A pilot RCT on the management of term prelabour rupture of membranes

by

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Abstract in English

Background

About 10% of women experience term pre-labour rupture of membranes. Since it is believed that the risk of infection to mother and baby increases once the membranes are ruptured, two options are considered: (1) Inducing labour soon after the rupture of membranes (active management), and (2) Watchful waiting for spontaneous labour while monitoring maternal and fetal wellbeing (expectant management). There is controversy as to which one is associated with higher rates of normal birth and less infection. Further evidence shows that the number of vaginal examinations is one of the strongest correlators of chorioamnionitis.

Objective

To develop and pilot test the protocol for an RCT on expectant management and minimal vaginal examinations for term prelabour rupture of membranes.

Methods

Firstly, a systematic review on expectant management and the effect of vaginal examinations was carried out. Secondly, consultations with women, clinicians, and managers took place. Simple thematic analysis was undertaken, and the results informed the study protocol. A pilot RCT was then conducted. Women were allocated to the following groups: 1) Expectant management and minimal vaginal examinations, 2) Expectant management and routine vaginal examinations, 3) Active management and minimal vaginal examinations and 4) Active management and routine vaginal examinations during labour. Low vaginal swabs were taken before the first vaginal examination and after every examination to assess for the presence of exogenous bacteria. Women who were eligible to take part in the RCT but declined, were offered participation in an observational study that involved routine clinical practice to aid sample size calculation for the main study. The acceptability of the interventions in the RCT was

assessed with the Childbirth Experience Questionnaire (CEQ) and 10 study-specific questions.

Results

The systematic review revealed that there is no prior RCT on both expectant management and minimal vaginal examinations during labour. Stakeholder input was crucial in the development of the study protocol. There were 85 eligible women, of those 51% (n=43) took part in the pilot RCT, 40% (n=34) took part in the observational study, and 9% (n=8) did not take part in either. There were 33 (80.5%) questionnaires returned. No safety issues were encountered and the interventions were acceptable to women.

Conclusion

The results from the systematic review and the pilot RCT suggest that a definitive study in this area, using the protocol developed during this study, is needed, feasible, and acceptable to women.

Resumen en Español

Introducción

Aproximadamente, el 10% de las mujeres experimenta rotura prematura de membranas. Se cree que el riesgo de infección para la madre y el recién nacido aumenta una vez que se ha producido la rotura de membranas; por lo tanto, se consideran dos opciones: 1) Inducir el parto poco después de la rotura de membranas (manejo activo) o 2) Esperar a que el parto se inicie espontáneamente y de manera natural mientras se observa el bienestar materno-fetal (manejo expectante). Existe controversia sobre qué tipo de manejo está relacionado con una mayor proporción de partos normales y menor proporción de infeccion. Existe evidencia científica que muestra que existe una gran correlación entre el número de exploraciones vaginales realizadas y el desarrollo de la corioamnionitis.

Objetivo

Desarrollar el protocolo y prueba piloto para un ensayo clínico controlado y aleatorizado (ECCA) sobre el manejo expectante y el mínimo número de exploraciones vaginales para la rotura prematura de membranas.

Métodos

En primer lugar, se llevó a cabo una revisión sistemática de la literatura sobre el manejo expectante y los efectos de las exploraciones vaginales. A continuación, se organizaron grupos de discusión para consultar y hacer partícipe a las mujeres, personal clínico y gerentes en el desarrollo del protocolo. Se realizó un análisis temático simple y los resultados sirvieron para informar el protocolo del estudio. Después se llevó a cabo un ECCA piloto. Las mujeres que tomaron parte en el estudio, fueron asignadas de manera aleatoria a los siguientes grupos: 1) Manejo expectante y mínimas exploraciones vaginales, 2) Manejo expectante y exploraciones de manera rutinaria, 3) Manejo activo y mínimas exploraciones vaginales y 4) Manejo activo y exploraciones vaginales de manera

rutinaria. Se tomaron muestras vaginales (hisopos) antes de la primera exploración vaginal y después de cada exploración vaginal para evaluar la presencia de bacterias exógenas.

Las mujeres que cumplían con los criterios de inclusión pero que rechazaron participar en el ECCA piloto, se les ofreció tomar parte en un estudio observacional que consistía en el manejo rutinario del hospital con el objetivo de ayudar a calcular el tamaño muestral del futuro estudio principal. La aceptabilidad de las intervenciones del ECCA fue evaluada a través del cuestionario CEQ (Childbirth Experience Questionnaire) y 10 preguntas específicas del estudio.

Resultados

La revisión sistemática de la literatura reveló que no se ha llevado a cabo ningún ECCA sobre el manejo expectante y mínimas examinaciones vaginales durante el parto. La contribución de las partes interesadas fue crucial en el desarrollo del protocolo del estudio. Hubo 85 mujeres que cumplieron con los criterios de inclusión, de ellas, el 51% (n=43) tomo parte en el ECCA piloto, un 40% (n=34) tomó parte en el estudio observacional, y un 9% (n=8) no tomó parte en ninguno de los estudios. El 80.5% (n=33) de las participantes en el ECCA completó y envió el cuestionario. El estudio ECCA piloto resultó ser seguro, y las intervenciones realizadas fueron aceptables para las mujeres.

Conclusión

Los resultados de la revisión sistemática y del estudio ECCA piloto sugieren que un estudio definitivo en este área, utilizando el protocolo desarrollado durante este doctorado, es necesario, factible y aceptable para las mujeres.

Résumé en Français

Introduction

Environ 10% des femmes font l'expérience d'une rupture prématurée des membranes à terme. Puisque l'on croit que le risque d'infection pour la mère et le bébé augmente une fois que les membranes se rompent, deux options sont envisagées : (1) L'induction du travail peu de temps après la rupture des membranes (attitude agressive), et (2) l'attente vigilante d'un travail spontané tout en surveillant le bien-être maternel et fœtal (attitude expectative). Il y a controverse quant à savoir laquelle est associée à des taux plus élevés de naissance normale et une moindre infection. Des recherches supplémentaires montrent que le nombre d'examens vaginaux est un des plus forts corrélateurs de chorioamniotite.

Objectif

Développer et tester dans le cadre d'un essai pilote un protocole pour la création d'un ERC (essai randomisé contrˆôlé) dans le cadre de l'attitude expectative et d'un nombre minimal de touchers vaginaux menant à la rupture prématurée des membranes à terme.

Méthodes

En premier lieu, une revue systématique de l'attitude expectative et de l'effet de touchers vaginaux a été menée. Deuxièmement, des consultations avec des femmes, cliniciens, ainsi que de cadres supérieurs de l'hôpital où a été mené l'essai pilote, ont eu lieu. Une simple analyse thématique a été entreprise, et les résultats ont apporté les données nécessaires au développement du protocole pour l'ERC. Ensuite, un ERC pilote a été mené. Les femmes étaient réparties dans les groupes suivants : (1) Attitude expectative et nombre minimal de touchers vaginaux; (2)Aattitude expectative et nombre de touchers vaginaux de routine; (3) Attitude agressive et nombre minimal de touchers vaginaux; et (4) Attitude agressive et touchers vaginaux de routine pendant le travail. Des prélèvements du vagin inférieur ont été pris avant le premier

toucher vaginal et après chaque toucher vaginal pour évaluer la présence de bactéries exogènes. On a offert aux femmes, qui répondaient aux critères d'admission de l'ERC mais avaient refusé d'y participer, de prendre part à une étude observationnelle, qui incluait la pratique clinique habituelle pour aider le calcul de la taille de l'ERC de l'étude principale. L'acceptabilité des interventions dans l'ERC a été évaluée avec le questionnaire CEQ (Childbirth Experience Questionnaire) et 10 questions spécifiques à cette l'étude.

Résultats

La revue systématique a révélé qui il n'y a pas d'ERC en attitude expectative avec un nombre minimal de touchers vaginaux pendant le travail. La contribution des parties intéressées était cruciale pour le développement du protocole de l'étude. Il y avait 85 femmes qui répondaient aux critères d'admission, desquelles 51% (n=43) ont pris part à l'ERC, 40% (n=34) ont pris part à l'étude observationnelle, et 9% (n=8) n'ont pris part ni à l'un ni à l'autre. 33 questionnaires (80.5%) ont été rendus. Il n'y avait pas de problèmes de sécurité et les interventions de l'ERC étaient acceptables aux femmes qui ont particip´é `à cette étude.

Conclusion

Les résultats de la revue systèmatique et de l'ERC pilote montrent qu'une étude définitive dans ce domaine en appliquant le protocole élaboré au cours de cette recherche est nécessaire, possible et acceptable par les femmes.

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Glossary

AM: Active management

ARM: Artificial rupture of membranes

ATB: Antibiotics

BBA: Born before arrival

BMI: Body mass index (kg/m^2)

CASP: Critical appraisal skills programme

CTG: Cardio-toco-graph machine to record contractions and fetal heart rate

CEO: Chief executive officer

CS: Caesarean section

EBL: Estimated blood loss

EM: Expectant management

FHR: Fetal heart rate

GBS: Group B *streptococcus*, its scientific name is *Streptococcus agalactiae*

IOL: Induction of labour

IV: Intravenous

MESH: Medical subject heading

MLC: Midwifery led care

MLU: Midwifery led unit

NCT: National childbirth trust

NICE: National Institute for Clinical Excellence

NS: Not significant

OLC: Obstetric led care

PICO: Problem, intervention, control and outcome.

PIS: Participant information sheet

PPH: Post-partum haemorrhage

PPI: Patient and public involvement

PROM: Prelabour rupture of membranes

RCT: Randomised controlled trial

SROM: Spontaneous rupture of membranes

SSD: Statistically signicant difference

SVB/SVD: Spontaneous vaginal birth/delivery

VE: Vaginal examination

WHO: World Health Organisation

List of Definitions

BBA: Born before arrival. This is when a baby is born unattended, either at home before the arrival of the midwife (when a planned home birth), or en route to the maternity unit, for example in the car (when a birth in a maternity unit was planned).

Prelabour rupture of membranes at term: Spontaneous rupture of membranes in the absence of contractions at term (37-42 weeks gestation).

Latent phase: The period of time between the rupture of membranes and the onset of regular and strong contractions

Normal birth: A birth that is spontaneous in onset, that does not require augmentation, no ARM, no epidural, no episiotomy and baby is born spontaneously by maternal effort only.

Suspected clinical chorioamnionitis: Axillary temperature of 38°C or more in the absence of any other cause of pyrexia and 2 of the following:

- Maternal tachycardia: more than 100 bpm
- Foetal tachycardia: more than 160 bpm
- Uterine tenderness
- Foul smelling liquor
- White blood count/Leucocytosis: 16,000 cells/mm^3 or more

Confirmed chorioamnionitis: Clinical signs of chorioamnionitis and histopathologic findings in placenta

Suspected clinical neonatal infection: At least 2 of the following:

- Apnoea
- Temperature instability (less than 36°C or more than 38°C)
- Lethargy
- Feeding problems
- Signs of respiratory distress

Confirmed neonatal infection: Clinical signs of infection and positive blood cultures

Active first stage of labour: Regular and strong contractions at least 3 contractions in 10 minutes, that last for at least 60 seconds, and with a cervix dilation of at least 3cm.

Adequate uterine activity: 3-4 regular contractions in 10 minutes

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Chapter 1: Introduction

1.1 Introduction

This chapter presents the general topic, the management of prelabour rupture of membranes and scope of this thesis (the development, design and set up of a pilot RCT on the management of term prelabour rupture of membranes). In addition, it evaluates the current situation in maternity care, outlines the research question and the problem to be addressed, highlights the importance of this research and its contribution to knowledge.

This chapter also outlines the motivation of this study. A brief overview of the objectives, and the methods is also provided. Furthermore, it gives an overview of the structure of the thesis. The manuscript is divided into eight chapters, and a brief summary of each chapter is presented ahead.

1.2 Background

The incidence of induction keeps rising, increasing in England from 20.4% in 2007-2008 to 32.6% in 2017-2018 (NHS Digital, 2018). Prelabour rupture of membranes at term is a common cause for routine induction of labour due to national guidelines' recommendations (NICE, 2017). The spontaneous rupture of membranes (SROM) at term is a normal physiological event that most of the time happens during labour or it happens before but it is followed by uterine contractility and the onset of labour quickly afterwards. However, according to Hannah et al. (1996), in 8% of term pregnancies, the membranes rupture and labour commences later within the next few hours or days. Ottervanger, Keirse, Smit, and Holm (1996) explain that the incidence of this event can vary from 6-19% of term pregnancies, depending on the population studied,

the latent period required to be considered prelabour rupture of membranes and on what gestational age is considered to be term. Despite the frequency of this event, its management remains a controversial issue in current practice. Historically, it is commonly believed that when the membranes rupture there is an increased risk of infection (Shubeck et al., 1966). However, intact membranes and normal amniotic fluid do not fully protect the fetus and the mother from infection, as the risk of infection for both mother and baby is still present, and it is estimated to be approximately 0.5 % (NICE, 2017). One of the issues with intervening to reduce the possibility of infection is that such interventions might limit the potential for women and babies to experience the short and longer-term benefits of spontaneous labour and birth. The features of labour that are deemed to be normal are, to an extent, socially defined (Downe, 1996). Therefore, prelabour rupture of membranes is either seen as a high risk situation, or as a variation of normal labour, depending on the local labour philosophy. Downe (1996) explains that abnormality is becoming more often defined as a deviation from the average, with a potential or a risk for pathology rather than an actual problem/pathology. The "risk of abnormality/pathology" approach, labels women who deviate from the average, as "high risk", when in reality this could be physiologically normal for her.

The increased medicalisation of pregnancy and birth in our current maternity care system, often interferes with the physiological process, and in doing so, may introduce unncessary risks for healthy mothers and babies (Romano & Lothian, 2008). The consequence of this approach is that women may no longer have the confidence in their ability to go into spontaneous labour and give birth naturally, as Romano and Lothian (2008) highlight. Therefore, it is crucial to question if a certain routine intervention is based on the most recent research evidence and why is happening and whether it is for the convenience of clinicians and the smooth running of the hospital or if in fact, it is in the best interest for women and babies (Romano & Lothian, 2008).

In addition, spontaneous labour is associated with higher maternal satisfaction than induction of labour (Shetty, Burt, Rice, & Templeton, 2005). Therefore, new studies aimed at providing women with more information and choices on how to manage certain situations in pregnancy and childbirth should be supported.
Government initiatives support the right of women to be informed and given choice during childbirth (Cumberlege, 2016; Department of Health, 1993; Department of Health, 2007).

1.3 The case for spontaneous labour and normal birth

Although the possibility of infection is generally seen as the main clinical outcome, the mode of birth is also a crucial outcome that should not be overlooked. This section aims to discuss the benefits of spontaneous labour and physiological birth and why it is one of the main outcome measures in this RCT.

Physiological birth matters for many psychological and social reasons that have been explored by Kitzinger (2006) and Humenick (2006) amongst others. Birth is a deeply touching experience, which is likely to influence how women feel about themselves, and it can have a profound impact in the mother-child relationship. Therefore, it is important that women have a positive and empowering experience. On the other hand, it is also important to consider that having a normal birth is not just important so women feel good about themselves and can look after children appropriately in the future. It is also important because having a physiological birth plays an important role into our biological and physical development as individuals and as a human species. The biological and clinical benefits of normal labour and birth have not been studied in a randomised controlled trial (Humenick, 2006). However, there are many studies that have shown the negative consequences of unnecessary interventions (Boulvain et al., 2001) and studies that aim to reduce the increasing rates of operative and instrumental births. It appears that the discourse so far is very much focused on interventions, either to reduce negative outcomes, such as for example stillbirth or to reduce caesarean sections rates (Walker et al., 2016). There seems to be a lack of studies, where the main outcome measure is "normal-physiological birth" and therefore, there are very few studies that have looked directly at the consequences of the mode of birth specifically. Perhaps because the positive consequences of the mode of birth are seen in the long term, we as a society give it less importance.

In contrast, growing literature on both the epigenetic and the microbiome consequences of labour and birth suggests that how babies are born may have long-term effects, and these issues are starting to receive more and more attention. Epigenetics changes include alterations to DNA molecules that do not change the sequence but do influence gene expression (Clark, Adamian, & Taylor, 2013). Researchers have begun to look more deeply at the process of birth and epigenetics. Recent studies have linked mode of

birth, and in particular caesarean section to increasing rates of asthma, eczema, Type 1 diabetes, infant bronchiolitis, multiple sclerosis and obesity (Cardwell et al., 2008; Dahlen et al., 2014; Hyde et al., 2012). In addition, the mode of birth also plays a part in the development of the microbiome in the infant. Dominguez-Bello et al. (2010) found different types of microbiomes depending on the type of birth of the newborn.

There is some controversy as to what is understood by a physiological birth, also commonly known as "normal birth". The World Health Organization (1996), in page 4, defined normal birth as: "*spontaneous in onset, low-risk at the start of labour and remaining so throughout labour and delivery. The infant is born spontaneously in the vertex position between 37 and 42 completed weeks of pregnancy. After birth mother and infant are in good condition*". The definition developed by WHO includes by definition a birth that might include some interventions such as augmentation, the use of epidural and opioids and artificial rupture of the membranes (ARM).

Beech (1997), chair of AIMS (The Association for Improvements in Maternity Services), suggested a different definition that excluded augmentation, opioids and ARM (artificial rupture of membranes). Beech (1997) published a paper that highlighted the degree of disagreement that exists as to how normal birth should be defined. For example, many would say that any birth that didn't require a caesarean section, forceps or ventouse, was a normal birth, regardless of the interventions needed, whereas others would understand by normal birth something different, a birth that happens physiologically without the need of interventions. That paper also noted that very few women experienced a physiological birth by this definition, in contrast to reported "normal birth" rates of more than 70% in the UK.

Therefore, given the lack of agreement on the definition for normal birth, in 2007, the Royal College of Midwives, Royal College of Obstetricians and Gynaecologists, and the National Childbirth Trust, set up a Maternity Care Working Party to establish a consensus statement (Maternity Care Working Party, 2007).

In this document, a definition for "normal delivery" was agreed with the aim of having a working definition to be able to audit "normal delivery" rates and make comparisons. The maternity care working party agreed on the following definition: "*women whose labour starts spontaneously, progresses spontaneously without drugs, and who give birth spontaneously*"(Maternity Care Working Party, 2007, p. 3). This definition was seen as a step forward for some maternity groups, even though labours and births with

interventions such as augmentation of labour, opioids, and artificial rupture of membranes (ARM) could be termed a "*normal delivery*" under its criteria. This thesis uses a definition of normal birth that excludes interventions such as augmentation either by drugs or mechanically by artificially rupturing the membranes (ARM) and epidural or opioids. This is because it is important to have a definition that truly reflects a physiological process where birth takes places spontaneously. There is a list of all the definitions being used in this thesis on page 21.

1.4 Motivation for this Study

Clinical practice and research form a synergistic relationship, where they inform each other (Stricker & Keisner, 1985). This is further emphasised in the evidence base practice movement initiated by Cochrane (1972). During my career as a clinical midwife, I worked in the community providing continuity of care to a small group of women, also called caseloading. The women I looked after were either under the age of 16, or were booked to have their babies at home. The inspiration for this study came from my experience with the latter. I encountered several women who had broken their membranes (their waters in lay terms) before the labour started and were keen to have the baby at home and avoid the induction. In providing them with evidence based information so they could make informed decisions, I had to search for the latest evidence in regards to the management of prelabour rupture of membranes. Therefore, I found out what the national guidelines (NICE, 2017) recommended as well as the results from the TERMPROM trial conducted by Hannah et al. (1996) and the latest Cochrane systematic review at the time. Several women in my caseload opted for expectant management, which resulted in normal births with no complications. These experiences deeply inspired me to commence this PhD. I realised that the latest big study on the matter was carried out more than 20 years ago, and that it would be beneficial to revisit this clinical situation and carry out a new RCT with a fresh approach.

1.5 The Scope of this Thesis

Because of the lack of data on expectant management, minimal vaginal examinations and women being monitored and visited at home as a bundle of care for prelabour

rupture of membranes, it is unknown the effectiveness and efficacy of these interventions. A randomised controlled trial is the gold standard method to assess the efficacy and effectiveness of an intervention in health care (Cochrane, 1972). In order to conduct an excellent and well designed RCT, a series of steps need to be undertaken prior to the main trial. This thesis presents the development, design and set up of a pilot RCT on expectant management and minimal vaginal examinations for the management of prelabour rupture of membranes at term.

The randomised controlled trial (in its main phase) will assess the efficacy and effectiveness of these interventions, and it will aim to answer the question of what type of management is associated with higher rates of normal birth and less infection for the mother (chorioamnionitis).

However, since the scope of this thesis is the development, design and pilot testing of the protocol for the future main trial. This thesis addresses a different set of research questions. Why this research is necessary? Has it been done before? Will women take part and engage in such study? Will clinicians engage in this study if carried out at big scale? Does the protocol work as a whole? Is it safe?

Running a full scale RCT is a very expensive and time consuming undertaking. As with many PhD studies, the work undertaken for this thesis was conducted on self-funding basis with minimal resources, and within a set time-limit, therefore there were some obvious limitations in terms of access to resources, such as translators, laboratory technicians, and formal research support in the hospital that hosted the study. The thesis reports on the pilot stage of the study, as the basis for obtaining full funding for a definitive RCT in the future.

The next sections in this chapter outline the unique contribution to knowledge of this PhD, how this thesis is structured and what can be found in each chapter.

1.6 Unique contribution to knowledge

This thesis has made several contributions to knowledge, with the first one being the importance of the research question. Why is it important to look at what type of care we provide to women who break their waters but do not go straight away into labour? Why is it worth looking at all the components that are related or that contribute to the management of prelabour rupture of membranes at term? There have been several studies published before that looked at the timing for the induction of labour or what procedures or drugs to use for the induction of labour. However, this research goes a step further and apart from comparing active management (induction at approximately 24 hours) vs Expectant management (induction of labour at approximately 96 hours while women staying at home and receiving home visits by a midwife) it goes beyond and compares what happens when we do routine 4-hourly vaginal examinations vs an approach to minimise vaginal examinations.

Secondly, the systematic review revealed that no previous studies had been published before that compared expectant management and minimal vaginal examinations for term prelabour rupture of membranes. Although a Cochrane systematic review has been published recently by Middleton, Shepherd, Flenady, McBain, and Crowther (2017), it did not include the intervention of vaginal examinations in the searches in combination with the management (active vs expectant).
In addition, the systematic review presented in this thesis, also looked at observational studies and whether normal/physiological birth was used as a primary outcome in any of the studies. Therefore, the systematic review presented in this thesis constitutes one of the main elements of originality and contributions to knowledge.

Nevertheless, the main contribution to knowledge of this thesis is the development and pilot testing of a study protocol for a randomised controlled trial (RCT) on expectant management, and minimal vaginal examinations.
Several studies have compared expectant management with active management in the past, however, this thesis proposes a new approach to the management of term prelabour rupture of membranes, in the form of a bundle of care, that is the combination of expectant management, home visits for monitoring maternal and fetal wellbeing and an approach of minimal vaginal examinations. The TERMPROM trial that was carried out by Hannah et al. (1996), whose primary outcome was neonatal infection

and main secondary outcome was caesarean section, looked at expectant management up to 96 hours, and did some sub-analysis on the number of vaginal examinations. However, the pilot RCT presented on this thesis compares expectant management up to approximately 96 hours and an approach of minimal vaginal examinations as an intervention. In addition, the primary outcomes in the study presented in this thesis were also unique in the context of term prelabour rupture of membranes trials, there were two, instead of just one as it normally occurs and these are normal-physiological birth and chorioamnionitis.

The use of normal-physiological birth as a primary outcome also constitutes one of the elements of originality because it has not been used before in this context (Term prelabour rupture of membranes) and it sets a precedence for future clinical trials to use normal-physiological birth as primary outcome, instead of caesarean section, when looking at the mode of birth.
In addition, although similar definitions for normal-physiological birth have been already stated in the past (Beech, 1997), this study sets a precedence of using it in the context of a clinical trial in the management of prelabour rupture of membranes, because this could inspire other researchers to use it in future studies.

1.7 Structure of the Thesis

This thesis is divided into 8 chapters, with chapter 1 being this introduction. This is followed by chapter 2 (Background chapter). This chapter provides a standard scoping review of the relevant literature. It also outlines the nature and consequences of prelabour rupture of membranes at term, and of the current literature regarding the variation in current practice in the management of prelabour rupture of membranes at term.

Chapter 3: (Systematic reviews) - In this chapter an in-depth systematic review of the management of term prelabour rupture of membranes is presented. This chapter describes and discusses the complex process followed for the systematic, followed by the results obtained and a discussion of the findings from the studies that were included. It also highlights the gap that this study intends to cover.

Chapter 4 (Developmental phase) - This chapter describes the process that was followed to involve women and clinicians in the development of the study protocol. It also

discusses the findings from the discussion groups with women and clinicians and the changes made in the protocol based on their input.

Chapter 5 (Methods) - This chapter outlines the study protocol that was used for the pilot RCT following the SPIRIT criteria set by Chan et al. (2013), as well as for the observational study.

Chapter 6 (Findings) - This chapter presents the findings from the observational study and the pilot RCT are provided in this chapter. Statistical analysis was performed on the variables collected to assess the fidelity to the protocol, the clinical results. The acceptability of the study and its interventions was assessed with a questionnaire that was sent to women.

Chapter 7 (Microbiology) - It presents the rationale for taking and analysing the low vaginal swabs taken from the participants in the pilot RCT, the rationale for choosing the bacteria to test against in this pilot RCT followed by the results obtained and a brief discussion.

Chapter 8 (Discussion) - In this chapter a key summary of the findings is presented in order to answer or address the research question. In addition, the strengths and limitations of the study are shown and discussed, followed by some recommendations for future research, and future practice.

1.8 Conclusion

The incidence of induction of labour keeps rising, increasing in England from 20.4% in 2007-2008 to 32.6% in 2017-2018 (NHS Digital, 2018). Prelabour rupture of membranes at term is a common cause for routine induction of labour due to national guidelines' recommendations (NICE, 2017). However, the last clinical trial with enough statistical power on this topic is more than 20 years old (Hannah et al., 1996), and antibiotics and induction procedures have evolved since. The problem of a routine induction of labour due to prelabour rupture of membranes is that it limits the possibility of experiencing a normal labour and birth and its benefits. Furthermore, spontaneous labour is associated with higher maternal satisfaction than induction of labour (Shetty et al., 2005).Therefore, new studies aimed at providing women with more information and choice should be supported. Government initiatives support the right of women

to be informed and given choice during childbirth (Cumberlege, 2016; Department of Health, 1993; Department of Health, 2007). It is deemed that this study, in its main phase, will be able to provide more quality evidence to allow women to make informed choices about their pregnancy and birth in the presence of prelabour rupture of membranes. The present thesis presents the process that was followed to develop and pilot test the research protocol for a future main study on the management for prelabour rupture of membranes. The next chapter gives a general scoping overview of the relevant literature around prelabour rupture of membranes and the impact of vaginal examinations.

Chapter 2: Background

2.1 Introduction

The previous chapter stated the topic of this research, gave an overview of the current situation in maternity care and outlined the research question and the problem that this program of research aims to address. This chapter provides a standard scoping review of the relevant literature. It begins with some basics in anatomy, physiology and microbiology that are fundamental to understand the nature of the event, and potential consequences for women and neonates. It also outlines the nature and consequences of prelabour rupture of membranes at term, and of the current literature regarding the variation in current practice in the management of prelabour rupture of membranes at term. An in-depth systematic review of the management of term prelabour rupture of membranes has been undertaken and it is presented in next chapter.

2.2 Basics on anatomy, physiology and microbiology

Amniotic fluid is produced continuously due to the passage of fluid across the membranes (chorion and amnion), across the fetal skin, fetal urine production, and fetal pulmonary effluent since very early in the pregnancy. Amniotic fluid has multiple properties, provides protection against infection, and cord compression and protects the fetus from trauma. It also allows the fetus to move and breath, which is very important for its development. Figure below 2.1 on page 37 provides a graphical representation of the membranes (amnion and chorion).

The spontaneous rupture of membranes (SROM) at term is a normal physiological event that most of the time is followed with uterine contractility and the onset of labour. However, according to Hannah et al. (1996), in 8% of term pregnancies, the membranes

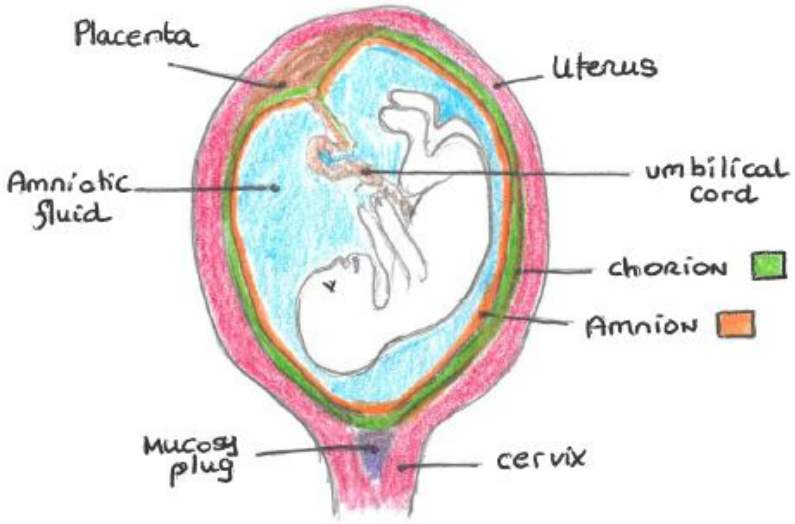


Figure 2.1: Fetal membranes (amnion and chorion) drawn by L. Ramirez-Montesinos

rupture before labour starts. Ottervanger et al. (1996) explain that the incidence of this event can vary from 6-19% of term pregnancies, depending on the population studied, the latent period required to be considered prelabour rupture of membranes and on what gestational age is considered to be term. Despite the frequency of this event, its management remains a controversial issue in current practice. Historically, it is commonly believed that when the membranes rupture there is an increased risk of infection (Shubeck et al., 1966). However, intact membranes and normal amniotic fluid do not fully protect the fetus and the mother from infection, as the risk of infection for both mother and baby is still present, and it is estimated to be approximately 0.5% (NICE, 2017).

