2	169	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Parity - Multiparae	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Parity - unknown	15	2580	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.57, 1.20]
6 Neonatal death or serious neonatal perinatal morbidity	18	3696	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.59, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Parity - Primiparae	1	100	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.18, 1.83]
6.2 Parity - Multiparae	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Parity - unknown	17	3596	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.60, 1.23]

Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy (Primiparae/Multiparae)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spontaneous onset of labour	1	69	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.88, 1.96]
1.1 Parity - Primiparae	1	69	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.88, 1.96]
1.2 Parity - Multiparae	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Induction of labour	1	69	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.42]
2.1 Parity - Primiparae	1	69	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.42]
2.2 Parity - Multiparae	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Caesarean section	1	69	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.12, 3.85]
3.1 Parity - Primiparae	1	69	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.12, 3.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Parity - Multiparae	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Maternal death or serious morbidity	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.1 Parity - Primiparae	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Parity - Multiparae	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Amniotic membranes sweeping versus no treatment/sham Favourable cervix/unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spontaneous onset of labour	17	3170	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.08, 1.34]
1.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Unfavourable cervix	5	700	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.05, 2.47]
1.3 Cervix unknown	12	2470	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.04, 1.32]
2 Induction of labour	16	3224	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.58, 0.95]
2.1 Favourable cervix	1	96	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.66, 1.41]
2.2 Unfavourable cervix	4	589	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.37, 0.85]
2.3 Cervix unknown	13	2539	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	32	5499	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.85, 1.04]
3.1 Favourable cervix	1	101	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.35, 2.95]
3.2 Unfavourable cervix	7	1170	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.15]
3.3 Cervix unknown	24	4228	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.71, 1.00]
4 Spontaneous vaginal birth	26	4538	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.99, 1.07]
4.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Unfavourable cervix	5	755	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.95, 1.15]
4.3 Cervix unknown	21	3783	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.99, 1.08]
5 Maternal death or serious morbidity	17	2749	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.57, 1.20]
5.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Unfavourable cervix	4	885	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.30, 1.04]
5.3 Cervix unknown	13	1864	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.65, 1.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Neonatal death or serious neonatal perinatal morbidity	18	3696	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.59, 1.17]
6.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Unfavourable cervix	1	346	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.58]
6.3 Cervix unknown	17	3350	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.19]

Amniotic membranes sweeping versus vaginal/intracervical prostaglandins (Favourable cervix/unfavourable cervix)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spontaneous onset of labour	3	339	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.98, 1.57]
1.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Unfavourable cervix	2	252	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.13, 1.76]
1.3 Cervix unknown	1	87	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.78, 1.34]
2 Induction of labour	2	157	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.56, 1.45]
2.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Unfavourable cervix	1	70	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.44, 1.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Cervix unknown	1	87	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.47, 1.95]
3 Caesarean section	3	339	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.44, 1.09]
3.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Unfavourable cervix	2	252	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.41, 1.08]
3.3 Cervix unknown	1	87	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.23, 4.15]
4 Spontaneous vaginal birth	2	252	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.95, 1.32]
4.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Unfavourable cervix	2	252	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.95, 1.32]
4.3 Cervix unknown	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Neonatal death or serious neonatal perinatal morbidity	2	269	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.12, 1.33]
5.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Unfavourable cervix	1	182	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.02, 1.68]
5.3 Cervix unknown	1	87	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.13, 2.33]

Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy (Favourable cervix/unfavourable cervix)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spontaneous onset of labour	1	69	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.88, 1.96]
1.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Unfavourable cervix	1	69	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.88, 1.96]
2 Induction of labour	1	69	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.42]
2.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Unfavourable cervix	1	69	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.42]
3 Caesarean section	1	69	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.12, 3.85]
3.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Unfavourable cervix	1	69	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.12, 3.85]
4 Maternal death or serious morbidity	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Unfavourable cervix	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Amniotic membranes sweeping versus vaginal/oral misoprostol (Favourable cervix/unfavourable cervix)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section**Show forest plot**	1	96	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.31, 2.17]
1.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Unfavourable cervix	1	96	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.31, 2.17]

One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping (Favourable cervix/unfavourable cervix)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Induction of labour	1	234	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.76, 1.85]
1.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Unfavourable cervix	1	234	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.76, 1.85]
2 Caesarean section	1	234	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.60, 1.46]
2.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Unfavourable cervix	1	234	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.60, 1.46]
3 Spontaneous vaginal birth	1	234	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.86, 1.17]
3.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Unfavourable cervix	1	234	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.86, 1.17]
4 Maternal death or serious morbidity	1	234	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.30, 2.02]
4.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Unfavourable cervix	1	234	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.30, 2.02]

Amniotic membranes sweeping versus mechanical methods (Favourable cervix/unfavourable cervix)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal death or serious neonatal perinatal morbidity	1	234	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.18, 21.76]
1.1 Favourable cervix	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Unfavourable cervix	1	234	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.18, 21.76]

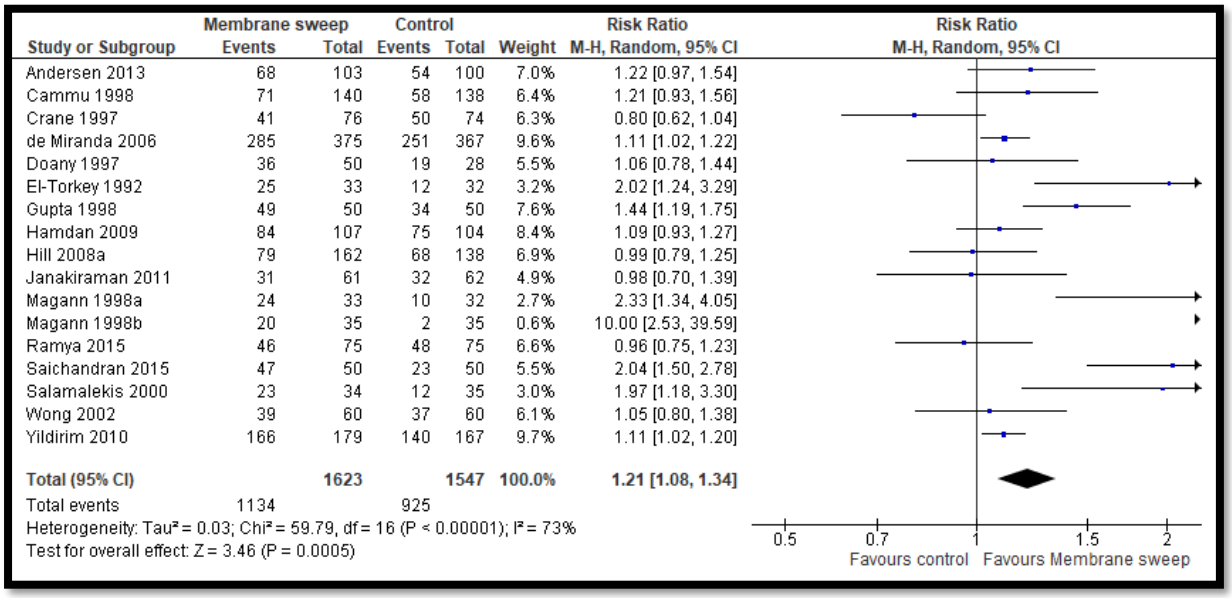
Amniotic membranes sweeping versus no treatment/sham- sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spontaneous onset of labour-sensitivity analysis	6	1884	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.98, 1.18]
2 Induction of labour-sensitivity analysis	6	1879	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.68, 1.24]
3 Caesarean section-sensitivity analysis	10	2480	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Spontaneous vaginal birth-sensitivity analysis	9	2379	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.97, 1.06]
5 Maternal death or serious morbidity - sensitivity analysis	4	661	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.57, 2.59]
6 Neonatal death or serious neonatal perinatal morbidity - sensitivity analysis	7	1941	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.65, 1.53]

Appendix 6.
Paper 1: Data and analyses - Forest plot illustrations

Analysis 1.1 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 1 Spontaneous onset of labour

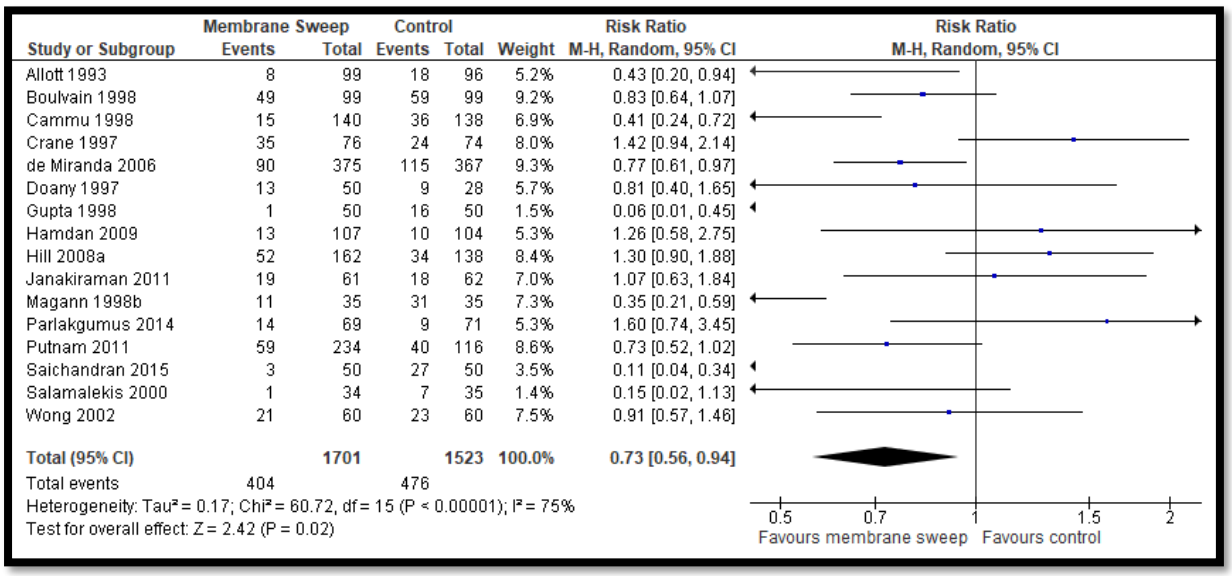


Study or Subgroup	Membrane sweep Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Andersen 2013	68	103	54	100	7.0%	1.22 [0.97, 1.54]
Cammu 1998	71	140	58	138	6.4%	1.21 [0.93, 1.56]
Crane 1997	41	76	50	74	6.3%	0.80 [0.62, 1.04]
de Miranda 2006	285	375	251	367	9.6%	1.11 [1.02, 1.22]
Doany 1997	36	50	19	28	5.5%	1.06 [0.78, 1.44]
El-Torkey 1992	25	33	12	32	3.2%	2.02 [1.24, 3.29]
Gupta 1998	49	50	34	50	7.6%	1.44 [1.19, 1.75]
Hamdan 2009	84	107	75	104	8.4%	1.09 [0.93, 1.27]
Hill 2008a	79	162	68	138	6.9%	0.99 [0.79, 1.25]
Janakiraman 2011	31	61	32	62	4.9%	0.98 [0.70, 1.39]
Magann 1998a	24	33	10	32	2.7%	2.33 [1.34, 4.05]
Magann 1998b	20	35	2	35	0.6%	10.00 [2.53, 39.59]
Ramya 2015	46	75	48	75	6.6%	0.96 [0.75, 1.23]
Saichandran 2015	47	50	23	50	5.5%	2.04 [1.50, 2.78]
Salamalekis 2000	23	34	12	35	3.0%	1.97 [1.18, 3.30]
Wong 2002	39	60	37	60	6.1%	1.05 [0.80, 1.38]
Yildirim 2010	166	179	140	167	9.7%	1.11 [1.02, 1.20]
Total (95% CI)		**1623**		**1547**	**100.0%**	**1.21 [1.08, 1.34]**
Total events	1134		925			

Heterogeneity: Tau² = 0.03; Chi² = 59.79, df = 16 (P < 0.00001); I² = 73%
Test for overall effect: Z = 3.46 (P = 0.0005)

Risk Ratio M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Favours control Favours Membrane sweep

Analysis 1.2 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 2 Induction of labour.

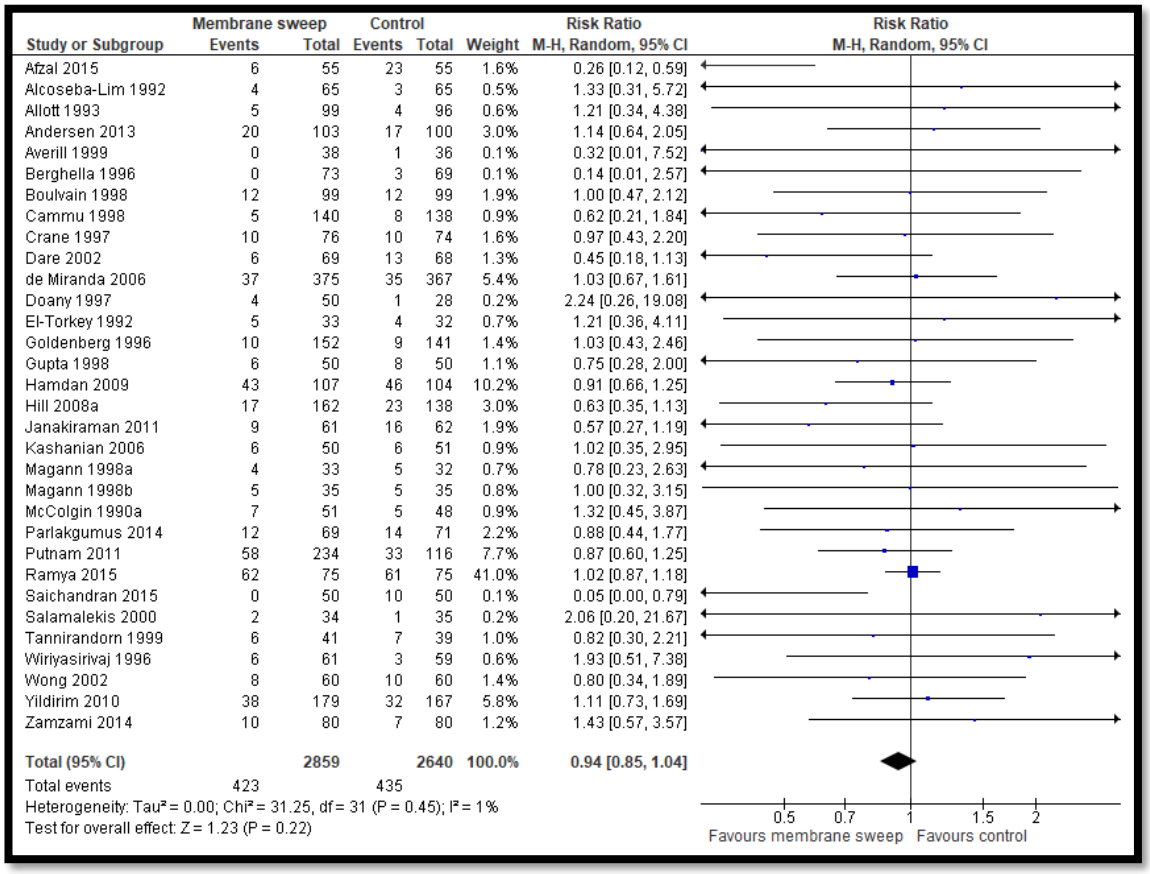


Study or Subgroup	Membrane Sweep Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Allott 1993	8	99	18	96	5.2%	0.43 [0.20, 0.94]
Boulvain 1998	49	99	59	99	9.2%	0.83 [0.64, 1.07]
Cammu 1998	15	140	36	138	6.9%	0.41 [0.24, 0.72]
Crane 1997	35	76	24	74	8.0%	1.42 [0.94, 2.14]
de Miranda 2006	90	375	115	367	9.3%	0.77 [0.61, 0.97]
Doany 1997	13	50	9	28	5.7%	0.81 [0.40, 1.65]
Gupta 1998	1	50	16	50	1.5%	0.06 [0.01, 0.45]
Hamdan 2009	13	107	10	104	5.3%	1.26 [0.58, 2.75]
Hill 2008a	52	162	34	138	8.4%	1.30 [0.90, 1.88]
Janakiraman 2011	19	61	18	62	7.0%	1.07 [0.63, 1.84]
Magann 1998b	11	35	31	35	7.3%	0.35 [0.21, 0.59]
Parlakgumus 2014	14	69	9	71	5.3%	1.60 [0.74, 3.45]
Putnam 2011	59	234	40	116	8.6%	0.73 [0.52, 1.02]
Saichandran 2015	3	50	27	50	3.5%	0.11 [0.04, 0.34]
Salamalekis 2000	1	34	7	35	1.4%	0.15 [0.02, 1.13]
Wong 2002	21	60	23	60	7.5%	0.91 [0.57, 1.46]
Total (95% CI)		**1701**		**1523**	**100.0%**	**0.73 [0.56, 0.94]**
Total events	404		476			

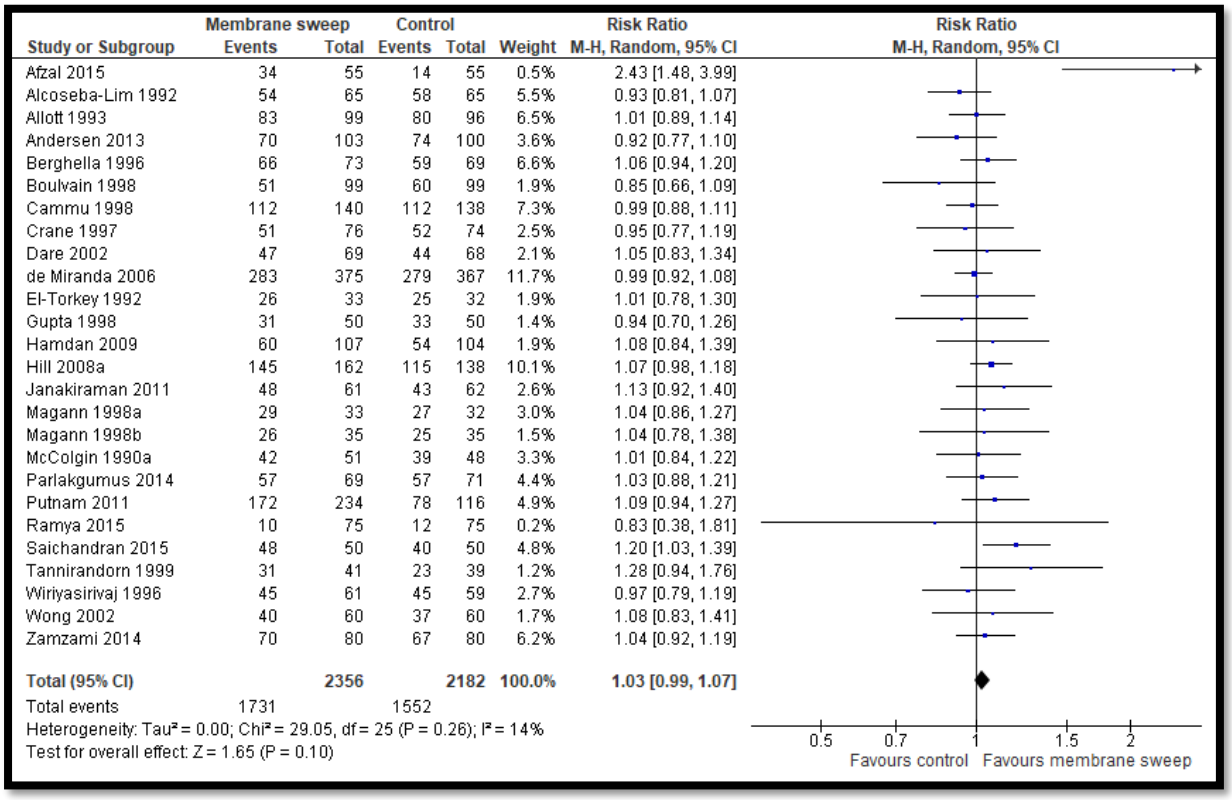
Heterogeneity: Tau² = 0.17; Chi² = 60.72, df = 15 (P < 0.00001); I² = 75%
Test for overall effect: Z = 2.42 (P = 0.02)

Risk Ratio M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Favours membrane sweep Favours control

Analysis 1.3 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 3 Caesarean section



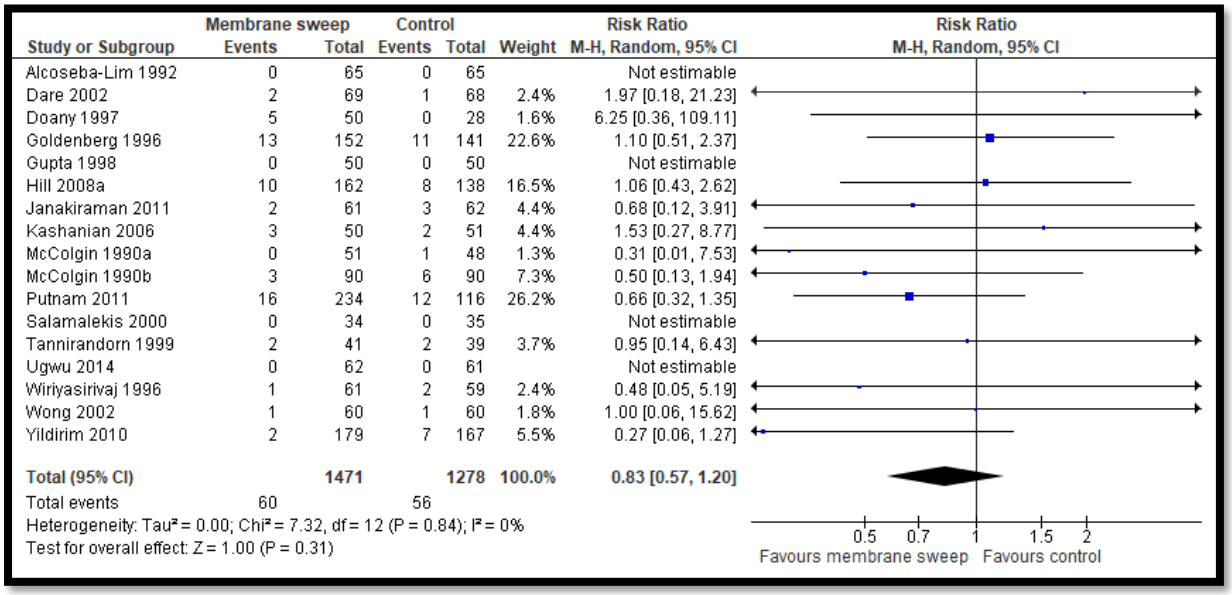
Analysis 1.4 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 4 Spontaneous vaginal birth.



Study or Subgroup	Membrane sweep Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Afzal 2015	34	55	14	55	0.5%	2.43 [1.48, 3.99]
Alcoseba-Lim 1992	54	65	58	65	5.5%	0.93 [0.81, 1.07]
Allott 1993	83	99	80	96	6.5%	1.01 [0.89, 1.14]
Andersen 2013	70	103	74	100	3.6%	0.92 [0.77, 1.10]
Berghella 1996	66	73	59	69	6.6%	1.06 [0.94, 1.20]
Boulvain 1998	51	99	60	99	1.9%	0.85 [0.66, 1.09]
Cammu 1998	112	140	112	138	7.3%	0.99 [0.88, 1.11]
Crane 1997	51	76	52	74	2.5%	0.95 [0.77, 1.19]
Dare 2002	47	69	44	68	2.1%	1.05 [0.83, 1.34]
de Miranda 2006	283	375	279	367	11.7%	0.99 [0.92, 1.08]
El-Torkey 1992	26	33	25	32	1.9%	1.01 [0.78, 1.30]
Gupta 1998	31	50	33	50	1.4%	0.94 [0.70, 1.26]
Hamdan 2009	60	107	54	104	1.9%	1.08 [0.84, 1.39]
Hill 2008a	145	162	115	138	10.1%	1.07 [0.98, 1.18]
Janakiraman 2011	48	61	43	62	2.6%	1.13 [0.92, 1.40]
Magann 1998a	29	33	27	32	3.0%	1.04 [0.86, 1.27]
Magann 1998b	26	35	25	35	1.5%	1.04 [0.78, 1.38]
McColgin 1990a	42	51	39	48	3.3%	1.01 [0.84, 1.22]
Parlakgumus 2014	57	69	57	71	4.4%	1.03 [0.88, 1.21]
Putnam 2011	172	234	78	116	4.9%	1.09 [0.94, 1.27]
Ramya 2015	10	75	12	75	0.2%	0.83 [0.38, 1.81]
Saichandran 2015	48	50	40	50	4.8%	1.20 [1.03, 1.39]
Tannirandorn 1999	31	41	23	39	1.2%	1.28 [0.94, 1.76]
Wiriyasirivaj 1996	45	61	45	59	2.7%	0.97 [0.79, 1.19]
Wong 2002	40	60	37	60	1.7%	1.08 [0.83, 1.41]
Zamzami 2014	70	80	67	80	6.2%	1.04 [0.92, 1.19]
Total (95% CI)		**2356**		**2182**	**100.0%**	**1.03 [0.99, 1.07]**
Total events	1731		1552			

Heterogeneity: Tau² = 0.00; Chi² = 29.05, df = 25 (P = 0.26); I² = 14%
Test for overall effect: Z = 1.65 (P = 0.10)

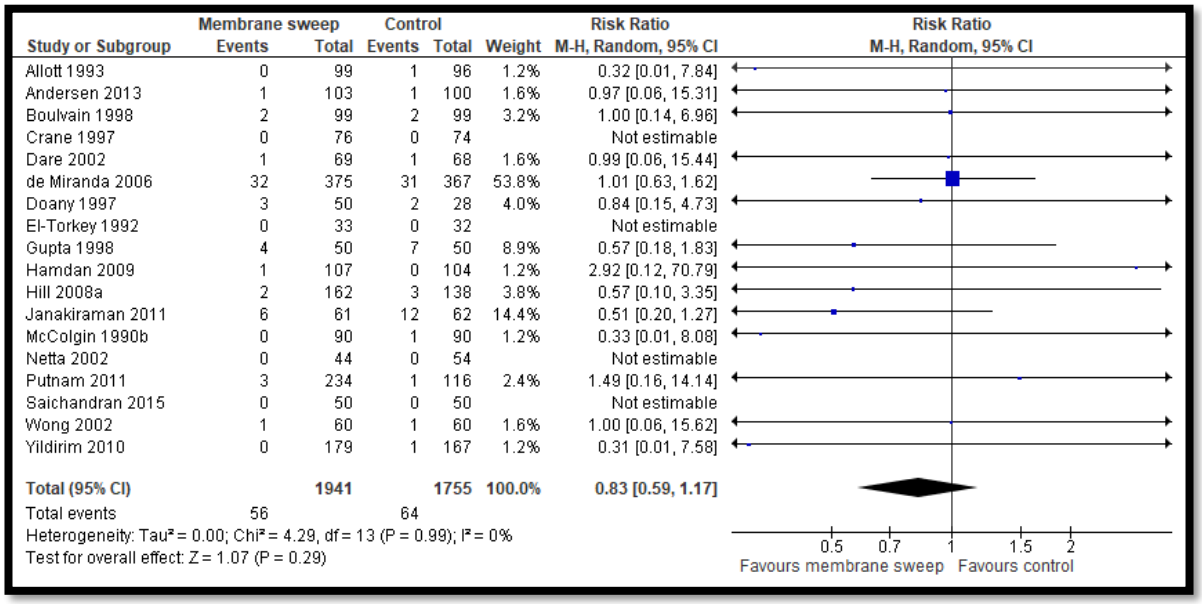
Analysis 1.5 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 5 Maternal death or serious morbidity.