Microorganisms are living entities that are too small to be seen by the naked eye without a microoscope. Microorganisms include bacteria, fungi and protozoa. Two other organisms are also considered microorganisms, these are viruses (which are not true living organisms) and helminths (parasitic flukes, round and flat worms which many can be seen by the naked eye (Wilson & Stucke, 2000). Some microorganisms are harmful to humans. However, many are not. The term "normal microbial flora" or "microbiota" refers to the population of microorganisms that inhabit the skin and

mucous membranes of healthy human beings (Brooks, Butel, & Morse, 2006). Up to the late 1960's, living organisms were classified into two kingdoms, the animal kingdom and the plant kingdom. At that time microorganisms were placed into the plant kingdom, hence the term "flora".Whittaker (1969) proposed that the categorisation should have five kingdoms, and microorganisms should have their own kingdoms. Therefore, the term "microbiota" is more appropriate, since microorganisms are no longer considered plants. The skin and mucous membranes have a variety of microorganisms that can be divided into 2 groups (Brooks et al., 2006). The resident microbiota consists of relatively fixed types of microorganisms regularly found in a certain area of the body, which if disturbed, it quickly re-establishes itself. The transient microbiota consists of both non-pathogenic and potentially pathogenic microorganisms that inhabit the skin or mucous membranes for hours, days or weeks without causing disease, and without establishing permanently. Members of the transient flora are generally of little significance as long as the permanent flora remains intact. However, if the resident flora gets disturbed, the transient microorganisms may colonise, proliferate and produce disease (Brooks et al., 2006). The microorganisms that are constantly present in body surfaces or mucous membranes are termed commensals (Brooks et al., 2006).

Romero et al. (2014) explain that the bacterial communities in the human vagina form a finely balanced mutualistic association. The degree to which they flourish in a given depends on physiologic factors such as temperature, moisture, the presence of certain nutrients, the relative acidity of the environment and so on. The resident microbiota of certain areas plays a crucial role in maintaining health and normal body functions. For example, members of the resident microbiota in the gut synthesize vitamin K or help with the absorption of nutrients, whereas in the vagina and genital tract, members of the resident flora such as Lactobacillus spp. create and maintain a relatively acid pH (pH<4.5), that helps to inhibit the growth of potential pathogens. Recent studies have revealed that a healthy microbiota hosts a surprisingly complex assemblage of microorganisms (Kim et al., 2009). These can be both aerobic and anaerobic, with *Lactobacilli spp.* being the predominant microorganisms found in a healthy vagina and cervix (Vasquez et al., 2002; Borges et al., 2014). As noted above, lactobacilli are beneficial because they can produce and tolerate high acidity (pH< 4.5), and this acidity limits the growth of other potentially pathogen bacteria. If *Lactobacillus spp.* are suppressed by the administration of antibiotics, antimicrobial drugs, antiseptics, etc, it can cause inflammation and irritation in the vagina and perhaps allow potential

pathogens to colonise the vagina. Recent studies conducted by Kim et al. (2009) have found that the vaginal microbiota is more heterogeneous than previously thought. They found that some groups of women had the traditional microbiota dominated by *Lactobacillus Spp.*, however there were other groups of women that had lower numbers of *Lactobacillus spp.* and had high numbers of *Pseudomonas spp.*

Most of the research in this area has studied the vaginal microbiota in non-pregnant women, therefore Romero et al. (2014) conducted a prospective longitudinal cohort study to characterize the changes in the composition of the vaginal microbiota of women with a normal pregnancy who were followed longitudinally during their pregnancy. The control group was non-pregnant women who were frequently sampled and also followed up. Romero et al. (2014) found that the normal microbiota of pregnant women is different from that of non-pregnant women and that the vaginal microbiota is more stable during pregnancy than in non-pregnancy states. They suggest that changes in the microbiota are a consequence of the physiological state of pregnancy. During the course of the menstrual cycle, stability of microbial communities is higher at the time when estrogen concentrations are high (14-21days) and even higher during pregnancy. This has been attributed to the effect of estrogens in the maturation of the vaginal epithelium, resulting in the accumulation of glycogen on the upper layer of the epithelium. Glycogen is a carbon source that can be metabolized into lactic acid by *Lactobacillus spp.* hence producing the low pH.

It has also been demonstrated that the precise make-up of the human vaginal microbiota is unique for each individual (Romero et al., 2014; Ravel et al., 2011). It is also known that the cervical mucus (mucosy plug) has antibacterial activity and contains lysozyme that prevents microorganisms from getting into the uterus (Brooks et al., 2006).

2.3 Management of prelabour rupture of membranes

In this section, a scoping review in chronological order of the literature on the management of this situation in relation to infection is presented. It covers what has been published through the years since the very first studies carried out on this subject until the most recent ones, in an attempt to understand this phenomenon fully.

Active management of prelabour rupture of membranes (PROM) involves an elective birth usually by induction of labour near to the time of the rupture of membranes.

Expectant management involves "watchful waiting", close observation of the mother and fetus for signs of infection while waiting for the spontaneous onset of labour.

Mozurkewich (2006) in her literature review explains that the management of prelabour rupture of membranes (PROM) has been the subject of great debate since the 1950s. Shubeck et al. (1966) and Webb (1967) published the results from their observational reports stating that when expectant management was undertaken there was an increase in maternal and fetal/neonatal mortality. The results from these studies must be taken with caution as the case series included mixed populations of term and preterm pregnancies, therefore some of the adverse outcomes could have been due to prematurity rather than infection. It should also be considered that some of those adverse outcomes could have been due to the methods used in the 1960s to accelerate or induce labour and also the lesser availability of antibiotics.

Mozurkewich (2006) also points out that microbiology during the 1960's could have been different to the current microbial milieu. Interestingly in the 1960's the majority of the reported deaths resulted from maternal sepsis related to *Escherichia coli*.
Group B *Streptococcus* (GBS) was not considered an important cause of infection in those years, in contrast to current concerns. The perinatal mortality rate associated with PROM was estimated as 2.6% to 11% (Mozurkewich, 2006). Although studies carried out by Shubeck et al. (1966) and Webb (1967) noted an increased risk of chorioamnionitis and maternal and fetal infection, prematurity was the most frequent cause of neonatal death found in these studies. This high incidence of infection reported in those studies in the 1960s clearly influenced common practice in the following years. According to Mozurkewich (2006), in the 1970's and 1980's active management of PROM became the standard practice, and as a result of this type of management, complications of labour related to the induction process began to rise. This rise in complications due to the induction process triggered further studies to ascertain if the infection risk was as high as previously reported and what was the best management.

Kappy et al. (1979) compared outcomes following induction and expectant management in a term population. The expectant management did not have a time limit. They found no difference in infection rates between the two groups and a higher rate of caesarean sections in the induced group. These results suggested that the risk of infection due to PROM might be smaller than previously reported, and that the caesarean section rate might be reduced if expectant management was used in case of unfavourable cervixes.

Kappy et al. (1979) stated that the conservative approach was safe and beneficial and that the lack of digital vaginal examinations may account for the low incidence of infectious morbidity. In addition, Ottervanger et al. (1996) pointed out that caesarean section in itself is a major contributor to infection in the mother and that a failed induction may contribute to infection, because a caesarean section is a major surgery.

The first RCT to address the question regarding neonatal infection was conducted by P. Duff, Huff, and Gibbs (1984). This study allocated 134 women who were not in labour 12 hours after rupture of membranes to immediate induction of labour with oxytocin or to expectant management. Those allocated to expectant management were admitted as inpatients until the onset of labour. P. Duff et al. (1984) found statistically significant increases in caesarean sections and chorioamnionitis in the induction group. This study did not have the statistical power to address the question of the risk of serious neonatal infection; however no trends toward differences in neonatal infectious complications were found. It is interesting to note that the results in terms of infection for babies from P. Duff et al. (1984) are consistent with the results obtained previously by Kappy et al. (1979). These findings therefore left the question regarding neonatal infection and the best management for PROM unanswered.

Morales and Lazar (1986) conducted a prospective randomised study with 317 women with prelabour rupture of membranes at $\geq$36 weeks gestation. In this study women were randomly allocated to immediate induction of labour or expectant management up to 48 hours. In this study there were no neonatal infections. They found that the active management group had a higher rate of caesarean sections (21%) compared to the expectant management group which had (7%). The rate of endometritis after caesarian section was 24% compared to 5% in the case of spontaneous vaginal birth. The overall maternal intrauterine infection rate was higher in the active management group (12%) compared to 4% in the expectant management group. Although the total time since the rupture of membranes until delivery was longer in the expectant management group, the mean time from the first vaginal examination to delivery was significantly higher in the active management group (17.4 hours) compared to (3.8 hours) in the expectant management group. This finding suggest that, contrary to previous assumptions, a prolonged interval between rupture of membranes and delivery does not increase the maternal and neonatal infection rate. However, the interval from digital examination to delivery may also be a critical risk factor in the incidence of infection, this concept was first introduced by Schutte et al. (1983). The mean number of vaginal examinations

was also significantly higher in the active management group in comparison to the expectant management group. The mean number of vaginal examinations in the active management group was 12 compared to four in the expectant management, showing that active management is associated with more interventions that may increase the risk of infection.

Six years after the findings of Shutte et al. (1983) in regard to the effects of vaginal examinations and infection, Wagner et al. (1989) conducted a randomised controlled trial (RCT) with 182 women. In this study, expectant management was allowed up to 24 hours, and active management was commenced at 6 hours after rupture of the membranes. In contrast to the previous study conducted by P. Duff et al. (1984), Wagner et al. (1989) found an increase in suspected neonatal infection in the expectant management group. However, this finding referred to suspected infection, not definite infection. The authors stated that this rise in suspected infection has probably more to do with the possible hospital policy of monitoring and screening infection in the newborns with latent periods of rupture of membranes greater than 24 hours, than with real cases of infected new-borns. Wagner et al. (1989) investigated the possible confounding factors for infection, and looked at the relationship between internal examinations and infection. In Wagner's study 14% of the participants, had an initial internal digital examination, and all the neonates who had a serious infection belonged to that group. Although this finding did not have enough statistical power to generalise data and conclusions around the effects of internal examinations, it suggests that vaginal examinations themselves may be associated with infection. During the 1980s and most of the 1990s, the debate continued around the best management for PROM to reduce the risk of infection for mother and baby, while reducing the risk of caesarean section (which in itself can cause infection). Therefore, the pendulum swung between induction of labour or expectant management, and 22 randomised and quasi-randomised studies were published on the matter. However, none of these studies had enough statistical power to address the questions around the best management for PROM and neonatal infection.

Hannah et al. (1996) carried out a big multicentre RCT in 72 countries, involving more than 5000 women and babies (the TermPROM trial). The aim was to have enough statistical power to address the question of neonatal infection and the best management for prelabour rupture of membranes at term. The study randomly allocated women to four groups: immediate induction with oxytocin; immediate induction with vaginal

PGE_2 gel; expectant management up to 96 hours with induction with oxytocin; and expectant management with induction with PGE_2 gel. The results from this study are consistent with those from Kappy et al. (1979) and P. Duff et al. (1984) in regards to neonatal infection. Hannah et al. (1996) found that the babies from the active management and expectant management groups had similar rates of infection. The rates of caesarean section were similar in both groups too. The women in the active management with intravenous oxytocin group had a lower risk of suspected chorioamnionitis (maternal infection) than those in the expectant management groups. However, some of the limitations of the TermPROM study affected the incidence of maternal infection. The threshold for diagnosis of suspected chorioamnionitis was 37.5°C on two or more occasions 1 hour apart or a temperature of more than 38°C. Generally, chorioamnionitis has been defined when the temperature raises over 38°C, therefore, defining chorioamnionitis as two temperatures of over 37.5°C could have resulted in an over-diagnosis of suspected chorioamnionitis. In addition, no histological examinations were carried out on the placentas, to confirm or rule out chorioamnionitis. Therefore, all the results in this study on chorioamnionitis are based on what is suspected on clinical judgement and since clinicians assessing chorioamnionitis were not blinded to the group allocation (because chorioamnionitis was a secondary outcome), the results on suspected chorioamnionitis can be highly influenced by the views or perception of risk on active or expectant management for prelabour rupture of membranes. Many women in the study had digital vaginal examinations upon entry to the study. As noted above, multiple digital vaginal examinations could be an independent risk factor for uterine infection (chorioamnionitis) as a secondary analysis of the termPROM data set carried out by Seaward et al. (1997) suggests. Seaward et al. (1997) found that when multiple vaginal exams are minimised, the time interval from ROM to birth had a minimal impact on development of chorioamnionitis. Having more than eight internal examinations was a strong predictor of clinical chorioamnionitis in this study.

Currently, the National Institute for Health and Clinical Excellence (NICE, 2017), bases the majority of its recommendations on the TermPROM trial.
NICE (2017), recommends active management 24 hours after rupture of membranes. However, it considers that expectant management up to 96 hours is a safe option that some women might want to choose. In accordance to NICE (2017), women with confirmed rupture of membranes and no uterine activity (contractions), are advised to wait for signs of labour at home and to come in to hospital for an induction of labour

if they are not in labour by 24 hours since the rupture of membranes. Therefore, the place where women spend that time between the rupture of membranes and the onset of labour is also of importance as it is discussed in the next section.

2.4 Place of care during the latent phase

The first study to look into the place of care during the latent phase (the period of time between the rupture of membranes and the onset of labour) was a randomised controlled trial conducted by Carlan et al. (1993). In this study, women with a preterm pregnancy were assessed for rupture of membranes by speculum examination and a fern or nitrazine test or positive pooling by a subjective decrease of Amniotic fluid on ultrasound. Cervical cultures were taken for *Neisseria gonorrhoeae, Group B streptococcus and Chlamydia trachomatis*. Everybody was initially admitted to hospital for the first 72 hours of expectant management and while awaiting results from the cultures, prophylactic antibiotics were given. If the cervical cultures were negative, the antibiotics were discontinued and if labour had not happened spontaneously by then, women allocated to the home management group were discharged home and followed up as outpatients in clinics. Both groups were induced by 37 weeks if the cervix was favourable but otherwise in the cases of unfavourable cervix, the pregnancy would progress until 40 weeks gestation. They were also offered pharmacologic acceleration of pulmonary maturation. Carlan et al. (1993) found that there were no significant differences in clinical outcomes or perinatal outcomes. However, there was a significant decrease in both the days of maternal hospitalization and maternal hospital expenses in the home group. Although the results of this study are based on preterm pregnancies, and these pregnancies have the added risk of prematurity, these results are of importance to the present study because they provide evidence on the safety of being at home during the time between the rupture of membranes and the onset of labour.

Subsequently, Hagskog et al. (1994), published a prospective study of 176 primiparous women with term ($\geq$37 weeks gestation) prelabour rupture of membranes. These women had conservative ambulatory management. Hagskog et al. (1994) wanted to provide information on the natural history of term PROM, therefore induction of labour was not performed routinely unless the participants reached 42 weeks gestation, at which point induction of labour was offered. Rupture of membranes was confirmed by speculum examination only and a cervical culture was taken to screen for Group B streptococcus.

Vaginal examinations were not performed until the women were deemed to be in active labour. Induction of labour was recommended if the results from the culture were positive or if any clinical signs of infection appeared during the latent phase. Women enrolled into the study, were given health advice and signs of infection to look for and what to do in case of any concerns. They were then discharged home. All the participants were seen in clinic as outpatients every second day. Hagskog et al. (1994) noted that women generally preferred to stay at home rather than in hospital, and that the costs of being monitored in the community or as an outpatient were lower than as an inpatient. They also highlighted that acquisition of a nosocomial infection in hospital was an important adverse outcome that should not be overlooked.

Jomeen and Martin (2002) conducted a RCT with 56 women with prelabour rupture of membranes at term to study the impact of home versus hospital admission for a period up to 24 hours. This study took place in a maternity unit in the UK where at the time; all women with prelabour rupture of membranes were admitted as inpatients to await spontaneous labour for a period up to 24 hours. In this study women who were randomly allocated to the home group were discharged home with a detailed information sheet with advice regarding general hygiene, instructions as to how to monitor temperature and signs of concern. A date and time were given to come back to hospital for induction of labour if spontaneous labour had not occurred within 24 hours. The women, who were randomly allocated to the hospital admission group, were admitted into the antenatal ward and were looked after as per the usual local hospital protocol. Both groups had a vaginal swab at the time when the rupture of membranes was confirmed by speculum examination and a second high vaginal swab was taken either at the onset of spontaneous labour or prior to the induction. Digital vaginal examinations were avoided until active labour was suspected.

Jomeen and Martin (2002) found that the only statistically significant difference between the groups was that at the 18-hour temperature reading, the hospital group had higher temperatures than the home group. There were no other statistically significant differences between the groups including no differences in rates of maternal or neonatal infection rates, type of birth or Apgar score.

Although this study did not have enough statistical power to detect differences in infection rates, it has provided some evidence on the safety of being at home during the time between the rupture of membranes and the onset of labour to both clinicians

and women. This suggests that it is reasonable to offer women the option of staying at home, where they might feel more comfortable, while awaiting the spontaneous onset of labour.

Hannah et al. (2000) conducted a secondary analysis of data from the International TermPROM study for women managed expectantly at home or in hospital. The aim was to find out whether adverse effects were greater in women expectantly managed at home compared to those expectantly managed in hospital. They also wanted to determine whether women's satisfaction was greater if women were managed at home rather than in hospital. They determined the effect of home and hospital management measuring maternal and neonatal infection and rates of caesarean section. In the TermPROM study, among 3333 women enrolled between January 15, 1994 and May 31, 1995, additional information was collected on whether they were managed partially or completely at home or in hospital. Among those 3333, 1670 (39.1%) were expectantly managed and 1017 (60.9%) were expectantly managed in hospital and 653 were partially or completely managed at home. One of the limitations of this study is that women who were partially or completely at home after entry were considered managed at home. Partial management at home included those admitted initially to hospitals, subsequently discharged, and later re-admitted when labour was established or for the induction of labour or initially discharged home and later on admitted to continue with the expectant management. The women who were assigned to expectant management were asked to check their temperatures twice a day and report if it reached 37.5 or more, whether there were any changes in the colour or smell of liquor or when complications developed. Some women had additional monitoring tests, but this was inconsistent across all the sites. If complications arose or if labour had not started after 4 days, labour was induced either with intravenous oxytocin or with vaginal prostaglandin gel. In the TermPROM study, women who were randomly assigned to expectant management returned home until labour was established or were admitted to hospital or had an individualized plan. There was heterogeneity regarding this aspect of the management depending on what was the usual practice in each local hospital. Women managed at home (partially or completely), 260/653 (39.8%) had one or more outpatient visits, whereas 364/653 (55.7%) had some form of telephone contact with a clinician. The results showed that women managed at home (partially or completely) had a higher rate of suspected chorioamnionitis compared to those managed in hospital (66/653 (10.1%) vs. 65/1017 (6.4%)) respectively, had a higher rate of neonatal infection

(20/653 (3.1%) vs. 17/1017 (1.7%)) respectively. However the women who stayed at home were more satisfied with their care than those who stayed in hospital. This is expressed in the questionnaire as "Did not like anything about care". The rate of agreement with this statement in the home group was 28/653 (4.3%) compared to the hospital group that was 88/1017 (8.7%). The limitations of this study are significant. It has been mentioned before that there is heterogeneity in the management of this aspect of the care, that could have an impact on the results, for example those women who were partially managed in hospital, who had to be initially admitted and then discharged and then had to come again, don't reflect the true nature of being at home during the expectant management. These women could have been less relaxed compared to those being at home all the time or could have been contaminated with hospital pathogens in one of the admissions. Therefore, full conclusions cannot be drawn. This study did not randomly assigned women to home or hospital. Therefore, the conclusions regarding the palce of care during expectant management should be taken with caution.

2.5 Prophylactic antibiotics during labour

This section presents a summary of the evidence behind the use of prophylactic antibiotics. It focuses on single studies because I wanted to provide a brief overview in chronological order of the main studies that have influenced practice through the years. This is followed by the conclusions from the most recent Cochrane systematic review published by Wojcieszek et al. (2014) in order to synthesize the evidence. In the study presented in this thesis, women did not receive antibiotics prophylactically due to the fact that the hospital where the study was hosted did not use them routinely because there is insufficient evidence to recommend its use. However, it was decided to write a brief summary of the evidence behind the routine use of prophylactic antibiotics for term prelabour rupture of membranes since it is an important element in the management of term prelabour rupture of membranes and some maternity units in the United Kingdom and rest of the world still use them nowadays.

The first study to ascertain whether the administration of prophylactic antibiotics was beneficial to both mother and infant in the context of prelabour rupture of membranes at term was a study conducted by Lebherz et al. (1963). It was a double-blind study that compared the use of tetracyclin with the use of a placebo. However, this antibiotic is no longer recommended in pregnancy. Although Lebherz et al. (1963) demonstrated reduction in endometritis and postpartum infections, tetracyclin was not effective against gram negative organisms that can cause chorioamnionitis.

Gordon and Weingold (1974) conducted a quasi RCT on the use of prophylactic antibiotics (Ampicillin) in both pre-term (less than 37 weeks gestation) and term (37 or more weeks gestation). A total of 268 women with uncomplicated and confirmed prelabour rupture of membranes were enrolled in the study. The participants were allocated to four groups: 1) Preterm pregnancy (treat): they received 1 gram of ampicillin intramuscularly every 12 hours for 48 hours. They were discharged to await labour on ampicillin 500mg orally every 8 hours for a total of 10 days. 2) Preterm pregnancy (control): They were hospitalised for 48 hours and then discharged to await labour. 3) Term pregnancy (treat): After a latent period of 12 hours, induction of labour begun. They received antibiotics (infusion of 1g of Ampicillin diluted in 1000ml of 5% dextrose until delivery. 4) Term pregnancy (Control): After a latent period of 12 hours, induction of labour begun, and the infant was delivered within 24 hours. Gordon and

Weingold (1974) claim that when prophylactic antibiotics are given, the incidence of amnionitis and other causes of pyrexia, and postpartum morbidity is reduced. On the contrary, when prophylactic antibiotics are only given during labour at term, they are not be expected to have the same effects and reduce antepartum infection and would only have a minimal effect on the postpartum period. Prophylactic antibiotics during labour seemed to provide no advantage to the survival of the fetus. However, Gordon and Weingold (1974) also explain that the major cause of death in their study was prematurity.

Ovalle et al. (1998) published a study that examined the effects of prophylactic antibiotics (cefuroxime and clyndamicin) in 105 women with prelabour rupture of membranes between 37 and 42 weeks' gestation. Women who were allocated to the treatment arm, received cefuroxime 750mg intravenous every 8 hours for 48 hours, and clindamycin 600mg intravenous every 6 hours for 48 hours. After these 48 hours, antibiotics were then given orally: cefuroxime 250mg every 12 hours and clindamycin 300 mg every 6 hours, up to 24 hours. Women had induction of labour with oxytocin within 24 hours after admission. In this study, women had a speculum examination at admission and digital cervical examinations were only performed once active labour (spontaneous or induced) was suspected. Ovalle et al. (1998) found that the rate of maternal infection (chorioamnionitis and/or endometritis) was lower in women who received antibiotics than in those who were given a placebo [1.8% (1/55) vs. 16% (8/50) p=<0.05] respectively. No other statistically significant differences were found and there were no cases of neonatal morbidity or mortality in either group. However, this study did not have enough statistical power.

Cararach et al. (1998) conducted a RCT on the use of prophylactic antibiotics in women with a gestation of $\geq$36 weeks presenting with prelabour rupture of membranes of less than 12 hours and no contractions. Women were allocated to two groups, treatment or control. In the treatment group, the antibiotic regime consisted of Ampicillin 1g intravenously every 6 hours and gentamicin 80mg intramuscularly every 8 hours. This antibiotic regime was to be given since the time of admission till delivery. Women allocated to control group would not receive antibiotics unless they became symptomatic in which case, they would receive the same antibiotic regime as the women in the treatment group. In both groups, the protocol was to induce labour if labour had not started by 12+/-3 h since the rupture of membranes. Women who required a caesarean section birth would be given prophylactic antibiotics after the extraction of the fetus, the

antibiotic treatment in the case of caesarean section varied depending on the hospital protocols. Cararach et al. (1998) concluded that the rate of chorioamnionitis was lower in those receiving prophylactic antibiotics since the time of admission, 12/371(3.2%) vs 17/362(4.7%) X^2 p=0.3, but the difference was not statistically significant. In the case of neonatal sepsis, it was found that the incidence of neonatal sepsis was lower in those receiving prophylactic antibiotics than in the control group, 1/371(0.3%) vs 7/362(1.9%) p=0.03. This difference was statistically significant. Cararach et al. (1998) concludes that antibiotic prophylaxis reduces the incidence of neonatal sepsis, however large numbers of women are needed to be treated prophylactically in order to prevent a small number of cases and suggests that the possibility of targeting the prophylactic antibiotics on specific groups of people may be more feasible.

Passos et al. (2012) carried out a single centre RCT that evaluated the use of prophylactic antibiotics in women with a gestation of $\geq$37 weeks and a rupture of membranes of less than 12 hours. In this study women were randomised to either prophylactic antibiotics or "no treatment". If allocated to prophylactic antibiotics, there were to commence at the time of admission and enrollment in the study. The antibiotic regime used in this study was to be given intravenously and consisted of ampicillin 1g every 6 hours and gentamicin 240mg every day. Women allocated to the control group were only given antibiotics (same regime as in treatment group), if clinical signs of infection appeared. In both groups, if women needed a caesarean section birth, women received intravenously one dose of cefoxitin 2g as a prophylaxis at the time of skin incision. One of the limitations of this study was that the decision of when to induce labour was arbitrary and it depended on the obstetrician responsible for the care of that particular woman instead of a clear protocol. This could affect the findings as the length of rupture of membranes is believed to affect the risk of infection. Passos et al. (2012) concluded that the incidence of chorioamnionitis was significantly lower in women who received prophylactic antibiotics in comparison to those who did not. 2.6% vs 10.8% (p=0.037). However, the incidence of endometritis was not significantly different, 0% vs 2/83(2.4%) (p=0.5). The incidence of neonatal infection was lower in those whose mothers had received prophylactic antibiotics 3/78(3.8%) compared to those in the control group 5/83(6%), but the difference was not statistically significant (p=0.375). They concluded that prophylactic antibiotics reduced chorioamnionitis but in the case of neonatal infection the difference was not statistically significant.

The most recent study on the topic was a study carried out by Nabhan et al. (2014).

This study assessed the effectiveness of a single dose of intravenously administered antibiotics (1,500mg of ampicillin) for women presenting with rupture of membranes of less than 12 hours and no contractions at ≥36 weeks gestation. The primary outcome was early onset of neonatal infection. Women were allocated to either prophylactic antibiotics on admission to the labour ward or placebo (the same solvent but without the antibiotics). The two groups were managed by immediate induction of labour or caesarean section as indicated, but the publication doesn't describe the indications. In contrast to previous studies on prophylactic antibiotics, in this study the vaginal examinations were restricted to a maximum of 4 during the first stage of labour, whereas in the other studies this was not controlled and could have had an impact on the incidence of chorioamnionitis. Definitive early onset of neonatal infection occurred in 9/820(1.1%) in the antibiotic group and 7/820(0.9%) in the placebo group. Clinical chorioamnionitis was present in 21/820(2.6%) in the antibiotics group and 19/820(2.3%) in the placebo group. Nabhan et al. (2014) concluded that the routine use of prophylactic antibiotics does not provide any benefit to either the mother or the infant.

Taking all these studies together, Wojcieszek et al. (2014) conducted a systematic review to compare outcomes for women and infants when antibiotics were administered prophylactically for prelabour rupture of membranes at gestations of ≥ 36 weeks. This Cochrane review included four studies outlined earlier (Cararach et al., 1998; Nabhan et al., 2014; Ovalle et al., 1998; Passos et al., 2012) with a total of 2,639 women. Given that in some of these studies the protocol was to induce labour immediately whereas in others the latency period was longer, the review carried out a subgroup analysis for early induction of labour (Induction within 12 hours since the rupture of membranes) and a subgroup analysis for late induction of labour (induction at 12 or more hours since the rupture of membranes). They also carried out a subgroup analysis for nulliparas, as the labour duration might be increased in this group and it is believed that the duration of labour is a correlator for infection. Maternal and neonatal infectious outcomes were still not significantly different whether women were given prophylactic antibiotics or not.

The conclusions from the Cochrane systematic review carried out by Wojcieszek et al. (2014) were that the use of prophylactic antibiotics showed no statistically significant differences on early-onset of neonatal sepsis, maternal infectious morbidity such as chorioamnionitis or endometritis, stillbirth, perinatal mortality, and serious maternal outcome. Therefore, this systematic review on the routine antibiotic prophylaxis showed

no significant evidence of benefit for women and their babies. Wojcieszek et al. (2014) in page 2, state that "*given the unmeasured potential adverse effects of antibiotics use, the potential for development of resistant organisms, and the low risk of maternal infection in the control group, the routine use of antibiotics for PROM at or near term in the absence of confirmed maternal infection should be avoided*". However, it is interesting to note that in the hospitals in the UK where antibiotics are still administered prohylactically for term prelabour rupture of membranes, these are given during labour and not from the time when the rupture of membranes is diagnosed. In contrast, the studies carried out on this topic report results when antibiotics are given since the time of enrollment in the study.

2.6 Vaginal examinations

Schutte et al. (1983) conducted a retrospective study to understand the risk of digital vaginal examinations to the infant in both preterm and term population. In this study, women did not receive any speculum or digital vaginal examination until they were deemed to be in active labour or unless delivery was expected to occur within 24 hours. Schutte et al. (1983) found that infection occurred more frequently if the interval between the first vaginal examination and the birth of the baby was longer than 24 hours at any gestational age. This difference was statistically significant. He also found two independent risk factors for infection: (1) Gestational age, preterm infants develop infections more frequently than those born at term and (2) the interval between the first vaginal examination and the delivery of the baby. This contradicts the common belief that it is the interval between the rupture of membranes to delivery the strongest predictor of infection (Akyol et al., 1999).

The international TERMPROM study conducted by Hannah et al. (1996) also found a relationship between the number of digital vaginal examinations and the incidence of chorioamnionitis. In this study, women had a speculum examination at the diagnosis of rupture of membranes but vaginal examinations were avoided until the onset of active labour. However, vaginal examinations were not intended to be reduced during labour. In a secondary analysis of the TERMPROM study, Seaward et al. (1997) found that having more than 8 internal examinations was a strong predictor of clinical chorioamnionitis. However, one of the limitations is that these findings were obtained through a retrospective logistic regression rather than by a prospective RCT.

These findings from Schutte et al. (1983) and Seaward et al. (1997) are also consistent with a more recent retrospective study conducted in Israel by Ezra et al. (2004). The aim of this study was to determine the significant predictors of clinical chorioamnionitis and neonatal infection in patients with prelabour rupture of the membranes at term. It was a retrospective case-control study, where the clinical notes from women who had prelabour rupture of membranes were reviewed. The case group were women who had evidence of maternal or neonatal infection whereas the control group were women with no evidence of infection. The analysis was focused on clinical chorioamnionitis and neonatal infection as the main outcome measure of the management strategy.
It compared risk factors for infection and 3 types of management retrospectively. Ezra et al. (2004) found that having more than seven vaginal examinations during labour or having caesarian section were independent predictors of infection.

Imseis, Trout, and Gabbe (1999) conducted a prospective study to determine whether vaginal digital examinations introduce microorganisms. In this study, 35 women with prelabour rupture of membranes at 34 or more weeks' gestation had a swab taken during a speculum examination at the beginning of the study and further swabs before and after every examination. They conclude that an immediate effect of digital examinations is the introduction of vaginal organisms into the cervix. This study has some limitations because it only looked at positive cultures and not at people who were symptomatic, (sometimes there can be positive culture but it does not cause a problem to the person and the person does not develop symptoms). The other limitation is that it was not a RCT that evaluated the effect of doing less or more digital examinations. Nevertheless, the results from this study are of interest since they indicate an increase in the growth of microorganisms after vaginal examinations. In summary, the studies reviewed in this section all tend to suggest that the number of vaginal examinations during labour could be associated with a risk of infection. However, these studies were not randomised controlled trials that directly assessed the effects of this intervention (having more or less vaginal examinations). In contrast, the pilot study presented in this thesis has controlled for this variable to establish the feasibility of including this element in the future main study.

2.7 Women's experiences of induction of labour

The first study to look at the experience of childbearing women during induction of labour was carried out by Cartwright (1979). This study was aimed at women undergoing induction for all kinds of reasons and not necessarily only due to prelabour rupture of membranes. However, many aspects of her study can be extrapolated to women undergoing induction for prelabour rupture of membranes. She concluded that most women prefer spontaneous labour over induction of labour, and that in regards to pain relief, in general, women found labour more painful when it was induced than when labour started spontaneously.

Later on, several other studies have also been conducted to investigate the women's experience of induction of labour vs. the experience of spontaneous labour (Gatward et al., 2010; Henderson & Redshaw, 2013; Hodnett et al., 1997; Shetty et al., 2005). These studies looked at the experience of induction of labour due to several clinical indications including post-dates pregnancy, hypertensive disorders, suspected growth fetal problems, as well as prelabour rupture of membranes. With the exception of Hodnett et al. (1997) who studied the experience of women who took part in the TermPROM study, the rest of the studies looked at women with prelabour rupture of membranes (PROM) and also women being induced due to other indications. Although these studies were looking at women being induced for a variety of reasons, similarities can be expected.

Shetty et al. (2005) conducted a study with 900 participants where, 450 participants underwent induction of labour with Prostaglandins E_2 tablets and 450 women laboured spontaneously. The group who were planning an induction were asked to complete a questionnaire prior to the start of the induction and another questionnaire post-delivery. The group who were labouring spontaneously completed the questionnaire only after the birth. The researchers found that women who laboured spontaneously had higher satisfaction rates, 22.6% of women who had an induction reported feeling very satisfied, compared to 34.3% of women having had an spontaneous labour p=0.008. Another study on the satisfaction of women with induction of labour was published by Gatward et al. (2010). The researchers studied the experiences of women being induced for post-date pregnancy. It is a qualitative study involving interviews from booking to after birthing with 23 participants who were booked for induction. Of those, 18 were

induced, and 5 went into spontaneous labour. They found that the women varied their responses from welcoming the induction to resisting it. The women wanted to have information that is meaningful to them and the process of induction. Women in the induction group lacked an understanding of what the procedures meant for them. The women in the spontaneous labour focused their worry on the impact of induction on the baby whereas the induction group focused their concerns on the effect on themselves and loss of a natural birth.

Henderson and Redshaw (2013) conducted a mixed method study about women's experience of induction of labour. This, involved a secondary analysis of data from questionnaires in regards to care in childbirth, using both closed (quantitative) and open (qualitative) questions. Women's experience of induction of labour was compared to those who had a spontaneous labour. The main outcomes were satisfaction with care, mode of delivery and experience of induction of labour. The survey was sent to a random sample of 10,000 women when their baby was approximately 3 months old. The response rate was 5,333/10,000 (55.1%), 20% of whom had their labours induced. The results indicated that, in general, the respondents favoured spontaneous labour over induction. Women who were induced had more worries in general. They were particularly concerned about the need for interventions. Those who were induced were less likely to be able to move around and find a comfortable position compared to those in spontaneous labour. Moreover, those who were induced had a perceived longer labour and generally rated their perception of interactions with staff more negatively. In regards to the mode of delivery, women who had spontaneous labour compared to those who were induced, had a higher rate of spontaneous vaginal delivery (SVD) 61% vs. 45.8% respectively, and a lower caesarean section rate 16.1% vs. 29.4% respectively. Qualitative data indicated the importance of giving balanced information, and of good communication with women. One respondent stated: "*my date to be induced was 15 days over my due date. I was already worried as the midwife had told me that after 10 days the placenta starts losing its nourishment, so there is a risk to the baby's health, so I was panicking as it was...*" (Henderson & Redshaw, 2013, p. 3). This quote from Henderson and Redshaw (2013) describes how the information provided to women can have an impact on their degree of worry and anxiety, which might make them more willing to accept interventions during childbirth and to worry if those interventions are delayed. This study is highly relevant as it provides valuable information in regards to the experience of women who undergo induction of labour and it compares it with

those who experience a spontaneous labour. It has a very high number of participants, but some of the limitations of this study are that it was performed at 3 months after the birth of their baby, and it relies on what they recall and there might be cases where there is a lack of clarity. The authors also acknowledge that their responses at 3 months could be influenced by their current emotional status and not reflect totally how they felt during the labour and birth. Another limitation of this study is that it has not taken into consideration the model of care that women had, in that women who had for example a caseloading model of care but needed to be induced might have had a better experience than her counterpart with fragmented care during spontaneous labour. Nevertheless, the number of women having caseloading or continuity of care by a named midwife is very small and it is unlikely that it would have altered the results.

Hodnett et al. (1997) conducted a study as part of the international TermPROM, to assess women's views in regards to the management of prelabour rupture of membranes at term within the clinical trial. As noted previously, the TermPROM study was a multicentre international trial to compare the outcomes of induction of labour versus expectant management for women with prelabour rupture of membranes at term. 5041 women took part in the TERMPROM trial. All the participants were given a questionnaire within the first few days postpartum and before discharge from hospital. A total of 4129/5041 (81.9%) completed and returned the questionnaire. There were no statistically significant differences between the response rates between treatment groups. Equally there were no statistically significant differences between number of respondents who were primiparas and multiparas, and response rates were high for all participating countries (from 77.1% in Canada to over 85% in the UK, Australia, Sweden and Denmark). The main outcome measures were: 1) The evaluation of the treatment received, 2) perceived control during childbirth and 3) experience of trial participation. Hodnett et al. (1997) found that all statistically significant differences favoured active over expectant management. The authors explain that this could be partially due to the additional time those in the expectant group had to worry about their health or that of their baby. They acknowledge that this might have been reinforced, as part of the consent process involved informing all the potential participants of the uncertainties about prelabour rupture of membranes and how it could lead to neonatal infection. The authors note that there were different levels of worry between countries. United Kingdom, Sweden, and Israel showed lower levels of worry when compared with Canada. This highlights the importance of societal norms

and culture in the development of women's attitudes towards normalcy in childbirth and risk. It further supports what has been mentioned earlier in the study conducted by Henderson and Redshaw (2013), in that the information provided to women and the way it is given can have an impact in the levels of anxiety and worry that women experience. One of the limitations of this study is that the information provided at the beginning of the study may be favouring active management over expectant management, and this can be seen as a source of bias. There was a lot of heterogeneity within the expectant management arms, some women were discharged home and advised to come back in 4 days without having regular check-ups, while others were admitted into hospital for 4 days to wait for labour to start spontaneously. In order to be able to make fair comparisons in regard to the acceptability of expectant management a clearer and standard protocol should have been followed by all the sites.

2.8 Conclusion

Spontaneous rupture of membranes is a normal physiological event that in about 10% of the population, it happens before labour starts (Gunn, Mishell, & Morton, 1970). It is believed that prelabour rupture of membranes increases the risk of infection and therefore induction of labour is recommended in an attempt to reduce such risk. However, there is controversy as to the induction actually reduces that risk. Moreover the risk of infection is always there, even when the membranes are intact. The problem with the routine induction of women is that it limits the potential for women to experience a normal birth and its benefits. There is also controversy in regards to what is understood by "normal birth". Beech (1997) claims that "normal birth" can actually be seen as a rare event. In this study, what is understood by normal birth is a birth that started spontaneously and was not augmented either by drugs or mechanical means and when the baby is born spontaneously by maternal effort only. The management of prelabour rupture of membranes has been an issue of debate since the 60's and the pendulum has swung between inducing labour as soon as possible in an attempt to reduce the risk of infection and giving women time to start labour spontaneously in an attempt to reduce the risk of caesarean section that is associated with the induction of labour. This chapter has discussed the main studies over the past decades that have contributed to the current management in the UK. Vaginal examinations have been known to be associated with an increased risk of chorioamninionitis, one of the

first studies to highlight this issue was carried out by Schutte et al. (1983). They found out that what it was significant was the length of time since the first vaginal examination till the birth of the baby. That the vaginal examinations increase the risk of chorioamnionitis has also been demonstrated by Seaward et al. (1997).

The microbiologic effect of vaginal examinations has been explored by Imseis et al. (1999). It showed that the cultures taken after the vaginal examinations had a higher mean of number of different bacteria and greater growth. In an attempt to reduce the risk of infection, prophylactic antibiotics have been used and advocated in the past (Ovalle et al., 1998). In contrast, the most recent Cochrane systematic review on the matter carried out by Wojcieszek et al. (2014) do not support the use of prophylactic antibiotics during the latent phase or during labour due to the insufficient evidence of their benefit and on the potential long term negative consequences of antibiotic resistance. Due to the relatively common incidence of labour induction, several studies have explored the experience of women who have undergone induction of labour in general. As well as looking at the clinical outcomes, it is also important to assess the experience of women. Therefore, for the purpose of this thesis, the Childbirth Experience Questionnaire was used to evaluate it (Dencker et al., 2010; Walker et al., 2015). This traditional scoping review presented in this chapter facilitated the identification of interventions and outcomes to be addressed in the systematic review in the next chapter.

Chapter 3: Systematic Review

3.1 Introduction

This chapter follows on the previous chapter where the background and a traditional scoping review were presented. The scoping review facilitated the identification of the interventions and outcomes to be addressed in the systematic review. This chapter provides an overview of the systematic reviews carried out for this research. It contains a common background followed by two sections. The first section addresses the first systematic review and the second section addresses the consequently systematic reviews two, three and four. This is because initially, it was intended to be a single systematic review but it became evident that this was not going to be possible as there are no published studies (RCTs or observational) that answer the precise research question as a whole and it became necessary to break down the research question in three simpler questions. Therefore, this chapter presents the processes and results of four systematic reviews. The discussion at the end draws conclusions from both sections.

3.2 Background

There are different ways of re-viewing what has already been published in regards to a specific research question; they essentially differ on the methodology used to retrieve the information and the way the results are interpreted and analysed. A traditional literature review is a "*written appraisal of what is already known - existing knowledge on a topic with no prescribed methodology*" (Jesson, Matheson, & Lacey, 2011, p. 10). In contrast a systematic review has been performed using a systematic approach in order to minimise biases and random errors (Chalmers & Altman, 1995). Systematic reviews can be considered research in themselves because they follow a method, consisting of at least the following steps: a research question, a plan for the search, a list of inclusion

and exclusion criteria, and a quality assessment as well as an intention to synthesise the results from a group of studies (Jesson et al., 2011).

Meta-analysis is a type of synthesis; it is the statistical analysis of the results of the studies obtained by the search, which generally aims to produce an estimate of a treatment effect (Egger, Smith, & Sterne, 2001). Egger et al. (2001) explain that a systematic review may or may not include a meta-analysis as sometimes conducting a meta-analysis is inappropriate if there are large differences (heterogeneity) between trials in the inclusion criteria for participants, the intervention, the outcomes or the measurements of effect (Chalmers & Altman, 1995). It is important to make the distinction between a systematic review and a meta-analysis. It is always appropriate and desirable to locate systematically what has been written about a certain research question, whereas meta-analysis might sometimes be inappropriate or misleading if there is significant heterogeneity between the studies. In other words, the systematic review may or may not be followed by meta-analysis, whereas the meta-analysis should always be preceded by a systematic review. Egger et al. (2001) highlight that systematic reviews and meta-analysis can be performed on observational studies as well as on randomised controlled trials, as long as the meta-analysis is performed separately for both types of studies. Evidence-based practice requires the integration of three fundamental pillars: clinical experience, the best available research evidence, and the values and preferences of the woman, into the clinical decision-making process (Straus, Glasziou, & Richardson, 2011). Therefore, systematic reviews and meta-analyses have become increasingly important and valued since they fulfil the criteria of identifying the best reliable research evidence to aid clinical decision making. One of the principles of evidence-based medicine is that when taking into consideration the best research evidence in regards to a specific question it is more reliable to look at the results of a few studies rather than just one in order to avoid bias and increase the generability. This task of searching for the evidence and synthesising the results of those studies is time consuming and very demanding for the clinician. Therefore, Archie Cochrane in 1980, founded the Cochrane collaboration with the aim of providing readily available reliable systematic reviews of the evidence. Sometimes systematic reviews serve the purpose of highlighting where more research is needed, or even where there is a complete gap in knowledge, as in the case of this review, where a systematic search located no published studies reporting on the primary research question. In such cases, it is only possible to describe the process that lead to the identification of the gap. This chapter presents both the gap in the literature found by performing the systematic review and

the subsequent systematic review designed to answer the 3 more simple questions in which the initial research question was broken down.

3.3 Systematic review (complex question)

3.3.1 Aims

- To systematically identify primary research that answers the research question: **"For prelabour rupture of membranes at term and an otherwise healthy pregnancy, is expectant management and minimal vaginal examinations associated with a higher rate of physiological labour and birth and a reduced rate of chorioamnionitis (maternal infection) in comparison to active management and routine vaginal examinations?"**

3.3.2 Methods

The search strategy and selection criteria were designed to identify good quality primary quantitative research studies that answered the primary research question. The key databases were identified and the following databases were deemed as most appropriate: (1) Medline, (2) Embase, (3) CINALH, (4) Maternity and Infant care, (5) LILACS. Cochrane database was considered and the systematic review on this topic has been checked (Middleton et al., 2017), but since Cohrane database contains only systematic reviews and not primary research, it was not included. The search has been guided by the primary research question and by an adaptation of the PICO framework, as seen in the table 3.1 on page 62. As a result, a list of key search terms and synonyms was produced and the MESH headings and subject headings for each database have been considered and included when appropriate as explained later on.

Table 3.1: PICO diagram

P(problem) **PROM**	I_1**(Intervention)** **Expectant management**	I_2**(Intervention2)** **vaginal examinations**	C_1**(Comparison)** **Active management**	O_1**(Outcome1)** **Mode of birth**	O_2**(outcome2)** **Chorioamnionitis**
"prelabour rupture of membranes" or "prelabor rupture of membranes" or "premature rupture of membranes" or "PROM" or "ruptured fetal membranes" or "ruptured foetal membranes" or "ruptured membranes" or "prolonged rupture of membranes" or "prolonged rupture of membrane" or "fetal membranes" or "foetal membranes"	"expectant management" or "conservative management" or "wait and see" or "watchful waiting"	"vaginal examination" or "vaginal examinations" or "internal examination" or "internal examinations" or "cervical examination" or "cervical examinations" or "digital examination" or "digital examinations"	"active management" or "induction of labour" or "aggressive management" or "pitocin" or "oxytocin" or "prostaglandin" or "prostaglandins"	"mode of birth" or "normal birth" or "normal delivery" or "physiological birth" or "physiological delivery" or "spontaneous vaginal birth" or "spontaneous veginal delivery" or "SVD" or "vaginal delivery" or "natural birth"	"infection" or "maternal infection" or "infectious morbidity" or "maternal sepsis" or "intra-amniotic infection" or "chorioamnionitis"

It was difficult to ascertain the correct strategy due to the complexity and specificity of the research question that this systematic review aimed to answer. However, it is described ahead the process for finding a suitable strategy that could reveal what has been published so far about this topic. The first database that was approached was MEDLINE. Medline has MeSH heading function (Medical subject headings), these are the controlled vocabulary thesaurus produced by the US national library of Medicine and they are used for indexing articles. They are a set of terms naming descriptors that have a hierarchical structure based on specificity. The key words that appear in table 3.1 on page 62 were mapped to find the MeSH headings. It appeared that not all the key words could be mapped to a MeSH heading, therefore only certain MeSH headings were used as described below. The searches were carried out during 2014 and 2015, but they were run again on the 6th November 2018 prior to the submission of this thesis. The results that appear here are the results obtained on the 6th November 2018.

- Mesh heading: Fetal membranes, premature rupture/ 6,821 hits
- Mesh heading: labour, induced/ 8,939 hits
- Mesh heading: Watchful waiting/ 2,892 hits
- Mesh heading: Term birth/ 2,597 hits
- Mesh heading: Delivery, Obstetric/ 27,145 hits
- Mesh heading: Cesarian section/ 41,323 hits
- Mesh heading: Chorioamnionitis/ 2,751 hits

There were no MeSH heading for “expectant management”, “normal birth” or “vaginal examination” when I did this search in 2015. However, now in November 2018, there has been a new Mesh Heading introduced ”Watchful waiting”. The search was carried out for each of the domains of the PICO diagram as they appear in table 3.1 on page 62 of this document. The key words were combined with the MeSH headings using the bolean operator “OR” in order to maximise the retrieval of papers as in the search strategy stated in the next page.

Example strategy for Medline:

[Mesh heading: Fetal membranes, premature rupture/ OR (List of key terms for Prelabour rupture of membranes)] AND [Mesh heading: Watchful waiting/ OR (list of key terms for expectant management)] AND [(Mesh Heading: labour, induced) OR (list of key terms for active management)] AND [(List of key terms for vaginal examination)] AND [(Mesh Heading: delivery obstetric) OR (list of key terms for normal birth)] AND [Mesh heading: Chorioamnionitis/ OR (List of key terms for Infectious morbidity)] AND [Mesh heading: Term birth/ OR (List of key terms for Term pregnancy)] =

In the case of other databases such as Embase or Maternity and Infant care that uses "subject headings", these subject headings were identified and the search strategy followed the same principles as given in the example above, using the relevant subject headings for ecah database and the key words outlined in table 3.1 on page 62. When I updated the systematic review in November 2018, I also realised that CINAHL has "CINAHL headings", so these were added and the searches were re-runned using these. The following table, 3.2, on page 65 outlines the different subject headings that were used depending on the database.

Table 3.2: Subject headings used depending on the database

Key word	Embase	Maternity and infant care	Medline	CINAHL
Prelabour rupture of membranes	Membrane rupture/	Fetal membranes-premature rupture de.	Fetal membranes, premature rupture/	Fetal Membranes, Premature Rupture
Active management	Labour induction	Labour-induced.de.	labour,induced/	Labour, induced
Expectant management	No subject heading	Expectant management.de	watchful waiting/	No subject heading found
Vaginal examination	No subject heading found	Vaginal examination.de	No Mesh heading found	No subject heading found
Chorioamnionitis	Chorioamnionitis/	Chorioamnionitis.de	Chorioamnionitis/	Chorioamnionitis
Normal birth	Natural childbirth/	Normal birth.de.	Delivery, obstetric/	Vaginal Birth

3.3.3 Inclusion and Exclusion criteria for complex systematic review

The following inclusion and exclusion criteria outlined in table 3.3 on page 67, were designed to identify studies that were relevant to answer the research question:
For prelabour rupture of membranes at term, is expectant management and reduced number of vaginal examinations associated with a higher rate of physiological labour and birth and a reduced rate of chorioamnionitis (maternal infection) compared to active management and routine vaginal examinations?

Although strictly speaking a term pregnancy refers to a gestational age of $\geq$37 weeks, for the purpose of this systematic review, studies that included gestational age of $\geq$36 weeks were included. This is because in practice a woman with a pregnancy of at least 36 weeks gestation would be treated as a term pregnancy in terms of the management of PROM, and also because through the scoping review I identified some studies that either included gestations from 36 weeks onwards or included all gestations but reported results from term from 36 weeks.

In terms of the date of publication, it was decided to include all studies that have been published since the start of the databases, for example in the case of Medline, all the studies published since 1946. This is because the pendulum has been oscillating between active and expectant management throughout the years, and I wanted to see the evolution and trends in management through time.

To get a picture of what has been published worldwide, it was decided to include papers in all different languages. Therefore, all the published studies that met these criteria were listed regardless of language. However, I only read papers published in English, Spanish or French as these are the only languages that I speak, and due to the lack of resources, it was impossible to employ translators.

Table 3.3: Inclusion and exclusion criteria for systematic review

Number	Inclusion criteria	Exclusion criteria
1	Quantitative primary research (RCT or observational)	Non-primary research
2	Prelabour rupture of membranes (PROM)	Studies not focused on PROM
3	Gestational age ≥36 weeks	Gestational age <36 weeks
4	Studies that compare active vs expectant management	Other comparisons
5	Studies that analyse the effect of vaginal examinations in the context of PROM	Studies that do not analyse the effect of vaginal examinations in the context of PROM
6	Papers published in all languages	Not applicable
7	Papers published since the start of the database (No time limit)	Not applicable

3.3.4 Results

When the search strategy was implemented by combining the string of key words with the MeSH headings or subject headings (as applicable depending on the database), only 2 results results were retrieved, and they were not primary research, these were only literature reviews.

In view that no primary studies were retrieved, it was decided that the systematic review that answered the research question as a whole had to stop here. It served the purpose of finding the gap in the literature. However, it was also decided that it would be necessary to systematically find out what had been published in each subtopic by breaking down the research question into three more simple questions and making systematic searches in order to find out what had been published in each subtopic. This is explained in the next section of this chapter.

3.4 Systematic reviews 1, 2 and 3

3.4.1 Aims

- To identify primary research that answers the following three research questions:

    1) For term prelabour rupture of membranes, is expectant management associated with a lower rate of chorioamnionitis compared to active management?

    2) For term prelabour rupture of membranes, is expectant management associated with a higher rate of normal birth compared to active management?

    3) For term prelabour rupture of membranes are vaginal examinations associated with chorioamnionitis?

- To provide a narrative overview of the findings of included studies
- To provide an overview of the changes in management in time

3.4.2 Search strategy

Once it was identified that the primary question had to be broken down into three more simple questions, the following three PICO diagrams were designed and a list of key words was identified for each domain, as well as the relevant MESH/subject headings for each database, as outlined in tables 3.4 on page 70, table 3.5 on page 72 and table 3.6 on page 74.

The three research questions stated below refer to term pregnancy (36 weeks or more). The searches were performed in general without specifying gestational age but later were screened manually for term pregnancy. This is because it was the approach that identified more studies. The studies that referred to pre-term were excluded manually. The search was carried out in the same databases mentioned at the beginning of this chapter (Medline, Embase, Matenity and Infant care, CINALH, LILACS).

3.4.3 Inclusion criteria

The inclusion and exclusion criteria for these three simpler questions remained the same as explained in table 3.3 on page 67, with the execption of two criteria, criterionn number 4 (Studies that compare expectant vs active management) that it was only

applicable for research question 1 and 2, and criterion 5 (Studies that analyse the effect of vaginal examinations) that it was only applicable for question 3. Therefore for research questions 1 and 2 all the criteria listed in table 3.3 on page 67 applied except criterion 5, whereas for research question 3, all criteria applied except criterion 4. The three research questions refer to term pregnancy (36 weeks or more). The searches were performed in general without specifying gestational age but later were screened manually for term pregnancy. This is because it was the approach that identified more studies. The studies that referred to pre-term were excluded manually.

Question 1

For prelabour rupture of membranes, is expectant management associated with a lower rate of chorioamnionitis compared to active management?

Table 3.4: PICO diagram for question 1

P	**I**	**C**	**O**
problem	**Intervention**	**Control**	**Outcome**
Prelabour rupture of membranes	**Expectant management**	**Active management**	**Chorioamnionitis**
"prelabour rupture of membranes"	"expectant management"	"induction of labour"	infection
or	or	or	or
"prelabor rupture of membranes"	"conservative management"	"active management"	"maternal infection"
or	or	or	or
"premature rupture of membranes"	"wait and see"	"aggresive management"	"infectious morbidity"
or	or	or	or
"PROM"	"watchful waiting"	pitocin	"maternal sepsis"
or		or	or
"ruptured fetal membranes"		oxytocin	"intra-amniotic infection"
or			or
"ruptured foetal membranes"		prostaglandin	"intraamniotic infection"
or			or
"prolonged rupture of membrane"		prostaglandins	chorioamnionitis
or			
"prolonged rupture of membranes"			
or			
"fetal membranes"			
or			
"foetal membranes"			

[(Mesh heading: Fetal membranes, premature rupture/) OR (List of key terms for Prelabour rupture of membranes)] AND [(Mesh heading: Watchful waiting/) OR (List of key terms for expectant management)] AND [Mesh heading: labour, induced/ OR (List of key terms for Active Management)] AND [(Mesh heading: Chorioamnionitis/) OR (List of key terms for chorioamnionitis)]

Results

- Medline: 41 hits – out of these 41, read title and abstract and 19 are relevant.
- Embase: 51 hits, out of these, 24 were relevant after having read the title and abstract
- Maternity and Infant care: 36 hits, out of these, 22 were relevant after having read the title and abstract
- CINALH: 0
- LILACS: 0

Rest were excluded because of the following reasons: population was preterm, different topic or because it was a literature review and not primary studies.

Total search 1: 65, after removing duplicates = 31

Question 2

For prelabour rupture of membranes, is expectant management associated with a higher rate of normal birth compared to active management?

Table 3.5: PICO diagram for question 2

P	**I**	**C**	**O**
Problem	**Intervention**	**Control**	**Outcome**
Prelabour rupture of membranes	**Expectant management**	**Active management**	**Normal birth**
"prelabour rupture of membranes"	"expectant management"	"induction of labour"	"mode of birth"
or	or	or	or
"prelabor rupture of membranes"	"conservative management"	"active management"	"normal birth"
or	or	or	or
"premature rupture of membranes"	"wait and see"	"aggresive management"	"normal delivery"
or	or	or	or
"PROM"	"watchful waiting"	pitocin	"physiological birth"
or		or	or
"ruptured fetal membranes"		oxytocin	"physiological delivery"
or			
"ruptured foetal membranes"		prostaglandin	"Spontaneous vaginal birth"
or			or
"prolonged rupture of membrane"		prostaglandins	"spontaneous vaginal delivery"
or			or
"prolonged rupture of membranes"			SVD
or			or
"fetal membranes"			vaginal delivery
or			or
"foetal membranes"			natural birth

[(Mesh heading: Fetal membranes, premature rupture/) OR (List of key terms for Prelabour rupture of membranes)] AND [(Mesh heading: Watchful waiting/) OR (List of key terms for expectant management)] AND [Mesh heading: labour, induced/ OR (List of key terms for Active Management)] AND [Mesh heading: Delivery, Obstetric/ OR (List of key terms for normal birth)] =

Results

- MEDLINE: 51 hits – Read title and abstract and 24 are relevant.
- Embase: 10 hits- Read title and abstract and 5 were relevant
- Maternity and Infant care: Read title and abstract and 8 were relevant
- CINALH: 0
- LILACS: 0

Rest were excluded because of the following reasons: population was preterm, different topic or because it was a literature review and not primary studies. Total search 2: 37hits, after removing duplicates: 29 hits

Question 3

For prelabour rupture of membranes are vaginal examinations associated with chorioamnionitis?

Table 3.6: PICO diagram for question 3

P	I	C	O
problem	**Intervention**	**Control**	**Outcome**
Prelabour rupture of membranes	**Vaginal examination**	**Not applicable**	**Chorioamnionitis**
"prelabour rupture of membranes"	"vaginal examination"	Not applicable	infection
or	or		or
"prelabor rupture of membranes"	"vaginal examinations"		"maternal infection"
or	or		or
"premature rupture of membranes"	"internal examination"		"infectious morbidity"
or	or		or
"PROM"	"internal examinations"		"maternal sepsis"
or	or		or
"ruptured fetal membranes"	"cervical examination"		"intra-amniotic infection"
or	or		or
"ruptured foetal membranes"	"cervical examinations"		"intraamniotic infection"
or	or		or
"prolonged rupture of membrane"	"digital examination"		chorioamnionitis
or	or		
"prolonged rupture of membranes"	"digital examinations"		
or			
"fetal membranes"			
or			
"foetal membranes"			

[(Mesh heading: Fetal membranes, premature rupture/) OR (List of key terms for Prelabour rupture of membranes)] AND [(List of key terms for Vaginal examination)] AND [Mesh heading: Chorioamnionitis/ OR (List of key terms for Infectious morbidity)]

- MEDLINE: 47 hits. And after reading title and abstract, 19 were relevant and met inclusion criteria.
- Embase: 45 hits, 21 relevant and met inclusión criteria
- Maternity and Infant care: 36 hits, 18 relevant
- CINALH: 1
- LILACS: 0

Total search 3: 58 hits, after removing duplicates 36

3.4.4 Summary of the results obtained through these three searches

This section presents a summary of the results obtained through the breakdown of the overall research question into three more simple research questions. Figure 3.1 on page 76 presents a visual summary of the results obtained through the three searches mentioned earlier. This figure shows the number of papers that were relevant and met the inclusion criteria prior to assessing their quality.