Study or Subgroup	Membrane sweep Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Alcoseba-Lim 1992	0	65	0	65		Not estimable
Dare 2002	2	69	1	68	2.4%	1.97 [0.18, 21.23]
Doany 1997	5	50	0	28	1.6%	6.25 [0.36, 109.11]
Goldenberg 1996	13	152	11	141	22.6%	1.10 [0.51, 2.37]
Gupta 1998	0	50	0	50		Not estimable
Hill 2008a	10	162	8	138	16.5%	1.06 [0.43, 2.62]
Janakiraman 2011	2	61	3	62	4.4%	0.68 [0.12, 3.91]
Kashanian 2006	3	50	2	51	4.4%	1.53 [0.27, 8.77]
McColgin 1990a	0	51	1	48	1.3%	0.31 [0.01, 7.53]
McColgin 1990b	3	90	6	90	7.3%	0.50 [0.13, 1.94]
Putnam 2011	16	234	12	116	26.2%	0.66 [0.32, 1.35]
Salamalekis 2000	0	34	0	35		Not estimable
Tannirandorn 1999	2	41	2	39	3.7%	0.95 [0.14, 6.43]
Ugwu 2014	0	62	0	61		Not estimable
Wiriyasirivaj 1996	1	61	2	59	2.4%	0.48 [0.05, 5.19]
Wong 2002	1	60	1	60	1.8%	1.00 [0.06, 15.62]
Yildirim 2010	2	179	7	167	5.5%	0.27 [0.06, 1.27]
Total (95% CI)		**1471**		**1278**	**100.0%**	**0.83 [0.57, 1.20]**
Total events	60		56			

Heterogeneity: Tau² = 0.00; Chi² = 7.32, df = 12 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.31)

Analysis 1.6 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 6 Neonatal death or serious neonatal perinatal morbidity.

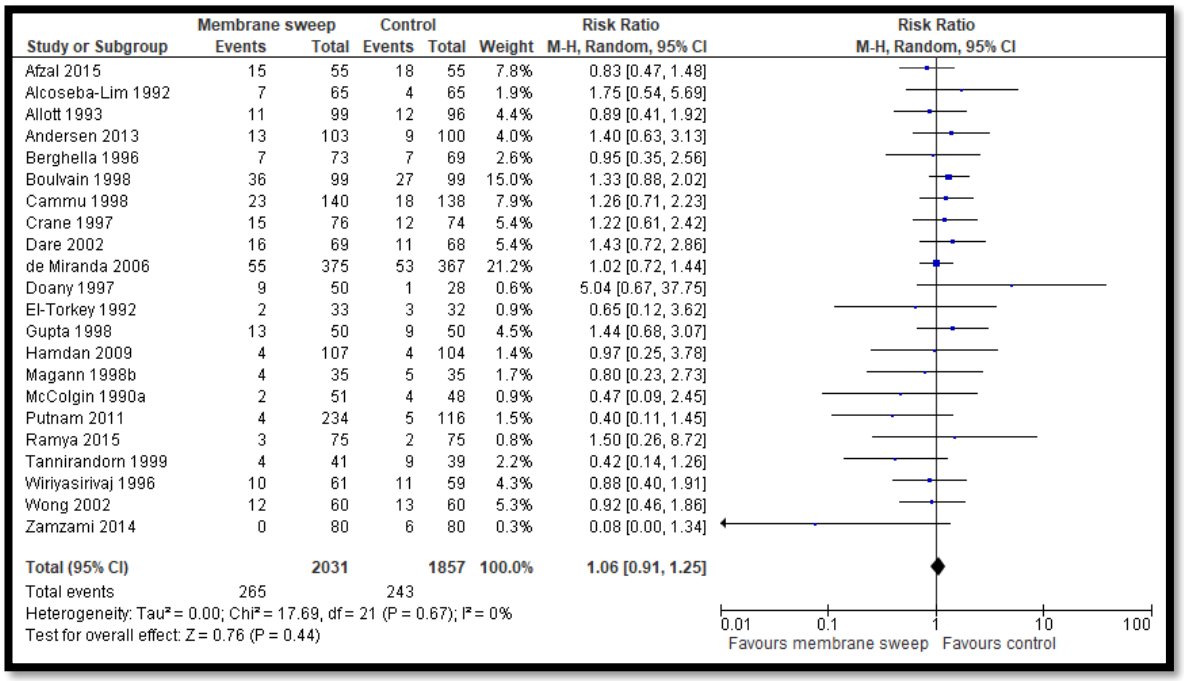


Study or Subgroup	Membrane sweep Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Allott 1993	0	99	1	96	1.2%	0.32 [0.01, 7.84]
Andersen 2013	1	103	1	100	1.6%	0.97 [0.06, 15.31]
Boulvain 1998	2	99	2	99	3.2%	1.00 [0.14, 6.96]
Crane 1997	0	76	0	74		Not estimable
Dare 2002	1	69	1	68	1.6%	0.99 [0.06, 15.44]
de Miranda 2006	32	375	31	367	53.8%	1.01 [0.63, 1.62]
Doany 1997	3	50	2	28	4.0%	0.84 [0.15, 4.73]
El-Torkey 1992	0	33	0	32		Not estimable
Gupta 1998	4	50	7	50	8.9%	0.57 [0.18, 1.83]
Hamdan 2009	1	107	0	104	1.2%	2.92 [0.12, 70.79]
Hill 2008a	2	162	3	138	3.8%	0.57 [0.10, 3.35]
Janakiraman 2011	6	61	12	62	14.4%	0.51 [0.20, 1.27]
McColgin 1990b	0	90	1	90	1.2%	0.33 [0.01, 8.08]
Netta 2002	0	44	0	54		Not estimable
Putnam 2011	3	234	1	116	2.4%	1.49 [0.16, 14.14]
Saichandran 2015	0	50	0	50		Not estimable
Wong 2002	1	60	1	60	1.6%	1.00 [0.06, 15.62]
Yildirim 2010	0	179	1	167	1.2%	0.31 [0.01, 7.58]
Total (95% CI)		**1941**		**1755**	**100.0%**	**0.83 [0.59, 1.17]**
Total events	56		64			

Heterogeneity: Tau² = 0.00; Chi² = 4.29, df = 13 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.29)

Risk Ratio M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Favours membrane sweep Favours control

Analysis 1.7 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 7 Instrumental vaginal birth.

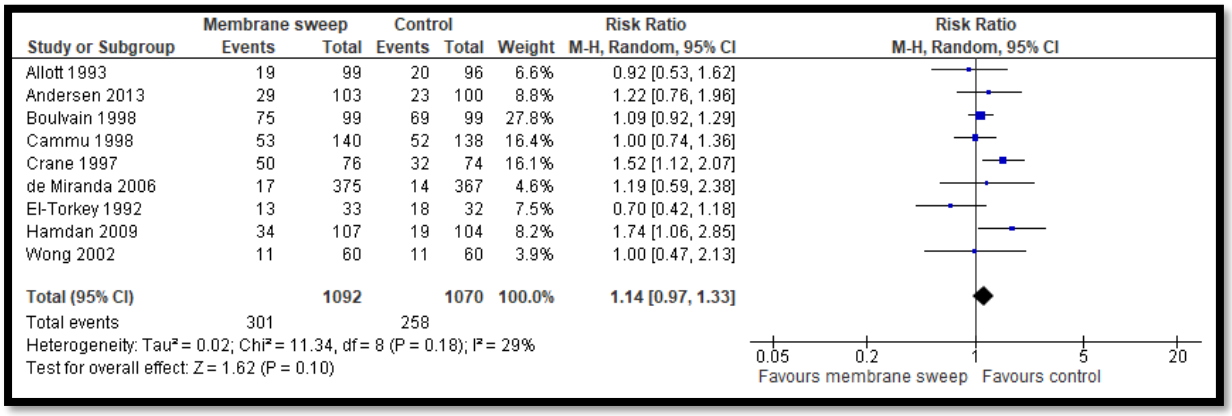


Study or Subgroup	Membrane sweep Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Afzal 2015	15	55	18	55	7.8%	0.83 [0.47, 1.48]
Alcoseba-Lim 1992	7	65	4	65	1.9%	1.75 [0.54, 5.69]
Allott 1993	11	99	12	96	4.4%	0.89 [0.41, 1.92]
Andersen 2013	13	103	9	100	4.0%	1.40 [0.63, 3.13]
Berghella 1996	7	73	7	69	2.6%	0.95 [0.35, 2.56]
Boulvain 1998	36	99	27	99	15.0%	1.33 [0.88, 2.02]
Cammu 1998	23	140	18	138	7.9%	1.26 [0.71, 2.23]
Crane 1997	15	76	12	74	5.4%	1.22 [0.61, 2.42]
Dare 2002	16	69	11	68	5.4%	1.43 [0.72, 2.86]
de Miranda 2006	55	375	53	367	21.2%	1.02 [0.72, 1.44]
Doany 1997	9	50	1	28	0.6%	5.04 [0.67, 37.75]
El-Torkey 1992	2	33	3	32	0.9%	0.65 [0.12, 3.62]
Gupta 1998	13	50	9	50	4.5%	1.44 [0.68, 3.07]
Hamdan 2009	4	107	4	104	1.4%	0.97 [0.25, 3.78]
Magann 1998b	4	35	5	35	1.7%	0.80 [0.23, 2.73]
McColgin 1990a	2	51	4	48	0.9%	0.47 [0.09, 2.45]
Putnam 2011	4	234	5	116	1.5%	0.40 [0.11, 1.45]
Ramya 2015	3	75	2	75	0.8%	1.50 [0.26, 8.72]
Tannirandorn 1999	4	41	9	39	2.2%	0.42 [0.14, 1.26]
Wiriyasirivaj 1996	10	61	11	59	4.3%	0.88 [0.40, 1.91]
Wong 2002	12	60	13	60	5.3%	0.92 [0.46, 1.86]
Zamzami 2014	0	80	6	80	0.3%	0.08 [0.00, 1.34]
Total (95% CI)		**2031**		**1857**	**100.0%**	**1.06 [0.91, 1.25]**
Total events	265		243			

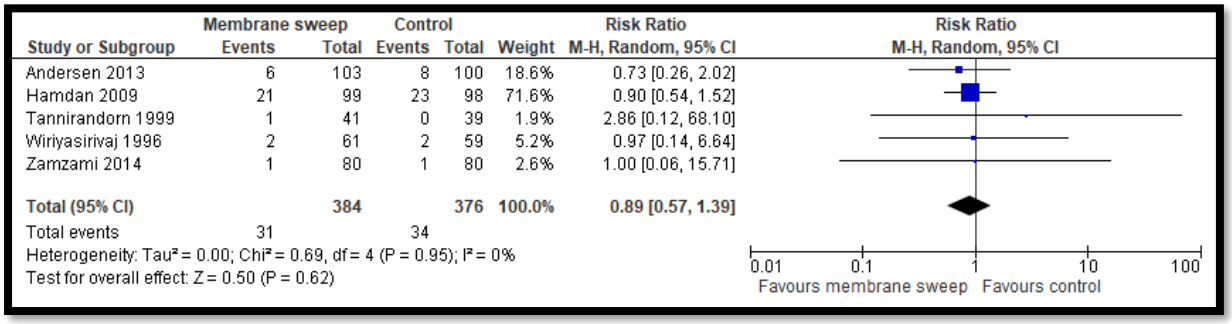
Heterogeneity: Tau² = 0.00; Chi² = 17.69, df = 21 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.44)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours membrane sweep Favours control

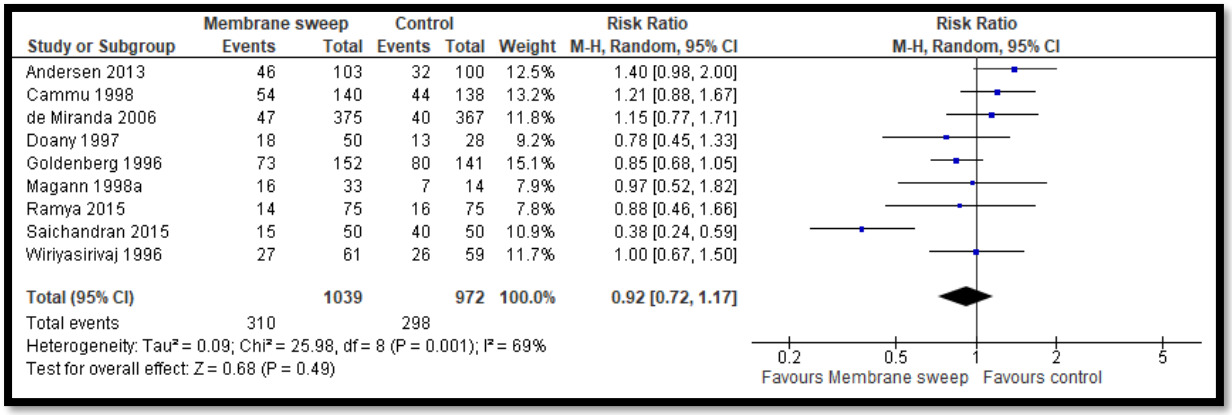
Analysis 1.8 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 8 Epidural analgesia.



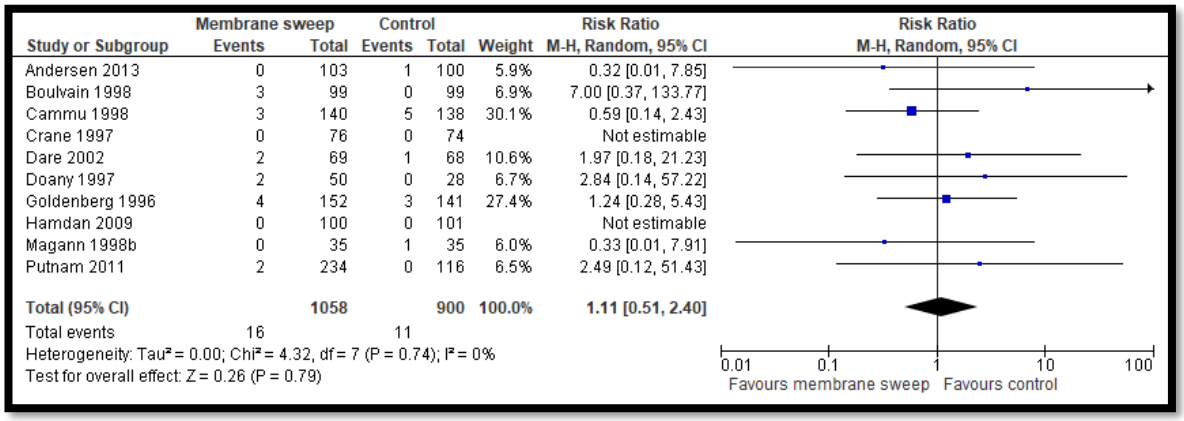
Analysis 1.9 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 9 Postpartum haemorrhage.



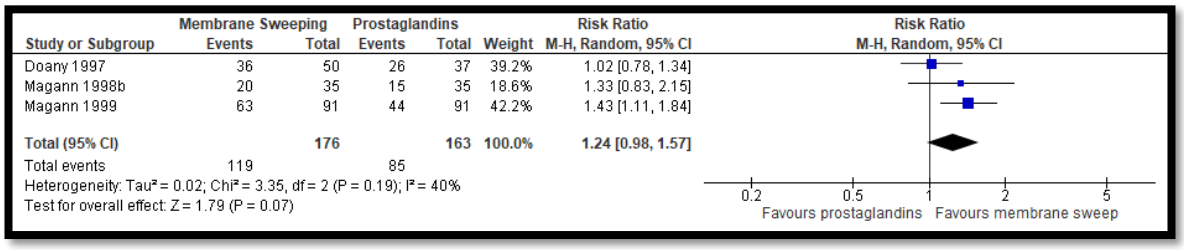
Analysis 1.10 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 10 Augmentation of labour.



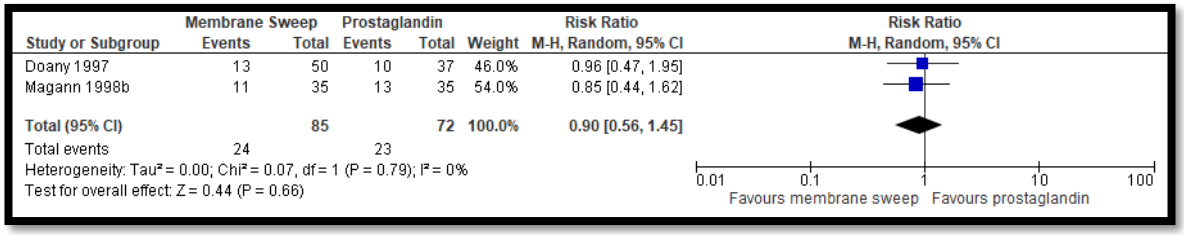
Analysis 1.11 Comparison 1 Amniotic membranes sweeping versus no treatment/sham, Outcome 11 Apgar score less than seven at five minutes.



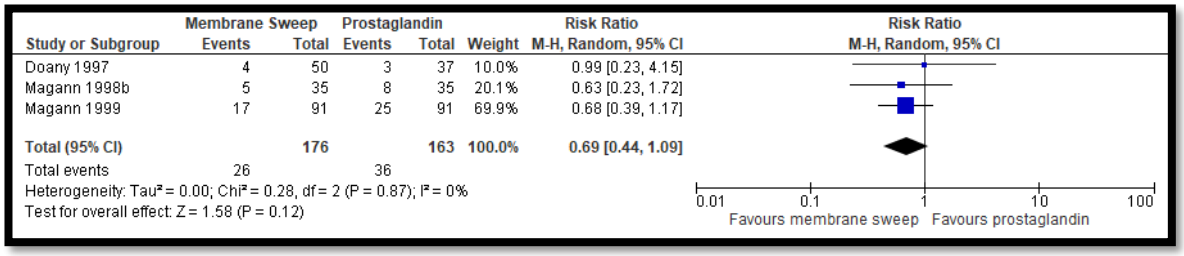
Analysis 2.1 Comparison 2 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins, Outcome 1 Spontaneous onset of labour



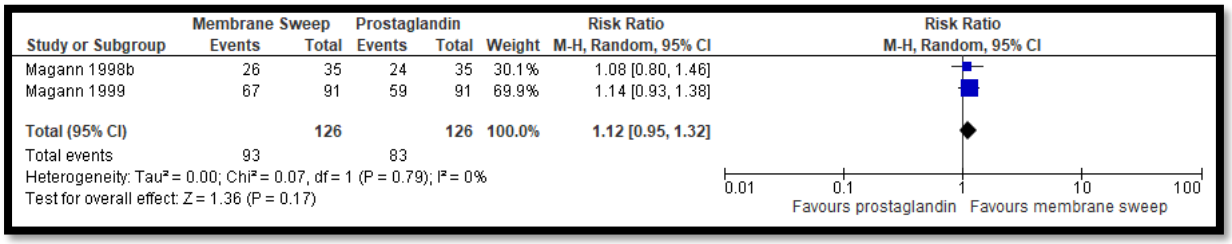
Analysis 2.2 Comparison 2 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins, Outcome 2 Induction of labour.



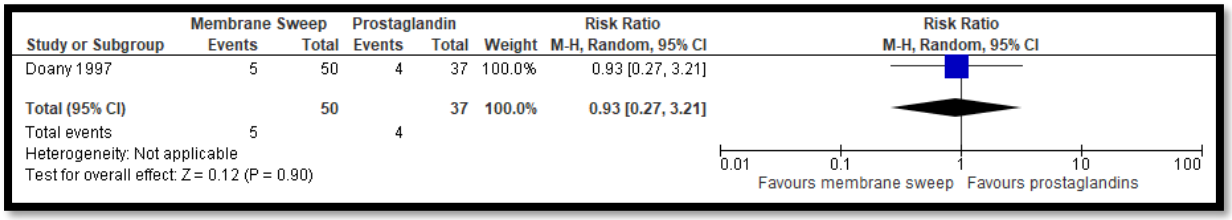
Analysis 2.3 Comparison 2 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins, Outcome 3 Caesarean section.



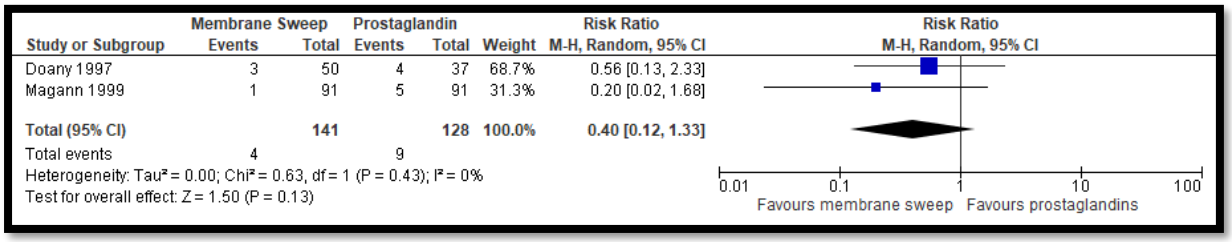
Analysis 2.4 Comparison 2 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins, Outcome 4 Spontaneous vaginal birth.



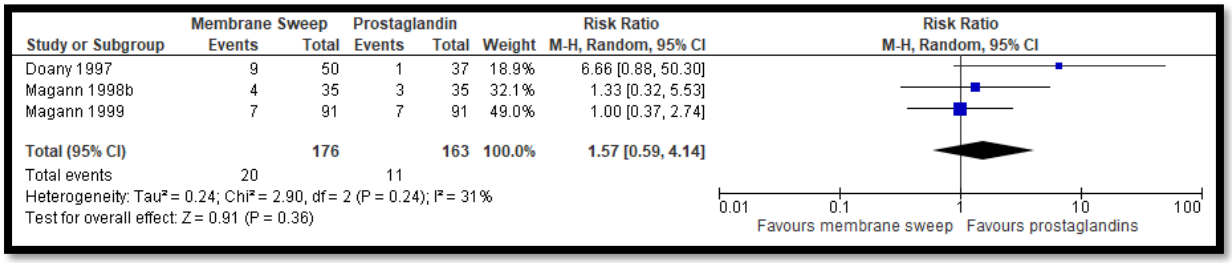
Analysis 2.5 Comparison 2 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins, Outcome 5 Maternal death or serious morbidity.



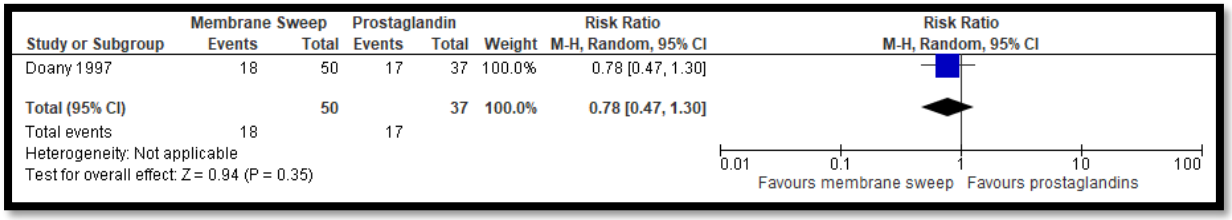
Analysis 2.6 Comparison 2 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins, Outcome 6 Neonatal death or serious neonatal perinatal morbidity.



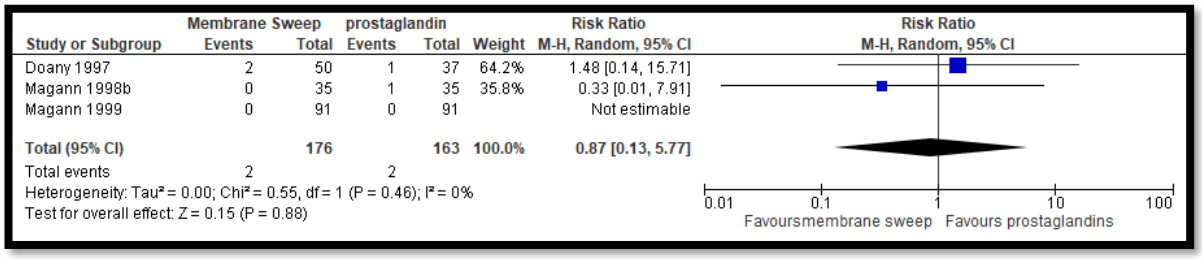
Analysis 2.7 Comparison 2 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins, Outcome 7 Instrumental vaginal birth



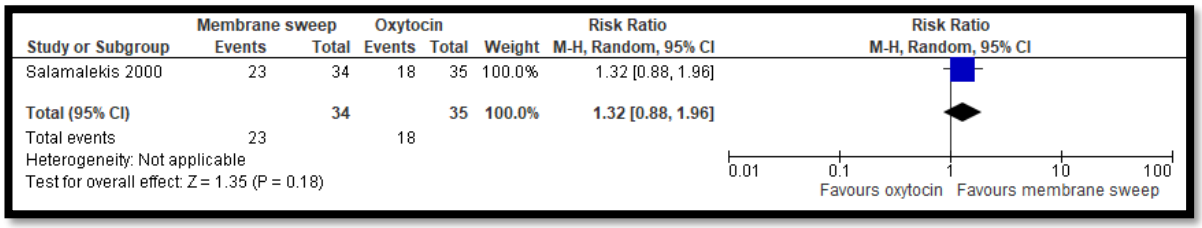
Analysis 2.8 Comparison 2 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins, Outcome 8 Augmentation of labour.



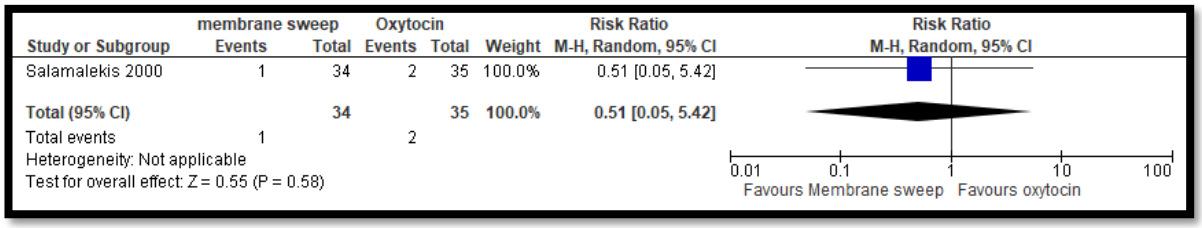
Analysis 2.9 Comparison 2 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins, Outcome 9 Apgar score less than seven at five minutes.



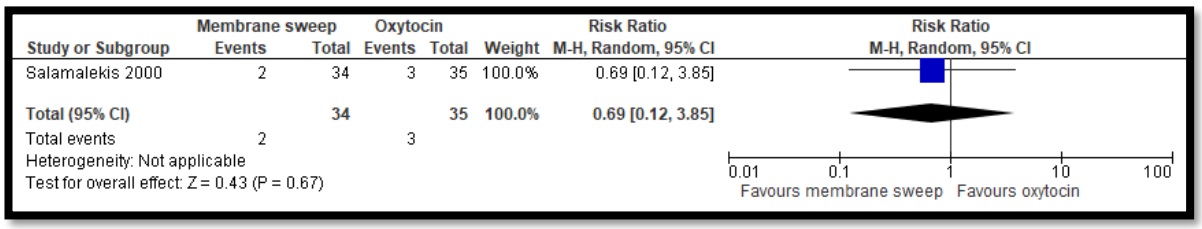
Analysis 3.1 Comparison 3 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy, Outcome 1 Spontaneous onset of labour.



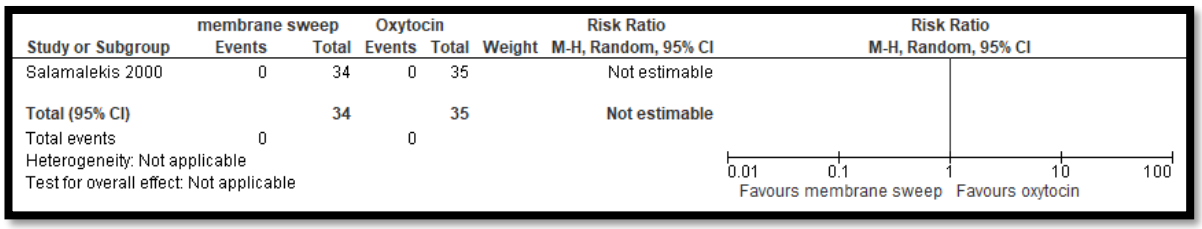
Analysis 3.2 Comparison 3 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy, Outcome 2 Induction of labour.