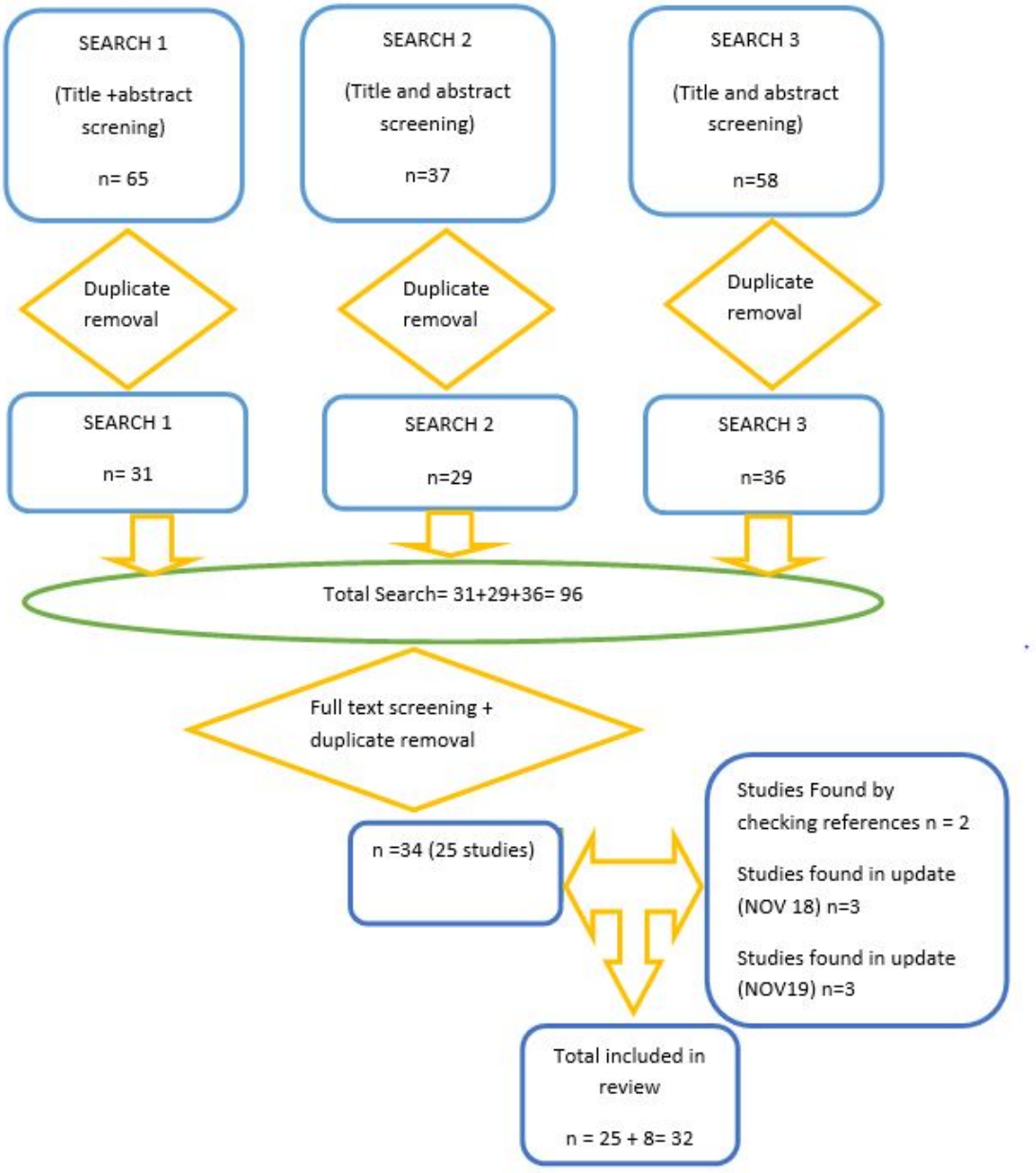


Figure 3.1: Summary of results from the three searches

3.4.5 Quality assessment

The quality assessment of the research studies is a crucial phase in systematic literature reviews, because in order to synthesise what has been published in regards to a topic, one has to make sure that conclusions are based on quality research that is reliable and can be trusted. There are several published tools to aid the quality assessment of research studies, as well as different tools depending on the type or methodology of the research.

The quality assessment process carried out in the systematic review included in this thesis, has been drawn upon the CASP tools (Critical Appraisal Skills Programme, 2018a; Critical Appraisal Skills Programme, 2018b; Critical Appraisal Skills Programme, 2018c), and the Cochrane risk of bias assessment tool developed by Higgins et al. (2019). This was because this systematic review included observational studies, as well as randomised controlled trials, and I wanted to develop a list of questions that was easy to use and that it would cover and assess the main risks of bias in the clinical trials as well as in the observational studies. Therefore I created a list of 13 questions for the RCTs and a list of 12 questions for the observational studies. Tables 3.7 on page 79 and 3.8 on page 80 present the questions that were used to assess the quality of the RCT and observational studies respectively, and which published tool they came from.

Although the risk of bias assessment tool developed by Higgins et al. (2019) is well known and well acepted by the academic community to assess the quality of RCT, I decided to add some of the questions and concepts developed by the Critical Appraisal Skills Programme because they would contribute to assess the quality of all the studies included in this systematic review including the observational studies. The implications of this choice are that two similar lists of questions were created that made the process of assessing the quality of the studies less complicated, without compromising the quality assessment. Both, the Cochrane risk of bias assessment tool and the Critical Appraisal Skills Programme are deemed good tools to assess the quality of the studies. Furthermore, the results from the systematic review presented in this thesis are in agreement with a recent cochrane systematic review published by Middleton et al. (2017) in that the quality of most studies in this topic is generally low.

Since there was a high degree of heterogeneity in the outcomes to be measured and it was not possible to do meta-analysis, I decided to list in this thesis all the studies that were found in the searches that met the criteria, and no studies have been omited

due to their quality. Tables 3.9, 3.10, 3.11, 3.12, 3.13, 3.14 and 3.15 in pages 81 to 93 present and provide a brief summary of all the studies that were found that met the inclusion criteria stated on table 3.3 on page 67.

As mentioned earlier, a total of 13 questions were formulated to be answered by each RCT study, and 12 questions for observational studies, therefore, all the studies were given a score between 0 and 12 or 13, in which 0 indicated very poor quality and 12-13 extremely good quality and then a percentage was obtained, for example 8/13 (61.5%). In these tables the main quality standards are described, such as how the group allocation took place, outcomes or any other bias that were identified. In order to maintain consistency and rigor, in the case of RCT studies where it was not clear what the primary and secondary outcomes were or in cases where these were not stated, these papers were given a score of 0 as an answer to question: "Were the primary and secondary outcomes clearly stated?". Also in the case of RCT studies, if the randomisation system used was either not stated or the allocation to treatment was done by the day of the week, or the number of the hospital number or by means of sealed envelopes, these studies were given a score of 0 as an answer to the question "In the case of RCT, was the allocation to treatment randomised?". It was decided a priori that studies that had a total score of eight or over would be considered good quality. Table 3.16 on page 101 presents a summary of the studies of good quality.

Table 3.7: Quality assessment questions for RCT studies

Question Number	Question	Original tool
1	Did the study address a clearly focused issue?	CASP
2	Did the study clearly stated primary and secondary outcomes?	Cochrane
3	Did the study have enough statistical power?	Cochrane
4	If it was a trial, was the assignment of patients to treatments randomised?	CASP
5	Were participants or staff blinded?	CASP
6	Was there any blinding for the outcome assessment?	Cochrane
7	Were the characteristics of the groups similar?	CASP
8	Were the groups treated differently (except for the intervention)?	CASP
9	Were all the participants accounted for at its conclusion?	CASP
10	Number of participants with missing outcome data	Cochrane
11	Selective reporting?	Cochrane
12	Other important bias identified?	Cochrane
13	Were all the clinically important outcomes considered?	CASP

Table 3.8: Quality assessment questions for observational studies

Question Number	Question	Original tool
1	Did the study address a clearly focused issue?	CASP
2	Did the study clearly stated primary and secondary outcomes?	Cochrane
3	Did the study have enough statistical power?	Cochrane
4	Were participants or staff blinded?	CASP
5	Was there any blinding for the outcome assessment?	Cochrane
6	Were the characteristics of the groups similar?	CASP
7	Were the groups treated differently (except for the intervention)?	CASP
8	Were all the participants accounted for at its conclusion?	CASP
9	Number of participants with missing outcome data	Cochrane
10	Selective reporting?	Cochrane
11	Other important bias identified?	Cochrane
12	Were all the clinically important outcomes considered?	CASP

Table 3.9: RCT studies comparing Immediate IOL vs EM up to 12h.

First author, year Country	**Type of study**	**Total N of participants n per group**	**Intervention & comparison**	**Outcomes**	**Results**	**Quality**
Poornima, 2011 India	RCT Doesn't state randomisation method	N=100 n_1=50 n_2=50	G_1: Immediate IOL with PGE_2 (Max 2 doses/6h apart) G_2:Expectant up to 12h. Followed by IV oxytocin if needed	Primary & secondary not stated Outcomes: Length of SROM Length of time between SROM and cervical dilatation=3cm Length of active labour Clinical chorioamnionitis clinical neonatal infection Definitions for chorioamnionitis and neonatal infection not given Number of VEs NOT reported	More Spontaneous labours, more vaginal births, less CS in EM. No significant differences in infections. CS: G_1=40% G_2=27% Clinical chorioamnionitis: G_1=0 G_2=0 Clinical neonatal infection: G_1=2/50(4%) G_2=2/50(4%)	5/13 (38.5%)
Ray, 1992 USA	RCT Randomisation list mantained by pharmacy staff	N=140 n_1=40 n_2=55 n_3=45	G_1: Immediate IOL with PGE_2 (max 2 doses/6h apart) G_2: Immediate IOL with oxytocin G_3: Expectant up to 12h G_1 & G_3 were blinded	Primary & secondary not stated Outcomes: Length of SROM CS, Chorioamnionitis and neonatal sepsis Number of VEs not reported	No SSD between the 3 groups in CS No cases of neonatal infection Shorter length of SROM with PGE_2 than IV oxytocin or placebo definition of chorioamnionitis only temperature $\geq 38^{\circ}$C reported maternal infection instead of chorioamnionitis Results provided only % not absolute numbers. CS: Nulliparous: G_1= 14.5% G_2=20.7% G_3=19% Multiparous: G_1=0 G_2=15.3% G_3=12.5% Maternal infection: Nulliparous: G_1=9.5% G_2=34.5% G_3=33.3% Multuparous: G_1=0 G_2=11.5% G_3=8.3%	5/13 (38.5%)

Table 3.10: RCT studies comparing IOL at 12h vs EM up to 24h.

First author, year Country	**Type of study**	**Total N of participants n per group**	**Intervention & comparison**	**Outcomes**	**Results**	**Quality**
Granstrom, 1995 Sweden)	RCT allocation by drawing a sealed & numbered envelope	N=181 n_1=91 n_2=90	G_1:IOL at 12h G_2:IOL at 24h	Primary & secondary not stated Outcomes: Length of SROM Length of labour CS Number of VEs NOT reported	EM resulted in higher incidence of spontaneous ripening of the cervix combined with spontaneous onset of labour and spontaneous vaginal delivery maternal and neonatal complications were similar in both groups No significant differences in: length of SROM length of labour or instrumental births. More CS in G_1 CS: G_1:11/91(12%) G_2:7/90(8%) No definition of chorioamnionitis, suspected infection, or neonatal infection Swabs were taken from all babies with or without symptoms of infection Positive bacterial cultures in neonates were similar in both groups: G_1:30/91(33%) vs G_2:26/90(29%)	7/13 (53.8%)
Moberger, 1997 Sweden	Quasi-RCT Allocated at random doesn't say how according to the cervix (favourable/unfavourable) Unclear if stratification by cervical ripeneness	N=380 n_1=Doesn't say n_2=Doesn't say	G_1: IOL at 12h. G_2: IOL at 24h.	Primary: Neonatal outcome other: CS Number of VEs NOT reported	Perinatal mortality=0 No SSD in admissions to NICU spontaneous births, inductions, instrumentals, length of labour antibiotics in the mother Chorioamnionitis not defined or reported only signs of infection in the mother, doesn't say when or which signs Neonatal infection not clearly reported, suspicious and definitive neonatal infection reported together Neonatal infection: G_1=9 cases G_2=6 cases CS:G_1=8% G_2=6%	3/13 (23.1%)

Table 3.11: RCT studies comparing Immediate IOL vs EM up to 33h

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Akyol, 1999 Turkey	RCT	N=126 (underpowered) n_1=52 n_2=74	G1: Inmediate IOL with IV oxytocin G2: Expectant up to 24h followed by IOL with IV oxytocin Participants in EM were offered an elective CS if necessary	Primary: Definitive or probable neonatal infection Secondary:CS Reports number of VEs	Selective reporting: It does not mention cases of probable or definitive neonatal infection CS: G1(AM)=10/52(19.2%) G2(EM)=21/74 (28.4%)	7/13 (53.8%)
Ayaz, 2008 Saudi Arabia & Pakistan	Quasi RCT Participants chose 1 of 2 cards labelled as S or C S=Study C=Conservative	N=84 n_1=42 n_2=42	G1: Immediate IOL with oral misoprostol (every 4h, max 4 doses) G2: Expectant up to 24h	Does not specify primary or secondary outcomes Reports: Interval from SROM to onset of labour interval from SROM to delivery CS and vaginal delivery maternal & neonatal complications No definition for: neonatal sepsis or chorioamnionitis No mention of N of VE	The interval between SROM and onset of labour and between SROM and delivery was significantly shorter in the study group Higher rate of CS in EM Women were offered a CS if not in labour by 24h of EM	5/13 (38.5%)
Bashir, 2017 Pakistan	Quasi-experimental allocation by randomisation	N=120 n_1=60 n_2=60	G_1: Immediate IOL (PGE2 or oxytocin) G_2: Expectant up to 24h	Primary/secondary not stated Outcomes: Mode of delivery Neonatal infection Endometritis Fetal dystress NICU admission $\geq$24h. Post-partum pyrexia Endometritis Mean Hospital stay	No significant difference in: Mode of delivery Neonatal infection Endometritis hospital stay endometritis more postpartum fever in EM Number of VEs NOT reported	6/13 (46.2%)
Chung, 1992 Hong Kong	RCT Allocated by computerized set of random numbers	N=59 n_1=30 n_2=29	G1: Inmmediate IOL (during the first 12h) with PGE2 G2: Expectant up to 24h with placebo (KY jelly)	Length of SROM at onset of labour and at delivery Length of labour CS rate No mention of Number of VEs	Women who received PGE2 went into labour sooner and gave birth earlier. 1 case of uterine rupture in G1 Chorioamnionitis not reported No significant differences in: duration of labour operative delivery There were no cases of neonatal infection	6/13 (46.2%)

Table 3.11: RCT studies comparing Immediate IOL vs EM up to 33h

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Da Graca Krupa, 2005 Brazil	RCT Randomised by envelopes	N=150 n_1=75 n_2=75	G_1: Inmediate IOL with misoprostol (PGE1) max 4 doses of 25mg at 6h intervals followed by IV oxytocin if needed G_2: Expectant up to 24h followed by IOL with IV oxytocin if needed	Primary: Time from recruitment to delivery Secondary: Latency period length of hospitalization CS rate contractility pattern labour and delivery complications maternal & neonatal morbidity Chorioamnionitis was not reported No mention of Number of VEs	Latency period and time from recruitment to birth was shorter in G1 More hypercontractility and tachysystole in G1 No significant differences in CS or Apgar scores No cases of neonatal infection or admissions to NICU reported)	7/13 (53.8%)
Fatima, 2015 Pakistan	RCT Lottery method	N=200 n_1=100 n_2=100	G_1: Immediate IOL with PGE1 (Misoprostol) G_2: Expectant up to 24h	Primary/secondary not stated Outcomes: IOL to labour interval Length of labour Mode of delivery Apgars at 5min NICU admission	Shorter IOL to labour interval in G1 Maternal fever: G2 (10%) vs G1(3.33% No significant diferences in: Length of labour Modeo of birth admissions to NICU Apgar score Neonatal complications Number of VEs NOT reported)	6/13 (46.2%)
Grant, 1992 UK	RCT Opaque & sealed envelopes	N=444 n_1=219 n_2=225	G_1: Immediate IOL with oxytocin G_2: Expectant up to the following morning (9–33h) followed by IV oxytocin if needed	Primary: CS Other: Length of latent phase Length of active labour Analgesia VEs Maternal pyrexia (T$\geq$ 37.1°C) in $\geq$1 occassions neonatal infection	Fewer women in G_2 had $\geq$4VEs Neonatal infection assessed by neonatologist not aware of allocation, but definition not given. Chorioamnionitis not reported. CS: G1:38/219(17%) G2:25/225(11%) SVD: G1:113/219(52%) G2:141/225(63%) VEs: (continuous) M(SD): G1:2.84(1.36) G2:3.37(1.42) Neonatal infection: G1:0 G2:1/225(0.4%)	9/13 (69.2%)

Table 3.11: RCT studies comparing Immediate IOL vs EM up to 33h

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Javaid, 2008 Pakistan	RCT Does not mention how randomisation or allocation took place	N=100 n_1=50 n_2=50	G_1:Immediate IOL (oral misoprostol) G_2: Expectant up to 24h	Primary outcome not stated only mentions "maternal & fetal outcomes" It looks at: CS Length of hospital stay need for augmentation clinical chorioamnionitis (not defined) Postpartum fever Infected wound after CS PPH Neonatal morbidity (not defined) Admission to NNU	No tables provided No absolute numbers provided Only percentages or higher/lower statements but not specific numbers Chorioamnionitis: G_1:3% G_2:7.8% CS: G_1:24% G_2:34%	2/13 (15.4%)
Mahmood, 1995 Scotland (UK)	RCT Randomised list & sealed envelopes	N=100 n_1=50 n_2=50	G_1: Immediate IOL with PGE2 (1mg/dose, 6h apart, max 2doses) G_2: Expectant up to 24h.	Primary & secondary not stated Outcomes: Length of SROM need for IV oxytocin need for analgesia Number of VEs NOT reported chorioamnionitis NOT reported No definition of neonatal infection	Time from SROM–onset of labour & total length of SROM longer in EM No significant differences in: CS, need for IV oxytocin meconium intrapartum pyrexia length of 2nd stage PPH, apgars and IV ATB for baby	5/13 (38.5%)
Maqbool, 2014 Pakistan	RCT allocated by "lottery method"	N=560 n_1=280 n_2=280	G_1: Immediate IOL with PGE1 (misoprostol) 100 µg up to 5 doses/4h apart G_2 :Expectant up to 24h	Primary & secondary not stated Outcomes: Type of birth chorioamnionitis No definition for chorioamnionitis Number of VEs not reported	More CS and chorioamnionitis in EM	4/13 (30.7%)

Table 3.11: RCT studies comparing Immediate IOL vs EM up to 33h

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Shetty, 2002 UK	RCT (Sealed envelopes)	N=61 n_1=30 n_2=31	G_1: Immediate IOL with oral misoprostol G_2: Expectant up to 24h Followed by Prostaglandins or IV oxytocin depending on Bishop score	Primary: Number of women in active labour within 24h since rupture of membranes Assess patient's preference for management Secondary:Total length of SROM (from SROM till Birth) Spontaneous vaginal delivery Instrumental CS Number of VEs Maternal Pyrexia Chorioamniniotitis not defined Chorioamnionitis not reported Admission to NNU Neonatal infection not defined Neonatal infection not reported	More active labour within 24h in G_1 G_1:28/30 (93.3%) G_2:17/31(54.8%) No significant difference in: satisfaction maternal or neonatal outcomes Number of VEs	7/13 (53.8%)
Wagner, 1989 USA	Quasi–RCT Randomised by last digit in participants' medical records even number: EM odd number: AM	N=182 n_1=86 n_2=96	G_1: Immediate IOL with oxytocin G_2: Expectant up to 24h.	Doesn't state primary/secondary ouctomes Outcomes: Length of SROM CS Intra–amniotic infection neonatal infection endometritis Number of VEs reported	No significant differences in CS, neonatal infection & endometritis No cases of clinical intra-amniotic infection All placentas had histologic exam 25% showed inflammatory signs (Histologic chorioamnionitis) None symptomatic All neonatal infections ocurred in those who had a VE on enrolment in the study CS: G1=12/86(14%) G2=15/96(15.6%) Neonatal infection: G1=0 G2=5/96(5.2%)	5/13 (38.5%)

Table 3.12: RCT studies comparing Immediate IOL vs EM up to 48h.

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Natale, 1994 Canada	RCT Does not mention how randomisation took place	N=262 (Underpowered) n_1=129 n_2=133	G_1: IOL at 8h since SROM G_2: Expectant up to 48h	Primary: CS Secondary: Clinical neonatal-maternal infection Number of VEs NOT reported	No SSD in CS More spontaneous labours in EM Neonatal sepsis not defined Neonatal sepsis not reported Only reported admissions to NICU Reported antibiotics given—not necessarily related to treatment but to hospitals' protocols Chorioamnionitis not defined only reported findings from histological exam of placentas not how many participants had clinical signs of infection CS: G_1=11.2% G_2=13.1% Histologic chorioamnionitis: G_1=20.2% G_2=33.3%	8/13 (61.5%)
Ottervanger, 1996 The Netherlands	RCT randomisation by sealed & opaque envelopes)	N=123 n_1=61 n_2=62	G_1: Immediate IOL with oxytocin G_2: Expectant up to 48h	Primary: CS Secondary: Instrumental births use of analgesia maternal infectious morbidity neonatal infectious morbidity neonatal re–admission Number of VEs NOT reported Powered to CS stopped earlier interim analysis revealed significant differences in CS	More spontaneous labours in EM More CS and Instrumentals in AM Similar length of labour in both groups Chorioamnionitis not defined Only reported maternal infectious morbidity Not clear if that relates to chorioamnionitis endometritis or both Neonatal infection not defined No cases of neonatal infection All participants had cervical cultures and all babies had gastric aspirates' cultures and section of the cord was sent to histopathology High rates of positive cultures and histological examination Low numbers of clinical signs of infection in women or babies CS: G_1=4/61(6.6%) G_2=2/62 (3.2%) Maternal infectious morbidity: G_1=1/61(1.6%) G_2=2/62(3.2%) neonatal infectious morbidity: G_1=0 G_2=0	8/13 (61.5%)

Table 3.12: RCT studies comparing Immediate IOL vs EM up to 48h.

First author, year Country	**Type of study**	**Total N of participants n per group**	**Intervention & comparison**	**Outcomes**	**Results**	**Quality**
Van der Walt, 1989 South Africa	Quasi–RCT (allocated according to a numerical list kept on Labour ward)	N=60 n_1=20 n_2=20 n_3=20	G_1: Immediate IOL with IV oxytocin G_2: Immediate IOL with PGE_2 G_3: Expectant up to 48h.	Does not state primary or secondary outcomes Outcome of labour maternal & neonatal welfare Time between SROM and active labour (3cm) Length of labour (3cm–delivery) CS Endometritis defines chorioamnionitis but does not report it Number of VEs NOT reported	In G_3(EM):90% had spontaneous labour No cases of CS Active labour was shorter in G_3 than G_1 and G_2 EM and AM with PGE_2 more effective than AM with IV oxytocin No CS in G_2 and G_3 No significant maternal morbidity 1 case of neonatal positive blood cultures but does not say which group Bias: Failed IOL defined as no spontaneous labour within 12h in G_1 whilst participants in G_2 were given 18h (3 doses/6h apart) No cases of neonatal death No cases of endometritis EM not led to higher infection rate CS: G1:6/20(30%) G2=0 G3=0 Neonatal sepsis: G1: 1/20 (5%) G2=0 G3=0	3/13 (23.1%)

Table 3.13: RCT studies comparing Immediate IOL vs EM up to 96h.

First author, year Country	**Type of study**	**Total N of participants n per group**	**Intervention & comparison**	**Outcomes**	**Results**	**Quality**
Hannah, (1996)) TERMPROM International multicentre 9 published papers	RCT	N=5,041 n_1=1,258 n_2=1,259 n_3=1,263 n_4=1,261	G_1: Immediate IOL with IV oxytocin G_2: Immediate IOL with prostaglandins G_3: EM up to 96h folllowed by IOL with IV oxytocin G4: EM up to 96h followed by IOL with prostaglandins if needed	Primary: Neonatal infection Secondary: CS + Women's views Number of VEs were reported	No significant differences for: neonatal infection CS and chorioamnionitis (when using prostaglandins)	9/13 (69.2%)
Rydhstrom, 1991 Sweden	RCT (Sealed envelopes)	N=369 (under powered) n_1=139 n_2=138	G_1: Immediate IOL with oxytocin G_2:Expectant up to 80h.	Primary:obstetric intervention: composite of CS or Instrumental birth and short term neonatal morbidity Other: Length of SROM fever, antibiotics neonatal morbidity: Pneumonia, sepsis meningitis. Number of VEs not reported Power calculation based on reducing rate of obstetric intervention and abnormal CTG by 50% (N=700) Stopped sooner because interim analysis revealed hypothesis could not be tested	No statistical differences in: CS, instrumentals, CTG traces. No definition of abnormal CTG trace. Chorioamnionitis not reported. Only intrapartum fever $\geq 38^{\circ}$C during 1st stage of labour, more cases of fever in those with epidural. No SSD in endometritis. More neonatal infectius morbidity in G_2, but doesn't say exactly what, as it is a composite could be: pneumonia, sepsis, meningitis pemphigus or impetigo does not define sepsis. CS: G_1=4/139(2.9%) G_2=5/138(3.6%) Neonatal infection: G_1=1/139 G_2=6/138(4.3%)	5/13 (38.5%)

Table 3.13: RCT studies comparing Immediate IOL vs EM up to 96h.

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Yasmin, 2013 Pakistan	Quasi-experimental Participants could choose allocation group if they didn't want to the clinician chose 87% were unable to decide	N=100 n_1=50 n_2=50	G_1: Immediate IOL with PGE_2 G_2: Expectant up to 72h	Primary & secondary not stated maternal & fetal complications length of hospital stay mode of birth costs mentions number of VEs less in EM but not significantly different but doesn't report figures	No definition for SVD. More SVD in EM, less CS in EM. No significant differences in: CS, Instrumentals, neonatal sepsis Chorioamnionitis not reported. Although it says 1st cause of CS was chorioamnionitis. Only mild intrapartum fever reported, doesn't give exact figures and doesn't specify what mild fever is. More mild intrapartum fever in EM. Doesn't report results on epidurals. Costs were higher in AM SVD: G1=30/50(60%) G2=40/50(80%) p<0.05 CS: G1=11/50(22%) G2=6/50(12%) p=0.28 Neonatal sepsis: G1=1/50(2%) G2=1/50(2%)	5/13 (38.5%)

Table 3.14: RCT studies comparing Immediate IOL vs EM with no time limit

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Alcalay (1996) Israel	Quasi RCT Randomised by table of random numbers	N=154 n_1=74 n_2=80	G1: Immediate IOL with IV oxytocin G2: EM (no limit)	Doesn't specify primary or secondary outcomes Reports: SVD, CS, Number of VEs, Neonatal infection and Chorioamnionitis	More SVD in EM EM is safe No statistically significant differences in CS, neonatal infection or chorioamnionitis	7/13 (53.8%)
Duff, 1984 USA	Quasi-RCT Group allocation based on the day of the week of patien's admission to hospital	N=134 n_1=59 n_2=75	G_1: IOL by 12h with IV Oxytocin G_2: EM with no time limit	Primary/secondary not stated Outcomes: Length of labour Length of SROM CS Intra-amniotic infection Endometritis proven neonatal sepsis Number of VEs NOT reported	G_1had more intra-amniotic infection, more CS and longer labours. CS: G1=12/59(20%) G2=6/75(8%) p<0.005 Intra-amniotic infection: G1=10/59 (17%) G2=3/75(4%) p<0.005 Proven neonatal sepsis: G1=1/59(1.7%) G2=0	7/13 (53.8%)
McCaul, 1997 USA	RCT Computer generated random group allocation	N=96 n_1=36 n_2=25 n_3=35	G_1: Expectant (Unclear how long) G_2:IOL with Oxytocin at least 4h after SROM G_3:IOL with PGE2 at least 4h after SROM	Primary & secondary not stated Outcomes: CS, Length of SROM Length of labour Length of hospital stay VEs were analysed in G_1 and G_2 but not in G_3 selective reporting	No significant differences in CS, length of labour, neonatal morbidity or neonatal stay No infant required ventilation or treatment for sepsis Longer length of SROM and length of maternal stay in EM than in AM groups neonatal sepsis not defined	4/13 (30.7%)
Morales, 1986 USA	Quasi-RCT Allocated to AM or EM according to day of the week of admission and the hospital case number	N=317 n_1=150 n_2=167	G_1:Immediate IOL with oxytocin G_2:Expectant (No time limit)	Primary & secondary not stated Looks at: Intra-amniotic infection Failed IOL Failure to progress CS Neonatal infection Number of VEs NOT reported	No neonatal infections Less intra-amniotic infection in EM Less CS in EM No difference in length of hospitalization CS: G_1=31/150(21%) G_2=11/167(7%) Intra-amniotic infection: G_1=18/150(12%) G_2=7/167(4%)	5/13 (38.5%)

Table 3.14: RCT studies comparing Immediate IOL vs EM with no time limit

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Tamsen, 1990 Sweden	RCT Does not mention how randomization took place	N=93 n_1=43 n_2=50	G_1:Immediate IOL with oxytocin G_2:Expectant (no time limit)	Primary & secondary not stated Looks at: Time from SROM to active labour Time from active labour to birth Time from SROM to birth Results subdivided by parity Need for augmentation SVD Vacuum extraction CS Admission to NNU >7days Maternal infection not defined Neonatal infection not defined	Shorter time from SROM to birth in AM for both Primiparas & multiparas SVD: G_1=40/43(93%) G_2=40/50(80%) CS: G_1=0 G_2=4/50(8%) Maternal infection: G_1=0 G_2=1/50(2%) Neonatal infection: G_1=0 G_2=2/50(4%)	6/13 (46.2%)

Table 3.15: Observational studies (n=5)

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Ezra (2004) Israel	Observational: retrospective case-control	N=411 n_1=132 (cases) n_2=279 (control)	G1: Cases of PROM with clinical chorioamnionitis or neonatal infection Bias: since either maternal or neonatal infection would clasify to be a case was difficult to analyse which treatment would be best for chorioamnionitis G2 Control: Cases of PROM with no evidence of chorioamnionitis or neonatal infection. Chorioamnionitis def: at least 2 of the following: Maternal temperature > 37.8°C Maternal white cell count > 15,000 Foul smelling liquor Maternal tachycardia >100bpm Fetal tachycardia >160bpm Uterine tenderness	Main outcome measures: Clinical chorioamnionitis and neonatal infection. 2^{o}: C/S, instrumental It compared 3 management options: 1) Immediate IOL 2)Expectant up to 24h 3) Expectant over 24h With 3 comparisons EM>24h vs EM up to 24h EM>24h vs Immediate IOL EM up to 24h vs Immediate IOL The number of VE is reported but only as women with more than 7VEs	The rate of EM for over 24h vs EM up to 24h was higher for cases than controls (46/92 (50%) vs 81/230 (35.2%) The rate of inmmediate IOL vs EM up to 24h was higher for cases than controls (149/198 (75%) vs 46/86 (53%) No statistically significant differences for EM > 24h vs Immediate IOL (46/86 (53%) vs 81/130 (62.3%)	8/12 (66.6%)
Paraiso, 2013 Spain	Observational study Retrospective	N=115 n_1=Doesn't say n_2=Doesn't say	G_1:Immediate IOL with oxytocin G_2:Expectant up to 24h.	Outcomes: CS, maternal & neonatal infection Number of VEs NOT reported	No significant differences in: CS or instrumental births 67% of women in EM went into spontaneous labour Only 1 case of neonatal sepsis in G_1. No cases of endometritis in the study Significant higher incidence in intrapartum pyrexia in G_1 (IOL group) They think it's because IOL process is associated with longer labours and more VEs than spontaneous labours Length of labour not reported Number of VEs not reported Chorioamnionitis not defined fever definition not given neonatal infection not defined Exact figures and proportions not reported Shorter length of SROM in G_1	1/12 (8.3%)

Table 3.15: Observational studies (n=5)

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Sadeh-Mestechkin, 2016 Israel	Observational Retrospective	N=325 n_1=112 n_2=213	G_1: Immediate IOL G_2: Expectant up to 48h.	Primary: maternal or fetal signs of infection chorioamnionitis neonatal sepsis endometritis prolonged materal hospitalizacion Secondary: CS Reported number of VEs	No cases of neonatal infection no significant differences in chorioamnionitis neonatal infection: G1=0 G2=0 Prolonged hospitalizacion: G_1:2/112(1.8%) G_2:15/213(7%)	9/12 (75%)
Shalev, 1995 Israel	Observational study Prospective Non-randomised	N=566 n_1=298 n_2=268	G_1: IOL at 12h. with IV oxytocin G_2:IOL at 72h. followed by oxytocin	Unclear outcomes length of SROM chorioamnionitis pregnancy outcome chorioamnionitis, CS IOL rate length of hospitalization Number of VEs NOT reported	No significant differences in: CS, chorioamnionitis Apgars at 5min, neonatal sepsis Higher IOL in G_1 than G_2 Higher length of hospital stay in EM as women were admitted to hospital whilst waiting for labour to start clinical chorioamnionitis defined as: abdominal pain, fever uterine irritability microbiology invasion of uterine cavity from cultures taken at birth and histologic placental inflamation. Not stated where temperature was taken and what was considered fever. Neonatal sepsis defined as: positive blood culture or cerebro-spinal fluid CS: G_1=14/298(4.7%) G_2=18/268 (6.7%) NS Chorioamnionitis: G_1=35/298 (11.7%) G_2=34/268 (12.7%)NS Neonatal sepsis: G_1=6/298 (2%) G_2=2/268(2.2%) NS	7/12 (58.3%)

Table 3.15: Observational studies (n=5)

First author, year Country	Type of study	Total N of participants n per group	Intervention & comparison	Outcomes	Results	Quality
Zamzami, 2006 Saudi Arabia	Observational case-control	N=344 N_S=172 n_{EM}=118 n_{AM}=54 N_C=172	G_S: Divided in 2 groups chosen by consultant G_{S1}:Immediate IOL with oxytocin G_{S2}:Expectant up to 24h G_C:Women in spontanous labour with intact membranes	Primary & secondary not stated Outcomes: Length of labour Fetal dystress Intrapartum pyrexia CS Apgars Number of VEs NOT reported	No significant differences between control & study groups in CS 3 cases of intrapartum pyrexia in study groups 2 in AM & 1 in EM 0 in control	4/12 (33.3%)

3.4.6 Narrative overview of the results

There were 24 studies included in the review found by the 3 search strategies in 2014 and 2015 explained earlier in this chapter and two found by checking references of references. I updated the systematic review in November 2018, and I run the 3 searches in the 5 databases and found three new studies (Bashir et al., 2017; Fatima et al., 2015; Sadeh-Mestechkin et al., 2016), making a total of 29 studies.

In November 2019, I updated the systematic review again, and run the 3 searches in CINAHL, EMBASE, LILACS, Maternity and Infant care, and MEDLINE, but nothing new was found. In addition, the searches were also performed on CENTRAL. However, it was only possible to use the key terms as the search engine did not allow me to use MESH terms. I found 4 extra RCTs that had been published (Javaid et al., 2008; Shetty et al., 2002; Doungtone & Tanaput, 1999; Tamsen et al., 1990) and 2 RCT that were found on CENTRAL linked to "clinicaltrials.gov", the results from these studies don't seem to have been published, therefore they have not been included in this systematic review. Their titles are: "Nitric Oxide Donor Isosorbide Mono Nitrate for Induction of Labor With Pre-labor Rupture of Membranes" whose principal investigator is Waleed M El khyat and "Premature Rupture of Membranes With a Bishop Score<6: comparison of Medical Induction/Expectant Management" whose principal investigator is Amir Weissman. The studies carried out by Javaid et al. (2008) and Shetty et al. (2002) have been added to table 3.11 on page 83, and the study carried out by Tamsen et al. (1990) has been added to table 3.14 on page 92. The full text from Doungtone and Tanaput (1999) was not found, despite the efforts from the librarias. As a consequence, it has not been added to any of the tables or the review. Therefore, a total of three studies have been added through the last update in November 2019 by adding another database (CENTRAL), making the total number of studies included in this review 32.

Therefore, in total, there are 32 studies included in this review, 27 studies were RCT (Randomised controlled trials) or Quasi-randomised and 5 were observational studies (Ezra et al., 2004; Paraiso et al., 2013.; Sadeh-Mestechkin et al., 2016; Shalev et al., 1995; Zamzami, 2006). In this thesis, what is understood by randomised controlled trial is a study that has a truly random method of allocating participants to the different treatment groups, such as a random list of computer generated numbers or a computer that does the randomisation online, which means it cannot be predicted the treatment

group that the participant will be allocated to. On the other hand, a quasi-randomised trial, is one in which the allocation of participants can be easily predicted, because the study uses a method of allocation that is not random, for example, when the allocation of participants is based on the last digit of the date of birth, or the last digit of the medical record number, for example odd numbers are allocated to group 1 and even numbers to group 2. Using these easily predictable methods to allocate participants to different treatment groups can introduce selection bias into the study. In this systematic review several studies were deemed to be quasi-randomised controlled trials, such as (Moberger et al., 1997; Ayaz et al., 2008; Wagner et al., 1989; Yasmin et al., 2013; P. Duff et al., 1984; Morales & Lazar, 1986).

The 32 studies were conducted all over the world, the TERMPROM was an international multicentric study that was carried out in 6 countries (Canada, UK, Australia, Sweden, Denmark, and Israel), six were undertaken in Europe, five in the USA, one in Canada, one in South America, two in Africa, six in Middle East, and four in Asia. The debate seems very much centred in what management is associated with better clinical outcomes and it compares active versus expectant management. Most of the papers compare immediate induction of labour or up to 12 hours since the rupture of membranes with a length of time in which labour is to start spontaneously (expectant management). Tables 3.9, 3.10, 3.11, 3.12, 3.13 and table 3.14 present the RCT studies found, organised in different tables according to the length of SROM in the expectant management

In regards to the length of time of the expectant management, out of those 27 RCT studies, two studies had expectant labour up to 12 hours, two studies compared IOL at 12 hours vs IOL at 24 hours, 12 studies has a EM up to 33 hours, three studies had an expectant arm up to 48 hours, three RCT had an expectant management up to 96 hours and five RCT did not state a time limit on the expectant management (Alcalay et al., 1996; P. Duff et al., 1984; McCaul et al., 1997; Morales & Lazar, 1986; Tamsen et al., 1990). The other aspect of study in these research studies was what agent/drug is associated with better clinical outcomes, being the three main drugs used to initiate labour: Intravenous oxytocin, prostaglandings (PGE_2) and misoprostol (PGE_1). The systematic review included in this thesis, was not focused on what drugs were used during the induction of labour but on the comparison between expectant and active management. In regards to the primary outcome the majority of studies focused on caesarean section or neonatal infection whereas no studies use "normal birth" or chorioamnionitis as a primary outcome. Making the choice of primary outcomes used

in the study included in this thesis is one of the elements of originality of this PhD. In regards to the quality of studies, the majority of the studies were of poor quality and only four studies had a score of 60% or more, these are (Grant et al., 1992; Hannah et al., 1996; Natale et al., 1994; Ottervanger et al., 1996). The main problems being the lack of clarity or focus in that in most of the times, the primary and secondary outcomes were not stated, the lack of definitions of the outcomes, studies that are not properly randomised (i.e studies where the allocation could be predicted, for example allocation by the day of the week, or the number at the end of the case notes) or cases of selective reporting amongst other issues. The small sample size, was another issue, with the exception of the TERMPROM trial, other studies whose primary outcome was neonatal infection were underpowered. For example, the trial carried out by Akyol et al. (1999), had a sample size of n=126. This is considered underpowered for neonatal infection.

In the case of the TERMPROM, it was found that chorioamnionitis is reported as being higher when women have expectant management in comparison to those who have active management and are induced with IV oxytocin. However, what is not reported is that the difference in chorioamninitis between Active management and Expectant management [78/1259 (6.2%) vs 99/1261 (7.8%)] when inducing with prostaglandins is not statistically significant (X^2=2.446, Dof=1; p=0.104). Figure 3.2 on page 99 provides a graphical representation of these results.

Instead, the results found when inducing with intravenous oxytocin have been generalised, when in fact, if women are induced with prostaglandins, the difference is not significant. Moreover, nowadays women are induced with prostaglandins. Therefore, the results that are relevant to current practice are those in relation to when the induction starts with prostaglandins. However, the rates of chorioamnionitis when the induction is started with prostaglandins have not been actively reported by Hannah et al. (1996).

Seaward et al. (1997) also highlighted that the number of vaginal examinations is the strongest correlator of chorioamnionitis. Figure 3.3 on page 100 shows a graphical representation of the relationship between VEs and chorioamnionitis.

In terms of the clinical outcomes, table 3.16 on page 101, gives a quick overview of the studies with the highest quality and their outcomes.

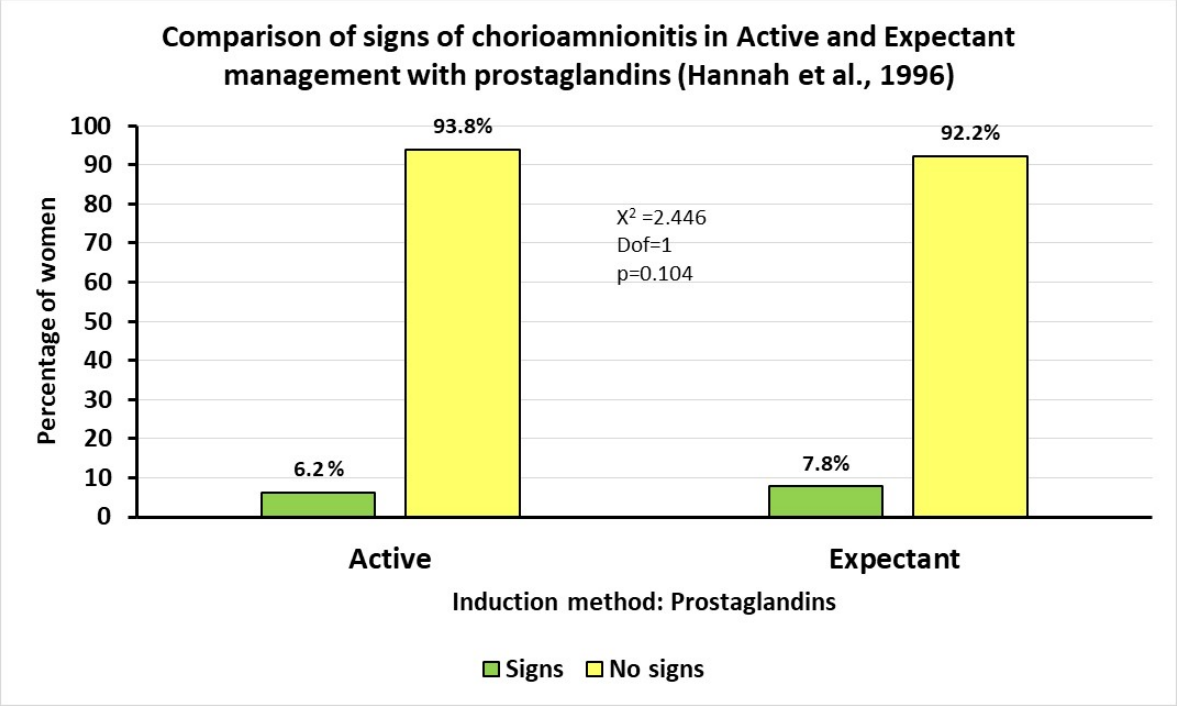


Figure 3.2: Chi-square test results on chorioamnionitis in TERMPROM study

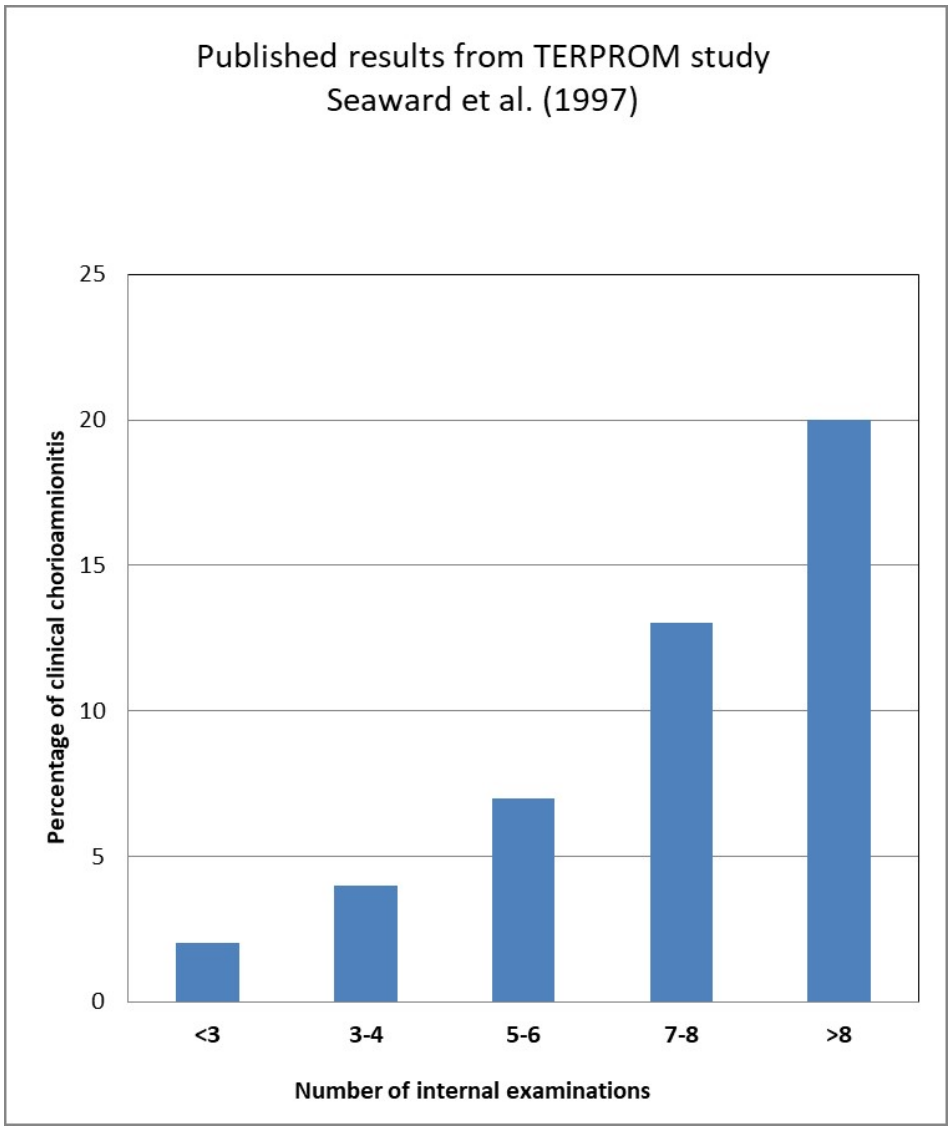


Figure 3.3: Relationship between number of VEs and chorioamnionitis

Table 3.16: Overview of the studies of highest quality

Study ID	First author & year of publication	Chorioamnionitis	Neonatal infection	Caesarean section
Z	Hannah (1996) TERMPROM	Not statistically significant differences when comparing AM vs EM when induction with prostaglendins	Not statistically significant differences	Not statistically significant differences
46	Natale (1994)	More hystologic chorioamninitis in EM Doesn't report how many women had symptoms	Not reported	Not statistically significant differences
47	Ottervanger (1996)	Not statistically significant differences	Not statistically significant differences	G1(AM): 4/61 (6.6%) G2: (EM): 2/62 (3.2%) Not statistically significant differences
Y	Grant (1992)	Not analysed	Not statistically significant differences	Not statistically significant differences

The main study that has informed practice and national and international guidelines is the TermProm study (Hannah et al., 1996) (Hannah et al., 1996) due to its big sample size, as it is the only study that has enough sample size to address neonatal infection as a primary outcome.

The studies conducted by Grant et al. (1992), Natale et al. (1994) and Ottervanger et al. (1996) had CS as a primary outcome but only the studies conducted by Grant et al. (1992) and Ottervanger et al. (1996) had enough statistical power to address CS as a primary outcome.

The number of vaginal examinations during labour appeared to be retrospectively analysed in some studies (Akyol et al., 1999; Grant et al., 1992; Hannah et al., 1996). While a secondary analysis performed by Seaward et al. (1997) on the TERMPROM trial concluded that vaginal examinations are associated with higher rates of infection, I did not find any studies that prospectively do any intervention to try to minimise chorioamnionitis by reducing the number of vaginal examinations.
The studies performed by Akyol et al. (1999) and Grant et al. (1992) reported the number of vaginal examinations, the former as a categorical variable and the latter as a continuous variable. Neither of them conducted any analysis to see if the number of vaginal examinations was associated with chorioamnionitis. Akyol et al. (1999), Hannah et al. (1996), and Grant et al. (1992) analysed the number of vaginal examinations whereas the studies conducted by Natale et al. (1994) and Ottervanger et al. (1996) did not.

3.5 Discussion

The systematic review that addressed the first overall research question helped to show that there is a gap in the literature, because it does not seem to be any prospective studies that have answered the question of whether expectant management and a reduced number of vaginal examinations are associated with a higher rate of normal birth and a lower rate of chorioamnionitis. Therefore, this pilot study and subsequent main study will aim to answer this question and cover this gap in the literature.

Through the process of searching and gathering studies, it also become evident that there are no studies on this topic that looked at normal birth as an outcome, most of the studies looked at reducing caesarean section as opposed to increase normal birth. The Lancet midwifery series supports more studies with normal birth as an outcome

The studies found in section 2 of this chapter, through the breakdown of the overall research question into three more simple questions, identified that the management of prelabour rupture of membranes is a matter of global interest, as there were studies published in the five continents, both in developed and high income countries, as well as in developing countries. Apart from the fact that the use of epidural was reported more often in Europe than other parts of the world, there were no particular trends depending on the country, making the findings more generalisable.

On the other hand, most of the studies were published more than ten years ago, and although the issue of prelabour rupture of membranes has not changed, and women continue to break their waters before going into labour, the practices around birth have developed and nowadays there are different antibiotics specially in the light of the current issues around antibiotic resistance. Concerns around antibiotic resistance further reinforces the need for a conscious and appropriate management of prelabour rupture of membranes and especially new approaches to minimise the risk of infection by reducing vaginal examinations during labour.

It is also important to highlight that most of the studies found were of poor quality, very few had computerised randomisation, the primary and secondary outcomes were not stated or these were not clear, the diagnosis of chorioamnionitis or neonatal infection was not blinded and it was based on clinical signs of infection, the definitions for

chorioamnionitis and neonatal infection varied a lot and in some cases the definitions were not appropriate. These weaknesses meant that it was not possible to perform a meta-analysis due to the high degree of heterogeneity.

3.6 Conclusion

There are no published studies (RCTs or observational) that have looked at expectant management and minimal vaginal examinations during labour. Therefore, it became necessary to break down the question in three simpler questions, and hence, this chapter reports the results of four systematic reviews.

There were 32 studies included in this review, most of them of very poor quality. The poor quality of the available evidence on this matter is consistent with the findings from the most recent Cochrane review on term prelabour rupture of membranes (Middleton et al., 2017). Due to its big sample size and higher quality, the study that still dominates the results of the systematic review is the TERMPROM study conducted by Hannah et al. (1996). The TERPROM study showed that the there is no statistically signifant differences in the rates of neonatal infection. Expectant management with IV oxytocin was associated with a higher incidence of chorioamnionitis than when compared with active management and IV oxytocin (8.6% vs 4% $p<0.001$). However, nowadays most women are induced with prostaglandins. The TERMPROM did not carry out an analysis between chorioamnionitis and prostaglandins, however the descriptive statistics in the form of percentages were presented.

This chapter presents the results from a significance test (chi-square) to determine if the difference in the incidence of chorioamnionitis between expectant management with prostaglandins and active management with prostaglandins is statistically significant. It showed that the difference is not statistically significant (7.8% vs 6.2% $p=0.119$). Due to the high degree of heterogeneity of the main outcomes (Mode of birth and chorioamnionitis), it was not possible to conduct a meta-analysis and simple thematic analysis was carried out instead. The results suggest that expectant management is a safe option for women who want to avoid the induction of labour. Evidence suggests that the rates of infection in mothers and babies were similar when labour was induced with prostaglandins, compared to when labour was allowed to start spontaneously.

Chapter 4: Developmental and Feasibility phase

4.1 Introduction

The previous chapter has shown the results from the systematic reviews and has highlighted the gap that this research is going to cover. This chapter describes the rationale for conducting a feasibility and developmental phase, the methods that were used, the findings and how the findings have helped to inform the study protocol and subsequent phase in this study, the pilot phase. Patient and public involvement (PPI) has been critical in this phase, and this chapter aims to explain how PPI contributed to shape to the design of the study protocol. At the end of the chapter conclusions are drawn followed by a brief discussion about how PPI can contribute to better research.

4.2 Background

The preliminary work carried out prior to a large-scale definitive clinical trial is a critical part in the development of any intervention in health care (Whitehead, Sully, & Campbell, 2014). The term "preliminary work" carried out prior to the large-scale clinical trial, is a very broad concept as it can focus on multiple areas of the future study and can have different aims. Therefore, terms like developmental phase, feasibility and pilot phases or studies are sometimes not very clear and often authors tend to re-define those (Whitehead et al., 2014). This research study has carried out a feasibility phase (the focus of this chapter), followed by a pilot RCT (the focus of the next chapter). The NIHR definitions were adopted.

Feasibility studies as defined by NIHR (2017) are "pieces of research done before a main study in order to answer the question "Can this study be done?". NIHR (2017) outlines some of the objectives that can be addressed by undertaking a feasibility study.

In this study in particular, the focus of the developmental phase was on exploring the willingness of participants to be part of the study, as well as the willingness of clinicians to recruit participants. It also focused on determining the number of eligible patients. Although it is not one of the objectives of the feasibility phase as stated by NIHR (2017), the feasibility phase of this study also focused on developing the study design and documentation for participants by involving the clinicians and the public. Carrying out preliminary work prior to the main study has become a crucial part prior to applying for funding, since many large public funding bodies nowadays expect substantial work to have been done prior to the application for funding as Whitehead et al. (2014) explain. In line with current best practice in RCTs, a feasibility phase was designed. It was decided to undertake this feasibility phase so that the main issues around the implementation of such a study could be explored and addressed before the pilot and main study phases took place. Clinical trials in general face many challenges, such as problems with recruitment (Kaur, Smyth, & Williamson, 2012), loss of participants, poor adherence to the study protocol and a potential poor return of the questionnaires. To address these challenges, I thought that it would be beneficial to involve the staff, patients and the public in a consultation role as part of the feasibility phase, as it could improve the quality of research as well as making it more relevant to the service users (Brett et al., 2014). Involving patients and the public in research can make the research more ethical (Staley & Minogue, 2006), as it explores what is acceptable to service users and what is not, before carrying out the research.

Patient and public involvement has grown in popularity in recent years, and nowadays researchers are encouraged to involve service users in their research due to the belief that it contributes to increase the quality of the research (Brett et al., 2014). In 1996, a government funded program called INVOLVE was established. The National Institute for Health research funds it to support active public involvement in research in the NHS, public health, and social care. Public involvement in research is defined as: *"research being carried out "with" or "by" members of the public rather than "to", "about" or "for" them"* (INVOLVE, 2012, p. 6).

Although the concept of patient and public involvement in research seems to be relatively new, it is in fact something that the World Health Organisation has been advocating since the 1970's. In 1978, the Alma-Ata declaration, stated that *"people have the right and duty to participate individually and collectively in the planning and implementation of their care"* (World Health Organization, 1978, p.1). The updates for the Alma-Ata

declaration, both in 1998 with "Health 21" and in 2005 "Health for all: Policy framework for the WHO European region" maintained the core values of equity, solidarity and participation (World Health Organization, 1998; World Health Organization, 2005;).

The developmental phase was also designed to aid with the design of the information resources for participants, the study questionnaire and the design of the pilot phase that would establish the acceptability and feasibility of the planned study and its procedures. Therefore, in this developmental phase, service users and clinicians took part in discussion groups, where matters such as: the barriers and facilitators to recruitment were discussed, and the acceptability of the information and resources given to participants was checked. The intention was to make sure that the information that future participants were going to receive, met their needs, was relevant and was easy to understand.

4.3 Aims

- To explore the practicalities around the implementation of the planned pilot and main RCT
- To develop a sound recruitment strategy
- To involve women and clinicians in the development of the study
- To develop the information and resources given to participants (participant information sheets, consent forms and participants diary)
- To develop the study questionnaire and perform a face validity check

4.4 Methods

This section describes how the patient and public involvement strategy was undertaken. The developmental stage was subdivided into three stages: The first, exploratory stage addressed the views of women about this study and found out what information they would like to see in the documents that future participants would be be given in the future pilot and main RCT. It also found out what the current practice is and gained ideas for the study design by involving the clinicians in a consultation. The second stage, the design stage focused on developing the study design and study documentation

building on the information obtained in the discussion groups with both women and clinicians. The third and final stage, the consolidation stage, focused on testing that all the documentation was reader friendly and that in contained all the information that women would like to receive. These stages are presented ahead.

Inclusion criteria to take part in the consultation groups

The inclusion criteria to take part in the discussion groups with women were: pregnant women or women who have given birth within the past 12 months, who could speak and understand written English, who were healthy and did not have any mental health issues or learning disabilities and aged 18- 45 years old. For the discussion group with clinicians, there were no other inclusion criteria, other than:

- For the community midwives group: To work as a community or caseloading midwife
- For the hospital midwives group: To work as a core hospital/MLU midwife
- For the managers group: To work as a Band 7 midwife or above
- For the neonatologists group: To work as a neonatologist
- For the obstetricians group: To work as an obstetrician

The recruitment for these discussion groups followed an opportunistic approach. In the case of the discussion groups with women, I contacted the consultant midwife at the host Trust who then put me in contact with one of the local antenatal and postnatal groups that run in the area. These groups are women-led and although hosted by NCT, they are free to attend and no membership is necessary. The woman organising these groups was then contacted and a mutually convenient time for me to attend one of their sessions was organised. Women were aware that I was going to come for a discussion with them prior to the date so they could choose to come or not come and whether to stay in the room where I was going to conduct the discussion or in a different one. Prior to the start of the discussion, I introduced myself and explained the purpose of the discussion as well as what would involve to take part. I also handed in an information leaflet for people to read. Verbal consent was taken by reading a script out loud and they were told that I was assuming consent if they decided to stay in the room. Women were aware that the discussion was intended to be voice recorded although they were given choice about it, if anybody wasn't comfortable with that, I told them that I could

take notes. They were also aware that no personal data was going to be taken, and they were aware of their right to leave the room at any point. The first and second groups were conducted with the same organisation, although completely different people took part (except from the person who led those groups who was present in both). This was because I wanted to capture different opinions and advice. Since they took place a few months apart, women who took part in the first group had finished their maternity leave by the time the second group took place, so although, the aim was to have different people, that is what happened naturally without having to force it.

The third group with women followed the same opportunistic strategy for its recruitment but it was conducted with a different group and organisation. This group was conducted after the meeting with the ethics committee and the purpose of this third meeting with women was to pilot- test the amendments made following the ethics recommendations and to make sure they were still reader friendly. I decided that since we were going to conduct a third group that it would be beneficial to include the voice of antenatal women as in the previous two groups there were only women who had recently given birth within the last 12 months approximately.
This third group was conducted with the help of an organisation called "One to One midwives" who I had conections with due to my work in Warrington. The CEO of that organisation was contacted and they agreed to pass around the participant information sheet for the discussion group around their clients and a group of women (antenatal and postnatal women) was formed and a mutually convenient date and time for the meeting was agreed for me to come to their venue.

In the case of the discussion groups with staff, they followed the same opportunistic principle and I arranged them by contacting the lead of each staff group and asking if I could come to talk to them before or after one of their meetings. For example, in the case of the discussion groups with the neonatologists they invited me to come to one of their monthly meetings where they discuss research. Staff were informed of the purpose of the discussion group in advance. At the beginning of the meeting, I introduced myself and the study and I explained that I intended to voice record the discussion and gave the choice of not recording should anyone felt uncomfortable. They were also informed that no personal data was going to be collected and that they could leave the room at any time. The consent script was read aloud, and consent was assumed if they decided to stay in the room. They all consented to be voice-recorded.