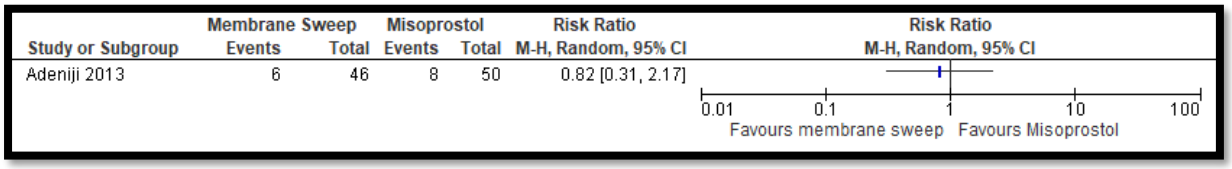
Analysis 3.3 Comparison 3 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy, Outcome 3 Caesarean section.



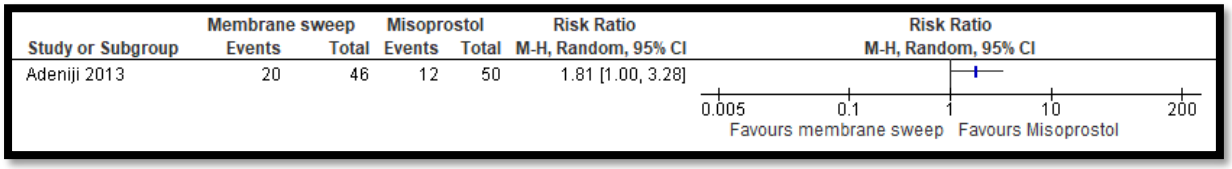
Analysis 3.4 Comparison 3 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy, Outcome 4 Maternal death or serious morbidity.



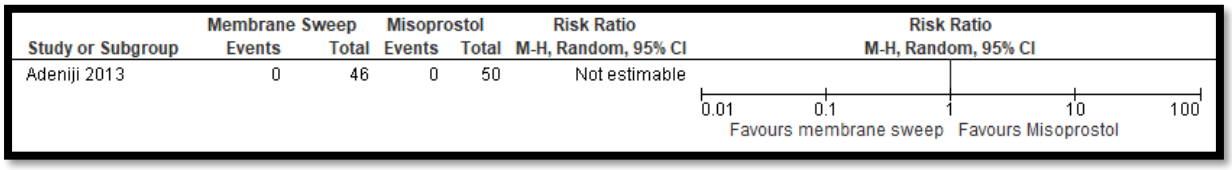
Analysis 5.1 Comparison 5 Amniotic membranes sweeping versus vaginal/oral misoprostol, Outcome 1 Caesarean section.



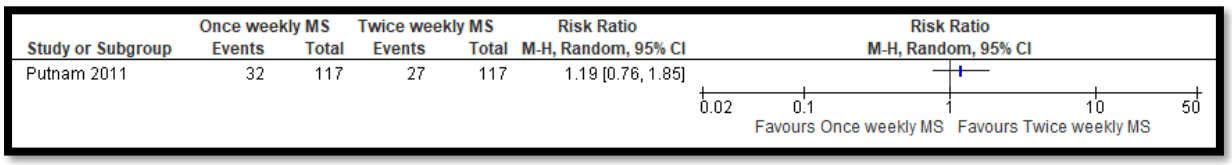
Analysis 5.2 Comparison 5 Amniotic membranes sweeping versus vaginal/oral misoprostol, Outcome 2 Augmentation of labour



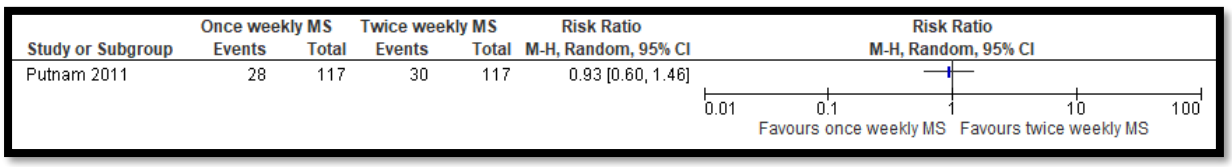
Analysis 5.3 Comparison 5 Amniotic membranes sweeping versus vaginal/oral misoprostol, Outcome 3 Apgar score less than seven at five minutes.



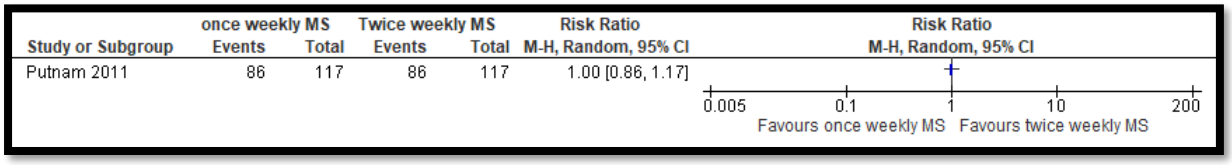
Analysis 7.1 Comparison 7 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping, Outcome 1 Induction of labour.



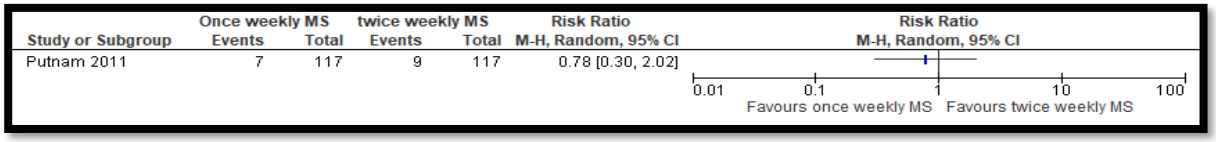
Analysis 7.2 Comparison 7 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping, Outcome 2 Caesarean section.



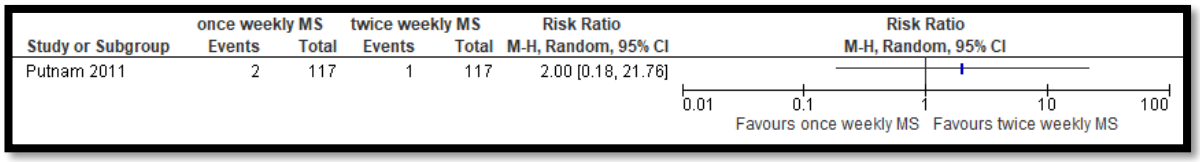
Analysis 7.3 Comparison 7 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping, Outcome 3 Spontaneous vaginal birth.



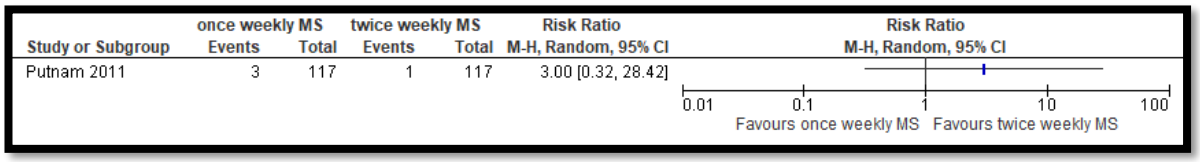
Analysis 7.4 Comparison 7 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping, Outcome 4 Maternal death or serious morbidity.



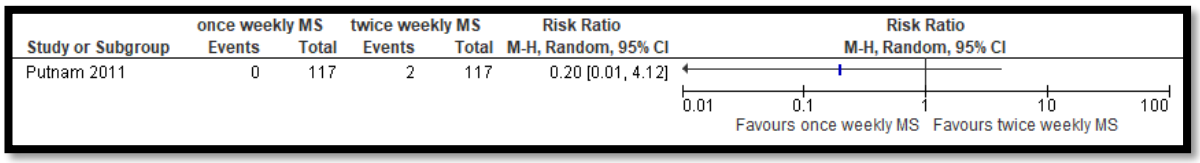
Analysis 7.5 Comparison 7 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping, Outcome 5 Neonatal death or serious neonatal perinatal morbidity.



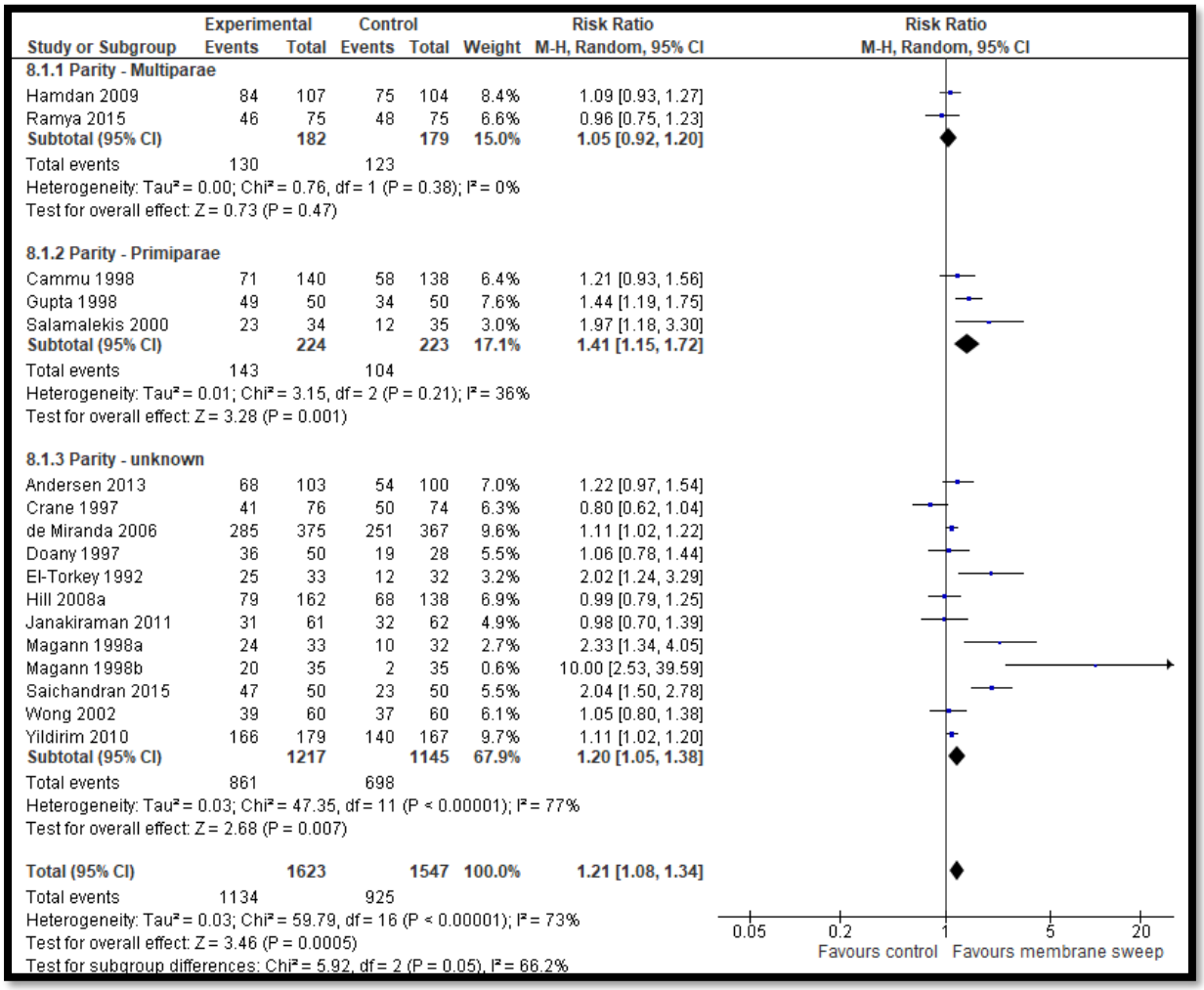
Analysis 7 .6 Comparison 7 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping, Outcome 6 Instrumental vaginal birth.



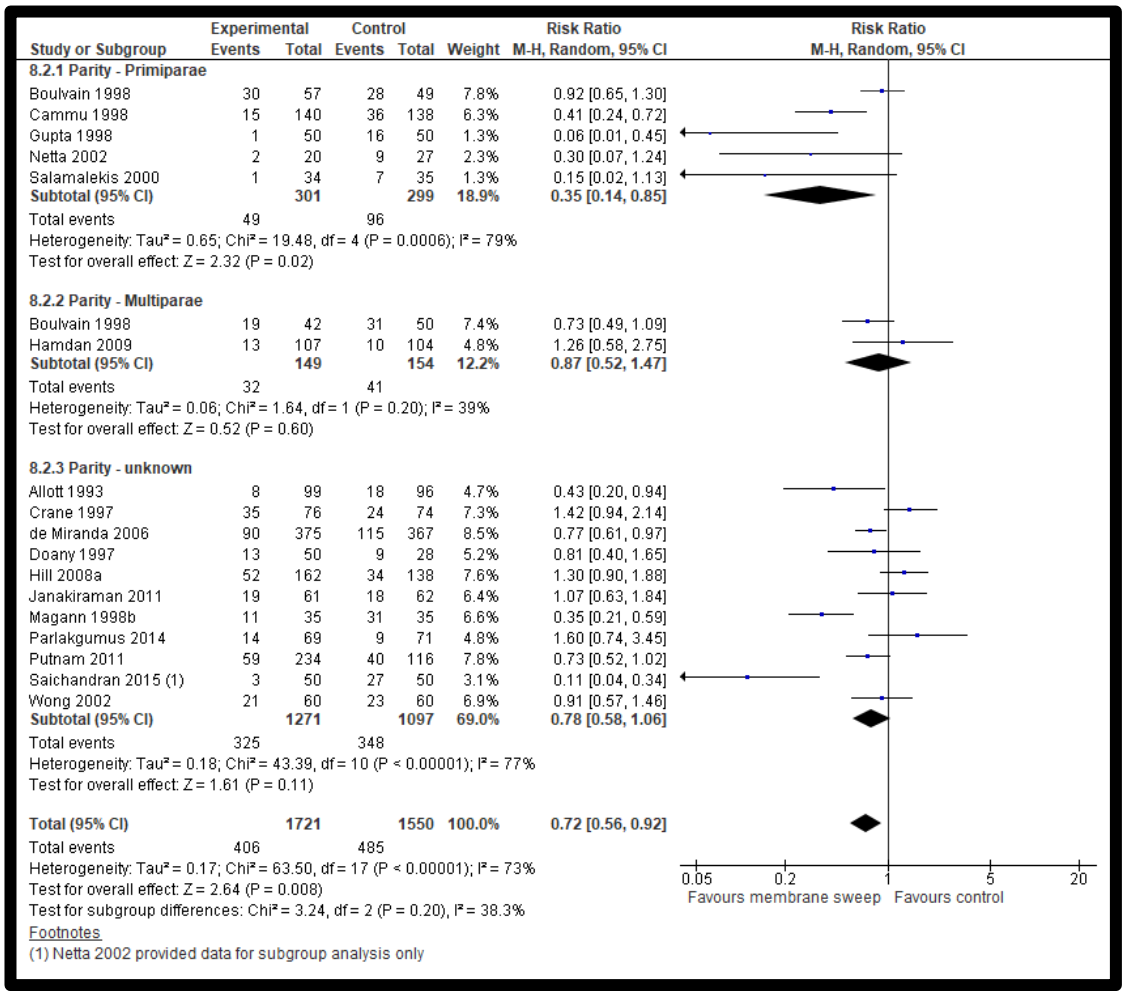
Analysis 7.7 Comparison 7 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping, Outcome 7 Apgar score less than seven at five minutes.



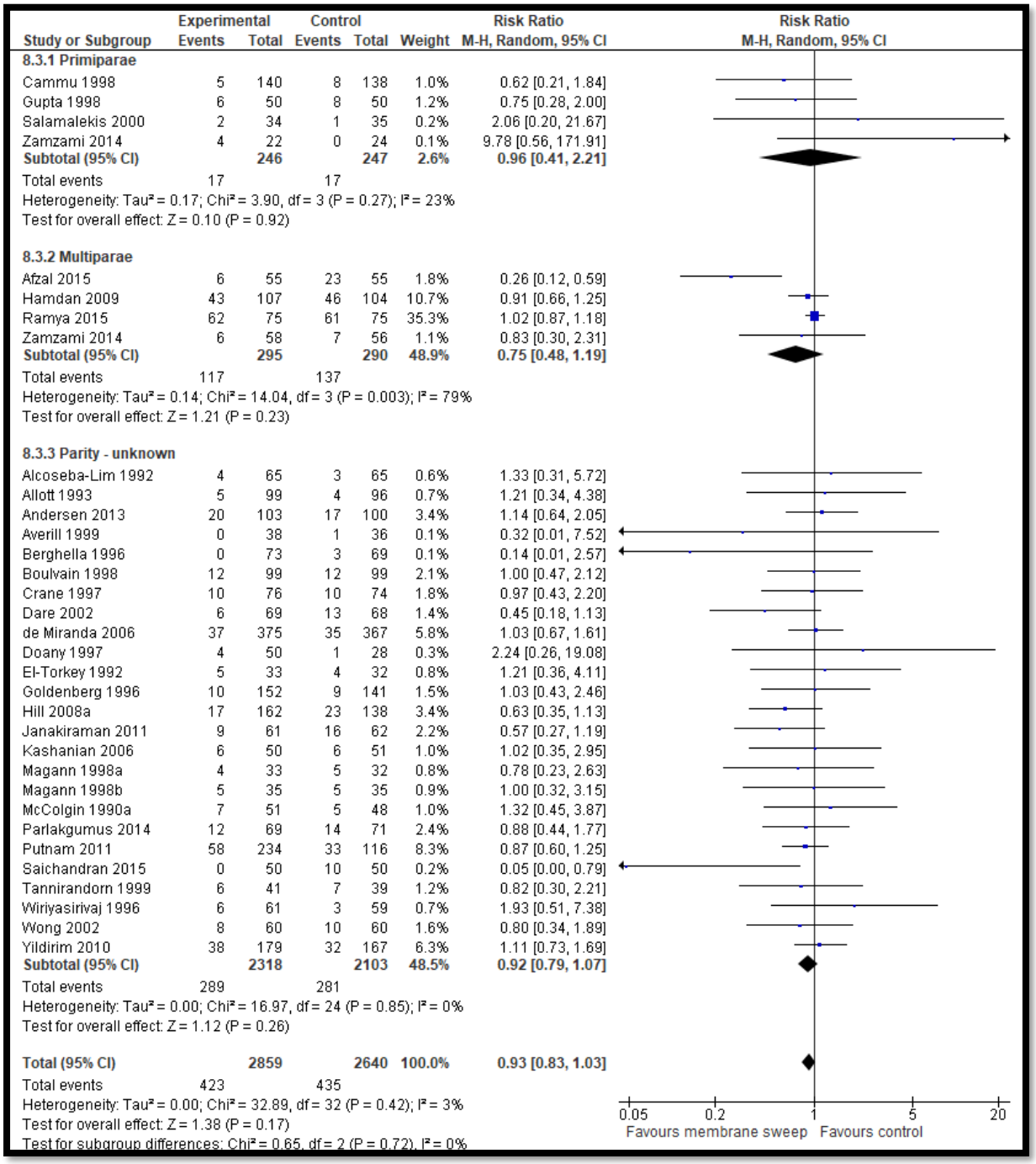
Analysis 8.1 Comparison 8 Amniotic membranes sweeping versus no treatment/sham (Primiparae/Multiparae), Outcome 1 Spontaneous onset of labour.



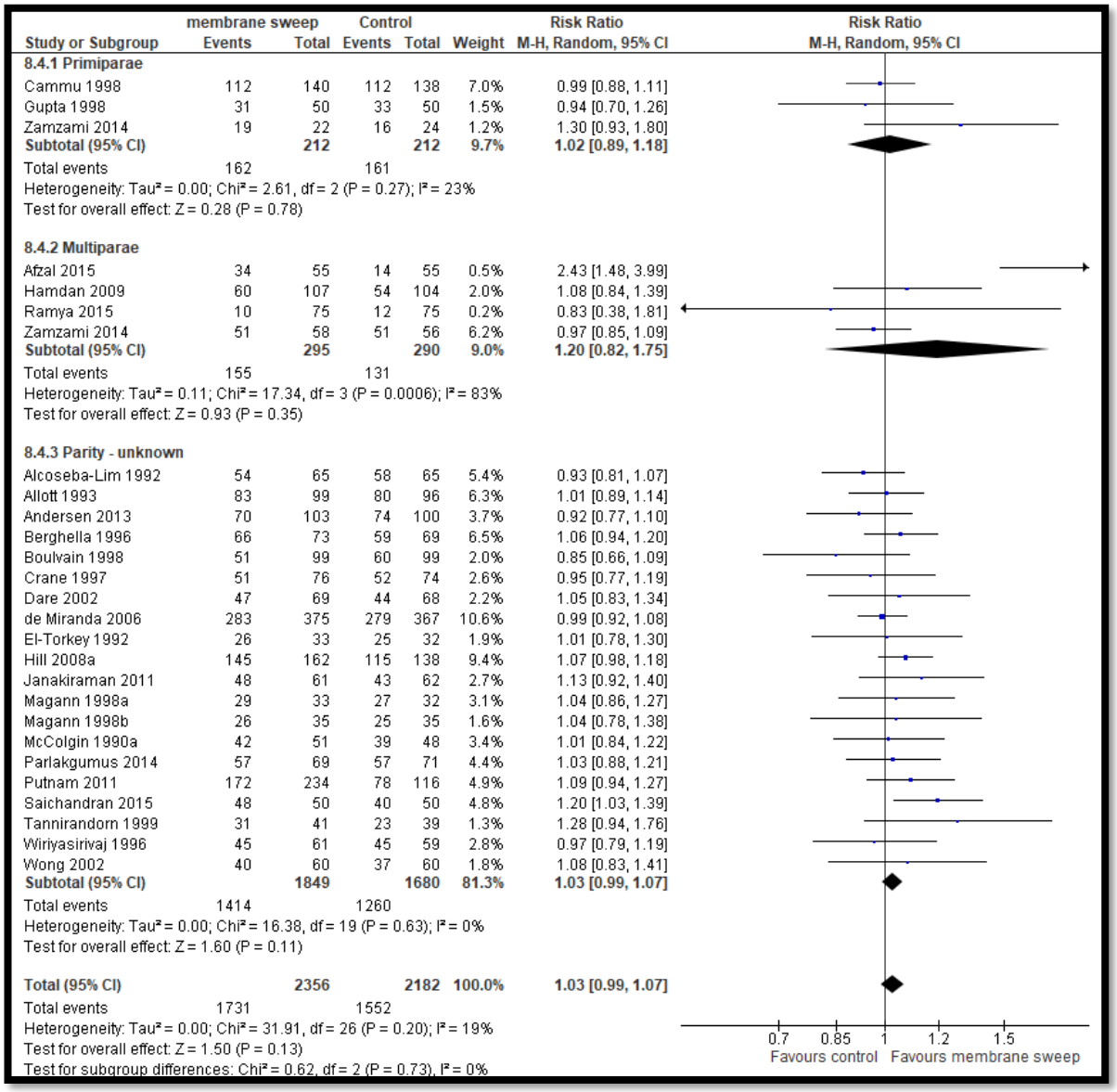
Analysis 8.2 Comparison 8 Amniotic membranes sweeping versus no treatment/sham (Primiparae/Multiparae), Outcome 2 Induction of labour.



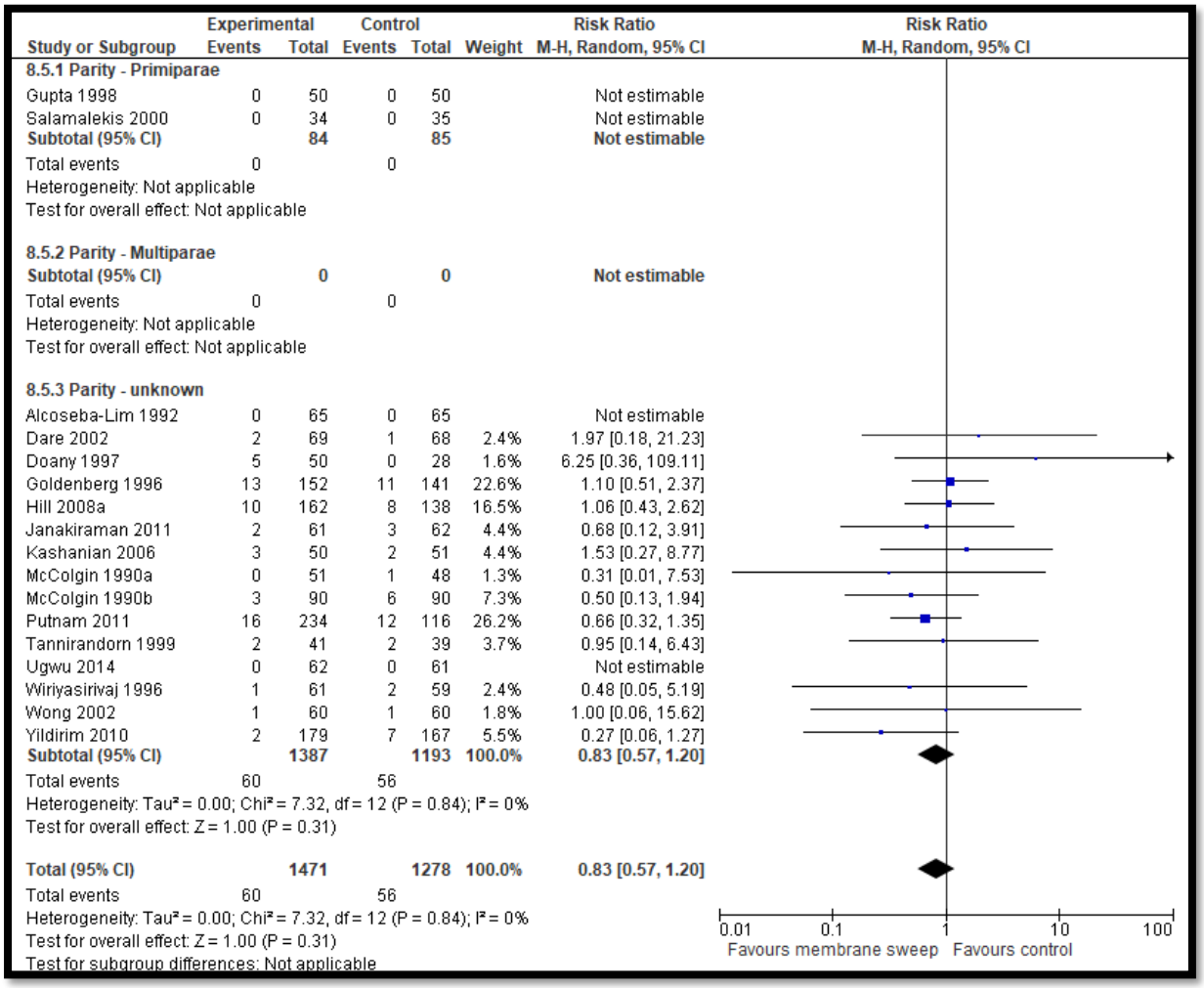
Analysis 8.3 Comparison 8 Amniotic membranes sweeping versus no treatment/sham (Primiparae/Multiparae), Outcome 3 Caesarean section.