4.4.1 Initial exploratory stage

This phase used qualitative methods (simple thematic analysis). It included, one discussion group with women, to get to know their views about this study, and find out what type of information they would like to see in the documents, that were to be given to participants in the pilot and future large-scale study. It also included five discussion groups with clinicians and stake-holders to understand what happens in current practice in that particular maternity unit and the practicalities that would need to be addressed for the study to run smoothly. In the discussion with women, consisting of pregnant women or women who have given birth in the past 12 months. The following topics were explored:

- If they were asked to join a study like this in the future, what would their thoughts and feelings be about taking part?
- In their view, which features of the management of prelabour rupture of membranes were likely to be important to women (Labour spontaneously, having their labour induced, being able to be assessed and monitored at home during the latent phase by community midwives, coming to hospital to get checked, continuity of care, more chances of having a normal labour, risk of adverse outcomes etc.
- What information the "participant information sheet" should contain to be relevant and useful to women who might be asked to take part in the study in the future.
- Type of information and resources that should appear in the "participant's diary".
- Type of questionnaire/data collection instrument that would be acceptable, understandable and useful for participants.

The five discussion groups with stake-holders were achived by setting up oportunistic discussion groups, to gather the input from the full range of staff likely to be involved in the care of women with prelabour rupture of membranes (community midwives, hospital midwives, managers, research midwives, obstetricians and neonatologists). These were set up at times that were convenient to them and usually before or after a meeting that was already taking place. For example, I was invited to the monthly meeting that neonatologists hold on regular basis, or to the weekly teaching sessions for obstetricians.

In addition, to these group meetings, and due to the suggestion of the head of midwifery,

a number of consultant obstetricians were approached, and one-to-one meetings were set up with them (n=5). This was to ensure that all the members of the multidisciplinary team were on board. Therefore, there were ten discussions in total (five discussion groups with different clinicians and five individual meetings with consultant obstetricians). Each discussion meeting lasted approximately 60minutes and the following topics were explored:

- How to make it as easy as possible for clinicians to call the researcher when identifying a potential participant with history of pre-labour rupture of membranes.
- The potential barriers and facilitators to recruitment
- The ideal process of randomisation, blinding and allocation concealment
- The minimally important difference in rates of chorioamnionitis, neonatal infection and normal birth
- The best place for the researcher to wait for eligible women to come in.
- How to make the protocol/procedures as easy as possible for clinicians.
- The optimal process of taking the swabs, storage and collection.
- For midwives working in the community and for managers: The best way of implementing the regular visits to the homes of women who are randomised to the intervention arm to assess and monitor them, as required by the protocol.

4.4.2 Design stage

Once these discussions groups were undertaken, the information was gathered and organised. The design phase occurred mainly in the office where the pilot RCT documents, such as participant's information sheets, consent forms and participant's diary were developed.

It was clear that the acceptability of the interventions and the experience of women taking part in the pilot RCT needed to be analysed. To do so, different methods and tools were examined during this stage. One to one qualitative interviews to women taking part in the pilot RCT were considered, however due to the time limitations of the doctoral degree, a questionnaire was deemed to be a more feasible choice.

Therefore, different questionnaires were considered such as the "Childbirth experience questionnaire" (CEQ) developed by Dencker et al. (2010), the "Mother-generated index (MGI) developed by Symon and Dobb (2011), and "Women's views of birth labour satisfaction questionnaire" (WOMBLSQ) developed by Smith (2001). The childbirth experience questionnaire was chosen due to its simplicity, the fact that it is focused on the labour and birth process, the high return rate shown in the original study in Sweden (Dencker et al., 2010) and the fact that it was a questionnaire that is available at least in two other languages (Swedish and Spanish), which meant that if the future main study becomes an international study, it will be a questionnaire that has potential to be used in other countries.

During this phase it was also decided how the acceptability of the trial's interventions was going to be measured, and the hence, ten questions were developed for the study specific questionnaire.

Based on the descriptive and thematic analysis of these discussion groups, the following materials were developed:

- Information leaflet for the Pilot RCT
- Consent form for the pilot RCT
- Information leaflet for the observational study
- Consent form for the observational study
- Participant's diary
- Questionnaire

4.4.3 Consolidation stage

Once the resources were designed in draft, the acceptability of the information and resources given to participants was tested during this stage. This was achieved by undertaking a second and third discussion groups, with pregnant women or women who have given birth within the last 12 months. These discussions had a duration of 1 hour approximately, and women were asked to try out and talk about their views on the following material:

- Information leaflet for future participants for the Pilot RCT
- Consent form for the pilot RCT
- Information leaflet for the observational study
- Consent form for the observational study
- Participant's diary
- Questionnaire

The final version of these documents can be seen in the appendix.

The following table 4.1 on page 114 summarises the meetings held as part of the patient and public involvement strategy.

Table 4.1: Overview of the meetings held

Date	Location	Stake-holder	Number of atendees	Details
07/05/2015	Education centre (Trust)	Hospital based midwives	n=15 (approx.)	Consultation
28/05/2015	Birth Centre	Community midwives	n=6	Consultation
17/06/2015	Neonatal Pod (Trust)	Neonatologists	n=12	Consultation
24/07/2015	Nursery (Preston)	Women	n=7	Consultation
19/08/2015	Teaching room (Labour ward)	R&D/HoM/Cons. MW	n=6	Consultation
29/08/2015	Teaching room (Labour ward)	Managers	n=15 (approx.)	Consultation
08/09/2015	Cons. office (Trust)	Consultant obstetrician	n=1	Consultation
14/09/2015	Cons. office (Trust)	Consultant obstetrician	n=1	Consultation
16/09/2015	Cons. office (Trust)	Consultant obstetrician	n=1	Consultation
17/09/2015	Meeting room (Trust)	Consultant obstetrician	n=1	Consultation
22/09/2015	Education centre (Trust)	Junior obstetricians	n=3	Consultation
24/09/2015	Cons. office (Trust)	Cons. O&G (Head of research)	n=1	Consultation
15/01/2016	Nursery (Preston)	Women	n=4	Pilot documents
21/06/2016	Pregnancy advice centre (Warrington)	Women	n=4	Pilot documents

4.5 Analysis

Simple descriptive and thematic analysis was performed for all the discussion groups that were carried out during this phase. The findings have been organised according to each of the sub-phases and the topics that each stage needed to address: 1) Findings from the exploratory stage, 2) the findings from the design stage, and 3) the findings from the consolidation stage.

4.6 Results from the exploratory stage

This section provides a narrative presentation of the findings obtained during the consultation groups.

4.6.1 Discussion with women

This subsection describes the findings from the first discussion group that was undertaken with women. The topics that were explored during the discussion group and the main results are summarised ahead and also in table 4.2 and 4.3 on page 144 and 145 at the end of this chapter.

A) **Research question and overall study design/method**

Women appeared very positive and keen in the study. They all indicated that if they were pregnant again, had prelabour rupture of membranes and were ask if they would like to take part in this RCT, they would.
The main reasons they gave were: the desire to help others, and the belief that taking part in a study would result in having better care. They thought this topic of research is uncommon and that more research is needed in this area so there is more and new knowledge available on the management of prelabour rupture of membranes. So women will be better informed in the future.

They also believed that *"when you take part in studies like these, you are more likely to get better care, and a point of contact, as you are likely to be better monitored and should any of these women develop any problems, these would be addressed properly and promptly"*. When the women were informed about the rationale for conducting a randomised clinical trial, and were asked if the randomisation would "put them off" from taking part in this study, they understood the rationale and thought that it was not an issue, as in normal practice, women generally are not given choice about which management they would prefer, and are generally told that they need to be induced within 24 hours. They mentioned that by taking part in this study, women would have the chance of getting what they would normally get and the chance of waiting a bit longer for spontaneous labour. Women thought that it was all beneficial.

Knowing that it was important for women to know more about the management of prelabour rupture of membranes, validated the research question, the study design and the decision to undertake a RCT.

B) **Study design and features of the management of prelabour rupture of membranes that are important to women**

1. **Induction of labour vs spontaneous labour**

   The participants acknowledged that some women prefer to get on with labour as soon as possible but that more and more women nowadays prefer to give birth as naturally as they can, so being able to go into spontaneous labour would be important to those women. They also thought that women are starting to *"get fed up with all the interferences"* and feeling like a *"cow in the production line"*. When talking about the induction, they thought that an induction is harder than spontaneous labour because the body is not ready for labour yet. They also mentioned that an induction is not like a scheduled caesarean section, in that there is no certainty about when the baby is going to be born. In an induced labour *"you go to hospital to be induced but you don't know what's going to happen either, you sometimes have to wait, etc.. . . "*. They thought that some women prefer to be left alone (in the sense of not being interfered with) and this is why more and more women are choosing to go to birth centres. In the group, there was a woman who experienced prelabour rupture of membranes and said that she was planning to give birth in the birth centre and that was taken away because of the induction. She mentioned that some of her friends who were induced felt that they had missed out on something because their labours were induced.

   Knowing that it is important to some women to be given the opportunity to go into spontaneous labour, validated the study design and the rationale of comparing active vs expectant management to gain more knowledge about both approaches.

2. **Study intervention: Home visits vs coming to hospital to get checked**

   The participants thought they would be more comfortable and relaxed in their own homes. Since women allocated to the expectant management arms, would be taking their own temperatures, and doing their own checks, they thought participants would be doing similar checks to what the hospital staff would do for them if they were admitted to hospital. They did not like the idea of coming to

hospital just to get checked and thought that more people would prefer to stay at home and be seen by the community midwife at home. Their reasons as to why they thought coming to hospital would be an inconvenience were: finding childcare in the case of having other children, finding parking and having to pay for it, having to wait around, sit around see other people around, and seeing other women stressed out who would stress them out. They thought it would be less hassle to be seen at home.

It was useful to know that the participants preferred to be visited at home rather than to come to hospital to get checked because this validated the study intervention and design. It also meant that, when I had to negotiate with the hospitals, I knew the home visits were important for women, and that they should not be compromised.

3. **Continuity of carer**

All participants agreed that they prefer to have continuity of care as opposed to have a different midwife at each appointment and for the birth. They felt that having continuity of care would be beneficial for the study and something that future participants would appreciate. The reasons they gave were: they wanted to build rapport with someone, they wanted their midwife to know them, so they don't have to tell their story repeatedly to different people; that this made care safer, as if the midwife knew them, they thought the midwife would be more likely to spot quickly when something was not right with them. They also expressed that having the same midwife throughout pregnancy made them more relaxed and reduced their stressed and put them at ease. They also mentioned that when women see different midwives are more likely to receive conflicting information and that makes people confused.

It was useful to know that having the same midwife throughout the antenatal period and for the birth was important for women. This helped to shape the design and although in the end for pragmatic reasons the study was hosted by a Trust where they do not have caseloading model of care, and therefore true continuity of care was not going to be possible to achieve. However, when the clinical midwives were trained in the study procedures, they were advised that if it was possible, the same midwife should visit the participant.

4. **Study intervention: Vaginal examinations**

They thought that having more/less vaginal examinations would not be an issue for people, as it varies a lot anyway depending on where women give birth, some women in the group reported having more than what they would have liked whereas others had very few because they were in a birth centre. They also noted that it is a very personal issue, as some women might like the reassurance of being told that they are dilating and making progress whereas others hate having vaginal examinations and to be touched internally.

It was useful to recognise that the ideal potential participant would be someone who would be ok with both approaches to vaginal examinations. I also realised that it will be important to reassure potential participants that regardless of the group that they are allocated to, that they would receive the necessary vaginal examinations, and that should they don't want or want a vaginal examination their desires would be respected and honoured.

5. **Study intervention: Vaginal swabs**

Initially the study was designed to take "high vaginal swabs" with the help of the speculum just before the first vaginal examination and just after each vaginal examination. Women in this discussion group were not sure about that intervention as they thought that some potential participants might dislike the high vaginal swabs because they involve the need to use a speculum to reach the cervix and could be seen as another interference. They reported that some

women do not like vaginal examinations and do not like to be touched. On the contrary, another woman reported that once she got to active labour and her cervix was about 7cm dilated, she did not care anymore and had a different attitude compared to the early labour, she reported that her attitude during the active phase of labour when asked by the midwife about the need to break her membranes artificially (also known as ARM) was *"get on with it, do whatever you need to do"*. They thought that if it was just a swab without the speculum would be fine and women would not mind that.

This was discussed with women at this group and at subsequent groups. In view that the use of the speculum did not seem to be acceptable, it was decided to take low vaginal swabs that would not require the use of speculum.

6. **Risk of adverse outcomes**

When presented with the evidence on the infection risk for women and babies when there is prelabour rupture of membranes at term, participants thought that the risk of infection was small. They appeared to be surprised about of how little it was in comparison to how big professionals make this risk looks like. One participant who had experienced prelabour rupture of membranes stated that then *"You start panicking because they make you panic, because they make it such a big risk"*. The rest of the participants agreed that potential future participants need to have clear and objective information about the risks of infection in the information leaflet. They also agreed that the leaflet needs to provide information about what is going to happen to women who agree to take part, and what would happen if they decided not to take part in the study. They thought that a lot of people who are asked, would say yes to taking part in this study because the alternative would be an automatic induction of labour, and this can be seen as an adverse outcome.

Knowing this information helped to shape the participant information leaflets as I made sure that they clearly explained the risks and what would happen if women decided to take part in the study but also what would happen if they decided not to take part.

7. **What is important for women during labour and birth in general?**

Participants thought that this question would depend a lot on the preferences of individual women. One mentioned that she knew that some of her friends preferred to be looked after in hospital from early labour onwards, whereas other friends and herself preferred to stay at home until labour was well established. Some women mentioned that it was important to have a fan in the room, others appreciated being able to move, or being able to eat and drink during labour. In contrast, one of them recalled that she *"was not allowed"* to eat or drink because she was being induced and had a high chance of having a caesarean section. She remembered being very thirsty and hungry. She thought that the inability to push in the second stage of labour following labour induction might be due to exhaustion and lack of energy as a consequence of being starved in labour. All the participants agreed that being able to move freely, eat and drink was very important for them.

Having this information helped the design of the study protocol as it made sure that women were given the freedom to move, eat and drink during labour as they pleased, and no restrictions were applied in these areas to increase their comfort during labour and birth.

C) **Recruitment, tools and resources for future participants**

1. **Ideas to maximise recruitment**

They gave me four main ideas to enhance recruitment: 1) They thought that it would be a good idea to be able to discuss the study with the researcher in their own home, for example if the potential participant was given the leaflet at the 34-36 weeks appointment that it would be good if I could be available in case someone would like to discuss it antenatally, that they could call me and if they wanted to know more that I could go and see them at home. 2) They thought it was very important to be able to consent future participants day and night and not just during the day, as some women may break their waters during the night as it was the case of one of the women who took part in the discussion group. 3) They suggested using social media to raise awareness about the study, they named a few private local groups in social media where I could put some information about the study so women would be aware about this study taking place and they can also discuss it amongst themselves. 4) they thought it would be a good idea to leave some leaflets in children centres and clinics where women go for their antenatal appointments and scans so they could pick one up themselves to increase the number of women receiving the leaflet antenatally.

Some of these ideas were taken for the process of recruitment. In particular, being available to recruit participants day and night and being available to discuss the study at the potential participants' homes in case anyone would feel more comfortable discussing the study in their homes. Other ideas such as putting information in social media could not be implemented as the study had some inclusion and exclusion criteria and I thought that it would be more efficient to target the people who meets these criteria, rather than people who would might not meet the inclusion criteria for example; women who live outside the hospital's catchment area.

2. **Participant information sheet (PIS) for future participants**

Participants thought that the PIS should contain the following information: 1) Background explaining the situation and the risks. The risks need to be presented as they are and without exaggeration, 2) what taking part in the study involves, 3) what is going to happen if they decide to take part and if they decide not to take part, so if they decided not to take part at least they had a bit of more information than what women are normally given. They would also like to know the groups or treatment groups that they would be allocated to and the fact that there is still a chance that they might be induced at 24 hours. They also thought that it would help if there was a flow chart with all the steps of the study, so future potential participants would be able to see the study interventions at a glance.

One of the women thought that it would be interesting to mention how many women are induced every year, because in her experience, before being induced, she thought that the process of being induced was very rare, when in reality, it is not, so knowing this might put people at ease. She thought that some people might not want to take part in the study because they don't want to be induced, because for example they want to go to the birth centre, but if it is explained that the normal practice is to induce labour at 24 hours, they might change their minds because this study gives a 50% chance of not being induced until 96 hours after the rupture of membranes. It was also mentioned that it is important that the study is discussed in depth in person, as sometimes leaflets are given to women, but not discussed and not everyone reads them.

This information was very useful as it gave me a guide about what would be important for women to know to be able to decide whether to take part or not. The participant information leaflets answered the questions that women had and were later shown to another group to test whether the information they contained was easy to understand and whether they contain enough information.

3. **Participant's package**

They thought that having a diary to log on the temperatures and checks would be a good idea because it would give reassurance and a sense of control to the participants, as they would know what to look for and equally, if they noticed something was wrong or they were unsure, they would know what to do and who to contact. Women were asked if they would also like an extra leaflet with more information, but they thought that since the participants would have read the participants information leaflet, then would have spoken to me and discussed everything in depth that adding more material to read might not be beneficial, and said that *"sometimes less is more"*. They preferred just the diary to guide them through the checks that they had to do, and a number to contact in case they had any worries. Some others said that the diary could have some information about what to do if they start having contractions and what would happen next and also some information about the process of induction. Informing them of what happens during the process of induction and what to expect.

Having this discussion with women made it clear that it was important to design a participant's diary not only for the study but for the participants as it was evident that it would give them a sense of control, because they would know what to look for, it would give them reassurance when things were well, and it would guide them about what to do and who to contact in case they had any worries. In regards adding more information, I decided not to add more leaflets, as I agreed with some of them, that it wouldn't be a good idea to overload them with information, and also because what happens during spontaneous labour and birth and the process of the induction is something that I will ask midwives to discuss during the home visits in person.

4. **Questionnaire**

Women were shown the "Childbirth Experience Questionnaire" (Dencker et al., 2010). This is a questionnaire that was developed and published in Sweden, and later on translated and validated in the UK by (Walker et al., 2015). Women thought it looked like other questionnaires that they were given in the past, so it

seemed ok for them. One of the women reported that would have had difficulties trying to complete the questionnaire as felt very different when she was in labour at home compared to once she was in hospital with the drips and rest of the interventions, she felt happy, capable and strong until she got to hospital and once in hospital excruciating pain, felt she had no control, and like everything was awful. When they were asked about possible statements to measure satisfaction in relation to the study specific interventions, they thought that similar statements could be used but to specify "during the latent phase" or "from the time when the waters broke till when they were in labour or being induced". They also suggested that in the questionnaire, I could ask what treatment they preferred before taking part in the study and then see what they were allocated to, and compare the satisfaction amongst people who got what they wanted with people who didn't get what they wanted. When women were asked about when to give the questionnaire and how, they thought it would be good idea to give it a few weeks after the birth so women have some time to reflect about their births, also because during the first two weeks women might go through a lot of changes, baby blues and sometimes feel generally down, but that it is due to the hormonal changes and not the study, and that people could look at the study with more objectivity a few weeks after the birth than within the first hours or days after the birth.

It was very useful to know this information, the childbirth experience questionnaire was chosen because women found it acceptable and in regards to the study specific questionnaire, questions were designed taking into consideration what they suggested about making them specific as to what phase or time the questions were referring to. Also, following this discussion group, it was decided that the questionnaire would be given between four and six weeks postnatal to give women time to settle and reflect about their births and obtain a more objective opinion.

4.6.2 Discussions with clinicians

This section describes and discusses the findings obtained from the discussion groups with clinicians (neonatologists, community midwives, hospital midwives,

obstetricians, and managers). The results are presented together and organised by each of the areas or topics that I wanted to address. This is mainly because although the discussion groups took place separately and each group of clinicians met in different dates, all the members of staff were asked similar questions with the aim of addressing the same issues from different perspectives.

1. **Exploring routine practice in the host trust for mothers**

   In order for the study to run smoothly and to maximise the compliance to the protocol, it was crucial to know what the routine practice was in regards to the management of prelabour rupture of membranes. This helped to develop a study protocol that would fit in well with what normally happens in daily practice and avoid making unnecessary changes in their practice. Therefore, the following areas were explored: 1) Process and advice that women are given when they call saying that they think their membranes have ruptured and how this is confirmed, 2) Vaginal examinations, 3) Placental histology to aid the diagnosis of chorioamnionitis and 4) Protocol for babies born to mothers who experience prelabour rupture of membranes.

   In regards to the process and advice that women are given when they call saying that they think their membranes have ruptured and how this is confirmed; Community and hospital midwives explained that women are advised to phone the place where they are booked to give birth when they think they have ruptured their membranes, if they give a good history over the phone, they would be invited to come in straight away, if they give an equivocal history over the phone, they are normally advised to put a pad on and observe it and call again in a couple of hours, if then the pad is wet, they would be then invited to come in to get checked, if the pad is dry, then no further action would be required. Once they arrive to the Birth Centre/Triage, then they would take routine observations (Blood pressure, pulse, respiratory rate, and temperature), observe for contractions and palpate them by performing an abdominal palpation and listen to Foetal Heart Rate (FHR). In order to confirm or diagnose the rupture of membranes, they would check the pad and listen to her history, if the pad is wet and gives a good history, they would generally diagnose “rupture of membranes” by clinical signs only, although some midwives had mentioned that they would

use the new "Actim-PROM test" to confirm the rupture of membranes as they find it a non-invasive procedure and they get extra confirmation. They would also carry out the test "Actim-PROM" in those cases where the history is uncertain and/or the pad is not wet. The community and hospital midwives and the doctors confirmed that they don't routinely take swabs and they don't perform routine Cardio-toco graph (CTG) on women with a healthy pregnancy. Once it has been confirmed that the membranes ruptured and if there are no signs of active labour, women are generally told that they need to come in after 24 hours since the rupture of membranes for an induction and expectant management is not discussed unless the woman asks about alternatives or declines to be induced. The induction would then be booked (unless they decline it) and Women would be informed of how to and what to look for, they would be told to check their temperatures every four hours when they are awake and check the colour and smell of the liquor as well as how they feel in general. If the women have any concerns with their observations or feel generally unwell they are advised to call the place where they are booked to give birth and speak to one of the midwives.

Knowing what happens in standard practice, was useful for the development of the study protocol

2. **Exploring routine practice in the host trust for babies**

The current protocol for the baby depends on the length of time of the rupture of membranes by the time the baby is born and whether the baby shows any signs of infection in the early neonatal period. If the membranes have been ruptured for less than 24 hours, it is not considered a risk factor, and the baby would not require observations. However, if the membranes have been ruptured for 24 hours or more, it would be considered one risk factor for infection and the baby would need to be observed for 12 hours. If during that time, all the observations are within normal limits, the baby would not need further investigations and could be discharged with the mother. However, if during that time, the baby shows any signs of infection, the baby would require blood tests and would start on antibiotics until the

results from the cultures are back. If the results are negative, then the antibiotics would be discontinued.

> It was useful to know the normal procedures in regards to the newborn as this will be explained when discussing the study with potential participants and also taken into consideration when developing the study protocol

3. **Diagnosis of chorioamnionitis**

   In regards to this topic, there seemed to be a variety of opinion, some midwives said that they would routinely send the placentas for histology but others said that they would take a swab from the placenta and others said that they would only send it if the baby was born in poor condition.

> It was decided that we would emphasise the need to send the placenta to histology as part of the briefings about the study and this will be clearly stated in the protocol to avoid misunderstandings

4. **Study intervention: Home visits**

   The study intervention requires midwives to visit the participants allocated to expectant management at home every day (approximately every 24 hours) during the expectant period of 96 hours. There was a variety of opinion around this topic. Some midwives understood the rationale for the visits, and that there won't be too many participants due to the small sample of this study, and the fact that about 50% of the participants, are expected to give birth within the first 24 hours after the rupture of membranes, regardless of the arm they are allocated to. Some others, and specially the managers, expressed some resistance towards the home visits, due to concerns with increasing the work load, or not having enough midwives or not being paid for the extra work.

Since women preferred to be visited at home, it was decided to honour women's preferences and it was decided to keep the home visits

5. **Study intervention: vaginal examinations**

In regards to vaginal examinations, two types of discourses were observed, the community midwives would say that they always try to minimise vaginal examinations whereas the midwives who work on the delivery suite and the obstetricians would perform vaginal examinations routinely every four hours. However, obstetricians noted that a couple of examinations could be avoided, they agreed that if during the last vaginal examination, the cervix was found to be six centimetres dilated and four hours later, that woman was pushing, you could see anal dilation, passing of stools, vaginal gaping that in that case, perhaps the vaginal examination was not necessary to confirm full dilatation. They also thought that during the process of induction, if a woman has had ARM (artificial rupture of membranes) and had the prostaglandins but if after four hours of walking around, she is not having contractions that it wouldn't be necessary to carry out a vaginal examination and could start with IV oxytocin straight away.

Due to the fact that the study protocol asks for both approaches to vaginal examinations for the study and control arms (an approach where these are minimised and an approach where they are routinely performed), it was noted that community midwives were more comfortable with the "minimal approach" and the obstetricians and "labour ward midwives" were more comfortable with the "routine four hourly examinations approach", and both groups of people expressed some degree of resistance towards what was new or demanded a change in their usual practice.

6. **Study intervention: vaginal swabs**

Initially the study protocol requested high vaginal swabs with the help of a speculum and this was discussed with the midwives and they thought that it

would be very difficult to carry out high vaginal swabs during labour because they would need to use a speculum and it might be very uncomfortable for the women. They suggested low vaginal swabs instead.

The neonatologists thought that the bacteria that the study was planning to test for, were enough and did not suggest any extra bacteria. They suggested that it would be a good idea to have a protocol agreed with what to do if we find a positive result amongst our tests and the baby has been already discharged home.

In view of this feedback, it was decided to take low vaginal swabs

7. **Barriers and facilitators to recruitment**

It is well known in the literature that one of the biggest challenges in randomised controlled trials is recruitment (Kaur et al., 2012). This is mainly because not everyone is comfortable with not being able to choose the treatment. To address the issue of recruitment from an early stage, it was decided to include this topic in all the discussion groups with both women and clinicians to obtain their opinions and advice as to how to maximise recruitment. In this section, the barriers and facilitators to recruitment as well as the proposed strategy to overcome the problems are summarised below.

Barriers:

The obstetricians mentioned that one of the barriers to recruitment might be the patient's expectations, in that if they have had a friend with this problem, they would like to have the same treatment as her friend, they agreed that giving this information antenatally at the 34-36 weeks appointment would help, and also because women might not take in new information when they come into hospital with prelabour rupture of membranes as sometimes is a stressful situation for some of them. It was suggested by the neonatologists that women might not like the randomisation, in that some women might have a preference towards one treatment against the other and that this might make some people not to take part in the trial, or if they decide to

take part, that some might drop off if they didn't get the treatment that they wanted. It was also suggested that they might have concerns towards the health of their baby, and that the leaflet needs to explain this in a clear and positive way.

Facilitators:

One of the facilitators that was mentioned in all the discussion groups was that the Participant Information Sheet (PIS) should be attractive and explain the problem, the risks and the different management options in a positive way, informing women also about what happens during the process of induction. It should also mention that women might also need to wait for the induction until a place becomes available in the delivery suite. It was also agreed that giving this information antenatally would help, as some women might be very stressed when they come in with the rupture of membranes and might not be receptive to take part in a clinical trial at that stage. The midwives suggested speaking to as many midwives as possible by attending all the ward, delivery suite and birth centres meetings and talk to the midwives about the study, so as many people as possible are aware of the study. And to ask the coordinators to mention the study at hand-overs. It was suggested that posters are a good way of reminding midwives about the study, when and how to contact me as well as the inclusion and exclusion criteria.

These findings have helped to develop the recruitment strategy. A table outlining the barriers and facilitators and the strategy for recruitment is outlined at the end of this section.

8. **How to minimise the risk of bias**

It was suggested by the midwives that the thing to do was to offer the study to everyone and not just the "good candidates" like high social class. The neonatologists thought that the important thing was to make sure the study provided very explicit protocols with instructions so procedures are carried out in a consistent manner to leave as little as possible to personal judgement, because then it becomes "my personal practice" and what might

be necessary for one person, might not be necessary for another. They suggested to have a definition for suspected and confirmed chorioamnionitis and suspected and confirmed neonatal infection, a set criteria or a definition of "internal examinations only when necessary" and a set criteria of "routine examinations", also having a list of circumstances that would warrant to do an examination and a list of possible circumstances that wouldn't require an examination. They also mentioned that they do not need to know the exact duration of the rupture of membranes when examining a baby, that all they need to know is whether the duration of the rupture of membranes was less than 24 hours or 24 hours or more, as it is considered the same level of risk and the management doesn't change whether the duration of membranes was for example 25 hours than 60 hours. The obstetricians thought that it would be good to have a few people taking consent, and that maybe junior doctors could help me with it. They also thought that it was important to have as many people as possible aware of the study and to have the protocol around so the staff is aware of what they need to do. They also agreed that it would be very interesting to get the results from the histopathology on the placentas to confirm the chorioamnionitis objectively, as at the moment they would start women on IV antibiotics if they have two temperatures of over 37.5c one hour apart. They also thought that it would be interesting to get that data to see how many people are being overtreated.

It was good to know this information. The study will be offered to everyone and not just the good candidates, and the help from other midwives was sought for recruitment. The study protocol was made as explicit as possible, the criteria for performing vaginal examinations were outlined in the protocol.

9. **Minimal clinically significant difference for chorioamnionitis**

The junior obstetricians thought that since the baseline incidence of chorioamnionitis is low (6.7%) that they wouldn't suggest to aim to reduce it by a lot, that 1-2% reduction would be significant enough. The community midwives and consultant obstetricians thought that a 50% reduction in

infection rate and interventions would be clinically significant.

It was decided to go with a reduction of 50% of chorioamnionitis as the sample would be more feasible and also it was what the midwives and some senior obstetricians thought, and these were more experienced

4.7 Results from the design and Consolidation stage

Once all the information collected through all the discussion groups and meetings was synthesised, the resources and tools were designed and later on, were tested in two stages to make sure that these were reader friendly. Therefore, this section is divided in two subsections:"Testing resources and tools (pre-ethics)", describes the findings from a second discussion group that was carried out at the local NCT group in Preston, and where women looked at the resources that were going to be submitted to the ethics committee and section "Testing resources and tools (post-ethics)", presents the findings from a discussion group that was carried out with women from a different group (Pregnancy advice centre in Warrington). In this group women were asked to look at new material that was developed taking into consideration the suggestions from the ethics committee. It is important to note that the ethics committee did not ask the research team to conduct another discussion group, it was my decision since a new version of the material was developed and I wanted to make sure that it was still reader friendly.