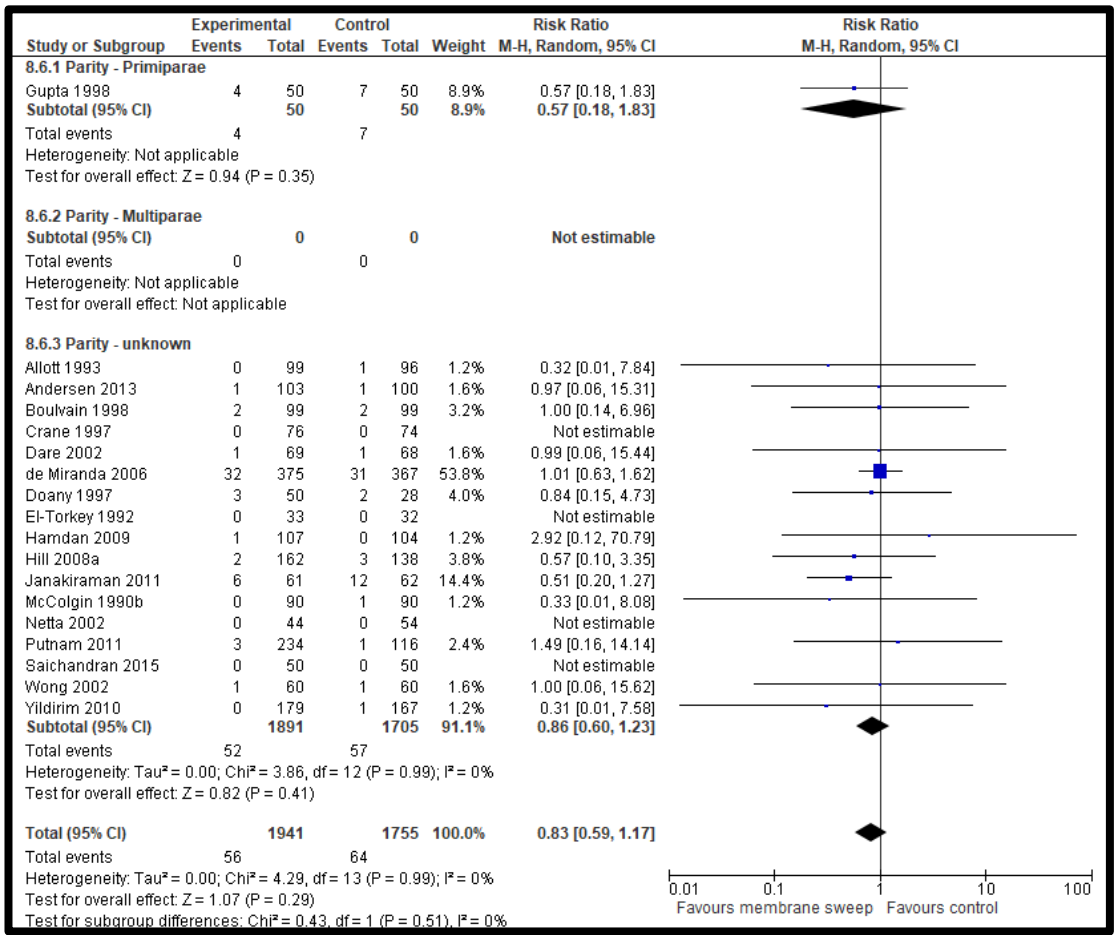
Analysis 8.4 Comparison 8 Amniotic membranes sweeping versus no treatment/sham (Primiparae/Multiparae), Outcome 4 Spontaneous vaginal birth



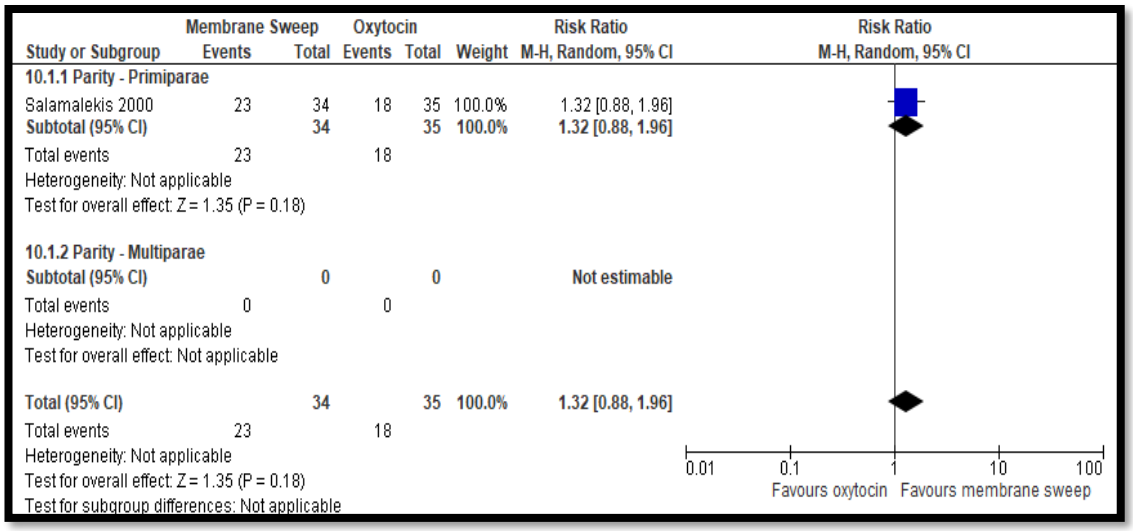
Analysis 8.5 Comparison 8 Amniotic membranes sweeping versus no treatment/sham (Primiparae/Multiparae), Outcome 5 Maternal death or serious morbidity.



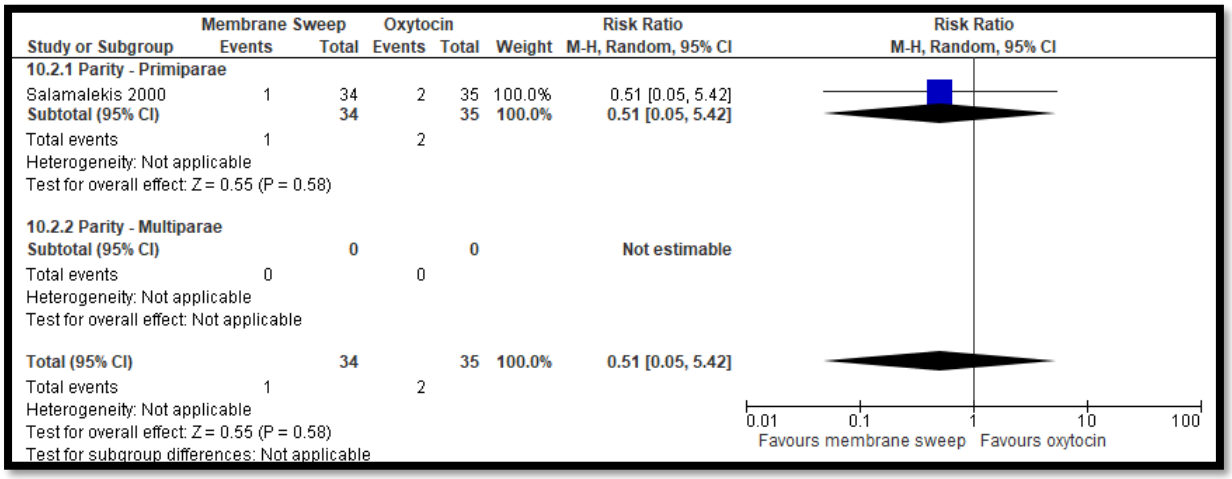
Analysis 8.6 Comparison 8 Amniotic membranes sweeping versus no treatment/sham (Primiparae/Multiparae), Outcome 6 Neonatal death or serious neonatal perinatal morbidity.



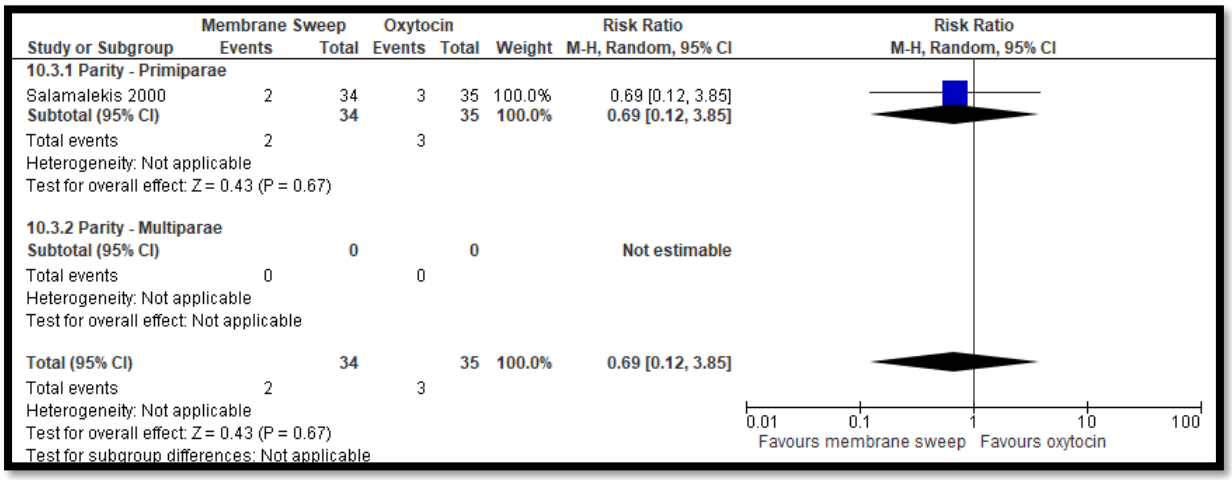
Analysis 10.1 Comparison 10 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy (Primiparae/Multiparae), Outcome 1 Spontaneous onset of labour.



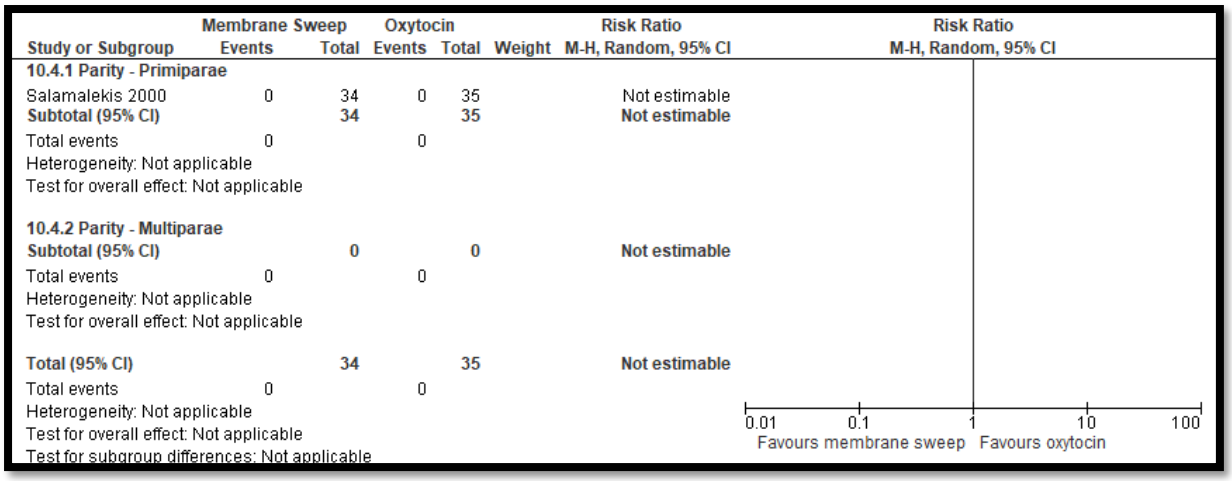
Analysis 10.2 Comparison 10 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy (Primiparae/Multiparae), Outcome 2 Induction of labour.



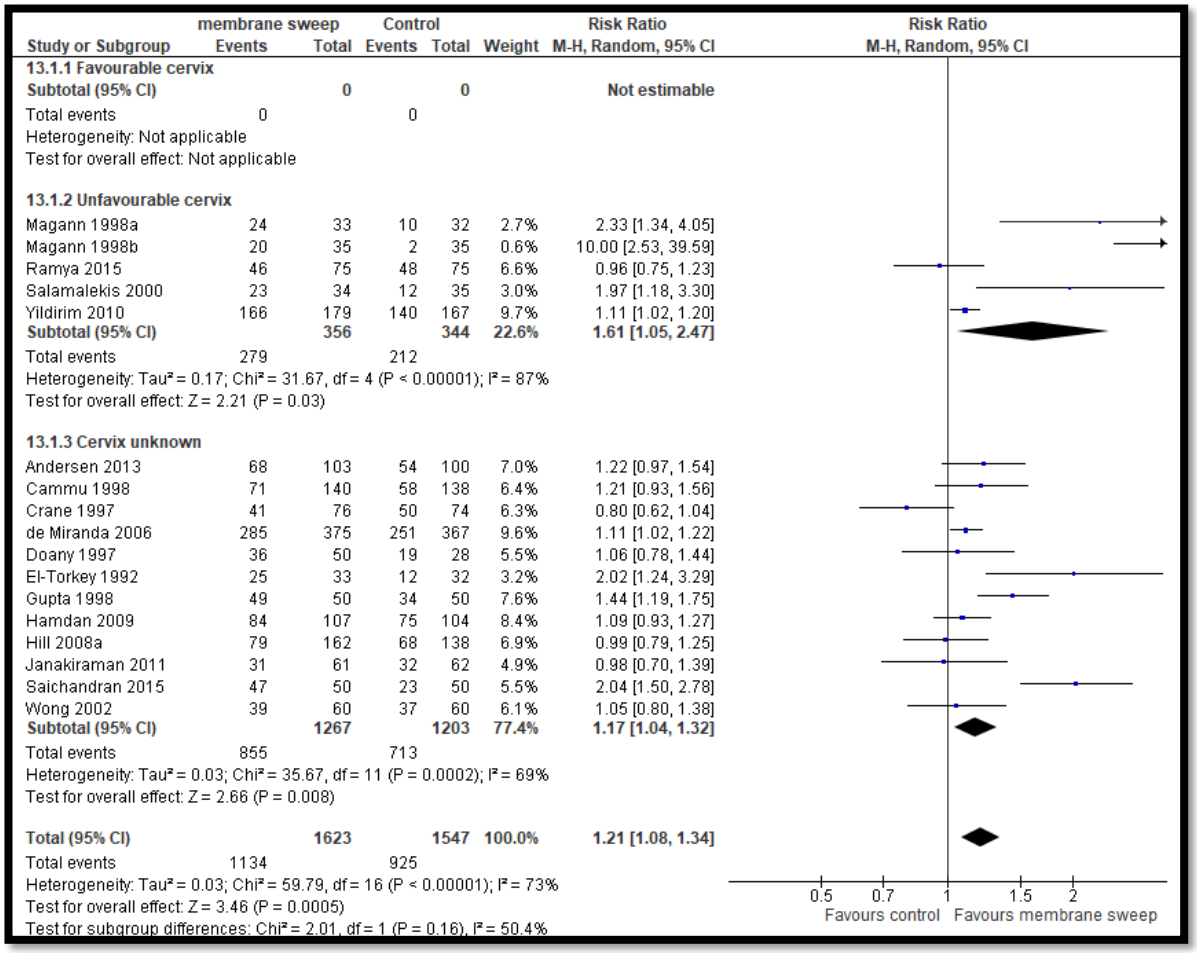
Analysis 10.3 Comparison 10 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy (Primiparae/Multiparae), Outcome 3 Caesarean section.



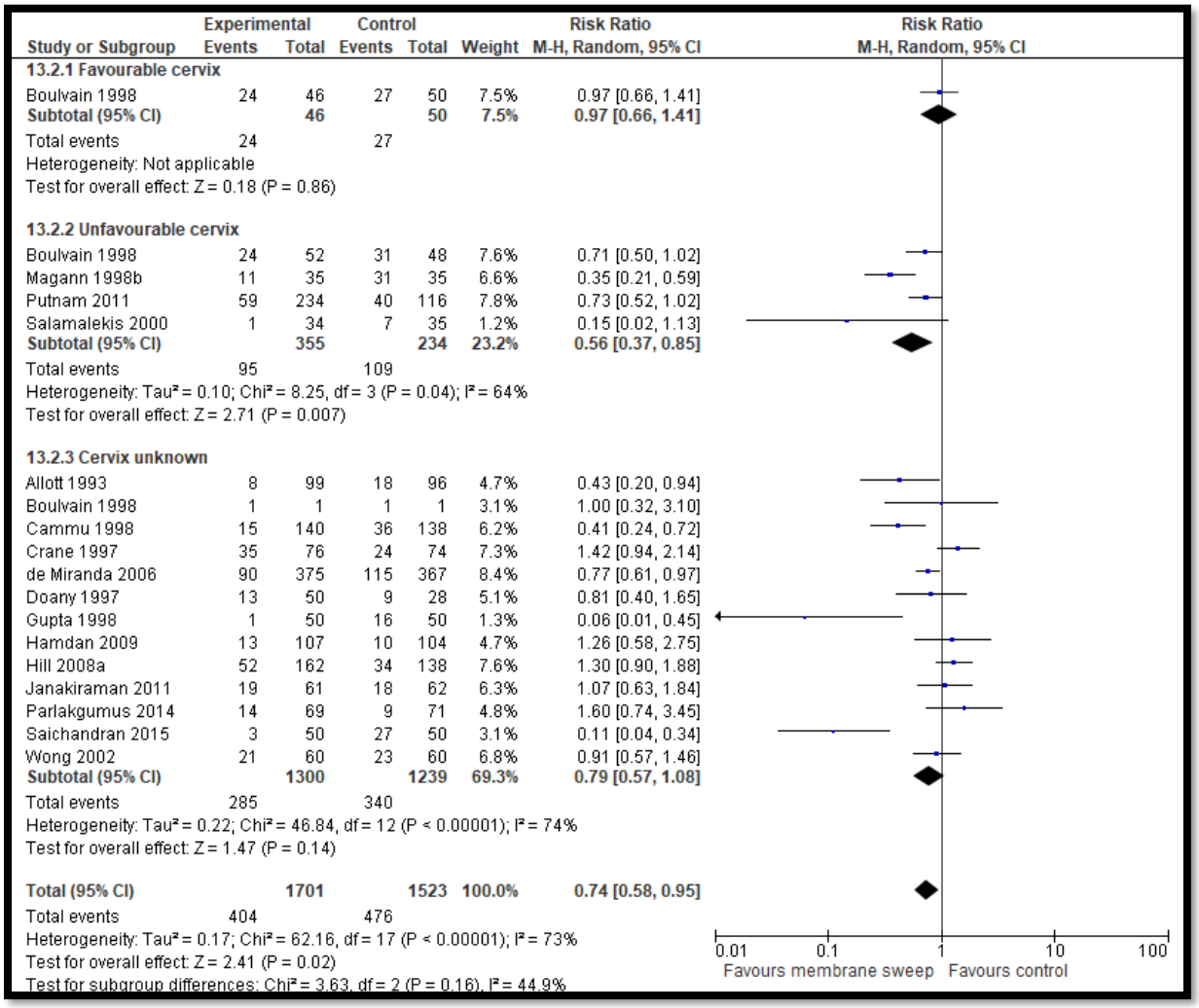
Analysis 10.4 Comparison 10 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy (Primiparae/Multiparae), Outcome 4 Maternal death or serious morbidity.



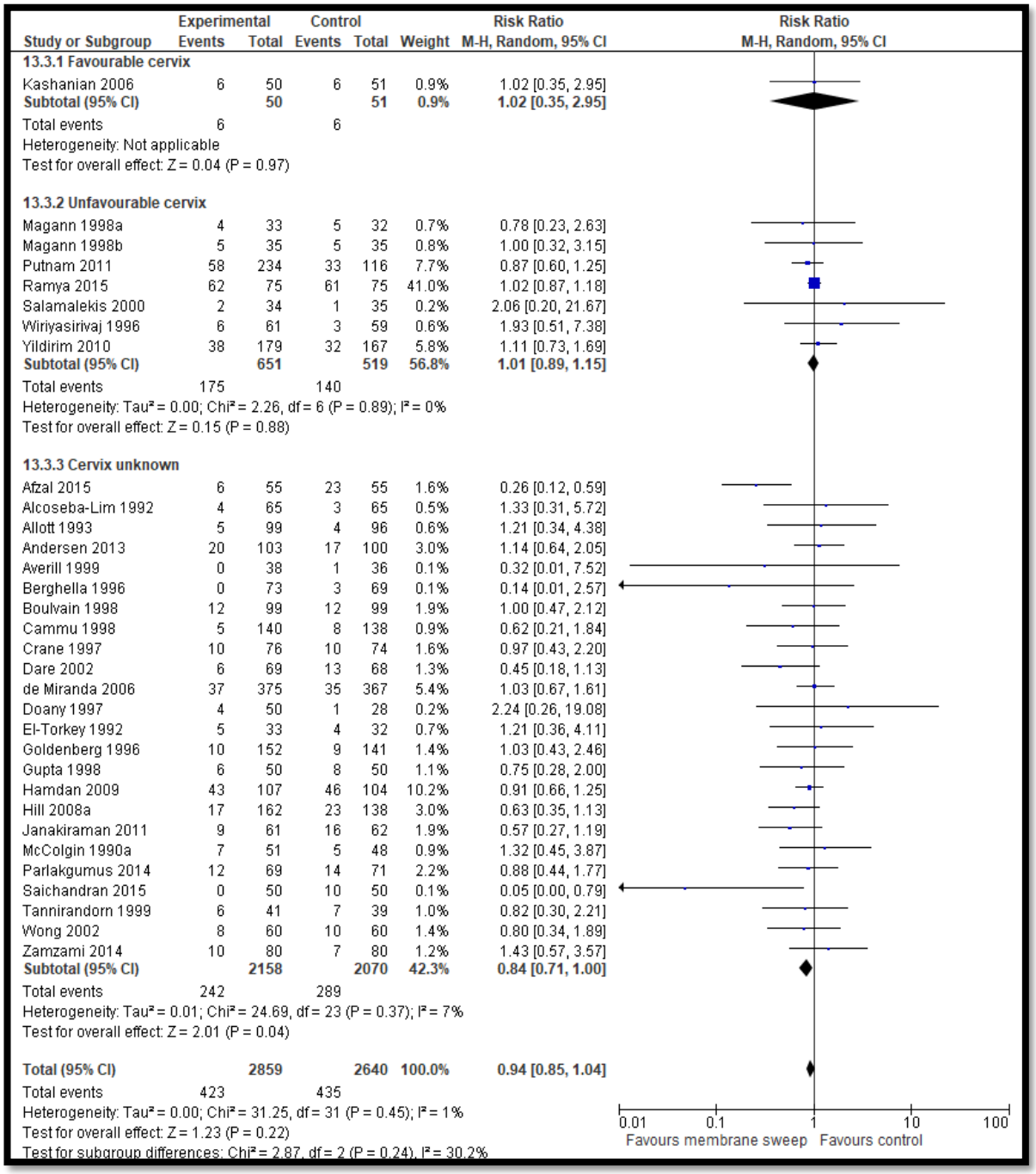
Analysis 13.1 Comparison 13 Amniotic membranes sweeping versus no treatment/sham Favourable cervix/unfavourable cervix, Outcome 1 Spontaneous onset of labour.



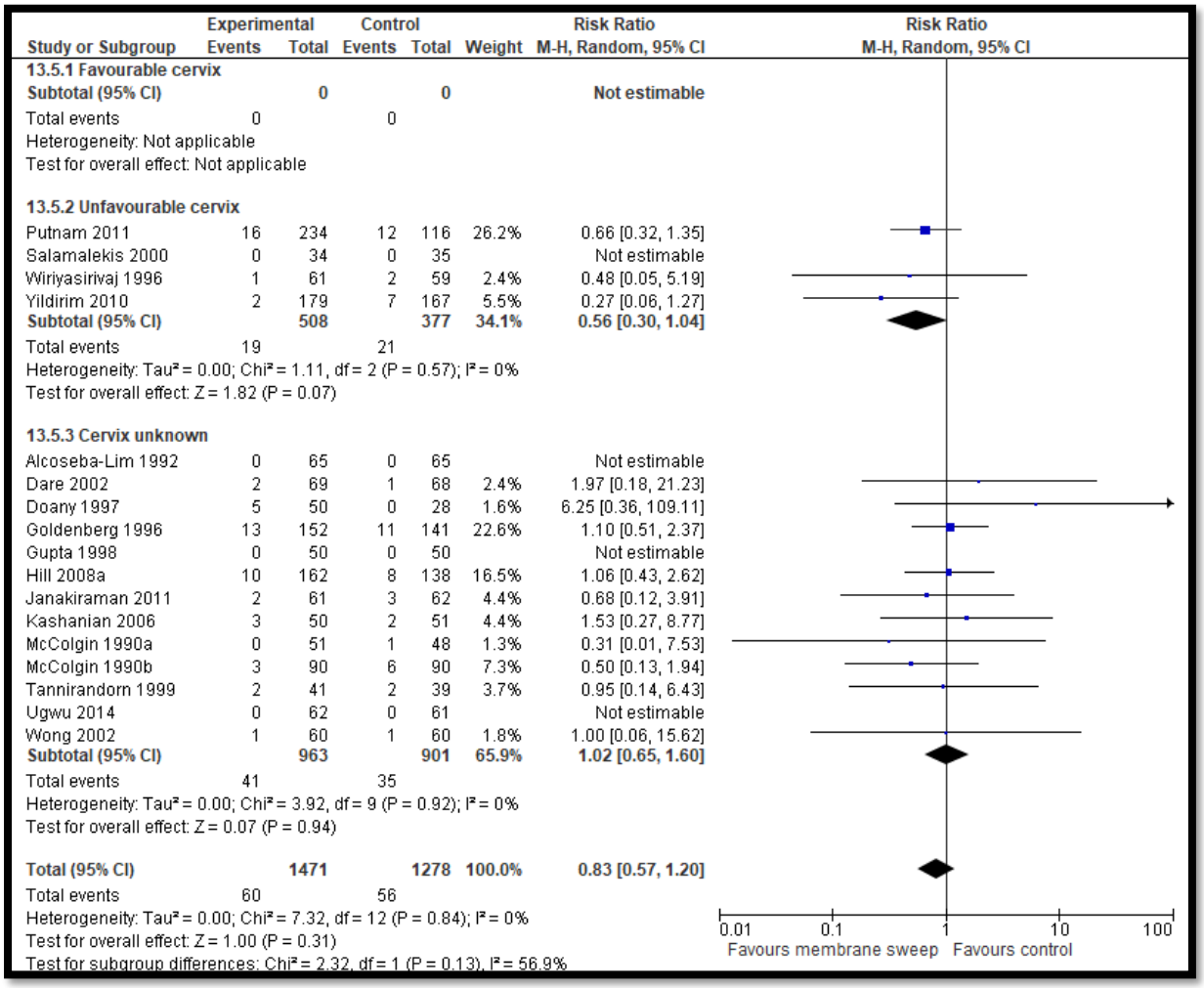
Analysis 13.2 Comparison 13 Amniotic membranes sweeping versus no treatment/sham Favourable cervix/unfavourable cervix, Outcome 2 Induction of labour.



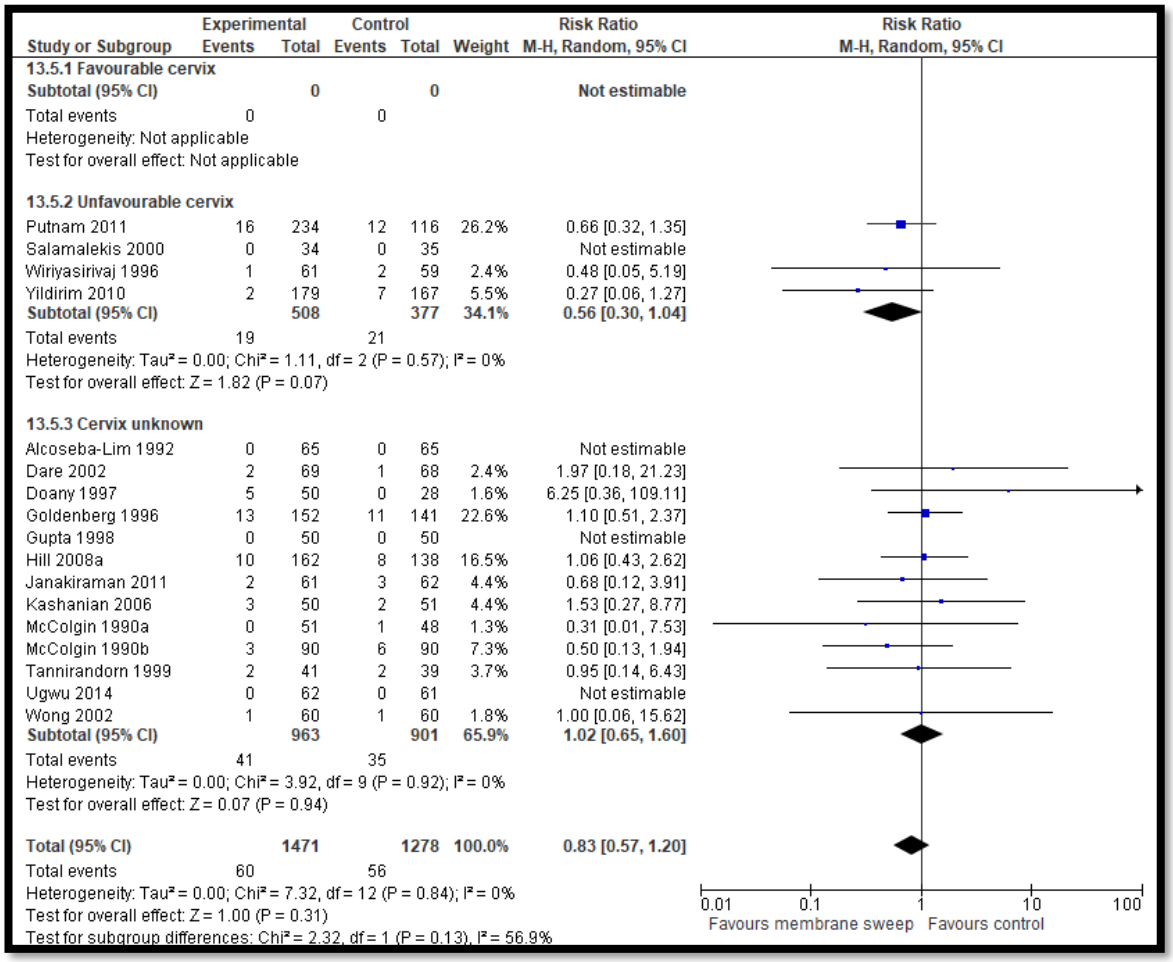
Analysis 13.3 Comparison 13 Amniotic membranes sweeping versus no treatment/sham Favourable cervix/unfavourable cervix, Outcome 3 Caesarean section.



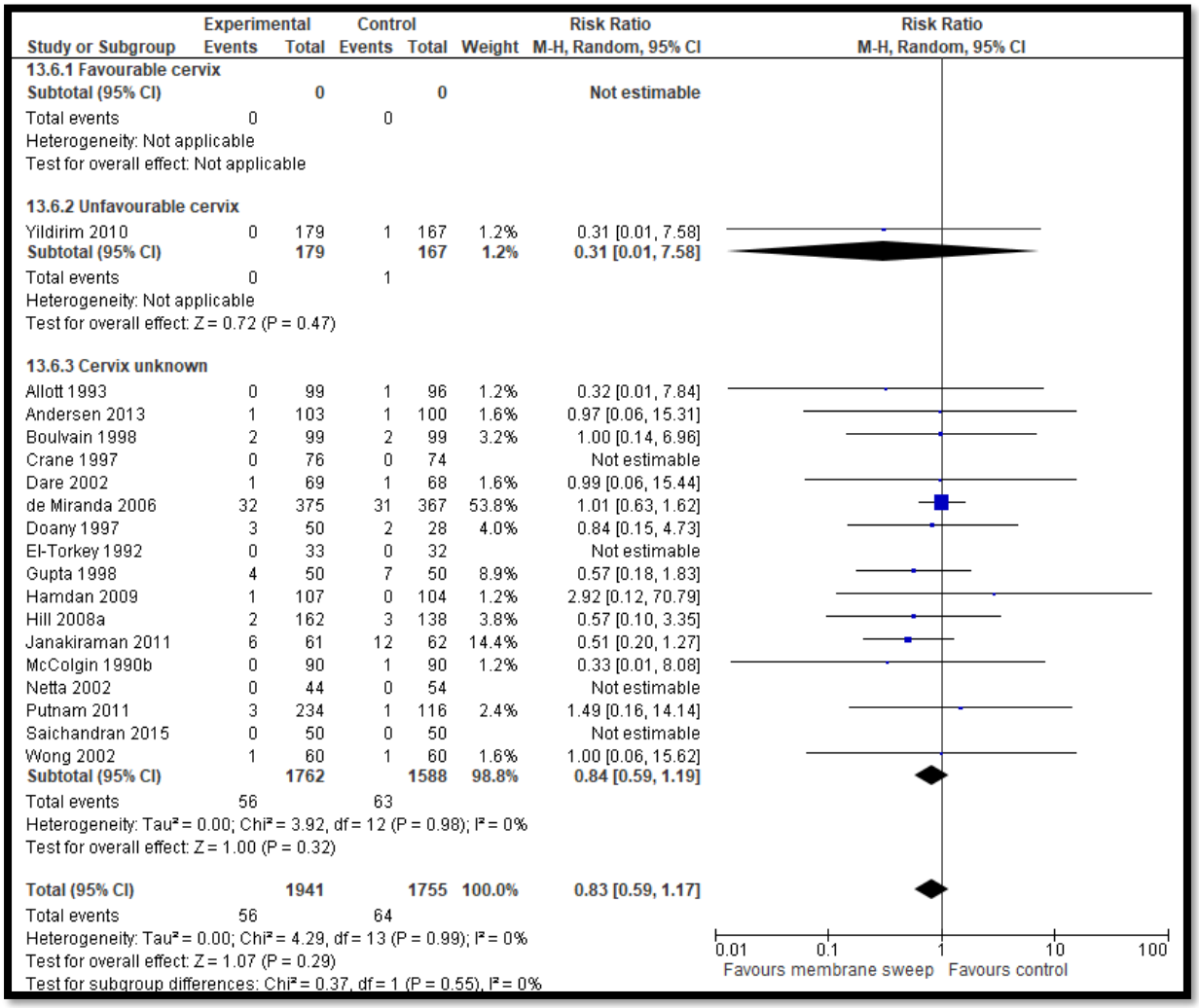
Analysis 13.4 Comparison 13 Amniotic membranes sweeping versus no treatment/sham Favourable cervix/unfavourable cervix, Outcome 4 Spontaneous vaginal birth



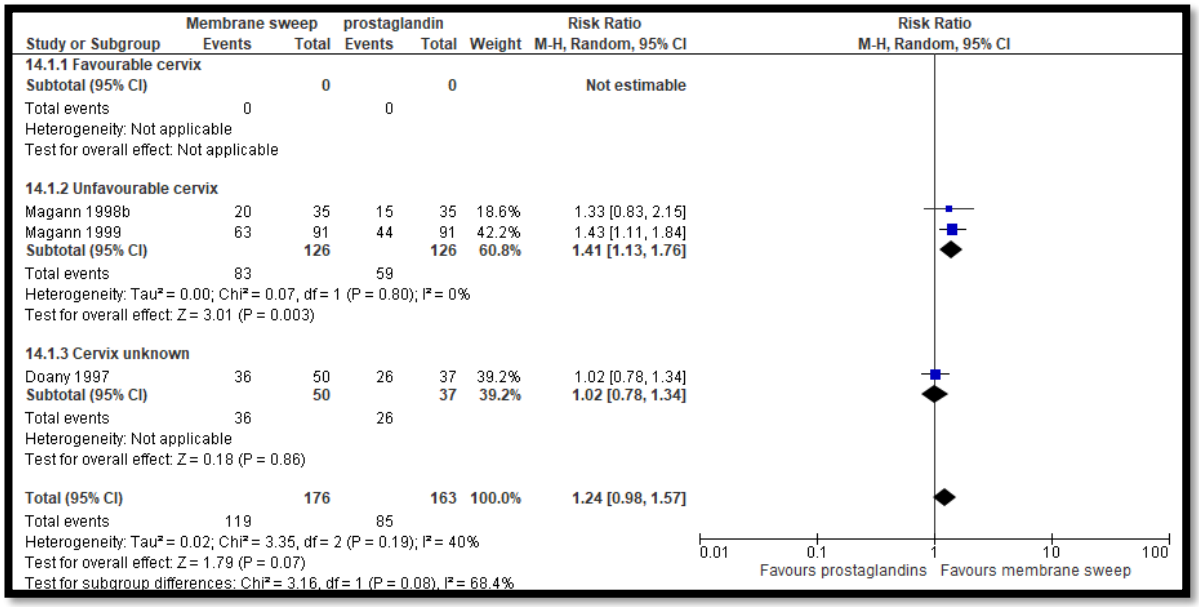
Analysis 13.5 Comparison 13 Amniotic membranes sweeping versus no treatment/sham Favourable cervix/unfavourable cervix, Outcome 5 Maternal death or serious morbidity.



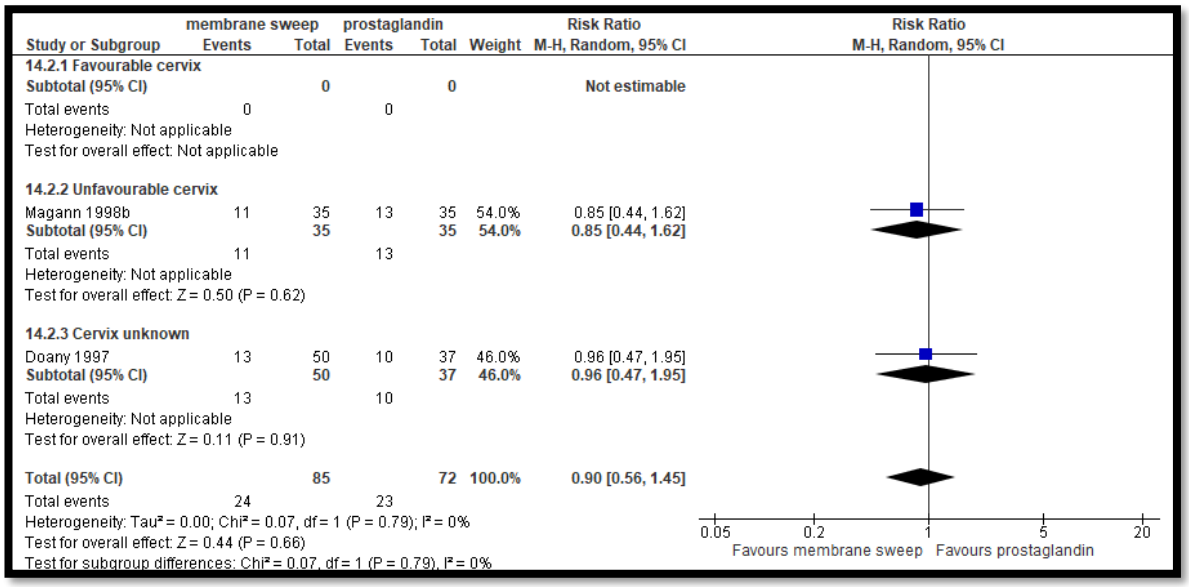
Analysis 13.6 Comparison 13 Amniotic membranes sweeping versus no treatment/sham Favourable cervix/unfavourable cervix, Outcome 6 Neonatal death or serious neonatal perinatal morbidity.



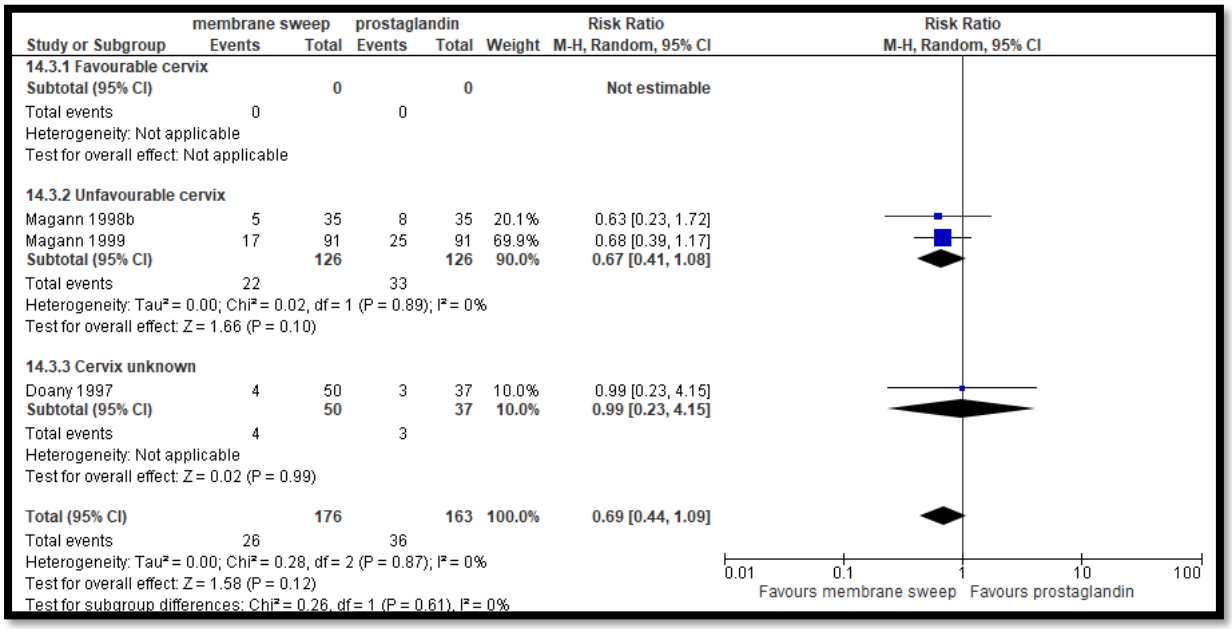
Analysis 14.1 Comparison 14 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins (Favourable cervix/unfavourable cervix), Outcome 1 Spontaneous onset of labour.



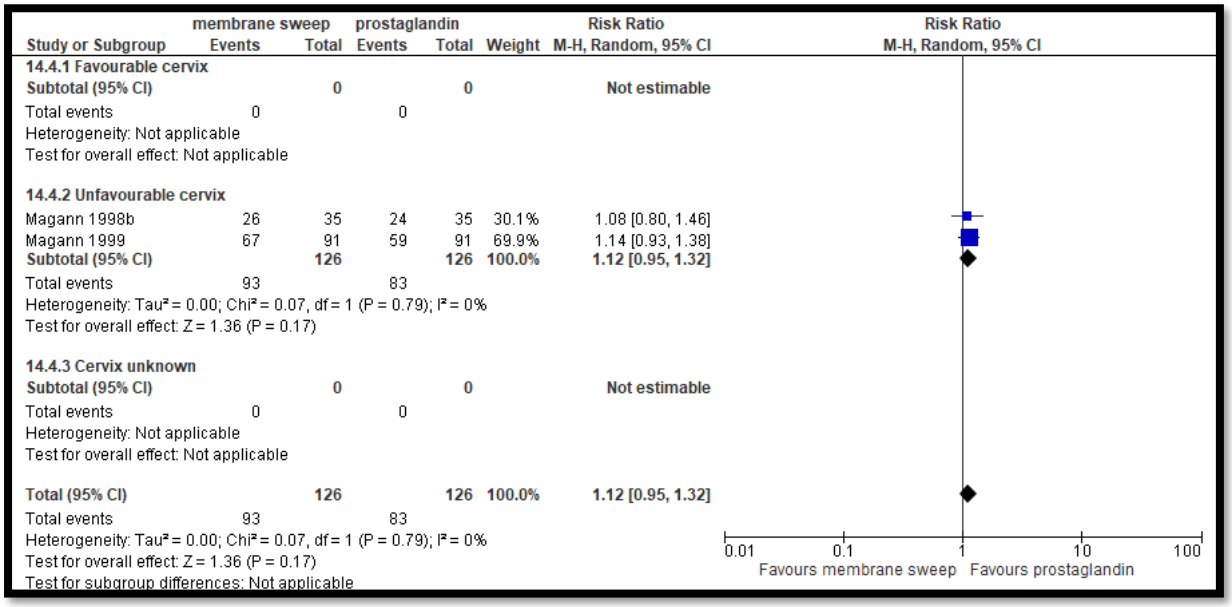
Analysis 14.2 Comparison 14 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins (Favourable cervix/unfavourable cervix), Outcome 2 Induction of labour.



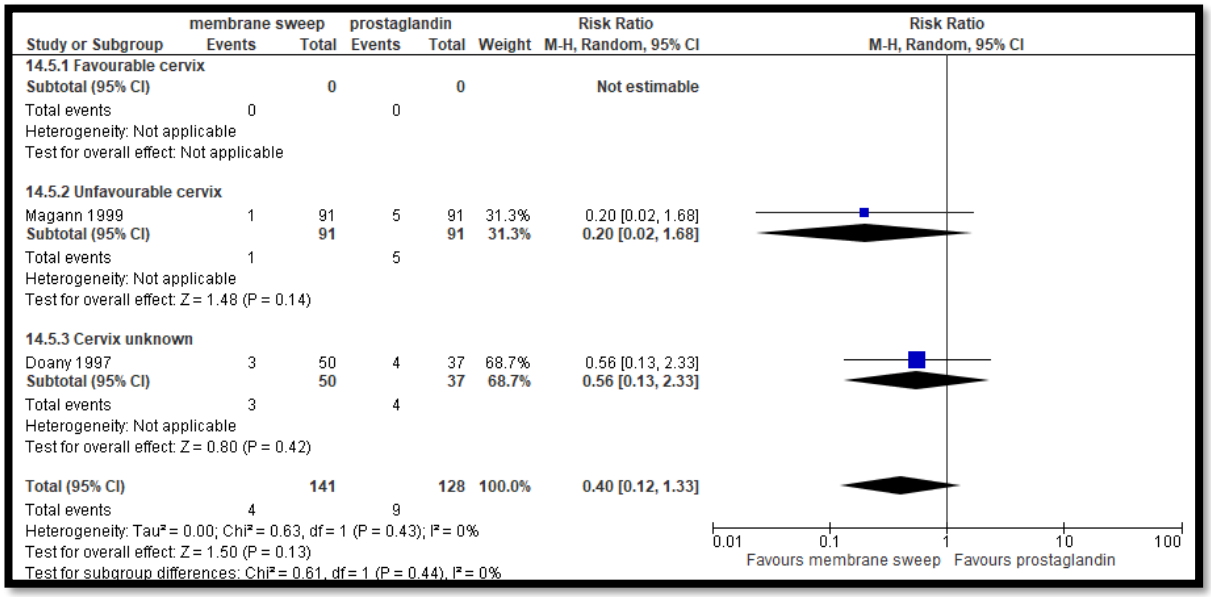
Analysis 14.3 Comparison 14 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins (Favourable cervix/unfavourable cervix), Outcome 3 Caesarean section.



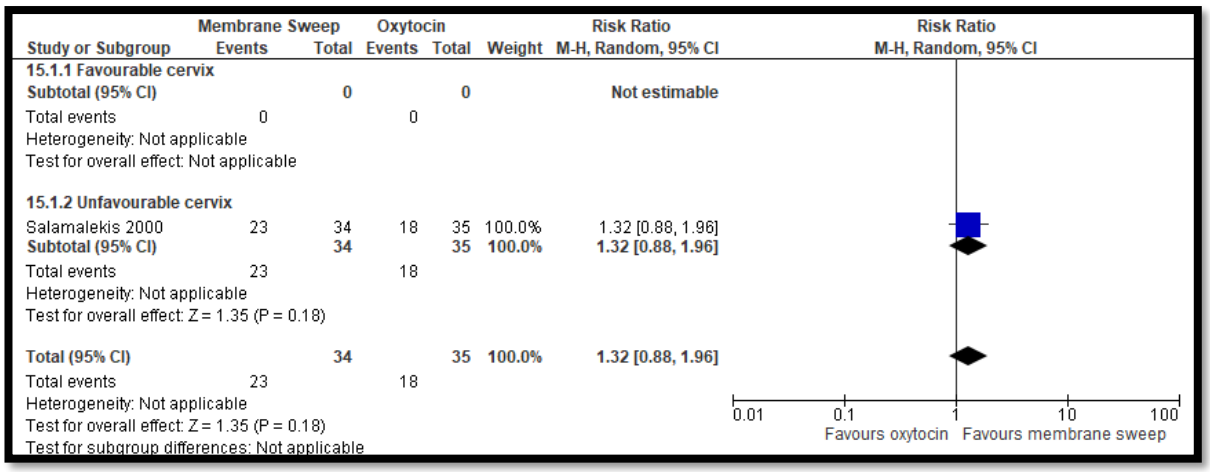
Analysis 14.4 Comparison 14 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins (Favourable cervix/unfavourable cervix), Outcome 4 Spontaneous vaginal birth



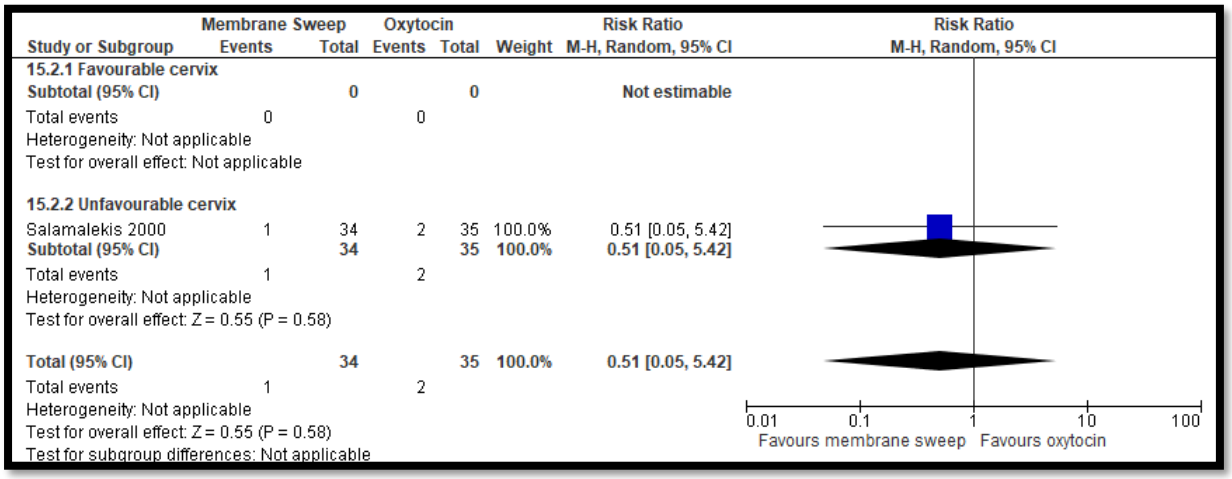
Analysis 14.5 Comparison 14 Amniotic membranes sweeping versus vaginal/intracervical prostaglandins (Favourable cervix/unfavourable cervix), Outcome 5 Neonatal death or serious neonatal perinatal morbidity.



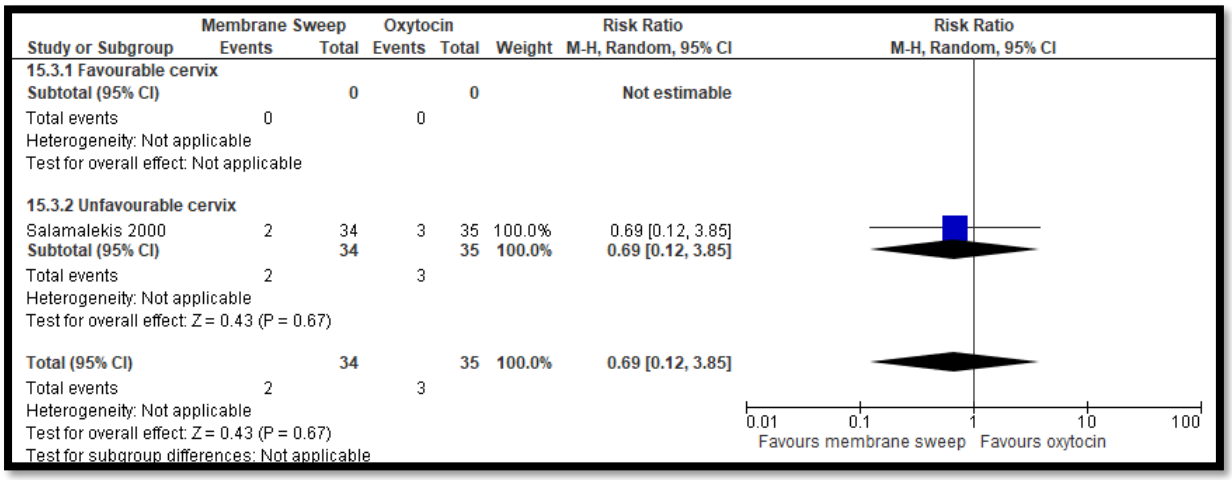
Analysis 15.1 Comparison 15 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy (Favourable cervix/unfavourable cervix), Outcome 1 Spontaneous onset of labour.



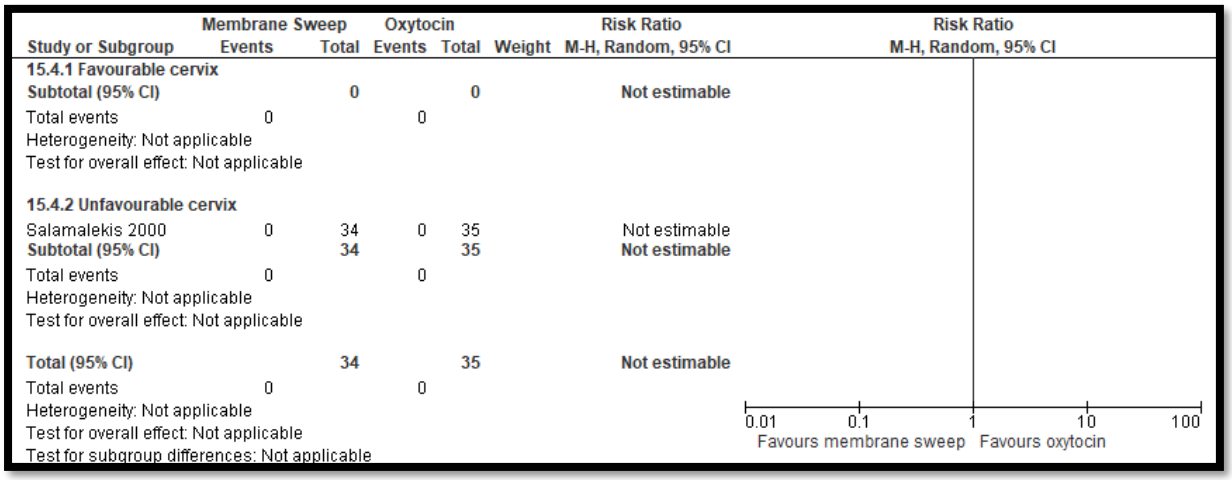
Analysis 15.2 Comparison 15 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy (Favourable cervix/unfavourable cervix), Outcome 2 Induction of labour.



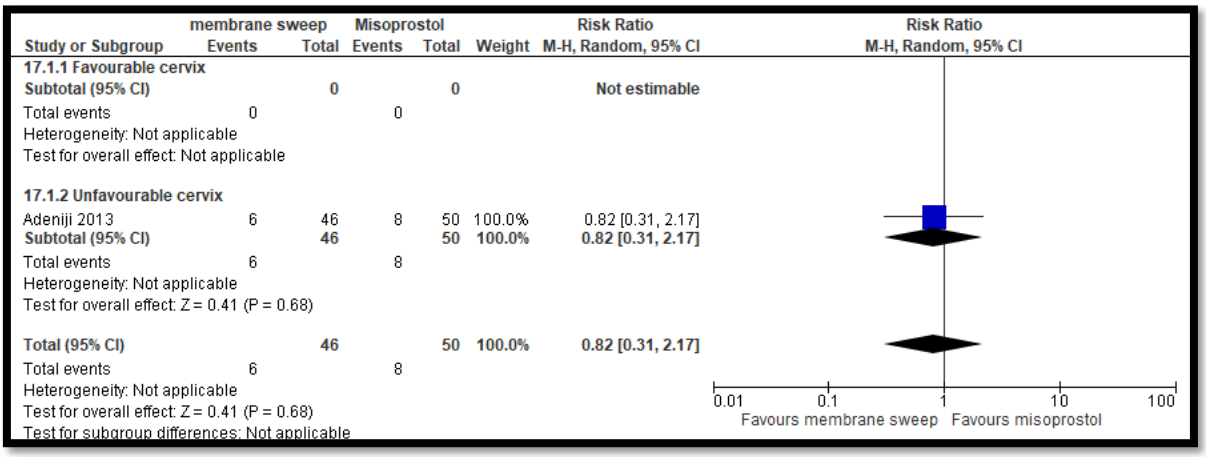
Analysis 15.3 Comparison 15 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy (Favourable cervix/unfavourable cervix), Outcome 3 Caesarean section.