4.7.1 Testing resources and tools pre-ethics

This section of the chapter describes the findings from the second discussion group with women from the local NCT group. The findings from this discussion group are presented and organised by the resources and tools that women were asked to look at.

1. **Participant information sheet for pilot RCT**

   They thought that it was all well explained and easy to understand, and they particularly liked the graphs and the time line. They liked the structure and suggested perhaps breaking down the text in small paragraphs or bullet points. One of the women suggested using more simple terminology, and pointed out

that some people might not understand the term "liquor" and might be better to use the term "waters" or instead of the question: "What are the possible disadvantages and risks of taking part?" to say "will my baby or me be put at risk?". In regards to the content of it, a woman suggested that it was important to emphasise that the study would maintain the same level of quality/standard of care to make sure potential participants understand that their care is not going to be compromised by taking part in the study, as the term "standard care" and "study intervention" might be confusing for some people, mainly because the word "standard" can be used to denote quality but also it can be used referring to what normally happens. They thought it was important to point out that, regardless of the treatment group that future participants will be allocated to, that they will receive the necessary vaginal examinations and that the clinician would not necessarily wait for four hours if it was needed immediately. Although it was acknowledged by the group that probably potential participants were aware that by taking part in the study they might get better care because they will be better informed and more monitored.

Knowing this information was helpful to make sure the terminology used in the leaflet was easy to understand by a lay audience. The term "liquor" was changed for the term "waters" and the question about the risks was simplified. In regards to making sure that future participants understand that they will receive a high standard of care regardless of the treatment group they allocated to, I made that explicit and a sentence was there explaining that concept.

2. **Participant's diary**

Women thought that it was easy to complete and the instructions were clear. They suggested to include a chart stating what is normal and what is not and a person and a contact number to call in case of any issues or worries. They suggested getting the partners or birth partners involved in helping the women to carry out the observations, this will increase the motivation and commitment to carry out the observations as sometimes pregnant women might be tired and perhaps might forget about them. They also pointed out that generally, men like

to be busy doing something, and it would be a good entertainment for them.

Following this discussion group, a few amendments were made on the diary, some more information was added explaining what is normal and what is not and I took note to involve the birth partners in the observations that needed to be done and in how to record them in the diary.

3. **Questionnaire**

At the time when this discussion group took place, it was thought that the questionnaire would be given twice to women, at 24-72 hours following the birth and again the same questionnaire at 4-6 weeks following the birth. Women commented during this group, that it was okay to give it soon after the birth but that I might obtain a different result at 6-8 weeks after the birth.

In regards to the Childbirth Experience Questionnaire (CEQ), they found it straight forward and easy to complete, although some of the statements ambiguous, for example statements: "Labour and birth went as I expected", they thought that it seemed to imply that women expect good things, when for example someone might have expected to have a very painful labour and birth and then had a very painful labour, and in this case she might have answered "yes, it went as expected" and although the birth met her expectations, she might have not been satisfied with her birth experience. On the contrary, someone might have expected to give birth at home in the water, but then was transferred into hospital and needed a Caesarean section, and she might have answered "no, it didn't go as expected" and was disappointed and unhappy.

They were unsure about the statement "I felt strong", and asked me what it referred to, when I explained them that the statement was trying to find out whether the women felt anxious or miserable or whether they felt like "I can do it". They replied that it might be better to be more specific like "I felt focused", or "I felt physically capable" or "I felt in control", or "I felt mentally capable", "I felt like in a good emotional place". They acknowledged that emotions are hard to judge because of their changeable and impermanent nature, in that one minute someone can be very happy and content and the next minute felt miserable. They

suggested that it might be a good idea to put a few emotions and ask participants to circle how they felt. They agreed that it would be good idea to ask future participants whether they liked the management or type of care that they were allocated to.

Women in this discussion group were also asked about how they would prefer to receive the questionnaire. There was a variety of opinion regarding this topic, some women expressed that when they had the baby they did not open their computers for days, but that would check the post every day and part of their routine was going for walks to put the baby to sleep, and that sending the questionnaire by traditional post would fit in well with their daily schedule. Other women said that when they had the baby there would be days when they did not check the post, but that if the questionnaire could be sent by email with a link to the questionnaire and this could be completed on their smart phones, that many women might find that handy as it could be easily completed during the night feeds.

In view that some women and other colleagues that I checked this questionnaire with found the statement "Labour and birth went as I expected" very ambiguous I decided to contact the author and our discussion can be seen in the reflection box ahead. There was another statement that came to my attention as problematic, this was not highlighted during this discussion group, but by a colleague at University "My midwife devoted enough time to my partner", it was highlighted that not all women have their partners with them, some might be a lone parent, or the partner might be in the army at the time, and that another person or family member might be with them during the birth. It was suggested that perhaps the term "birth partner" might be relevant to more people and prevent some people from getting offended.

I contacted the author of the questionnaire to discuss these two statements that seemed problematic and we had some correspondence. The author, thought that the statement "Labour and birth went as I had expected" was clear and insisted that the questionnaire had been validated.

It was acknowledged that perhaps there was a problem with the translation of the questionnaire from Swedish to English, as there is a slight difference between the verb "to expect" and "to hope", in that the first can imply both positive and negative things, and the latter refers mainly when someone expect positive things.

I suggested that perhaps it would be better to phrase the statement that appears on the questionnaire as "Labour and birth went as I hoped" because if someone expected the labour to be very painful, but in the end it was not. That person could potentially answer "I strongly disagree with the statement" which would mean that they would have a low score in that question, when in reality it meant that they were satisfied with the experience, which is what the questionnaire is trying to measure. Nobody would hope for a painful labour, but many would expect it to be painful.

I therefore, suggested that if an updated version of the questionnaire was to be made that this point should be taken into consideration. In my study, in order to clarify any issues, I would put a little note at the beginning saying that the statement meant "Whether labour and birth went as they hoped".

We also discussed the statement "My midwife devoted enough time to my partner", the author agreed that it refers to "birth partner", that is anyone who will accompany the woman during the labour and birth i.e. family member, friend, husband, partner, boyfriend, doula, mother, other etc...

In my study, to make sure that women understood what is meant by it and to prevent single mothers feeling judged or upset, a little note would be added to explain what is meant by partner, and that it refers to anyone who accompany them during the labour and birth.

In regards to the issue about how to send the questionnaire to women, it was decided that since there was a variety of opinion there, that the best would be to ask women in the study how they would prefer to complete the questionnaire. This was implemented in the study protocol and the researcher called the women at about four weeks after having their babies to find out how they would prefer to receive the questionnaire.

4.7.2 Testing resources and tools post-ethics

This section of the chapter describes the findings from the third discussion group with women from the "Pregnancy advice centre" in Warrington. The aim of this discussion group was to test the new resources that were developed, including the participant information leaflet for the observational study and the new participant information leaflet for the pilot RCT including the suggestions made by the ethics committee.
The findings from this discussion group are presented and organised by the resources and tools that women were asked to look at followed by a short summary of how those results influenced the development of the resources and the study design.

1. **Title**

   The long/scientific title was one of the things that the NHS ethics committee suggested changing, originally the study's long title was: "A pilot RCT on expectant management and minimal vaginal examinations for prelabour rupture of membranes at term", and the short title: "A pilot RCT on the management of term prelabour rupture of membranes". Women could choose from the following titles:

   - Long title: "A pilot RCT on expectant management and minimal vaginal examinations for prelabour rupture of membranes at term"
   - "A pilot RCT on the management of term prelabour rupture of membranes"
   - "Establishing best practice for prelabour rupture of membranes at term", they thought this was too vague.

   It was useful to have their opinion about the study title. In the end, I decided to have the long and scientific title as "Active vs expectant management and routine vs only-when-necessary vaginal examinations during labour for prelabour rupture of membranes at term, a pilot RCT study" and I kept the short title that had been approved by the ethics committee "A pilot RCT on the management of term prelabour rupture of membranes", and since women liked this title, I decided to use this short title in all the documents that will be seen by the participants and to keep the scientific title for the study protocol, and correspondence with ethics.

2. **Participant information sheet for RCT**

In this group women were given a leaflet with different paragraphs saying the same but with different wording, some of those paragraphs were written by me and others by my director of studies. Women were asked to choose which paragraphs were simpler and easier to understand. In regards to the wording of the question, what are the possible disadvantages and risks of taking part? They thought it was the most important question and gave a few suggestions. As a few examples of their suggestions and input, they thought that it was better to say "starting labour off with drugs and other treatments" as opposed to saying just pessaries or breaking the waters, because being more general it includes more things. They also suggested to break down the text in a few paragraphs, and they suggested the following structure for the answer, 1) "There are no extra risks to the health of you or your baby", 2) "According to the studies, both options of care are safe options for women and their babies as the chances of getting infected are very similar for both mother and baby when we induce labour with drugs or other treatments compared to when we wait for labour to start on its own", 3) Regardless of the group you will be monitored by a team of midwives and doctors.

Some women thought that it was good to make the language as easy as possible for women, whereas other women thought that it was good to put a bit of the vocabulary that the clinicians use so women understand the clinicians when they speak to them about possible treatments. They thought it was better to say that vaginal examinations could contribute to the development of the infection rather than "we don't know" because women generally expect clinicians to know things and it could make women not have faith in the clinicians. They suggested adding a sentence to say that midwives and doctors will know about this study as they thought that it could increase anxiety if women felt there was a lack of communication amongst the staff working at the hospital.

In regards to the question, what happens once I enroll into the study? They thought that I might struggle to get the necessary participants because people cannot choose the treatment group, they thought that most women would have a preference and not so many people might be happy with either In regards to the question – What does taking part in the study involve? They suggested not putting "24 hours (routine practice) and 96 hours (study)", and instead just

saying "around 24 hours or around 96 hours". They explained that as soon as people read the word "routine", some people might be thinking that if they are allocated to the "study group", they are not doing what they are supposed to be doing and they might resist to the study. They thought that it does not matter to the participant whether it is routine or not. Women were asked what they thought about the low vaginal swabs, they thought that they would be fine as after having had a vaginal examination, "a swab would be nothing". Women thought that the home visits were a very good idea and that women would like that, because it would be easier and less stressful than having to come to the hospital, find a parking space, pay for parking, wait around and later on to be told to go home. Overall, they thought that it contained the necessary information for helping women to decide whether to take part or not.

On reflection, it was a good approach to give women a few paragraphs to choose from, as it seemed as if women gave more feedback than just asking them to comment. The structure that they suggested for the question about the risks of taking part in the study was followed and the suggestions they made in regards the wording were taken.

3. **Participant information for observational study**

A woman stayed and looked at this Participant information leaflet as the rest had to go, and she gave the following feedback.

She suggested the following changes:

- To offer the possibility of just looking at the participant's notes, once the potential participant has declined the pilot RCT, as otherwise, people might choose the easiest option first.
- To keep this leaflet for the observational very short, simple and to give this leaflet once they have read the participant information sheet for the pilot RCT and have declined it, so the participant information sheet for the observational can be kept very short and simple assuming they have read the other one very recently.
- To add a sentence saying something along the lines "this study does not require you to actively do anything, the researchers will collect the necessary information from your records"

Following this meeting, the participant information sheet for the observational was made shorter and the recommendations given were implemented.

4. **Participant's diary**

Women liked the diary for future participants very much and thought it was very empowering because it would give women autonomy and control because future participants would know what to look for and how to do the observations. They also thought that it reinforces what the hospital would usually tell women, but in a written form which would be useful as when the instructions are only given verbally, some women might forget and get anxious because they think they might miss something.

Women suggested the following changes:

- Take the temperature under your armpit rather than "axillary temperature"
- "Amniotic fluid" rather than "waters", they thought everyone would understand by now amniotic fluid.
- "Lumps of meconium" rather than "clumps of meconium" – They thought that the staff at the hospital would use the term lumps, so better to use the same word.
- In regards to the show, they suggested the term "snot" rather than gelatinous.
- Bright red blood instead of Fresh blood
- Foetal movements rather than movements of the baby
- Change in foetal movements rather than just less

The changes that women suggested were implemented. The discussion with women helped to ensure the diary was user-friendly. It also validated the participant's diary

5. **Questionnaire**

Women thought that the introduction as well as the length of the questionnaire were fine. In regards to the best method to send it, they thought that the best would be to ask them how they prefer to receive it a week or two before I intend to send it. In regards to the study specific questionnaire, they liked that in regards to vaginal examinations, the statements regarding the frequency and whether the participants would have preferred to have more or less vaginal examinations were separate questions. They also liked that there was a statement for "mentally capable", "emotionally capable" and "physically capable" as it captures all the dimensions.

Women suggested to add a sentence saying that the questionnaire is anonymous and that whatever they say will not be seen by any other health care professionals. A sentence saying that the questionnaire was anonymous was added and it was decided that the best approach was to ask women a week or two before I intend to send the questionnaire how they would prefer to receive it. The discussion with the women gave face validity to the questionnaire.

Table 4.2: Summary of results obtained during the consultation

Area of enquiry	**Response**	**Implementation**
Research question	Women thought it was necessary to carry out research in this area	Validation of research question
Method: RCT (Randomisation)	Randomisation was not an issue as women saw it as an opportunity to have the same treatment and a 50% chance of having more time to go into labour spontaneously and potentially achieve a physiological labour and birth	Validation of method
Intervention: Expectant management	Women valued being able to have a normal labour and birth and given more time to achieve it. Women voiced some dissatisfaction with the process of induction. Women were keen in having home visits	Validation of study design
Intervention: Monitoring between SROM and onset of labour	Women preferred to be seen at home by community midwives rather than coming to hospital for check-ups	Home visits were implemented
Intervention: vaginal examinations (minimised vs routinely every 4 hours)	Women expressed that wanting to have more/less vaginal examinations was very personal but that both approaches were acceptable	Validation of study design
Intervention: Vaginal swabs	Initially these were going to be high vaginal swabs. Both women and clinicians thought that high vaginal swabs were too invasive during labour, and preferred low vaginal swabs	Low vaginal swabs were implemented
Bacteria being tested for	Clinicians were shown bacteria to be tested (*E. coli, S. albicans, P.areuginosa, S. aureous*). Clinicians thought that these were enough and did not suggest any others	Validation of study design
How to minimise the risk of bias? randomisation, blinding and allocation concealment	Midwives suggested offering the study to everyone and not just the "good candidates" Neonatologists suggested to make the protocol as explicit as possible and that neonatologists do not need to know the exact length of time of the rupture of membranes as for them once it has been 24 hours, the baby will have the same treatment whether it has been 24 or 72 hours Obstetricians thought that it would be good idea to have a few people consenting and recruiting the participants	Recommendations were implemented
Minimally clinically significant difference in chorioamnionitis	Junior obstetricians thought that even a reduction of 1-2% in chorioamnionitis would be clinically significant Midwives and obstetricians thought that a reduction of 50% in chorioamnionitis rates would be clinically significant	$\geq$ 2% reduction will be considered clinically significant

Table 4.3: Summary of consultation on barriers and facilitators to recruitment

Barriers	**Facilitators**	**Strategy**
Patient's expectations (women with friends and relatives who had PROM)	Give participant information sheet (PIS) at 34-36 weeks gestation.	To ask midwives to give PIS at the 34-36 weeks appointment
Randomisation	Participant information sheet (PIS) to be positive and explain clearly the possible treatment groups. PIS to explain that induction also takes some time and can be uncertain	To make the PIS clear, simple and positive
Clinician's preference towards a particular type of treatment	Flexible clinician with no particular preference Clinicians who are aware and engaged in the study	To attend as many meetings as possible To talk and engage as many clinicians as possible
Lack of formal support from researchh midwives	To be available to consent participants 24 hours/day	To be on-call 24h/ 5 days/week To seek help from clinical midwives who might be interested in helping with recruitment
Not applicable	To use social media to promote and raise awareness about the study	Decided against this as I would need specific ethical approval
Not applicable	To put posters in clinical and non-clinical areas to remind midwives about the study and the need to call me when they identify a potential participant	Posters to remind midwives about the study and the need to call me when they identify a potential participant. Poster also contained inclusion criteria
Not applicable	To leave PIS for women in clinics and children centres	Midwives to give PIS at the 34-36 weeks appointment

4.8 Discussion

Involving patients and the public in a consultation on the design of the clinical trial can be a complex but very rewarding process, as it can bring many benefits to the research. Enwistle et al, (1998) and Staley and Minogue (2006) discuss the reasons for involving service users as well as its benefits. Although the reasons can be politically mandated, for example, nowadays many funding organisations require evidence of having included patients and the public in the early designing stages of research, many researchers might still want to involve the public in their research because the views from lay people often differ from those of health professionals and researchers, and this can improve research significantly. These benefits include: It helps to make sure that the research question is important to service users, ensuring that public money is not wasted in research that is not relevant to the public, and its findings may become more accepted and therefore, this may encourage consumer groups to disseminate the research findings and in turn it may lead to its findings being more implemented (Entwistle, Renfrew, Yearley, Forrester, & Lamont, 1998). 2) If service users are involved in the early stages of the research, it can improve recruitment rates, it can lead to better return of questionnaires, better compliance with the protocol, etc. and 3) It can lead to more ethical research as Staley and Minogue (2006) explain. This is because for example it can improve the process of informed consent by making sure that the participants information leaflets are easy to understand by developing them with the target audience.

However, although there seems to be many benefits, Entwistle et al. (1998) also argues that there might be some objections, the main reasons can be summarised as: 1) The people interested in being involved in research are rarely typical, in that it is only a minority who is generally interested in this and their views might not represent those of the majority of the population, 2) The interests of the public can be represented by others such as health professionals who claim to know what the public wants, however studies show that this is not the case (Dolan, Bordley, & Miller, 1993) in (Entwistle et al., 1998; Hares et al., 1992), 3) Lay perspectives will not improve decision making in research, there is a view that lay people who are not medically trained or formally trained in research might not be able to add anything to decision making, however, everyone brings different skills and lay people may bring different points of view that researchers might not be able to see and 4) Lay input can be biased or partial, this is because lay people might have an opinion or a preference towards a specific treatment

and may favour their own preferences or not act in an objective way. Although this could also be seen in the scientists and professional researchers as being impartial is very difficult for the human being, what it seems to be important is to be able to acknowledge when there is a preference.

There is a systematic review on the impact of PPI in research, carried out by Brett et al. (2014). This systematic review included 66 studies reporting having used PPI. The conclusion of this systematic review is that, involving the public enhanced the quality and appropriateness of research. In my opinion the positives outweigh the negatives, because I believe that the service users bring a unique perspective that us as professionals might not be aware of. However, as Staley and Minogue (2006) and Brett et al. (2014) explain, this is not exempt from challenges, the research team first have to decide on the role of the involvement, as there are different levels. These levels of involvement are described by INVOLVE: (1) Consultation (the type of involvement that was chosen in this research), where service users are asked about their views on the research and documents, (2) Collaborative, where service users are involved as active partners and (3) User-controlled research, where the locus of power, initiative and decision making rests on the service users as opposed to the professional researchers. These different levels of involvement are all appropriate, but depending on the study characteristics and the topic of the research, one type of involvement might be more appropriate than others. Therefore, the first strategy to minimise the challenges is to choose the appropriate level of involvement for the research from the early stages of the research in order for all the members of the team to be aware of their role. In the case of this study, a consultation role was preferred due to the pilot nature of the study, also because of lack of funding, because I wouldn't have been able to afford to pay for transport or other expenses to the lay collaborators. Challenges described by Brett et al. (2014) were mainly due to the differences between the professional researchers and the service users working together and due to both groups having different priorities, motivations, different ways of working, because these differences caused conflicts and power struggles. It is therefore, very important for each member of the team to know their role. For example the professional researcher needs to be aware of his/her responsibility of conducting scientific research of high quality and to be able to justify the design and should also be able to negotiate changes suggested by the lay members and to incorporate these in a logical manner (Brett et al., 2014).

4.9 Conclusion

Carrying out preliminary work prior to the main clinical trial is critical (Whitehead et al., 2014). It is considered to improve the quality of the research (Brett et al., 2014). A total of five discussion groups with clinicians, and three discussion groups with women took place. In addition, five individual meetings with consultant obstetricians and others with senior managers were conducted with the overall aim of increasing the involvement of as many clinicians as possible. During this developmental and feasibility phase the following areas were addressed: how to maximise recruitment, maximise the engagement and involvement of clinicians and hence enhance the adherence to the study protocol, and make sure that the study interventions seemed acceptable to women. This preliminary work also helped in the development of the participant information sheet, the diary and the questionnaire and to make sure everything was relevant and easy to understand. The next chapter, called "methods", will describe the study protocol for the pilot RCT, this protocol, takes into consideration the findings from the feasibility phase and the discussion groups

Chapter 5: Methods

5.1 Introduction

This chapter builds on from the previous chapter (Developmental phase). This is because the pilot RCT has taken into consideration the findings from the discussion groups with clinicians and women to develop the design and the recruitment strategies, and the documents for the participants. This chapter also discusses the rationale for the pilot RCT, and it describes in detail the study protocol that was followed. It also outlines the plan for the statistical analysis. At the end, it has a section where the processes for developing study protocols and recruitment strategies are discussed, followed by a brief conclusion where a summary of this chapter is given.

5.2 Background

The study protocol for the pilot RCT has been developed following the guidance given by "The systematic development and scope of SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) developed by Chan et al. (2013).

The final design of the pilot clinical trial has taken into consideration the findings from the PPI (Public and patient involvement) work that took place during the developmental phase. Prior to conducting the pilot clinical trial, extensive public and patient involvement (PPI) has taken place where the main implementation issues had been explored and addressed. Public and patient involvement is known to improve the quality of the research (Brett et al., 2014; Stewart et al., 2011), and this has been further corroborated in the case of this study as many insights have been gained for the development of this study, as detailed in the previous chapter. As part of the public involvement, eight discussion groups with different groups of clinicians and service users took place

(Community midwives, hospital-based midwives, obstetricians, neonatologists, managers and research midwives and three discussion groups with women). During these discussion groups, issues such as ways to improve recruitment, study procedures, what was important for women and piloting of the documents amongst other issues were explored. These discussion groups also helped to decide on what would be the minimally clinically important difference for the primary outcomes in order to decide on what reduction in chorioamnionitis and what increase in normal birth would be considered clinically significant. It was important to determine this in order to be able to calculate the sample size for the future main clinical trial. It was also expected that the pilot RCT trial would also contribute to determine the necessary sample size for the main study. Since the prevalalence of chorioamnionitis and normal birth can vary significantly depending on the definition used and the population being studied, it was decided to also collect the data from 100 participants having normal/routine care to ascertain the prevalence and thus to be able to estimate more accurately the sample size needed for the full-scale trial. Clinicians also helped with their ideas on the recruitment processes and the recruitment processes outlined here have been developed taking their suggestions into consideration. Women helped with their thoughts on how to improve recruitment, by giving important insight about what information should the participant information leaflet contain.Two different group of women piloted the documents to make sure that these, were reader friendly.

In essence, pilot studies are a miniature version of the main study, although they have different aims and objectives than the full-scale study (Lancaster, Dodd, & Williamson, 2004). Pilot studies can be divided between two types, those undertaken inside the main study, and where the study is started and the first pre-determined number of participants entering the trial. Whereas external pilot RCT studies, are studies carried out separately and before the main study is started. External pilot studies, have many benefits, they are used to check that the randomisation procedure works, determine the consent rate, the acceptability of the intervention and of the concept of randomisation, selection of most appropriate outcome measure, to estimate sample size and to ensure the integrity of the study protocol (Lancaster et al., 2004).

It was decided to undertake a pilot trial prior to the main trial, to make sure that the study protocol works effectively and as a whole and also to test that all the components work well together before embarking into the main study. It was also decided that it was also important to test that the logistics work, that participants are being recruited,

that women accept the intervention, that the process for randomization and blinding works, that the collection and analysis of samples are carried out appropriately, that participants are being followed up according to the study protocol and that all the components run smoothly together (Arain et al., 2010).

5.3 Administrative information

Long Title: Active vs expectant management and routine vs only-when-necessary vaginal examinations during labour for prelabour rupture of membranes at term, a pilot RCT study.

Short Title: A pilot RCT on the management of term prelabour rupture of membranes

Trial registration: clinicaltrials.gov ref: NCT02872883

World Health Organisation (WHO) Universal Trial Number (UTN): U1111-1185-3426

Latest protocol version: Version 4.0

Funding: Self-funded study

Name and contact information for the trial Sponsor: University of Central Lancashire

5.4 Aims

This program of research will address the following objectives:

5.4.1 Aims for the pilot RCT

1. To estimate rates of recruitment
2. To estimate rate of fidelity to the study protocol
3. To estimate attrition rates
4. To test randomisation procedures
5. To test data collection and reporting forms
6. To test questionnaire out as well as the method to send it

7. To determine the acceptability of the intervention: Expectant management
8. To determine the acceptability of the intervention: Minimal vaginal examinations
9. To test the integrity of the study protocol for the future trial

5.4.2 Aims for the observational study

1. To provide information for the sample size calculation for the main clinical trial

5.4.3 Aims for the future main trial

1. To investigate which treatment will reduce the rate of definite chorioamnionitis
2. To investigate which treatment will increase the rate of normal birth
3. To obtain information regarding other important and relevant secondary health outcomes
4. To assess the effectiveness and efficacy of the interventions (Expectant management and minimal VEs)

5.5 Methods: Participants, interventions and outcomes

5.5.1 Trial design

The design of this pilot Randomised controlled trial is a miniature version of the main trial. This is a randomised controlled trial, with 4 arms. It is also a superiority trial. The participants had an equal chance (25%) to be allocated to any of the following 4 groups:

- Group 1: Expectant management and Minimal vaginal examinations during labour
- Group 2: Expectant management and Routine vaginal examinations during labour
- Group 3: Active management and Minimal vaginal examinations during labour
- Group 4: Active management and Routine vaginal examinations during labour

The following figure 5.1 on page 153 presents a diagram of the 4 treatment groups in the RCT

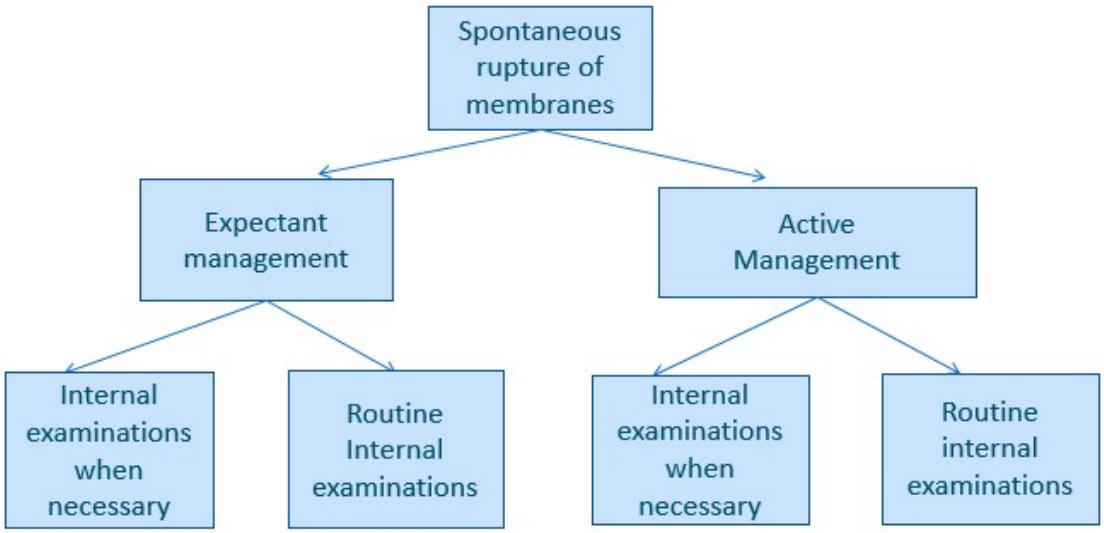


Figure 5.1: RCT diagram

5.5.2 Study setting

The study was carried out in the participating local tertiary hospital. Approximately 4,000 babies are born in the Trust each year.

5.5.3 Eligibility criteria

Table 5.1 below on page 154 presents the eligibility criteria for the RCT

Table 5.1: Eligibility criteria for RCT

Inclusion criteria	**Exclusion criteria**
Prelabour rupture of membranes (confirmed)	Intact membranes
Aged 18-45 years old	Aged $\leq$17 or $\geq$46 years old
Term pregnancy from 37+0 until 41+2 weeks (both inclusive)	Pregnancy $\leq$36+6 or $\geq$41+3 weeks gestation
Healthy/Normal pregnancy	Previous CS, Pre-eclampsia, Diabetes
Singleton pregnancy	Multiple pregnancy
Cephalic presentation	Breech presentation
No known current infections	Current infections:HIV, Hepatitis, Herpes
Not known to be colonised by GBS	Known to be colonised by GBS
Agrees for placenta to be sent to histology if deemed necessary by clinicians	Doesn't consent for placenta to be sent to histology if clinical signs of infection develop
Understands, and is able to read and write in English	Not fluent in the English language
Leaves within the Trust's geographical catchment area	Out of area
Not taking part in other clinical research at present that could interfere	Taking part in other clinical research that could interfere
Consents to take part	Doesn't consent to take part

5.5.4 Interventions

In this clinical trial (main trial), the effectiveness and efficacy of two interventions will be tested, separately and in combination, for healthy women and babies experiencing prelabour rupture of membranes at term.

- **Intervention 1: Expectant management**, defined as, in the presence of prelabour rupture of membranes at term, watchful waiting for labour to start spontaneously while monitoring maternal and foetal wellbeing by daily visits by the community midwives in the women's home for up to 96 hours, followed by induction of labour if labour hasn't started at approximately 96 hours since the rupture of membranes.
- **Control for intervention 1: Active management (routine/usual practice):** defined as, in the presence of prelabour rupture of membranes at term, watchful waiting for labour to start spontaneously while monitoring maternal and foetal wellbeing in the women's home for up to 24 hours, followed by induction of labour if labour hasn't started at approximately 24 hours since the rupture of membranes.
- **Intervention 2: Minimal vaginal examinations**, vaginal examinations only when clinically indicated with the aim of minimising the amount of examinations that women receive.
- **Control for intervention 2 (routine/usual practice)**: Vaginal examinations performed routinely every 4 hours and when clinically indicated.