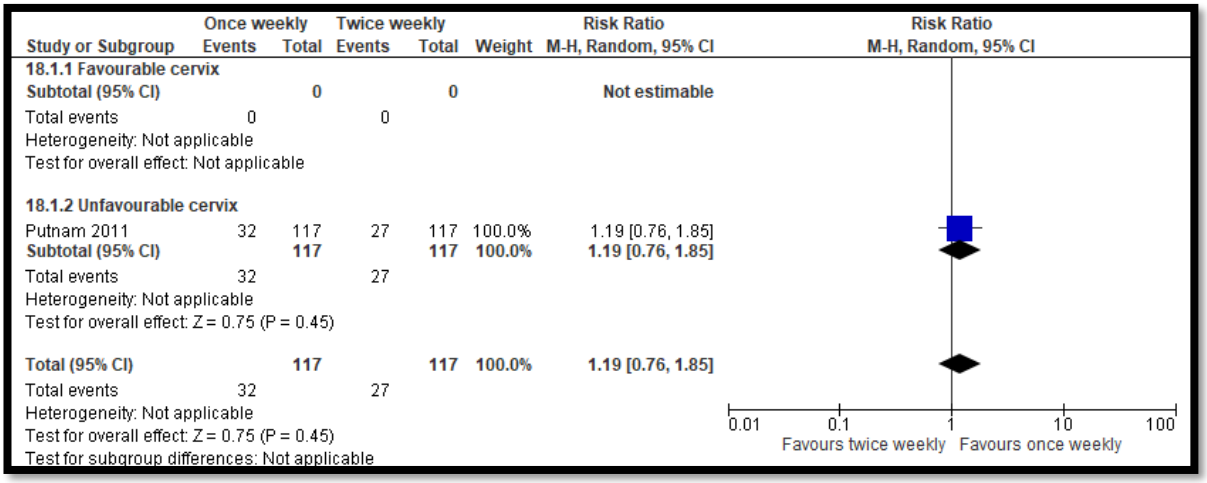
Analysis 15.4 Comparison 15 Amniotic membranes sweeping versus intravenous oxytocin +/- amniotomy (Favourable cervix/unfavourable cervix), Outcome 4 Maternal death or serious morbidity.



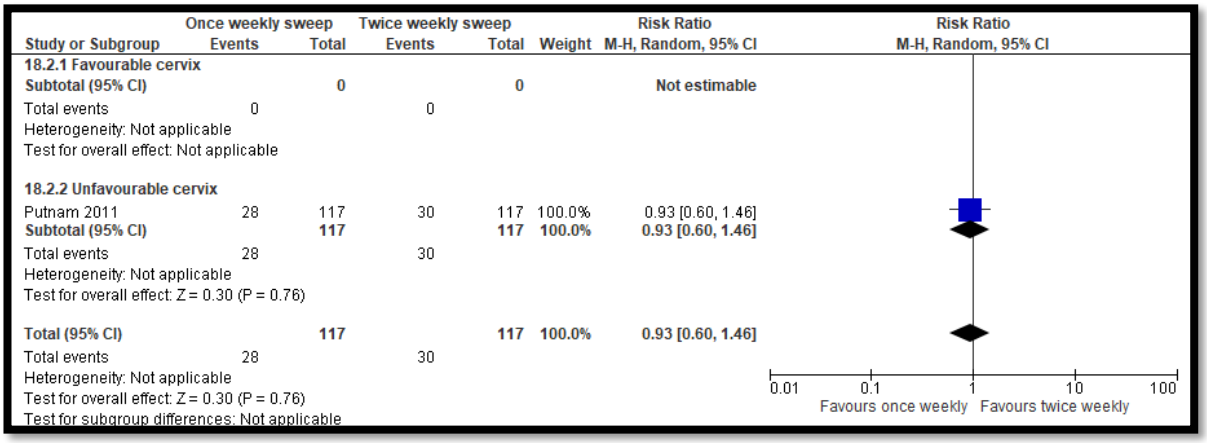
Analysis 17.1 Comparison 17 Amniotic membranes sweeping versus vaginal/oral misoprostol (Favourable cervix/unfavourable cervix), Outcome 1 Caesarean section.



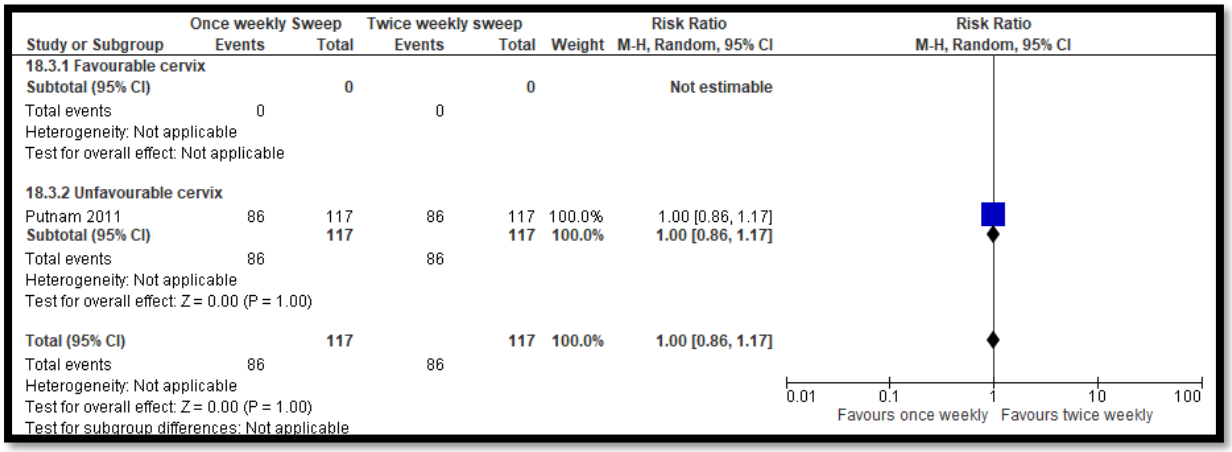
Analysis 18.1 Comparison 18 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping (Favourable cervix/unfavourable cervix), Outcome 1 Induction of labour.



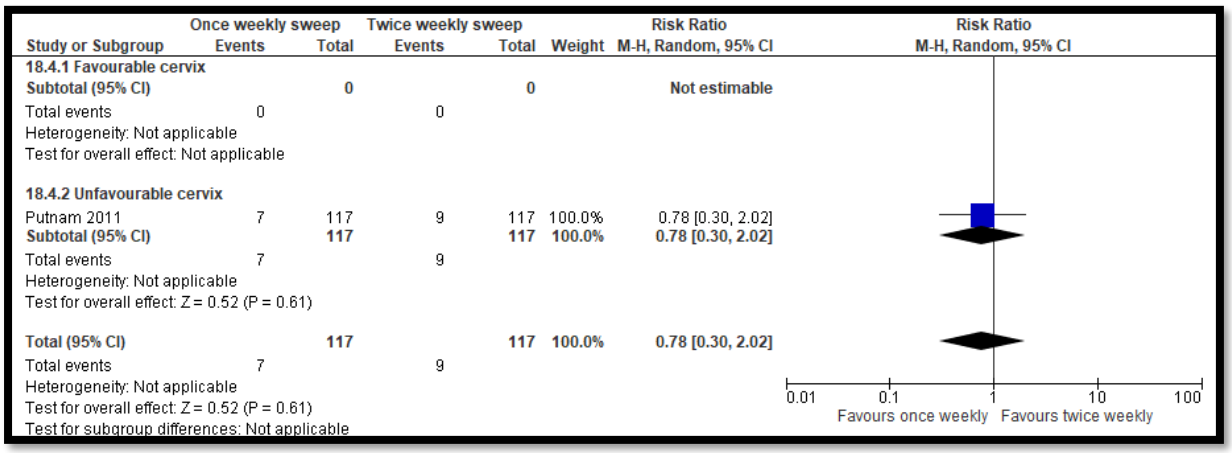
Analysis 18.2 Comparison 18 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping (Favourable cervix/unfavourable cervix), Outcome 2 Caesarean section.



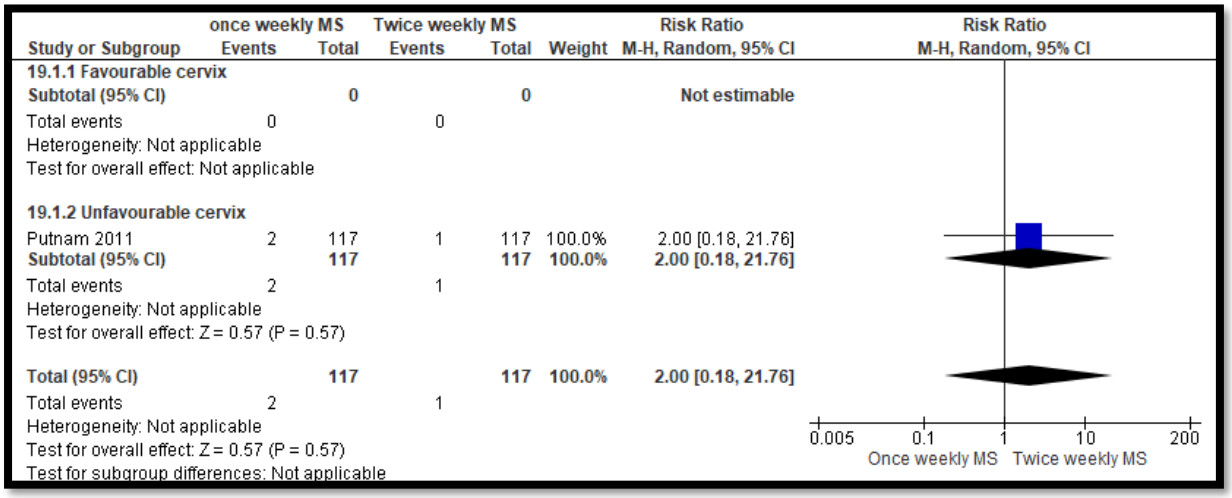
Analysis 18.3 Comparison 18 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping (Favourable cervix/unfavourable cervix), Outcome 3 Spontaneous vaginal birth.



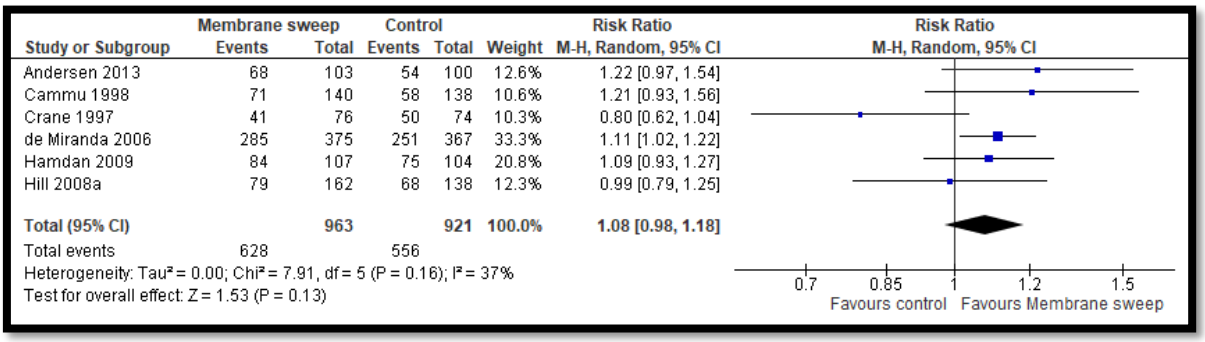
Analysis 18.4
Comparison 18 One frequency of amniotic membranes sweeping versus another frequency of amniotic membrane sweeping (Favourable cervix/unfavourable cervix), Outcome 4 Maternal death or serious morbidity.



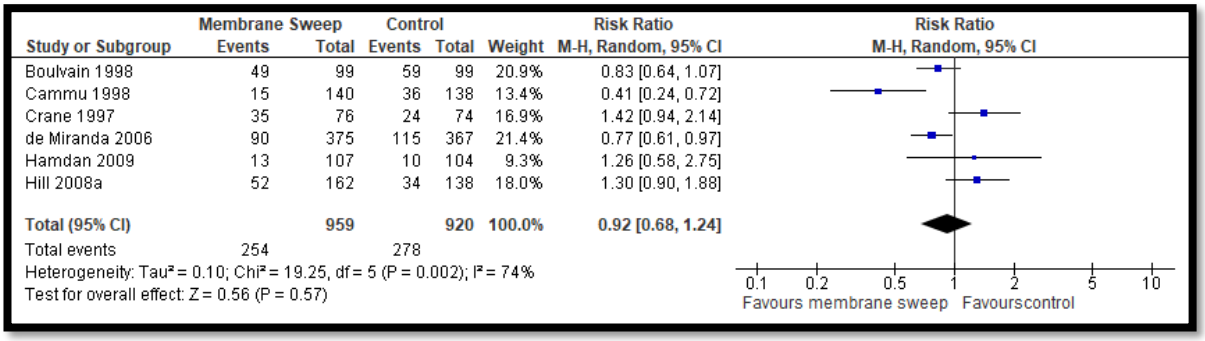
Analysis 19.1 Comparison 19 Amniotic membranes sweeping versus mechanical methods (Favourable cervix/unfavourable cervix), Outcome 1 Neonatal death or serious neonatal perinatal morbidity.



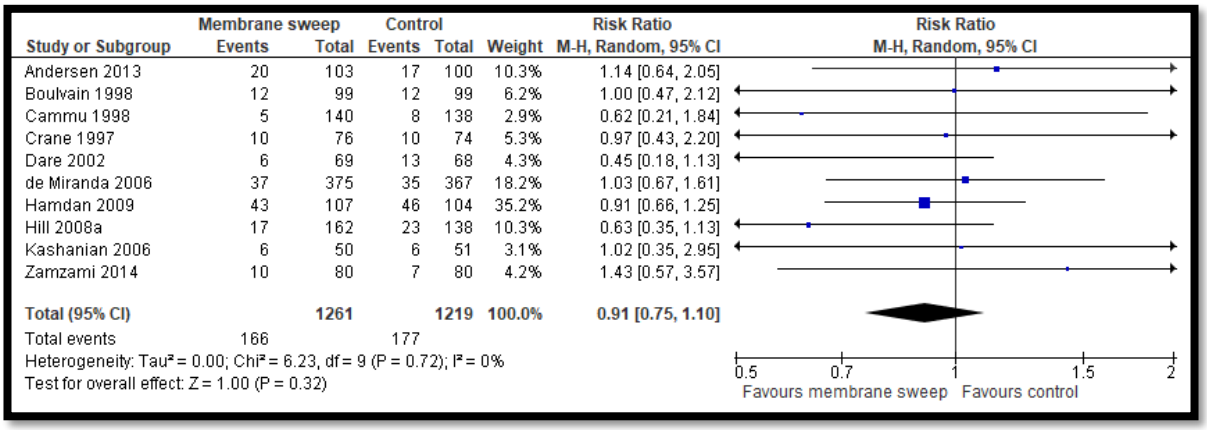
Analysis 20.1 Comparison 20 Amniotic membranes sweeping versus no treatment/sham-sensitivity analysis, Outcome 1 Spontaneous onset of labour-sensitivity analysis.



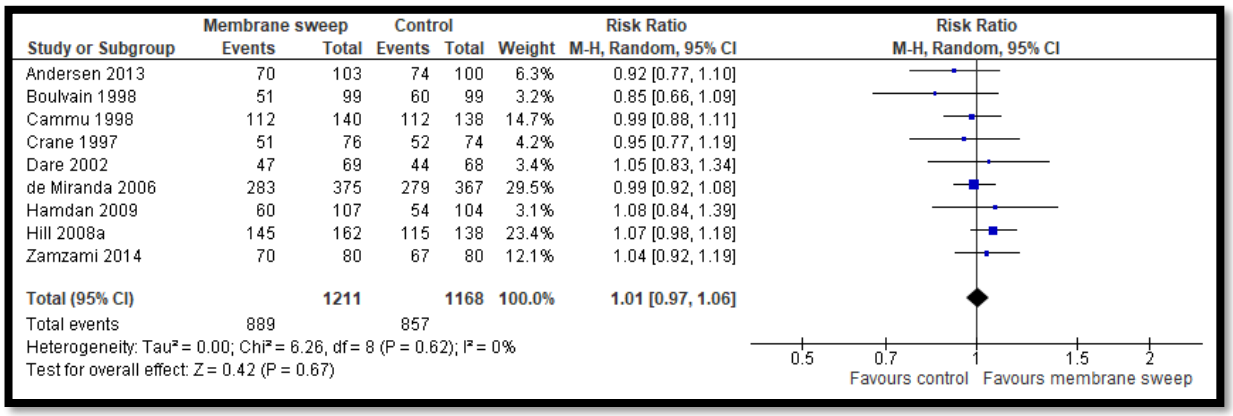
Analysis 20.2 Comparison 20 Amniotic membranes sweeping versus no treatment/sham-sensitivity analysis, Outcome 2 Induction of labour- sensitivity analysis



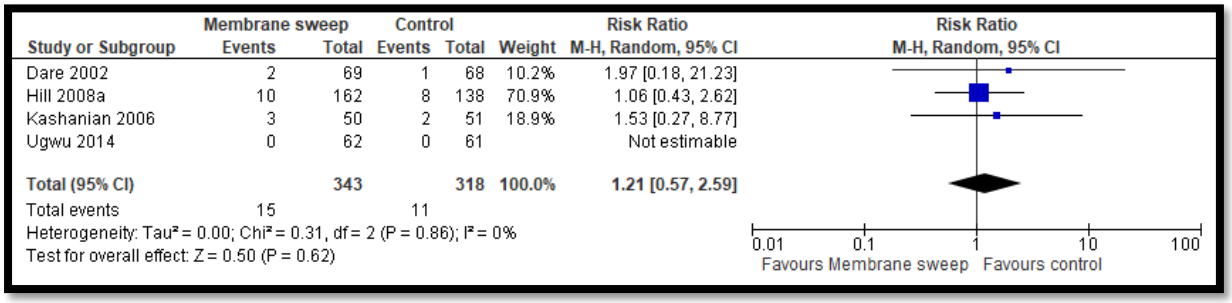
Analysis 20.3 Comparison 20 Amniotic membranes sweeping versus no treatment/sham-sensitivity analysis, Outcome 3 Caesarean section-sensitivity analysis.



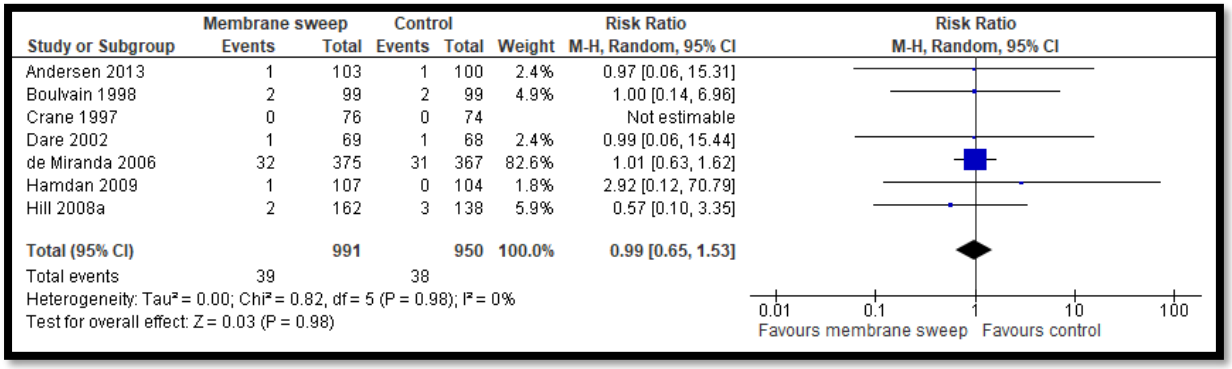
Analysis 20.4 Comparison 20 Amniotic membranes sweeping versus no treatment/sham-sensitivity analysis, Outcome 4 Spontaneous vaginal birth-sensitivity analysis



Analysis 20.5 Comparison 20 Amniotic membranes sweeping versus no treatment/sham-sensitivity analysis, Outcome 5 Maternal death or serious morbidity - sensitivity analysis.



Analysis 20.6 Comparison 20 Amniotic membranes sweeping versus no treatment/sham-sensitivity analysis, Outcome 6 Neonatal death or serious neonatal perinatal morbidity - sensitivity analysis.



Appendix 7.

Paper 2: The MILO Study - SPIRIT Checklist

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___2_____
	2b	All items from the World Health Organization Trial Registration Data Set	_1,17
Protocol version	3	Date and version identifier	___16__
Funding	4	Sources and types of financial, material, and other support	___17___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1___
	5b	Name and contact information for the trial sponsor	___17__
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___17___

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__15,17_

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____3__
	6b	Explanation for choice of comparators	__3 , 4
Objectives	7	Specific objectives or hypotheses	____5_
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__5,13,14

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___5___
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__5-6_
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,13,14__
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___11__

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_7,8,11_
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___12____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_8 - 10__
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____10__
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__8,11,14_

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____6_
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__6____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___6____

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___6____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	*neither clinicians nor women will be blinded to group assignment*
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__12____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___7____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___12___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_8 – 11 ____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13 - 15_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_7 _____

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not	__15__ *A copy of the DMC Charter is available from the correspon ding author on request*
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___11_
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___12__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___15__ *A copy of the DMC Charter is available from the correspon ding author on request*

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____16_

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___11,15_ *A copy of the DMC Charter is available from the correspon ding author on request*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__6,8,15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_N/A no ancillary studies included.
Confidentialit y	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12 - 14_
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___17_
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___17__
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__7,12, *A copy of The MILO Study indemnity insurance is available from the correspon ding author on request*

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16-17__
	31b	Authorship eligibility guidelines and any intended use of professional writers	_16-17_
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___17__
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A, No biological specimens will be collected.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Appendix 8.

Paper 2: Ethical approval letter from NUI Galway Research Ethics Committee

NUI Galway
OÉ Gaillimh

NUIG RESEARCH ETHICS COMMITTEE DECISION LETTER

REC Application Reference Number: 19-Jun-09
Title: Membrane sweeping for induction of labour: The MILO Study
Principle Applicant: Professor Declan Devane **School:** School of Nursing & Midwifery **Application Type:** New
Meeting Date: 19 June 2019
Decision: Full Approval

08 August 2019

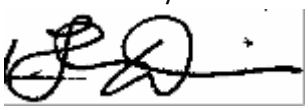
Dear Professor Devane,

I write to you regarding the above proposal, which was submitted for ethical review. Having reviewed your response to my letter, I am pleased to inform you that your proposal has been granted **FULL APPROVAL**.

All NUI Galway Research Ethic Committee approval is given subject to the Principal Investigator submitting annual and final statements of compliance. The first statement is due on or before 08 August 2020.

See annual and final statement of compliance forms attached. Section 7 of the REC's Standard Operating Procedures gives further details, and outlines other instances where you are required to report to the REC.

Yours sincerely



Dr Kevin Davison
Chair, NUIG Research Ethics Committee

Appendix 9.

Paper 2: Ethical approval letter from The Coombe Women and Infants University Maternity Hospital Research Ethics Committee

Coombe Women & Infants University Hospital
Excellence in the Care of Women and Babies
Foirfeacht i gCúram Ban agus Naíonán
Cork Street
Dublin 8
telephone +353·1·408 5200
fax +353·1·453 6033
www.coombe.ie

Prof Declan Devane **14th January 2020**
Professor of
Midwifery NUI
Galway
declane.devane@nuigalway.ie

Re: Study No. 15 – 2019 – Membrane sweeping for induction of labour: The MILO Study

Dear Prof Devane,
I have reviewed amendments and clarifications submitted in November and December 2019 in relation to your study '**Membrane sweeping for induction of labour: The MILO Study'.** Your study has now full approval from the Research Ethics Committee in the Coombe Women and Infants University Hospital.

Yours sincerely

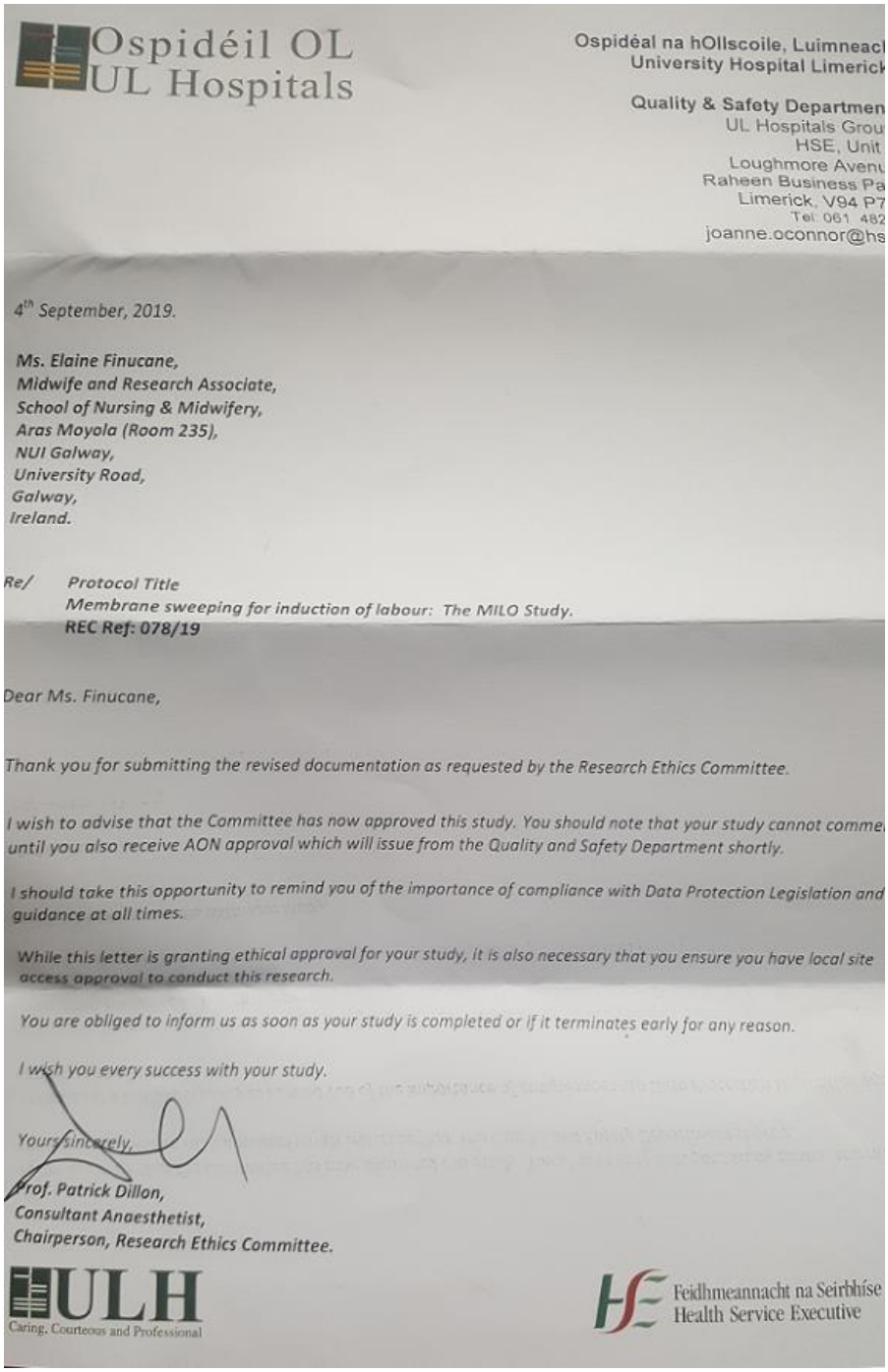
Professor Jan Miletin (IMC
241348) Consultant
Neonatologist
Chairman of the Research Ethics Committee
Coombe Women and Infants University Hospital (jmiletin@coombe.ie)

cc. *Prof Deirdre Murphy (MURPHYD4@tcd.ie), Professor of Obstetrics and* Gynaecology, Trinity College Dublin and Consultant Obstetrician, Coombe Women and Infants University Hospital, Dublin
Prof Amanda Cotter (Amanda.Cotter@ul.ie), Professor of Obstetrics and Gynaecology, University of Limerick and Consultant Obstetrician, University Maternity Hospital Limerick
Ms Elaine Finucane (elainemay.finucane@nuigalway.ie), Midwife and Research associate, NUI Galway
Prof Eleanor Molloy (molloyel@tcd.ie), Professor and Chair of Paediatrics, Trinity College Dublin, Ireland

Prof Martin O'Donnell (martin.odonnell@nuigalway.ie), Associate Director of the HRB Clinical Research Facility Galway, Associate Professor of Translational Medicine, NUI Galway

Appendix 10.

Paper 2: Ethical approval letter from University Maternity Hospital Limerick Research Ethics Committee



Ospidéil OL
UL Hospitals

Ospidéal na hOllscoile, Luimneach
University Hospital Limerick

Quality & Safety Departmen
UL Hospitals Grou
HSE, Unit
Loughmore Avenu
Raheen Business Pa
Limerick, V94 P7
Tel: 061 482
joanne.oconnor@hs

4th September, 2019.

Ms. Elaine Finucane,
Midwife and Research Associate,
School of Nursing & Midwifery,
Aras Moyola (Room 235),
NUI Galway,
University Road,
Galway,
Ireland.

Re/ Protocol Title
Membrane sweeping for induction of labour: The MILO Study.
REC Ref: 078/19

Dear Ms. Finucane,

Thank you for submitting the revised documentation as requested by the Research Ethics Committee.

I wish to advise that the Committee has now approved this study. You should note that your study cannot comme until you also receive AON approval which will issue from the Quality and Safety Department shortly.

I should take this opportunity to remind you of the importance of compliance with Data Protection Legislation and guidance at all times.

While this letter is granting ethical approval for your study, it is also necessary that you ensure you have local site access approval to conduct this research.

You are obliged to inform us as soon as your study is completed or if it terminates early for any reason.

I wish you every success with your study.

Yours sincerely,

Prof. Patrick Dillon,
Consultant Anaesthetist,
Chairperson, Research Ethics Committee.

ULH
Caring, Courteous and Professional

Feidhmeannacht na Seirbhíse
Health Service Executive

Appendix 11.

Paper 2: Participant Information Leaflet –The MILO Study.

Study information for Membrane sweeping for induction of labour: The MILO Study a randomised controlled trial

You are being invited to take part in a research study evaluating the effect of membrane sweeping on post-term pregnancy. Before you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully before deciding whether to take part and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Thank you for taking the time to read this.

Title of study:

Membrane sweeping for induction of labour: The MILO Study

Site:

The Coombe Women & Infants University Hospital.

About the research

Who will conduct the research?

The Principal Investigator for the Coombe Women & Infants University Hospital is Professor Deirdre Murphy.

What is the purpose of the study?

Post-term pregnancy refers to a pregnancy that continues past 42 weeks' gestation. It occurs in approximately 10% of pregnancies and is the most common reason for induction of labour. Post-term pregnancy is associated with higher risk of complications to mother and baby. Membrane sweeping is a simple clinical procedure, potentially promoting the onset of spontaneous labour, reducing the number of women requiring induction to avoid post-term pregnancy. Membrane sweeping is performed routinely by obstetricians or midwives in community or hospital settings. However, at present we do not know the best time during pregnancy or how often we need to perform a membrane sweep. We also do not know women's views or if membrane sweeping is cost-effective compared to other methods of induction. By performing this trial, we hope to begin the process of answering these questions.

This study will assess the feasibility of performing a randomised controlled trial to answer these questions.

Why have I been chosen?

You are eligible to take part in this study if you are over 18 years of age, are pregnant with a single fetus and your amniotic membranes are intact. Due to the unavailability of translational services, you must also have a competent level of fluency in English to take part in the study. The MILO study will be conducted in two Irish maternity hospitals over a 36-month period and will invite 132 women to take part.

Do I have to take part?

No. It is up to you to decide whether to take part. If you do decide to take part, you will be asked to sign a consent form and you should keep this leaflet. You are still free to withdraw at any time and without giving a reason. Whether or not you are in the study, the standard of care you receive will not be affected.

What does taking part involve?

If you are happy to take part in the study, you will be asked to sign a consent form. The person who takes consent will then enter your details into a computer system. This will allocate you to either the membrane sweep group or the no sweep group. If you are allocated to the membrane sweep group, you will be allocated to one of four pathways. 1) Weekly membrane sweeps beginning at 39 weeks gestation, 2) Weekly membrane sweeps beginning at 40 gestation, 3) a single membrane sweep at 39 weeks' gestation only and 4) a single membrane sweep at 40 weeks' gestation only. **Women allocated to the control arm will not receive a membrane sweep**. Other than allocation to the membrane sweep group or the no sweep group, all women will receive the same care. Participating in this trial will not alter the care you or your infant receive in labour or postnatally. The decision about which group you would go into will be made by chance, rather like the toss of a coin. This is important because it ensures that membrane sweeping can be tested fairly. We will also let your GP and consultant obstetrician know that you took part in the MILO study, with your consent.

What is an amniotic membrane sweep?

During a vaginal examination the clinician will insert a finger into the opening of your cervix (neck of your womb) and then gently through a circular motion separate the membranes of the amniotic sac surrounding your baby from your cervix. This separation stimulates the release of your own hormones to ripen the cervix naturally. All midwives and obstetricians taking part in the MILO study will be experienced in performing vaginal examinations, including cervical assessment, and will receive the MILO training programme, which will include training on how to perform a membrane sweep.

Where and when will the MILO Study take place?

The MILO Study will take place in The Coombe Women & Infants University Hospital, commencing on the XXXX.

Are there any benefits or risks to me taking part?

Your participation in this study may not result in any direct health benefits to you. We hope that the results from this study will be of benefit to other pregnant women in the future. While no physical risks are associated with participating in this study some women may

experience discomfort during the membrane sweeping procedure. The research team will respect the decision of all participants to walk away from the MILO study at any time.

Voluntary participation

Participation is entirely voluntary, and you have the right to withdraw from the study at any time. If you decide not to participate in this study there will be no negative consequences, and you will not be expected to give any reason for your decision and your care will not be affected in any way. If you do decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time without giving a reason and without detriment to yourself. However, it will not be possible to remove your data from the project once it has been anonymised as we will not be able to identify your specific data. This does not affect your data protection rights.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether to take part. If you decide not to take part, you do not need to do anything further. If you do decide to withdraw from the study at any time, I would ask that you send an email declaring withdrawal to the research team. Contact details are included towards the end of this Participant Information Sheet.

Confidentiality

What information will you collect about me?

In order to participate in this research project, we will need to collect information that could identify you, called “personal identifiable information”. Specifically, we will need to collect information about your antenatal care, your delivery and any problems you may have encountered during these periods. We will also collect data on you and your babies stay in hospital and postnatal experience. This is information that is routinely recorded in your hospital chart. Information will be collected by the research midwife and be kept confidentially. Your identity will remain confidential. All data will be coded, meaning that your name will not be published, and it will not be disclosed. All data retrieved from the MILO Study will be securely stored in the National University of Ireland, Galway under the stewardship of the research team and destroyed after a period of 7 years as in accordance with the National University of Ireland, Galway Data Retention Policy. In addition, The MILO Study has undergone a NUI Galway Data Protection Impact Assessment (DPIA) to ensure compliance to NUI Galway Data Protection Policies and Procedures.

Under what legal basis are we collecting this information?

We are collecting and storing this personal identifiable information in accordance with data protection law which protect your rights. These state that we must have a legal basis (specific reason) for collecting your data. For this study, the specific reasons are "consent” which is “freely given, specific, informed and unambiguous” and “a public interest task”.

What are my rights in relation to the information you will collect about me?

You have several rights under data protection law regarding your personal information. For example, you can request a copy of the information we hold about you.

If you would like to know more about your different rights or the way we use your personal information to ensure we follow the law, please consult the NUI Galway Data Protection Website https://www.nuigalway.ie/data-protection/

Will my participation in the study be confidential and my personal identifiable information be protected?

In accordance with data protection law, The National University of Ireland, Galway is the Data Controller for this project. This means that we are responsible for making sure your personal information is kept secure, confidential and used only in the way you have been told it will be used. All researchers are trained and your data will be looked after in the following way:
Only the Principle Investigator and co- investigators at The National University of Ireland, Galway will have access to your personal information, but they will anonymise it as soon as possible using a unique identifier code. Your name and any other identifying information will be removed and replaced with a random ID number. Only the research team will have access to the key that links this ID number to your personal information. All data will be entered onto a purposefully designed Excel database, within 7 days of your discharge, by the research midwives. All data collected during the study will be securely stored in the National University of Ireland, Galway under the stewardship of the Lead Co- Investigator and destroyed after a period of 7 years.
If any participant should disclose information during the research study regarding unacceptable work practices or issues of risk, the researcher is obliged to report this information to the appropriate management/ authority. In such cases, confidentiality may be broken.
Please also note that individuals from The National University of Ireland, Galway or regulatory authorities may need to look at the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data. All individuals involved in auditing and monitoring the study will have a strict duty of confidentiality to you as a research participant.

What will happen to the findings of this study?

The results of the study will be published in a scientific journal regardless of the findings. You will not be identified in any report or publication.

Compensation

This study is covered by standard institutional indemnity insurance. No payments are available for taking part in this study. Nothing in this document restricts or curtails your rights.

Has this study received ethical approval?

Yes, this study has received ethical approval from the following research ethics committee; The Coombe Women & Infants University Hospital, Research Ethics Committee (REC), the UL Hospitals Group, Research Ethics Committee and the NUI Galway, Research Ethics Committee.

Who is funding the research project?

The National University of Ireland, Galway is organising this research. The Health Research Board, Ireland is funding the research through the Definitive Interventions and Feasibility Awards (DIFA) and will be collecting any relevant safety information.

What if there is a problem?
If you take part in the study, then you will retain the same legal rights as any other patient within the Health Service Executive. If you are not satisfied with any aspect of the way in which you have been approached or treated during our study, then please speak first to the researchers (see contact details below).

Contact details for complaints
If you have a complaint that you wish to direct to members of the research team, please contact:

The MILO Study research team

(Insert name) Research Midwife, the Coombe Women & Infants University Hospital.
(Insert email allocated).
(Insert phone number allocated).

Professor Deirdre Murphy, the Coombe Women & Infants University Hospital.
Email: murphyd4@tcd.ie
Telephone: 01 4085200

Elaine Finucane, Midwife and PhD Fellow, NUI Galway
Email: elainemay.finucane@nuigalway.ie
(Insert phone number allocated).

Prof. Declan Devane, Professor of Midwifery, NUI Galway
Email: Declan.devane@nuigalway.ie
(Insert phone number allocated).
If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact:
Vice-President for Research, School of Natural Sciences, National University of Ireland, Galway. Tel: 353 91 495768 or by emailing: vpresearch@nuigalway.ie
If you wish to contact us about your data protection rights, please email: dataprotection@nuigalway.ie or write to The Data Protection Officer, NUI Galway, Room A129, The Quadrangle, NUI Galway, University Road, Galway and we will guide you through the process of exercising your rights.
You also have a right to complain to the Office of the Information Commissioner (https://www.oic.ie/) about complaints relating to your personal identifiable information:

Tel (01) 639 5689

Contact Details
If you have any queries about the study or if you are interested in taking part then please contact the researcher(s)
(Insert name) Research Midwife, the Coombe Women & Infants University Hospital.
(Insert email allocated).

(Insert phone number allocated).

Professor Deirdre Murphy, the Coombe Women & Infants University Hospital.
Email: murphyd4@tcd.ie
Telephone: 01 4085200

Elaine Finucane, Midwife and PhD Fellow, NUI Galway
Email: elainemay.finucane@nuigalway.ie
(Insert phone number allocated).

Prof. Declan Devane, Professor of Midwifery, NUI Galway
Email: Declan.devane@nuigalway.ie
(Insert phone number allocated).

Appendix 12.

Paper 2: Participant Information Leaflet – Women- The MILO Study, Focus Group Interview

Study information for Membrane sweeping for induction of labour: The MILO Study

You are being invited to take part in a focus group interview as part of a research study evaluating the effect of membrane sweeping on post-term pregnancy. Before you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully before deciding whether to take part and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Thank you for taking the time to read this.

Title of study:

Membrane sweeping for induction of labour: The MILO Study

About the research

Who will conduct the research?

The Principal Investigator for the Coombe Women & Infants University Hospital is Professor Deirdre Murphy.

Site:

The Coombe Women & Infants University Hospital.

What is the purpose of the study?

Post-term pregnancy refers to a pregnancy that continues past 42 weeks' gestation. It occurs in approximately 10% of pregnancies and is the most common reason for induction of labour. Post-term pregnancy is associated with higher risk of trauma to mother and baby. Membrane sweeping is a simple procedure potentially promoting the onset of spontaneous labour, reducing the number of women requiring induction to avoid post-term pregnancy. At present we do not know the best time during pregnancy or how often we need to perform a membrane sweep. We also do not know women's views or if membrane sweeping is cost-effective compared to other methods of induction. By performing this trial, we hope to begin the process of answering these questions.

The overall aim of this study is to assess the feasibility of performing a randomised controlled trial to answer these questions.

The focus group interview that you are being asked to participate in will inform the design of this trial as we are looking to recruit women, who are willing to discuss their experiences and views of taking part in the MILO study and membrane sweeping as a method of induction of labour.

Why have I been chosen?

You are eligible to take part in this study if you are over 18 years of age and have been a participant in the MILO study randomised controlled trial. Due to the unavailability of translational services, you must also have a competent level of fluency in English to take part in the study. The focus group interviews will be conducted in XXXX on XXXX at XXXXX. Twenty women (ten women from the Coombe Women & Infants University Hospital) will be invited to take part in the interviews.

Do I have to take part?

No. It is up to you to decide whether to take part. If you do decide to take part, you will be asked to sign a consent form and you should keep this leaflet. You are still free to withdraw at any time and without giving a reason. Whether or not you are in the study, the standard of care you receive will not be affected.

What does taking part involve?

Participation will involve taking part in one focus group interview with up to 9 other women who took part in the MILO study in the Coombe Women & Infants University Hospital. The purpose of the focus group interview is to explore participant's experiences and views of membrane sweeping as a method of induction of labour and of taking part in the MILO study. The interview will be facilitated by a researcher and by one- two members of the research team and will last approximately one hour. The interview will be audio recorded and then analysed later. This study does not involve any access to medical records.

Where and when will the focus group interview take place?

The focus group interview that you are invited to participate in is scheduled to take place in XXXX on the XXXX at XXXXX.

Are there any benefits or risks to me taking part?

No physical risks are associated with participating in this study. There is always a chance that talking about certain topics may upset you. If this occurs, you will be asked if you would like to take a break and have the audio recording paused. The research team will respect the decision of all participants to walk away from the focus interview at any time.

Voluntary participation

Participation is entirely voluntary, and you have the right to withdraw from the study at any time. If you decide not to participate in this study there will be no negative consequences, and you will not be expected to give any reason for your decision and your care will not be affected in any way. If you do decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time without giving a reason and without detriment to yourself. However, it will not be possible to remove your data from the project once it has been anonymised as we will not be able to identify your specific data. This does not affect your data protection rights.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether to take part. If you decide not to take part, you do not need to do anything further. If you do decide to withdraw from the study at any time, I would ask that you send an email declaring withdrawal to the research team. Contact details are included towards the end of this Participant Information Sheet.

Confidentiality

What information will you collect about me?

During the focus group we will explore your experiences and views of membrane sweeping as a method of induction of labour and of taking part in the MILO study.

Under what legal basis are you collecting this information?

We are collecting and storing this personal identifiable information in accordance with data protection law which protect your rights. These state that we must have a legal basis (specific reason) for collecting your data. For this study, the specific reasons are "consent" which is “freely given, specific, informed and unambiguous” and “a public interest task”.

What are my rights in relation to the information you will collect about me?

You have a number of rights under data protection law regarding your personal information. For example, you can request a copy of the information we hold about you. If you would like to know more about your different rights or the way we use your personal information to ensure we follow the law, please consult the NUI Galway Data Protection Website https://www.nuigalway.ie/data-protection/

Will my participation in the study be confidential and my personal identifiable information be protected?

In accordance with data protection law, The National University of Ireland, Galway is the Data Controller for this project. This means that we are responsible for making sure your personal information is kept secure, confidential and used only in the way you have been told it will be used. The MILO Study has undergone a NUI Galway Data Protection Impact Assessment (DPIA) to ensure compliance to NUI Galway Data Protection Policies and Procedures. All researchers are trained and your data will be looked after in the following way:
Your identity will remain confidential. All data will be coded, meaning that your name will not be published, and it will not be disclosed to anyone outside the focus group interview. Audio data from the focus group interview will be transcribed by an outside experienced research transcription service. The function of a transcription service is to write out everything that has been audio recorded within the interview. The transcriber for this study will have signed a confidentiality and non- disclosure agreement document for the study and they will only receive audio recording with pseudonym details. All data retrieved from the focus group interview will be securely stored in the National University of Ireland, Galway under the stewardship of the research team and destroyed after a period of 7 years as in accordance with the National University of Ireland, Galway Data Retention Policy. All data will be destroyed after a period of 7 years through confidential shredding.
If any participant should disclose information during the research study regarding unacceptable work practices or issues of risk, the researcher is obliged to report this

information to the appropriate management/ authority. In such cases, confidentiality may be broken.
Please also note that individuals from The National University of Ireland, Galway or regulatory authorities may need to look at the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data. All individuals involved in auditing and monitoring the study will have a strict duty of confidentiality to you as a research participant.

What will happen to the findings of this study?

The results of the study will be published in a scientific journal regardless of the findings. You will not be identified in any report or publication.

Compensation

This study is covered by standard institutional indemnity insurance. No payments are available for taking part in this study. Nothing in this document restricts or curtails your rights.

Has this study received ethical approval?

Yes, this study has received ethical approval from the following research ethics committees; The Coombe Women & Infants University Hospital, Research Ethics Committee (REC), the UL Hospitals Group, Research Ethics Committee and the NUI Galway, Research Ethics Committee.

Who is funding the research project?

The National University of Ireland, Galway is organising this research. The Health Research Board, Ireland is funding the research through the Definitive Interventions and Feasibility Awards (DIFA) and will be collecting any relevant safety information.

What if there is a problem?
If you take part in the study, then you will retain the same legal rights as any other patient within the Health Service Executive. If you are not satisfied with any aspect of the way in which you have been approached or treated during the course of our study, then please speak first to the researchers (see contact details below).

Contact details for complaints
If you have a complaint that you wish to direct to members of the research team, please contact:

The MILO Study research team

(Insert name) Research Midwife, the Coombe Women & Infants University Hospital.
(Insert email allocated).
(Insert phone number allocated).

Professor Deirdre Murphy, the Coombe Women & Infants University Hospital.
Email: murphyd4@tcd.ie
Telephone: 01 4085200

Elaine Finucane, Midwife and PhD Fellow, NUI Galway
Email: elainemay.finucane@nuigalway.ie
(Insert phone number allocated).

Prof. Declan Devane, Professor of Midwifery, NUI Galway
Email: Declan.devane@nuigalway.ie
(Insert phone number allocated).

If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance, then please contact:

Vice-President for Research, School of Natural Sciences, National University of Ireland, Galway. Tel: 353 91 495768 or by emailing: vpresearch@nuigalway.ie

If you wish to contact us about your data protection rights, please email: dataprotection@nuigalway.ie or write to The Data Protection Officer, NUI Galway, Room A129, The Quadrangle, NUI Galway, University Road, Galway and we will guide you through the process of exercising your rights.

You also have a right to complain to the Office of the Information Commissioner (https://www.oic.ie/) about complaints relating to your personal identifiable information
Tel (01) 639 5689

Contact Details

If you have any queries about the study or if you are interested in taking part then please contact the researcher(s)
(Insert name) Research Midwife, the Coombe Women & Infants University Hospital.
(Insert email allocated).
(Insert phone number allocated).

Professor Deirdre Murphy, the Coombe Women & Infants University Hospital.
Email: murphyd4@tcd.ie
Telephone: 01 4085200

Elaine Finucane, Midwife and PhD Fellow, NUI Galway
Email: elainemay.finucane@nuigalway.ie
(Insert phone number allocated).

Prof. Declan Devane, Professor of Midwifery, NUI Galway
Email: Declan.devane@nuigalway.ie
(Insert phone number allocated).

Appendix 13.

Paper 2: Participant Information Leaflet – Clinician- The MILO Study Focus Group Interview

Study information for Membrane sweeping for induction of labour: The MILO Study
You are being invited to take part in a focus group interview as part of a research study evaluating the effect of membrane sweeping on post-term pregnancy. Before you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully before deciding whether to take part and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Thank you for taking the time to read this.

Title of study:

Membrane sweeping for induction of labour: The MILO Study

Site:

The Coombe Women & Infants University Hospital.

About the research

Who will conduct the research?

The Principal Investigator for the Coombe Women & Infants University Hospital is XXXX.

What is the purpose of the study?

Post-term pregnancy refers to a pregnancy that continues past 42 weeks' gestation. It occurs in approximately 10% of pregnancies and is the most common reason for induction of labour. Post-term pregnancy is associated with higher risk of trauma to mother and baby. Membrane sweeping is a simple procedure potentially promoting the onset of spontaneous labour, reducing the number of women requiring induction to avoid post-term pregnancy. At present we do not know the best time during pregnancy or how often we need to perform a membrane sweep. We also do not know clinician's views or if membrane sweeping is cost-effective compared to other methods of induction. By performing this trial we hope to begin the process of answering these questions.

The overall aim of this study is to assess the feasibility of performing a randomised controlled trial to answer these questions.

The focus group interview that you are being asked to participate in will inform the design of this trial as we are looking to recruit clinician's, who are willing to discuss their experiences and views of taking part in the MILO study and membrane sweeping as a method of induction of labour.

Why have I been chosen?

You are eligible to take part in this study if you are an obstetrician or midwife who has participated in the MILO study randomised controlled trial in The Coombe Women & Infants University Hospital. The focus group interviews will be conducted in XXXX on XXXX at XXXXX. All clinicians who participated in The MILO Study will be invited to take part in the interviews.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part, you will be asked to sign a consent form and you should keep this leaflet. You are still free to withdraw at any time and without giving a reason.

What does taking part involve?
Participation will involve taking part in one focus group interview with colleagues from the Coombe Women & Infants University Hospital who also participated in The MILO Study. We will also facilitate one to one interviews with individuals if required. The purpose of the focus group interview is to explore clinician's experiences and views of membrane sweeping as a method of induction of labour and of taking part in the MILO study. The interview will be facilitated by a researcher and by one- two members of the research team and will last approximately one hour. The interview will be audio recorded and then analysed later. The audiotape will be destroyed once transcribed and this study does not involve any access to medical records.

Where and when will the focus group interview take place?
The focus group interview that you are invited to participate in is scheduled to take place in XXXX on the XXXX at XXXXX.

Are there any benefits or risks to me taking part?
No physical risks are associated with participating in this study. There is always a chance that talking about certain topics may upset you. If this occurs, you will be asked if you would like to take a break and have the audio recording paused. The research team will respect the decision of all participants to walk away from the focus interview at any time.

Voluntary participation

Participation is entirely voluntary, and you have the right to withdraw from the study at any time. If you decide not to participate in this study there will be no negative consequences, and you will not be expected to give any reason for your decision. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason and without detriment to yourself. However, it will not be possible to remove your data from the project once it has been anonymised as we will not be able to identify your specific data. This does not affect your data protection rights.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether or not to take part. If you decide not to take part you do not need to do anything further. If you do decide to withdraw from the study at any time, I

would ask that you send an email declaring withdrawal to the research team. Contact details are included towards the end of this Participant Information Sheet.

Confidentiality

What information will you collect about me?

During the focus group we will explore your experiences and views of membrane sweeping as a method of induction of labour and of taking part in the MILO study.

Under what legal basis are you collecting this information?

We are collecting and storing this personal identifiable information in accordance with data protection law which protect your rights. These state that we must have a legal basis (specific reason) for collecting your data. For this study, the specific reasons are "consent" which is "freely given, specific, informed and unambiguous" and "a public interest task".

What are my rights in relation to the information you will collect about me?

You have a number of rights under data protection law regarding your personal information. For example you can request a copy of the information we hold about you.
If you would like to know more about your different rights or the way we use your personal information to ensure we follow the law, please consult the NUI Galway Data Protection Website https://www.nuigalway.ie/data-protection/

Will my participation in the study be confidential and my personal identifiable information be protected?

In accordance with data protection law, The National University of Ireland, Galway is the Data Controller for this project. This means that we are responsible for making sure your personal information is kept secure, confidential and used only in the way you have been told it will be used. The MILO Study has undergone a NUI Galway Data Protection Impact Assessment (DPIA) to ensure compliance to NUI Galway Data Protection Policies and Procedures. All researchers are trained and your data will be looked after in the following way:
Your identity will remain confidential. All data will be coded, meaning that your name will not be published, and it will not be disclosed to anyone outside the focus group interview. Audio data from the focus group interview will be transcribed by an outside experienced research transcription service. The function of a transcription service is to write out everything that has been audio recorded within the interview. The transcriber for this study will have signed a confidentiality and non- disclosure agreement document for the study and they will only receive audio recording with pseudonym details. The audiotape will be destroyed once transcribed. All data retrieved from the focus group interview will be securely stored in the National University of Ireland, Galway under the stewardship of the research team and destroyed after a period of 7 years as in accordance with the National University of Ireland, Galway Data Retention Policy. All data will be destroyed after a period of 7 years through confidential shredding.
If any participant should disclose information during the research study regarding unacceptable work practices or issues of risk, the researcher is obliged to report this

information to the appropriate management/ authority. In such cases, confidentiality may be broken.
Please also note that individuals from The National University of Ireland, Galway or regulatory authorities may need to look at the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data. All individuals involved in auditing and monitoring the study will have a strict duty of confidentiality to you as a research participant.

What will happen to the findings of this study?

The results of the study will be published in a scientific journal regardless of the findings. You will not be identified in any report or publication.

Compensation

This study is covered by standard institutional indemnity insurance. No payments are available for taking part in this study. Nothing in this document restricts or curtails your rights.

Has this study received ethical approval?

Yes, this study has received ethical approval from the following research ethics committees; The Coombe Women & Infants University Hospital, Research Ethics Committee (REC), the UL Hospitals Group, Research Ethics Committee and the NUI Galway, Research Ethics Committee.

Who is funding the research project?

The National University of Ireland, Galway is organising this research. The Health Research Board, Ireland is funding the research through the Definitive Interventions and Feasibility Awards (DIFA) and will be collecting any relevant safety information.

What if there is a problem?
If you are not satisfied with any aspect of the way in which you have been approached or treated during our study, then please speak first to the researchers (see contact details below).
Contact details for complaints
If you have a complaint that you wish to direct to members of the research team, please contact:

The MILO Study research team

(Insert name) Research Midwife, the Coombe Women & Infants University Hospital.
(Insert email allocated).
(Insert phone number allocated).

Professor Deirdre Murphy, the Coombe Women & Infants University Hospital.
Email: murphyd4@tcd.ie
Telephone: 01 4085200

Elaine Finucane, Midwife and PhD Fellow, NUI Galway

Email: elainemay.finucane@nuigalway.ie
(Insert phone number allocated).

Prof. Declan Devane, Professor of Midwifery, NUI Galway
Email: Declan.devane@nuigalway.ie
(Insert phone number allocated).
If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact:
Vice-President for Research, School of Natural Sciences, National University of Ireland, Galway. Tel: 353 91 495768 or by emailing: vpresearch@nuigalway.ie
If you wish to contact us about your data protection rights, please email:
dataprotection@nuigalway.ie or write to The Data Protection Officer, NUI Galway, Room A129, The Quadrangle, NUI Galway, University Road, Galway and we will guide you through the process of exercising your rights.

You also have a right to complain to the Office of the Information Commissioner (https://www.oic.ie/) about complaints relating to your personal identifiable information Tel (01) 639 5689

Contact Details
If you have any queries about the study or if you are interested in taking part then please contact the researcher(s)
(Insert name) Research Midwife, the Coombe Women & Infants University Hospital.
(Insert email allocated).
(Insert phone number allocated).

Professor Deirdre Murphy, the Coombe Women & Infants University Hospital.
Email: murphyd4@tcd.ie
Telephone: 01 4085200

Elaine Finucane, Midwife and PhD Fellow, NUI Galway
Email: elainemay.finucane@nuigalway.ie
(Insert phone number allocated).

Prof. Declan Devane, Professor of Midwifery, NUI Galway
Email: Declan.devane@nuigalway.ie
(Insert phone number allocated).

Appendix 14.
Paper 2: Consent form– Participants in the MILO Study.

Appendices

Participant Consent form

Title of study: Membrane sweeping for induction of labour: The MILO Study
Site: The Coombe Women & Infants University Hospital
Participant Identification Number: _____ (to be completed by researcher)

Declaration of the participant – pleas tick (✓) the relevant box	YES	NO
I have read the participant information sheet for the MILO Study and I understand the contents.		
I have had the opportunity to ask questions and all my questions have been answered to my satisfaction.		
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason and without any negative consequences.		
I consent to the processing of personal data for research purposes and agree that the data collected from the MILO Study will be securely stored in the National University of Ireland, Galway, for a period of 7 years after the completion of this study.		
I consent to notifying my General Practitioner and consultant obstetrician that I am taking part in the MILO study as a participant in a randomised controlled trial.		
I consent to taking part in the MILO study as a participant in a randomised controlled trial in the Coombe Women & Infants University Hospital and I am over 18 years of age.		

If you take part in the MILO study, then you will retain the same legal rights as any other patient within the Health Service Executive. If you are not satisfied with any aspect of the way in which you have been approached or treated during the course of our study, then please speak first to the researchers (see contact details below).
(Insert name) Research Midwife, the Coombe Women & Infants University Hospital.
(Insert email allocated).
(Insert phone number allocated).

Professor Deirdre Murphy, the Coombe Women & Infants University Hospital.
Email: murphyd4@tcd.ie
Telephone: 01 4085200

Elaine Finucane, Midwife and PhD Fellow, NUI Galway
Email: elainemay.finucane@nuigalway.ie
(Insert phone number allocated).

Prof. Declan Devane, Professor of Midwifery, NUI Galway
Email: Declan.devane@nuigalway.ie
(Insert phone number allocated).
If you wish to contact us about your data protection rights, please email: dataprotection@nuigalway.ie or write to The Data Protection Officer, NUI Galway, Room A129,

The Quadrangle, NUI Galway, University Road, Galway and we will guide you through the process of exercising your rights.
You also have a right to complain to the Office of the Information Commissioner (https://www.oic.ie/) about complaints relating to your personal identifiable information Tel (01) 639 5689

Participant;
Participant name; _____
Participant signature; _____
Date; _____

Researcher / person taking consent;
Name of person taking consent; _____
Signature of person taking consent; _____
Date; _____

Appendix 15.

Paper 2: Consent form– Women in the focus groups.

Appendices

Participant Consent form

Title of study: Membrane sweeping for induction of labour: The MILO Study

Site: The Coombe Women & Infants University Hospital

Participant Identification Number: _____ (to be completed by researcher)

Declaration of the participant – pleas tick (✓) the relevant box	YES	NO
I have read the participant information sheet for this focus group interview and I understand the contents.		
I have had the opportunity to ask questions and all my questions have been answered to my satisfaction.		
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason and without any negative consequences.		
I agree to the focus group interview being recorded.		
I agree that the audiotape and transcript of the focus group interview will be securely stored in the National University of Ireland, Galway, for a period of 7 years after the completion of this study.		
I consent to taking part in the study through the completion of a focus group interview as a woman who participated in the MILO Study in the Coombe Women & Infants University Hospital and is over 18 years of age.		

If you take part in the MILO study, then you will retain the same legal rights as any other person accessing care from the Health Service Executive. If you are not satisfied with any aspect of the way in which you have been approached or treated during the course of our study, then please speak first to the researchers (see contact details below).

(Insert name) Research Midwife, the Coombe Women & Infants University Hospital.
(Insert email allocated).
(Insert phone number allocated).

Professor Deirdre Murphy, the Coombe Women & Infants University Hospital.
Email: murphyd4@tcd.ie
Telephone: 01 4085200

Elaine Finucane, Midwife and PhD Fellow, NUI Galway
Email: elainemay.finucane@nuigalway.ie
(Insert phone number allocated).
Prof. Declan Devane, Professor of Midwifery, NUI Galway
Email: Declan.devane@nuigalway.ie
(Insert phone number allocated).
If you wish to contact us about your data protection rights, please email: dataprotection@nuigalway.ie or write to The Data Protection Officer, NUI Galway, Room A129,

The Quadrangle, NUI Galway, University Road, Galway and we will guide you through the process of exercising your rights.
You also have a right to complain to the Office of the Information Commissioner (https://www.oic.ie/) about complaints relating to your personal identifiable information Tel (01) 639 5689

Participant;
Participant name; _____
Participant signature; _____
Date; _____

Researcher / person taking consent;
Name of person taking consent; _____
Signature of person taking consent; _____
Date; _____

Appendix 16.

Paper 2: Consent form– Clinicians in the focus groups.

Appendices

Participant Consent form

Title of study: Membrane sweeping for induction of labour: The MILO Study

Site: The Coombe Women & Infants University Hospital

Participant Identification Number: _____ (to be completed by researcher)

Declaration of the participant – pleas tick (✓) the relevant box	YES	NO
I have read the participant information sheet for this focus group interview and I understand the contents.		
I have had the opportunity to ask questions and all my questions have been answered to my satisfaction.		
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason and without any negative consequences.		
I agree to the focus group interview being recorded.		
I agree that the audiotape will be destroyed once transcribed and that the transcript of the focus group interview will be securely stored in the National University of Ireland, Galway, for a period of 7 years after the completion of this study.		
I consent to taking part in the study through the completion of a focus group interview as an obstetrician or midwife who participated in the MILO Study in the Coombe Women & Infants University Hospital and is over 18 years of age.		

If you are not satisfied with any aspect of the way in which you have been approached or treated during the course of our study, then please speak first to the researchers (see contact details below).

(Insert name) Research Midwife, the Coombe Women & Infants University Hospital.
(Insert email allocated).
(Insert phone number allocated).

Professor Deirdre Murphy, the Coombe Women & Infants University Hospital.
Email: murphyd4@tcd.ie
Telephone: 01 4085200

Elaine Finucane, Midwife and PhD Fellow, NUI Galway
Email: elainemay.finucane@nuigalway.ie
(Insert phone number allocated).

Prof. Declan Devane, Professor of Midwifery, NUI Galway
Email: Declan.devane@nuigalway.ie
(Insert phone number allocated).

If you wish to contact us about your data protection rights, please email: dataprotection@nuigalway.ie or write to The Data Protection Officer, NUI Galway, Room A129, The Quadrangle, NUI Galway, University Road, Galway and we will guide you through the process of exercising your rights.

You also have a right to complain to the Office of the Information Commissioner (https://www.oic.ie/) about complaints relating to your personal identifiable information Tel (01) 639 5689

Participant;
Participant name; _____
Participant signature; _____
Date; _____

Researcher / person taking consent;
Name of person taking consent; _____
Signature of person taking consent; _____
Date; _____

Appendix 17.

Paper 2:GP/Consultant letter – Participants in the MILO Study.

Appendices

Date

Dear Doctor

RE: Membrane sweeping for induction of labour: The MILO Study

Patient Name and DOB: _____

I am writing to inform you that your patient has agreed to participate in the above clinical trial at University Maternity Hospital Limerick. Post-term pregnancy occurs in approximately 10% of pregnancies and is the most common reason for induction of labour. Post-term pregnancy is associated with higher risk of trauma to mother and baby. Membrane sweeping is a simple procedure potentially promoting the onset of spontaneous labour, reducing the number of women requiring induction to avoid post-term pregnancy. However, we do not know the best time during pregnancy or how often we need to perform a membrane sweep. We also do not know women's views or if membrane sweeping is cost-effective compared to other methods of induction.

The MILO study, funded through the Health Research Board of Ireland, consists of four work packages (WP)

WP 1: A multicentre, pragmatic, parallel group pilot randomised controlled trial with an embedded 2x2 factorial design. Women will be randomised to receive an amniotic sweep or not.

WP 2: A health economic analysis examining the cost-effectiveness of membrane sweeping to prevent post-term pregnancy.

WP 3: A qualitative descriptive study using focus group interviews to explore women and clinicians experiences of and acceptability of membrane sweeping.

WP 4: A pilot study within a trial (SWAT). Trials often do not answer their question because they do not recruit enough participants. This WP will assess if the point at which women are invited to take part in the trial (i.e. when should women be asked?) affects the number of women participating in the trial.

The purpose of this study is to assess the feasibility of conducting a definitive trial to evaluate the effectiveness and optimal intensity (timing and frequency) of membrane sweeping to prevent post-term pregnancy. The MILO study will be conducted in two Irish maternity hospitals, University Maternity Hospital Limerick and The Coombe Women's and Children's Hospital, Dublin.

Your patient has been provided with an information sheet for the trial (copy enclosed) which explains why she has been approached to take part in the trial, that the participation is entirely voluntary, and emphasises that they are free to withdraw from the trial at any time without prejudicing their future medical care.

Should you have any questions or require further information about this research, please do not hesitate to contact xxx or xxxx, Research Midwives, the University Maternity Hospital Limerick.

Email: themilostudy@gmail.com

(Insert phone number allocated).

Yours Sincerely

_____

Encs: Patient Information Sheet

Appendix 18.

Paper 3: Participant Information Leaflet – The People's Trial (Survey)

Participant Information for The People's Trial Survey

You are invited to take part in a survey as part of a research study. Before you decide if you would like to take part, it is important to understand why this research is being done and what it would involve for you.

This Participant Information Sheet will explain the aim and purpose of the research, what taking part will involve, the voluntary nature of the study and the right to withdraw at any time.

Please take the time to read this information carefully and feel free to contact the research team if you have any questions. Contact details are included towards the end of this Participant Information Sheet.

Title of study: Citizen Science: The People's Trial

Who will conduct the research?

The People's Trial is a Health Research Board (HRB, Ireland) funded project based within the HRB Trials Methodology Research Network (HRB-TMRN) and is based in NUI Galway. The Principal Investigator of the project is Prof Declan Devane and the project is supported by a Steering Group.

Purpose of this research;

This research study wants to help enhance the public's understanding of randomised trials by facilitating the involvement of the public in an online, virtual trial.

These are exciting and challenging times for clinical trials. As the number and variety of treatments continues to grow, pressure increases on resources and on researchers to determine how these compare to current treatments. In addition, there is more demand for reliable and robust evidence on the benefits, harms and costs of health care, so that people can make informed choices. The need for and importance of patient and public involvement in health (and social) care research is now well established.

This research is important as its purpose is to enhance public understanding of randomised trials in a novel way by involving the public in all aspects of the trial research process. This includes the submission of common, fun, low risk questions, such as 'Does eating cheese cause nightmares?' as the potential research question The People's Trial will evaluate. Participants will also be involved in the prioritisation of research questions, decisions around methodology (e.g., deciding which outcomes to measure), data collection or tool development, selection of outcomes measures, interpretation of findings, crafting of the key messages and the dissemination of results. The survey that you are being asked to participate in will prioritise a research question for The People's Trial through an interactive, iterative, online process with public participants.

How do I know if I am eligible?

You are eligible to take part in this survey if you are over 18 years of age. Due to the unavailability of translational services, you must also have a competent level of fluency in English to take part in the study.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part, you will be asked to acknowledge your consent online. You are still free to withdraw at any time and without giving a reason.

What does taking part involve?

Participation will involve using an online survey to create a fun, low risk, trial question, such as 'Does eating cheese cause nightmares?', that you would like considered as the question for 'The People's Trial'. In the next stage, you will be presented with questions to review and will also be asked, over a further one to two rounds, to rate the importance of these questions for The People's Trial. The purpose of this process is to refine a selection of questions, with the question ranked at number one becoming the question for The People's Trial.

Where and when will the survey take place?

The survey that you are invited to participate will take place online and is scheduled to commence in summer 2019.

Are there any benefits or risks to me taking part?

Your participation will benefit you as The People's Trial offers an online format for you to learn about randomised trials and participate in a fun, educational trial. By participating in The People's Trial, you will interact with the website, take part in the planning and design process and participate in a trial offering the opportunity to learn more about the randomised trial process and the benefits of clinical trials. Participation in The People's Trial will inform you on key concepts of the research process providing you with the resources to understand and apply these concepts to claims about the effects of treatments when making personal health choices.

No physical risks are associated with participating in this study. Although it is not anticipated that any participants will suffer emotional distress, in the unlikely event that this does occur, you may contact a member of the research team (see contact details below). The research team will respect the decision of all participants to walk away from the survey at any time.

Voluntary participation

Participation is entirely voluntary, and you have the right to withdraw from the study at any time. If you decide not to participate in this study, or if you withdraw, there will be no negative consequences, and you will not be expected to give any reason for your decision.

Confidentiality

Your identity will remain confidential. All data will be coded, meaning that your name will not be published, and it will not be disclosed. All data retrieved from the surveys will be stored securely in the National University of Ireland, Galway under the stewardship of the research team and destroyed after a period of 7 years as in accordance with the National University of Ireland, Galway Data Retention Policy.

What will happen to the findings of this study?

The findings of the surveys will inform the question for The Peoples Trial. The findings of the survey may also be submitted to peer reviewed research journals for publication.

Compensation

No payments are available for taking part in this study. Nothing in this document restricts or curtails your rights.

Who is funding the research project?

The National University of Ireland, Galway is organising this research. This study has been funded by the Health Research Board, Ireland under a KEDS grant to the HRB-Trials Methodology Research Network.

Has this study received ethical approval?

Yes, this study has received approval from the National University of Ireland, Galway Research Ethics Committee Research Office Room 212 Research and Innovation Centre NUI Galway Tel: 353 91 495312

What if there is a problem?

Contact details for complaints If you have a complaint that you wish to direct to members of the research team, please contact:

The People's Trial Room 235, Áras Moyola, NUI Galway, University Road, Galway, Ireland Tel: +353 91 495691; Email: thepeoplestrial@nuigalway

If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact:

ice-President for Research, School of Natural Sciences, National University of Ireland, Galway, Ireland. Tel: +353 91 495768 or by emailing: vpresearch@nuigalway.ie If you wish to contact us about your data protection rights, please email: dataprotection@nuigalway.ie or write to The Data Protection Officer, NUI Galway, Room A129, The Quadrangle, NUI Galway, University Road, Galway, Ireland and we will guide you through the process of exercising your rights.

You also have a right to complain to the Office of the Information Commissioner (https://www.oic.ie/) about complaints relating to your personal identifiable information Tel +353 639 5689

Contact Details

If you have any queries about the study or if you are interested in taking part then please contact the researcher(s) thepeoplestrial@nuigalway

Appendix 19.

Paper 3: Privacy policy– The People's Trial

This Privacy Statement provides information about the ways in which *The People's Trial* process the personal information provided to us.

The People's Trial respects your privacy. Any personal information that you volunteer will be treated in confidence applying reasonable standards of security, in accordance with the Data Protection Act 1988-2018 and with effect from 25 May 2018, the General Data Protection Regulations ("GDPR"). Any information that you provide will not be made available to third parties except in accordance with applicable laws and regulations. The National University of Ireland Galway (NUI Galway) has overall responsibility for ensuring compliance with Data Protection legislation as the Data Controller of personal data collected during the conduct of the study. All data is subject to NUI Galway Data Protection Policies and Procedures.

Who we are?

The People's Trial is a Health Research Board (HRB, Ireland) funded project based within the HRB Trials Methodology Research Network (HRB-TMRN) and is based in NUI Galway, Ireland. The Principal Investigator of the project is Prof Declan Devane and the project is supported by a Steering Group.

What is the purpose of the study?

The People's Trial seeks to enhance the public's understanding of randomised clinical trials while giving people the opportunity to share their opinions and preferences about public engagement in randomised clinical trials.

Voluntary participation

Participation is entirely voluntary, and you have the right to withdraw from the study at any time. If you decide not to participate in this study there will be no negative consequences, and you will not be expected to give any reason for your decision. If you decide to take part, you are still free to withdraw at any time without giving a reason and without detriment to yourself. However, it will not be possible to remove your data from the project once it has been anonymised as we will not be able to identify your specific data. This does not affect your data protection rights.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether or not to take part. If you decide not to take part, you do not need to do anything further.

Confidentiality

What information will you collect about me?

To participate in this research project, we will need to collect information that could identify you, called "personal identifiable information". Specifically, we will need to collect your email address and demographic information.

The People's Trial will collect information through this website in three ways:

- Via email
- Via web technical logs
- Via web forms

This information includes: name, email, type of stakeholder, gender, age range and country.

Email: If you choose to contact *The People's Trial* via email, your details will be used only for the purposes for which you intended i.e. to receive a reply to your email request / communication. When your email has been actioned, the original message will be retained by *The People's Trial* for a reasonable period of time. In line with GDPR requirements, your details will not be added to any of our mailing lists and all members on our mailing list have expressed explicit active consent to join this list. All data will be coded, meaning that your name will not be published, and it will not be disclosed. All data retrieved from *The Peoples Trial* will be securely stored in NUI Galway under the stewardship of the research team and destroyed after a period of 7 years as in accordance with the NUI Galway Data Retention Policy.

Use of cookies

A cookie is a small text file that may be stored on your computer or mobile device that contains data related to a website you visit. It may allow a website "remember" your actions or preferences over a period of time, or it may contain data related to the function or delivery of the site. Cookies can be set by the owner of the website or in some cases by third party services the website owner allows to present other information, run content or provide other functionality such as analytics.

Further information on cookies can be found at: http://ec.europa.eu/ipg/basics/legal/cookies/index_en.htm

Purpose for which data is processed

We ask people who participate if we can stay in touch to better enable people to take part in all the different stages of *The People's Trial* using online software to identify people's

opinion. We ask if people participating are a health care professional or researcher, which country they are from, their gender and their age range because we would like to have a diverse group of people from different backgrounds taking part in the People's Trial. This helps us check how successful this has been.

Under what legal basis are we collecting this information?

We are collecting and storing this personal identifiable information in accordance with data protection law which protect your rights. These state that we must have a legal basis (specific reason) for collecting your data. For this study, the specific reasons are "consent" which is "freely given, specific, informed and unambiguous" and "a public interest task". We will collect the minimum amount of personal data required to carry out the research.

What are my rights in relation to the information you will collect about me?

You have a number of rights under data protection law regarding your personal information. For example you can request a copy of the information we hold about you. If you would like to know more about your different rights or the way we use your personal information to ensure we follow the law, please consult the NUI Galway Data Protection Website https://www.nuigalway.ie/data-protection/

Will my participation in the study be confidential and my personal identifiable information be protected?

In accordance with data protection law, NUI Galway is the Data Controller for this project. This means that we are responsible for making sure your personal information is kept secure, confidential and used only in the way you have been told it will be used. All researchers are trained with this in mind, and your data will be looked after in the following way:

Only the Principle Investigator and co- investigators at NUI Galway will have access to your personal information, but they will anonymise it as soon as possible using a unique identifier code. Your name and any other identifying information will be removed and replaced with a random ID number. Only the research team will have access to the key that links this ID number to your personal information. All data collected during the study will be securely stored in NUI Galway under the stewardship of the Lead Investigator and destroyed after a period of 7 years.

Please also note that individuals from NUI Galway or regulatory authorities may need to look at the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data. All individuals involved in auditing

and monitoring the study will have a strict duty of confidentiality to you as a research participant.

What will happen to the findings of this study?

The results of the study will be published in a scientific journal regardless of the findings. You will not be identified in any report or publication.

Compensation

No payments are available for taking part in this study. Nothing in this document restricts or curtails your rights.

Has this study received ethical approval?

Yes, this study has received ethical approval from the following research ethics committee; NUI Galway, University Road, Galway, Ireland.

Who is funding the research project?

The People's Trial is a Health Research Board (HRB, Ireland) funded project based within the HRB Trials Methodology Research Network (HRB-TMRN)

What if there is a problem?

If you have a complaint that you wish to direct to members of the research team, please contact:

The People's Trial research team,
School of Nursing & Midwifery, Room 235, Aras Moyola, NUI Galway, Galway H91 E3YV, Ireland info@thepeoplestrial.ie

If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact:

Vice-President for Research, School of Natural Sciences, National University of Ireland, Galway. Tel: +353 91 495768 or by emailing: vpresearch@nuigalway.ie

If you wish to contact us about your data protection rights, please email: dataprotection@nuigalway.ie or write to The Data Protection Officer, NUI Galway, Room A129, The Quadrangle, NUI Galway, University Road, Galway, Ireland and we will guide you through the process of exercising your rights.

You also have a right to complain to the Office of the Information Commissioner (https://www.oic.ie/) about complaints relating to your personal identifiable information: Tel +353 1 639 5689

Appendix 20.

Paper 4: Participant Information leaflet -The Reading Trial

Study information for *The People's Trial:* a randomised controlled trial

You are being invited to take part in a study evaluating **the effect on sleep of reading a book in bed**.

It is important for you to understand why the research is being conducted and what it will involve.

Please read the following information carefully before deciding whether to take part and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information.

Title of study: Citizen Science: The People's Trial

Who will conduct the research?

The study that you are invited to participate in will take place online and is scheduled to commence on Tuesday 3rd December at 09.00.

What is the purpose of the study?

This study wants to help enhance the public's understanding of randomised trials by facilitating the involvement of the public in an online, virtual trial.

In designing this trial, we involved the public in all phases of the research process. This included the submission of common, fun, low-risk questions as the potential research question. Public participants were then invited to prioritise the submitted questions.

Through this process, the public told us that they wanted to try to answer the question:

Does reading a book in bed make a difference to sleep in comparison to not reading a book in bed?

The research team determined, through a thorough review of the literature, that this question has not been answered previously. The public then made decisions around what 'reading a book in bed' (the intervention) and 'not reading a book in bed' (the comparator) actually meant and how we would measure the outcome 'sleep'.

Why have I been chosen?

You are eligible to take part in this study if you are over 18 years of age. Due to the unavailability of translational services, you must also have a competent level of fluency in English to take part in the study.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you choose to take part, you will be asked to indicate your consent on an online consent form, and you should keep this leaflet. You are still free to withdraw at any time and without giving a reason.

What does taking part involve?

If you are happy to take part in the study, you will be asked to indicate your consent on an online consent form. You will then be directed to a website which will allocate you to either the *reading a book in bed* group or the *not reading a book in bed* group.

If you are allocated to the reading a book in bed group, you will be asked to read a book for 15 to 30 mins in bed immediately before trying to go to sleep each day for one week. If you are allocated to the **not** reading a book in bed group, you will be asked to not read in bed for one week.

The decision about which group you would go into will be made by chance, rather like the toss of a coin. This is important because it ensures that reading a book in bed can be tested fairly.

If you take part, you will also be asked to complete a short questionnaire at the beginning of the trial and two short questionnaires at the end of the trial. The questionnaires take about 2-3 minutes each to complete.

Where and when will *The People's Trial* take place?

The People's Trial will take place online and is scheduled to commence on Tuesday 3rd December at 09.00. You may register to take part in *The People's Trial* anytime up until the 31st December at 17.00.

Are there any benefits or risks to me taking part?

Your participation will benefit you as *The People's Trial* will create a safe, respectful space online for you to learn about randomised trials.

No physical risks are associated with participating in this study. Although it is not anticipated that any participants will suffer emotional disruption, in the unlikely event that this does occur, you may contact a member of the research team.

Voluntary participation

Participation is entirely voluntary, and you have the right to withdraw from the study at any time. You will not be expected to give any reason for your decision. However, it will not be possible to remove your data from the project once it has been coded as we will not be able to identify your specific data. This does not affect your data protection rights.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether or not to take part. If you choose not to take part, you do not need to do anything further.

Confidentiality

Your identity will remain confidential. All data will be coded, meaning that your name will not be published, and it will not be disclosed. All data retrieved from *The People's Trial* will be stored securely in the National University of Ireland, Galway and destroyed after 7 years following the National University of Ireland, Galway Data Retention Policy. Also, *The*

People's Trial has undergone a NUI Galway Data Protection Impact Assessment (DPIA) to ensure compliance with NUI Galway Data Protection Policies and Procedures.

The National University of Ireland, Galway or regulatory authorities may need to look at the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data. All individuals involved in auditing and monitoring the study will have a strict duty of confidentiality to you as a research participant.

What will happen to the findings of this study?

The *People's Trial* aims to enhance the public's understanding of all aspects of randomised trials. As the publication of trial findings is an integral part of the research, we will involve the public in designing the dissemination strategy for *The People's Trial*.

Also, the results of the study will be published in a scientific journal, regardless of the findings. You will not be identified in any report or publication.

Compensation

This study is covered by standard institutional indemnity insurance. No payments are available for taking part in this study. Nothing in this document restricts or curtails your rights.

Has this study received ethical approval?

Yes, this study has received ethical approval from the following research ethics committee;

National University of Ireland, Galway Research Ethics Committee

Research Office

Room 212

Research and Innovation Centre

NUI Galway

Tel: 353 91 495312

Who is funding the research project?

The Health Research Board, Ireland, is funding the research.

Is there someone available to answer any questions that I may have about taking part?
Yes. You can get more information about the study, your participation in the study and your rights by contacting the research team. Contact details are as follows;
The People's Trial
The National University of Ireland,
Aras Moyola,
Room 235
NUI Galway
Email: thepeoplestrial@nuigalway.ie

Contact details for complaints

If you have a complaint that you wish to direct to members of the research team, please contact:

The People's Trial
The National University of Ireland,
Aras Moyola,
Room 235
NUI Galway
Email: thepeoplestrial@nuigalway.ie

If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance, then please contact:
Vice-President for Research, School of Natural Sciences, National University of Ireland, Galway. Tel: 353 91 495768 or by emailing: vpresearch@nuigalway.ie
If you wish to contact us about your data protection rights, please email: dataprotection@nuigalway.ie or write to The Data Protection Officer, NUI Galway, Room A129, The Quadrangle, NUI Galway, University Road, Galway and we will guide you through the process of exercising your rights.

You also have a right to complain to the Office of the Information Commissioner

(https://www.oic.ie/) about complaints relating to your personal identifiable information:

Tel (01) 639 5689

Appendix 21.

Paper 3: Ethical Approval – The People's Trial

Research Ethics Committee Decision Report

REC Application Reference Number: 19-Mar-09
Title: Citizen Science: The People's Trial
Principle Investigator: Declan Devane
Application Type: NEW
Meeting Date: 12 March 2019

NOTIFICATION OF REC DECSION

25 March 2019

Dear Professor Devane,

The Research Ethics Committee (REC) reviewed the above application at our most recent meeting. Following a detailed discussion, the Committee's decision regarding the application was FULL APPROVAL.

FULL APPROVAL (Application is approved without further revision)

No ethical issues were identified.

When the decision was taken I was chairing the meeting and the following members were also present:

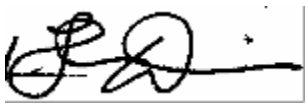
Dr Linda Biesty	Dr Gordon Bromley	Dr Cormac Forkan
Dr Caroline Heary	Dr Victoria Hogan	Dr Marcella Kelly
Dr Martina Kelly	Dr Marie Mahon	Dr Veronica McCauley
Dr Derek Morris	Dr Stacey Scriver	Dr Ioanna Tourkochoriti
Mr Patrick Towers	Dr Jane Walsh	Dr Evan Yacoub

All NUI Galway Research Ethic Committee approval is given subject to the Principal Investigator submitting annual and final statements of compliance. The first statement is due on or before 24 March 2020.

Annual and final statements of compliance forms are attached below. Section 7 of the REC's Standard Operating Procedures gives further details, and also outlines other instances where you are required to report to the REC.

If you have any questions regarding the Committee's decision and follow-up procedure, please email ethics@nuigalway.ie, including the reference number of your application.

Yours sincerely



Kevin Davison

Chair, Research Ethics Committee

Research Ethics Committee Decision Report

REC Application Reference Number: 19-Mar-09
Title: Citizen Science: The People's Trial
Principle Investigator: Declan Devane
Application Type: NEW
Meeting Date: 12 March 2019

Please note the following important points in regard to ACREC review of research proposals:

- Applicants must adhere fully to the approval decision, conditions or contingencies specified by the REC.
- The researcher must not commence data collection until FULL APPROVAL has been granted.
- Applicants must ensure that the research is not extended, modified, or altered in any way without obtaining prior approval for such amendments from the REC.
- It is the sole responsibility of the applicant to comply with all the Irish and European Law relating to research.
- Neither the University nor the REC or its individual members accept legal liability for any advice or assistance offered to the applicant or to any third party in the processing of the application or the carrying out of the research.
- As a minimum, the REC will require an annual statement of compliance from the Principal Investigator, but the Committee can agree to more frequent reporting at the time of approval.