Table 5.2: Table of RCT interventions (simple)

		Minimal vaginal examinations	
		YES	NO
Expectant management	YES	**Group 1** Expectant management + Minimal vaginal examinations	**Group 2** Expectant management + Routine vaginal examinations
	NO	**Group 3** Active management + Minimal vaginal examinations	**Group 4** Active management + Routine vaginal examinations

Table 5.3: Table of RCT interventions(detailed)

	Intervention		
Group	**Induction of labour (IOL)**	**Vaginal examinations (VEs) during labour**	**Lower vaginal swabs (LVS)**
Group 1	Expectant management: IOL at 96 hours or the next morning if SROM after midnight	VEs when clinically necessary or requested by the woman only	LVS prior to 1st VE and LVS after each VE
Group 2	Expectant management: IOL at 96 hours or the next morning if SROM after midnight	4 hourly routine VEs and when clinically necessary or requested by the woman	LVS prior to 1st VE and LVS after each VE
Group 3	Active management: IOL at 24 hours or the next morning if SROM after midnight	VEs when clinically necessary or requested by the woman only	LVS prior to 1st VE and LVS after each VE
Group 4	Active management: IOL at 24 hours or the next morning if SROM after midnight	4 hourly routine VEs and when clinically necessary or requested by the woman	LVS prior to 1st VE and LVS after each VE

5.5.5 General overview of study interventions, procedures and processes

1. Participants allocated to either active or expectant management, will be invited to go home to await for signs of labour. They will then be advised to monitor (every 4 hours during waking hours) their temperature, colour of amniotic liquor (waters), smell of liquor (waters), uterine tenderness and they will need to call the hospital or midwife if they have any concerns. Self-monitoring for signs of infection is part of the routine and normal care that would also happen outside the research, however while being part of this research they are advised to complete a diary (see appendix 4 on page 297).

2. Participants allocated to the active management will be invited to come back to hospital to be induced approximately 24 hours after the rupture of membranes to be induced as per hospital protocol. If the rupture of membranes happened during the night (after midnight), the participant will be invited to come at 8.00am the next morning, this is also part of the usual care.

3. Participants allocated to the expectant management will be visited at home approximately every 24 hours until they go into spontaneous labour. Ideally, the

home visits need to be carried out before 12pm every day, always following the principle that women should be seen by a midwife approximately every 24 hours, and no longer than 27 hours. If the midwife is unable to make the appointment on time, she should call the woman to make sure that everything is okay and should inform her of when she will visit her. Participants will be invited to come back to hospital to be induced approximately 96 hours after the rupture of membranes if they are not in labour or have not given birth by then. If the rupture of membranes happened during the night (after midnight), the participant will be invited to come at 8.00am the next morning (after the 96h since the rupture of membranes). For example if someone broke their waters on the 20th October at 10am, they will come back for induction at 10am on the 24th October, whereas if someone broke their waters at 3am on the 20th October, they will come back for induction at 8am on the 24th October. During this latent phase (also called waiting period) they will continue to monitor (every 4 hours during waking hours) the temperature, smell and colour of the liquor (waters), uterine tenderness and will call the midwife or hospital if they have any concerns.

4. Participants allocated to the arms where vaginal examinations during labour occur "routinely", will be offered vaginal examinations routinely every 4 hours and when deemed necessary (either by the clinician or the woman) for example: foetal heart abnormalities, hyper-contractility, lack of regular and strong contractions once active labour has been diagnosed or when any other concerns listed here arise, for example bleeding.

5. Participants allocated to the arms with minimal vaginal examinations, will receive vaginal examinations only when deemed as necessary (either by the clinician or the woman), for example: foetal heart abnormalities, hyper-contractility, lack of regular and strong contractions once active labour has been diagnosed or when any other concerns listed here arise, for example bleeding...

6. All the participants will be offered a low vaginal swab before the first examination takes place (to get a baseline of the microbiological state of the vagina) and then they will be offered a vaginal swab after every vaginal examination to monitor the impact of the vaginal examination on their microbiota. For the purpose of this study, during the process of induction or augmentation, if the hand is introduced twice (for example, once to assess the bishop score, and secondly to to introduce the prostaglandin), this should be counted as two vaginal examinations, and therefore a swab should be taken after assessing the bishop and another one after the administration of the prostaglandin. During the process of performing an artificial rupture of membranes (ARM), in this case, if the hand is introduced to assess cervical dilation and progress of labour, and then is removed and introduced again with the hook to perform the ARM. This should be regarded as two vaginal examinations, and therefore two swabs should be taken, one after the cervical assessment and another one after the ARM.

7. At about 4-6 weeks the participants who have given consent to be contacted will be phoned to let them know/remind them about the questionnaire. They will then be given the option as to what is their preferred way to complete the questionnaire: a) Complete it over the phone at that time or at a future agreed time, b) For the questionnaire to be sent in the post with a self-addressed and pre-paid envelope or c) for the questionnaire to be sent by email. In the event that the questionnaires sent by post or email are not received within 2 weeks from the date they were sent, the researcher will make contact with these participants to ensure that the

post or email was received and to see if they need any help with completing the questionnaire and/or whether they are still interested in completing it.

5.5.6 Outcomes

A) Outcomes related to the Pilot RCT

1. Proportion/percentage of eligible women who agree to take part in the study – The outcome will be measured with the help of the screening log, in which we will log the eligible participants that the researcher/research midwife meets for potential enrollment and following discussion give consent to take part.

2. Proportion/percentage of participants who stay in the allocation arm - Proportion of women who are allocated to expectant arm and do not request to be induced earlier than agreed or vice-versa, proportion of women who are allocated to the active arm and request to wait for longer instead of having the induction as agreed. The outcome will be measured with the following procedure: the clinician responsible for the care of the participant will notify researcher (LRM) by a phone call/text/email/conversation in person and this will be recorded in the participant's records by the clinician and logged in the CRF form by researcher (LRM) or research midwife. The outcome will be measured by the number (%) of deviations from the protocol, number (%) of each type of deviations and a description of whether they are clinically or scientifically significant.

3. Proportion/percentage of participants who drop out from the study - Formal request to abandon the study and request that we don't use their data. The clinician responsible for the care of the participant will notify researcher (LRM) by a phone call/text/email/conversation in person and this will be recorded in the participant's records by the clinician and logged in the CRF form by the researcher (LRM) or research midwife and the data from these participants won't be used.

4. Randomisation process – The outcome is defined as an effective randomisation process that allows participants to be randomised appropriately and in a timely manner. In the screening log, there will be a section in which the time that took to get the participant randomised will be logged (from the moment that the participant says yes, to being randomised). Three time frames will be used:

0-15min, 16-30 or 31or more min. It will also be recorded how the randomisation was obtained (by text or online) and in the case of using the phone, whether there is consistent coverage for the phone.

5. Data collection forms – The outcome is defined as: Case report forms (CRF), screening log, registration form and report of adverse event form that collect the necessary information and are easy to use. The CRF forms will be completed by the researcher (LRM) or research midwife by looking at the participant's records. The clinicians responsible for the care of the participant will be given a very simple and easy to complete form that they will need to complete with the extra data that the study requires and that it wouldn't be part of the usual care, then the researcher or research midwife will look into the records and in conjunction with that form that the clinicians have filled in will complete the CRF. The outcome will be measured by collecting feedback from clinicians and research team regarding the forms. These forms will have a question in regards to the form itself - did you find the form easy to complete? And will provide a box for addition comments. The forms will need to be deemed as easy to complete, efficient and collect the necessary information, have the necessary boxes and spaces to collect such information. The outcome will also be measured by the proportion/percentage of questions that were answered over the total of questions that should have been answered, as well as the clinical and scientifically significance of the information missing.

6. Return, efficiency and completeness of Questionnaire:
   The questionnaire is composed of a validated questionnaire (Childbirth experience questionnaire), and extra non-validated questions regarding the study.
   Participants will complete the questionnaire at 4-8 weeks after giving birth and we will measure percentage of completed questions and response rate. At the end of the questionnaire there will also be a box for the participants to make comments about the questionnaire itself and for them to tell us how easy it was to understand and complete. The outcome will be measured by the proportion/percentage of participants who complete and return the questionnaire, the proportion/percentage of questions that were answered and the method that was chosen by most of the participants to complete the questionnaire and which method appears to be associated with a higher response rate (post, survey monkey, completing it over the phone with researcher).

7. Acceptability of the interventions, this will be assessed together as a package of two interventions and separate for each. "Expectant management" and "Vaginal examinations only when necessary" – Proportion of women who find the intervention(s) acceptable and show higher scores of childbirth satisfaction on the "childbirth experience questionnaire". The childbirth experience questionnaire has been validated in the UK to measure satisfaction during childbirth, and people who is more satisfied will show higher scores than the people who is less satisfied. The questionnaire also has a question that asks whether they found the intervention(s) that they were allocated to, acceptable.

8. The integrity of the study protocol – This outcome will be assessed by synthesising the findings in relation to the other outcomes and findings from the trial. It will also be assessed by the changes that are needed to the protocol: 1) Changes that were implemented during the pilot phase and 2) Changes that are needed to address outstanding practical issues or unknowns for the main trial.

B) Outcome related to the observational study

- Sample size estimation for main RCT – The estimation of sample size for main trial will be obtained by looking at the records of 100 participants who decline to take part in the pilot RCT but give consent for their records to be looked at by the research team to be able to ascertain the current rate of definite chorioamnionitis and normal birth in that hospital.

C) Outcomes related to the main trial

Primary outcomes:

1. **Definite chorioamnionitis** – Primary outcome in which sample size is based, mainly because the incidence of chorioamnionitis is lower than the incidence of normal birth, therefore if the study is powered to chorioamnionitis, it will also be powered to normal birth. Confirmed/definite chorioamnionitis is defined as two or more of the following signs and symptoms and histopathologic findings in the placenta. • Maternal axillary temperature of $\geq$ 38°C in the absence of any other cause of pyrexia • Maternal tachycardia ($\geq$ 101 bpm) • Fetal tachycardia ($\geq$ 161bpm) • Uterine tenderness • Foul smelling liquor • White cell blood count/Leucocytosis: 17,000cells/mm3 or more The outcome will be measured by looking at the records of the participants and the reports from the pathologists

and the data will be logged into the CRF.

2. **Normal birth** – Primary outcome. Normal birth in this study is defined as a birth that meets all of the following criteria: • Spontaneous in onset • No augmentation • No ARM • No epidural anaesthesia • No episiotomy • Baby is born vaginally and spontaneously without forceps, ventouse or kiwi The outcome will be assessed by looking at the records of the participants and the data will be logged into the CRF.

Secondary outcomes related to main trial:

- **Definite Neonatal infection** – It is defined as two or more of the following clinical signs and symptoms and positive blood or cerebro-spinal fluid (CRF) cultures: • Signs of respiratory distress (tachypnea respiratory rate more than 60/min, rapid shallow breathing, nasal flaring, coastal retraction, cyanosis, grunting) • Temperature instability (less than 36.5c or more than 38c) • Lethargy • Feeding problems The outcome will be assessed by looking at the records of the participants and the data will be logged into the CRF.

- **Neonatal cord arterial and venous pH** – The neonatal cord pH normal values are: Arterial pH (7.05-7.35) and the venous pH (7.15-7.45). Cord pH will be taken if this is taken routinely as part of the normal practice, clinicians will write values in participant's records. The records of participants will be checked and the relevant information will be extracted and logged into the case report form (CRF) by researcher (LRM) or research midwife.

- **Caesarean section**– Surgical and abdominal birth of the baby. The records of participants will be checked by the researcher (LRM) or research midwife and the relevant information will be extracted and logged into the CRF.

- **Instrumental birth** – Delivery of the baby with the help of instruments such as forceps, ventouse or kiwi. The records of participants will be checked by the researcher (LRM) or research midwife and the relevant information will be extracted and logged into the CRF.

- **Spontaneous vaginal delivery** – Spontaneous birth of the baby that meets the following criteria: • Baby is born spontaneously without the help of forceps, or ventouse or kiwi • Labour can be induced or augmented with pharmacological

agents. • Labour can be induced or augmented with the help of ARM (artificial rupture of membranes) • Mother may have an epidural for pain relief • Birth of baby may be expedited with the help of an episiotomy

- **Number of vaginal examinations during latent phase** (if any, there should be none, but will record if there were any) – Number of vaginal examinations that the participant had from the time that her membranes were ruptured until the time when active labour was diagnosed. This period includes any vaginal examinations that were performed during the induction of labour process. The clinicians will write in the booklet all the vaginal examinations they perform and the reason why and the researcher/research midwife will extract these data and log them in the CRF.

- **Number of vaginal examinations during labour**– Number of vaginal examinations that the participant had from the time when active labour was diagnosed until the birth of the baby. The clinicians will write in the booklet all the vaginal examinations they perform and the reason why and the researcher/research midwife will extract these data and log them in the CRF.

- **Epidural**– Use of epidural anaesthesia during labour and/or birth. The records of participants will be checked by the researcher (LRM) or research midwife and the relevant information will be extracted and logged into the CRF.

- **Diamorphine/Pethidine** – Use of diamorphine and/or pethidine during labour and/or birth. The records of participants will be checked by the researcher (LRM) or research midwife and the relevant information will be extracted and logged into the CRF.

- **Length of latent phase** – The duration/length of time from the time when the membranes were ruptured until the diagnosis of active first stage of labour. The records of participants will be checked by the researcher (LRM) or research midwife and the relevant information will be extracted and logged into the CRF.

- **Length of active phase of labour** The duration/length of time from the time when active first stage of labour is diagnosed until the birth of the baby. The records of participants will be checked by the researcher (LRM) or research midwife and the relevant information will be extracted and logged into the CRF.

- **Estimated blood loss of more than 1,000ml** – Estimated blood loss during the third stage of labour in excess of 1,000ml. The records of participants will be checked by the researcher (LRM) or research midwife and the relevant information will be extracted and logged into the CRF.
- **Shoulder dystocia** – It is defined as a vaginal cephalic delivery that requires additional obstetric manoeuvres to deliver the baby the head has delivered and gentle traction has failed (RCOG, 2012). The records of participants will be checked by the researcher (LRM) or research midwife and the relevant information will be extracted and logged into the CRF.
- **Cord prolapse** – Umbilical cord prolapse occurs when the cord comes before the birth of the baby or with the presenting part. The records of participants will be checked by the researcher (LRM) or research midwife and the relevant information will be extracted and logged into the CRF.
- **Failed induction:** Defined as the inability to achieve active phase of labour, that is a cervical dilation of at least 4cm and regular contractions within 18hours of the start of the process of induction.
- **Uterine hyper-stimulation**6 or more contractions in 10 minutes
- **Uterine rupture:** disruption or tear in the uterus and peritoneum

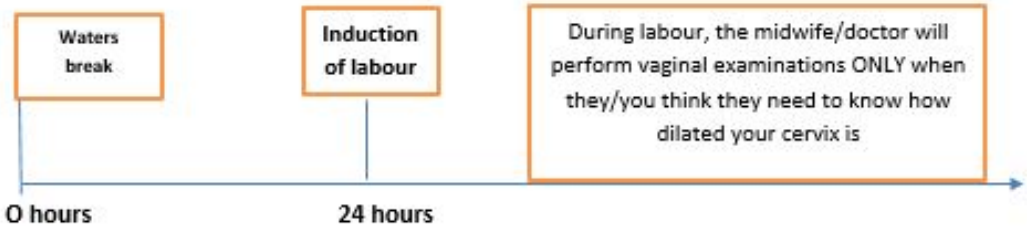
5.5.7 Participants timeline

The following figure 5.2 on page 165 shows the timeline that appears on the participants information leaflet, which gives a simple and graphic overview of the RCT

GROUP 1 = Expectant management and minimal vaginal examinations during labour

GROUP 2= Expectant management and routine vaginal examinations during labour

GROUP 3= Active management (Induction of labour at 24 hours) and minimal vaginal examinations during labour



GROUP 4 = Active management (Induction of labour at 24 hours) and routine internal examinations during labour. **This is the standard practice where you are looked after.**

Figure 5.2: Participants timeline

5.5.8 Sample size

It has been estimated that approximately 120 participants will be required for the pilot phase, this is 30 people per arm in order to meet the objectives stated earlier.

The target sample size of 120 participants for the pilot RCT will enable estimation of the recruitment rate (% of eligible participants randomized) to within no more than +/-6.9% (the precision will depend on the actual recruitment rate) with 95% confidence. This sample size will result in 30 people being allocated to each of the four arms and will give sufficient participants in order to fulfill the intervention-related objectives, assess the participant's satisfaction with the intervention and test that all the components of the study work individually as well as all together efficiently.

To support the preliminary sample size calculation for the main trial, we will also estimate the rate of definite chorioamnionitis and normal birth from 130 participants. 30 of these will be from the trial's control group (Active management and routine vaginal examinations group according to the diagram of the study that can be seen in figure 5.1 on page 153) and 100 will be from an additional review of the records of those who are eligible for the trial, but do not consent for the trial itself but do agree for their records to be used for this purpose. Assuming that the chorioamnionitis rate is 6.7% (Hannah et al., 1996), this will enable us to estimate the rate to within +/- 4.3%.

5.5.9 Recruitment

Following discussions with clinicians, managers and women as part of the PPI involvement during the developmental/feasibility phase of the study, it has been decided that the best approach to recruitment is as follows: Ideally, women who have singleton and low risk pregnancies will be informed briefly about this study at the 34-36 weeks appointment by their midwife and will be given 2 copies of the participant information sheet, one for her to read and one will stay in the notes (so we can track who has been given the leaflet and who has not). The notes of the women who have received the information leaflet will be flagged with a sticker that says they have received the leaflet. Women who want to find out more about the study can call me to ask any questions they might have. The study will also be mentioned and briefly explained by the clinical midwives and/or a member of the research team during the parent-craft sessions when possible, and a participant information leaflet was given to all the attendees. When

the women experience spontaneous rupture of membranes between 37 and 42 weeks gestation, they will phone the birth centre/labour ward and they will be asked to come in to get checked (this is standard practice in this hospital for confirming/ruling out the rupture of membranes). The clinician/midwife/doctor taking the call will also call the researcher (LRM) and/or research midwife so the researcher (LRM) and/or the research midwife can meet them once they have been seen by the midwife/doctor to see if they are eligible and to see if they are interested in taking part. At that meeting with the potential participant, the researcher (LRM) or the research midwife will assess eligibility and answer any questions that the potential participants might have, and the researcher (LRM) or the research midwife will take the consent if they decide to take part. Once the participant decides to take part the researcher (LRM) or the research midwife will then log in all the details in the screening form and will arrange the randomization to one of the 4 groups mentioned above with the help of a software called "sealed envelope" software. The woman, family and clinician will then be informed of the randomization.

Participants who meet the study criteria but decline to take part in the pilot RCT, will be asked if they would be happy for the researcher (LRM) to check their records so the information about chorioamnionitis, type of birth and number of Vaginal examinations and whether the baby got infected or not could be extracted from the records in order to have a more reliable baseline.

5.6 Methods: Assignment of interventions

5.6.1 Allocation sequence generation

Participants who agree to take part in the pilot RCT, will be allocated randomly to any of the 4 groups mentioned above in randomly permuted blocks of 4 and 8, and with stratification by parity (primipara and multipara). The randomisation will be carried out by an independent statistician using the online randomisation system (www.sealed envelope.com). The allocation list will be kept by (SD) and won't be available to the people responsible for the recruitment and enrolment of participants.

5.6.2 Allocation concealment mechanism

The researcher (LRM) or research midwives will go online into the randomisation system (sealed envelope.com), giving the necessary information in regards to the stratification, and the system will generate the group allocation for that participant.

5.6.3 Implementation

Participants will be enrolled by the researcher (LRM) or by the research midwives working at the Trust where the study will be taking place. Once the participant has signed the consent form the person enrolling the participant will go online into the IT system (called "sealed envelope"), and the automated system will generate the group allocation to that participant. The researcher (LRM) or the research midwife will then inform the participant and their care provided of the group allocation, will provide the necessary forms to complete for the participant and clinician. The person taking the consent and recruiting, will answer any further questions that the participant or clinician may have.

5.6.4 Blinding

Due to the nature of this randomised controlled trial it is not possible to blind participants or clinicians. However, blinding will take place in the situations where this can be possible. In regards to the primary outcome (definite chorioamnionitis), the placentas of the participants that show clinical signs of infection, will be assessed by a pathologist in the pathology department that won't know the duration of the rupture of membranes or the group that the participant has been allocated to or how many vaginal examinations the participant has had. This has been discussed with the pathologist and confirmed that knowing this information is not necessary in order to assess if a placenta has histological signs of inflammation. It is part of the routine practice to send the placentas of women who have shown signs of infection during labour and this information is not given routinely. In regards to the primary outcome, normal birth, it is not possible to blind the clinician or the participant because it is obvious. The clinician will have to tick the type of birth that the participant has had according to a list of criteria for each type of birth. In regards to the secondary outcome, definite neonatal infection, it is routine practice for the neonatologist to take blood cultures and/or a cerebro-spinal fluid cultures, the biomedical scientist analysing the neonatal blood or cerebro-spinal

fluid (CSF) cultures will not know the allocation of participants, duration of rupture of membranes or the number of vaginal examinations that the patient has had. The researcher analysing the swabs won't know either the group allocation of the swab as the samples will not contain that information.

5.7 Methods: Data collection, management and analysis

5.7.1 Data collection methods

The clinicians will fill in a form for the information that is not routinely collected, and the researcher and/or research midwife will pass that information on to the "Case report form" (CRF). The clinicians (midwives, obstetricians and neonatologists) will be trained in how to implement this study as well as the infection criteria for suspected chorioamnionitis and neonatal infection. In order to help with the diagnosis and with the intention to minimise bias, the placentas of the women who develop signs of infection during the waiting/latent phase as well as during labour will be sent to pathology to be examined histologically. The data from pathology will help to determine the rate of confirmed chorioamnionitis. In regards to neonatal infection, the neonatologists will be trained about the data that we will need to obtain for the study and the form that they will need to complete. In the case of suspected neonatal infection, we will collect the results from the blood cultures that are routinely obtained when infection is suspected in the neonate.

5.7.2 Data management

The researcher will look for the study forms and rest of necessary information in the case notes of the participants and will transfer the necessary information from the notes and the forms into the case report form (CRF). This process will happen in the hospital. Once the CRF is completed, the information from the anonymised CRF will be transferred into an electronic database. The anonymised paper CRF will be stored at the University of Central Lancashire in locked cabinets in rooms with restricted access to researchers only.

5.7.3 Statistical methods

The quantitative data collected during the study was analysed using statistical software (SPSS version 25).

Rates of recruitment, adherence to interventions in the study protocol, attrition, return of questionnaires and diaries and clinical outcomes (definite chorioamnionitis, definite neonatal infection and normal birth) will be presented in the next chapter as percentages, with 95% confidence intervals when appropiate. The completeness of the questionnaires will also be presented as percentages.

The acceptability of the interventions will be assessed by the study questionnaire (10 specific questions in regards to the study) and the Childbirth Experience Questionnaire (CEQ), a questionnaire that has been validated in the UK and that consists of 22 questions organised in 4 domains (Dencker et al., 2010; Walker et al., 2015). In the case of the study specific questionnaire, the results will be presented descriptively by providing absolute numbers and percentages. In the case of the CEQ the results will be presented as mean and standard deviation (SD) and analysed using the Krustal Wallis test. This was because the authors of this questionnaire deemed its answers to follow a non-parametric distribution and they recommended the use of Mann-Whitney-U-test (Dencker et al., 2010). However since in this case the pilot RCT has four different treatment groups, Krustal Wallis seemed more appropriate.

The number of vaginal examinations will be presented and analysed descriptively as a continuous variable. This is due to the small sample size of the study but is also in line with how it is presented in the literature (Dinsmoor & Gibbs, 1989; Shepherd & Cheyne, 2013; Lewin et al., 2005). Therefore, the mean and standard deviation of the number of vaginal examinations will be presented. Descriptive analysis will be performed for the demographic characteristics, as well as all primary and all other secondary outcomes. Descriptive analytic procedures will depend on the type of data:

- Continuos variables will be summarised with standard descriptive statistics such as mean and standard deviation (SD) or median and inter quartile range (IQR) as appropriate.
- Dichotomous outcomes will be presented by frequency tables and percentages

To test out the inferential analysis plan that will be used for the main study, dichotomous

outcomes will be analysed using a Chi-square test, and in the case of continuous variables a one-way anova or t-test will be performed. The pilot study will not have sufficient power to detect a difference in changes in infection rates and/or normal birth rates between the experimental and control arms, but its aim is to evaluate the feasibility and logistics of carrying out all the aspects of the study together.

The statistical analysis in the main study will follow an intention to treat analysis and as per protocol, to analyse the effectiveness and efficacy of the interventions. Both analyses are important, as they will reveal what happens under real life conditions but also what happens when the protocol is followed. It is not possible to predict how well the study protocol will be followed at this stage, however, the aim will be to look in depth at the effect of these interventions, so recommendations can be made for clinical practice in the future.

5.7.4 Recording of protocol deviations and violations

This section deals with two issues, protocol violations, and protocol deviations. Protocol violation is defined as any significant deviation from the protocol that may compromise the safety and wellbeing of the participants and/or the scientific analysis of the data. Protocol deviations, defined as any change, divergence or departure from the study design or procedures defined in the protocol, when it does not compromise the safety of the participants or the scientific value of the research. The following list of protocol violations will be recorded. This is list is not exclusive and it is intended to be given as a guidance.

- Home visits that are not taking place as per protocol. For example, when the visit is delayed more than 3 hours, or when the participant is asked to come to the unit rather than visited at home.
- Vaginal examinations not being minimised when allocated to the group were examinations are intended to be minimised.
- Lower vaginal swabs not carried out as per protocol, or when the correct swab has not been used.
- Being induced at a different time than allocated to the protocol for no clinical reason or due to maternal request.

All the violations and deviations to the protocol will be notified to the researcher (LRM), who will then approach the members of staff who were involved to understand the situation and the circumstances that lead to the protocol violation/deviation, and will put in place appropriate preventative and corrective actions depending on the nature of the deviation/violation, in order to prevent these deviations/violations from occurring again. Both violations and deviations from the protocol will be recorded in the CRF (case report form) and in the appropriate forms (see appendix). All violations/deviations from the protocol will be analysed during the analysis period.

5.8 Methods: Monitoring

5.8.1 Data monitoring

The data monitoring committee will be formed of researcher (LRM), director of studies, statistician, microbiologist and the link from the trust. The researcher will submit monthly reports of how the study is doing in terms of recruitment, retention, and will notify if any adverse outcomes appear. The data monitoring committee will meet every 3 months to review the progress of the study. Due to the nature of this study (Pilot RCT) there won't be an interim analysis as the number of participants being recruited is very small and there is not enough statistical power to make conclusions at this stage.

5.8.2 Harms

The reporting of adverse outcomes will be in line with the Good Clinical Practice principles. This pilot clinical trial will be collecting and analysing data for adverse events (AE) and will report "Serious adverse events" (SAE) as described below. SAE is defined by the Health Research Authority as an untoward occurrence occurring to a participant, that is deemed by the chief investigator (CI) and trial steering committee (STC) to be causally related to the study interventions and results in any of the following: a) results in death, b) It is life threatening, c) requires hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability or incapacity, e) consists of a congenital anomaly or birth defect or f) is otherwise considered medically significant by the investigator.

Serious adverse events (SAE) occurring to a participant will be reported to the sponsor and research ethics committee (REC) that gave favourable opinion, where in the opinion

of the chief investigator (CI) the event was:

- **Related:** that is, it resulted from administration of any of the research procedures

  AND

- **Unexpected:** that is, the type of event is not listed in the protocol as an expected occurrence.

It is expected that due to the nature of the phenomenon under investigation (prelabour rupture of membranes at term), some cases of confirmed chorioamnionitis, confirmed neonatal infection, and caesarean section will occur. These events will therefore be recorded as adverse events and will not be reported as "Serious adverse events" unless the chief investigator (CI) or trial steering committee (TSC) deem relevant. Cases where infection is suspected either in the mother or infant will be further investigated according to this study protocol and will be recorded once the diagnosis of confirmed infection according to this study protocol has been made by a physician. It is not anticipated that the study methodology or any of the interventions should result in any serious adverse events (SAEs). Previous studies (Hannah et al., 1996) (Hannah et al., 1996) have shown that active and expectant manage will result in very similar rates of maternal and neonatal infection. The different approaches to when to perform vaginal examinations are not expected to cause any serious adverse events either, mainly because vaginal examinations will be performed when clinically indicated in all participants.

The study will collect data regarding the primary and secondary outcomes, confirmed chorioamnionitis, confirmed neonatal infection, caesarean section, length of stay in hospital, deaths as part of the objectives and for the health economic analysis. Deaths will be collected on a different form so this participant is not contacted. Adverse events, primary and secondary outcomes will be routinely reviewed at the steering group, to consider whether there is any evidence suggesting a causal link to trial procedures. In the event that there was a substantial and significant difference in the number of adverse events in one of the arms of the study, the CI and TSC will consider stopping the trial.

5.8.3 Auditing

The researcher (LRM) will produce monthly reports of the progress made by the study and the data monitoring committee will meet every 3 months to review the progress of the study.

5.9 Ethics and dissemination

5.9.1 Research ethics approval

This program of research gained NHS ethical approval, R&D approval and University of Central Lancashire ethical approval. Please see appendix for details.

5.9.2 Protocol amendments

It is expected that due to the very nature of the pilot study, the study in itself will generate amendments. These amendments will be submitted to the ethical and governance committees.

5.9.3 Consent or assent

Consent will be obtained by the researcher or the research midwives employed by the Trust where this study will be hosted. Both the researcher (LRM) and research midwives have received full Good clinical practice (GCP) training, and their certificates are up to date. A sample of the consent forms are attached, and can be seen in appendix 3 on page 295 and appendix 8 on page 331.

5.9.4 Confidentiality

Confidentiality will be ensured by giving each participant a coded number (study participant number) and using the number identification. The list that contains the correlation between the number and the participant's personal details will be stored in the university and will not visible during the analysis period. Personal data will only be used when contacting the participants to remind them about the 6-8 weeks questionnaire and give the choice of how they prefer to complete it as well as to arrange follow up or collect questionnaires.

5.9.5 Declaration of interests

The researchers declare that they have no competing interests

5.9.6 Access to data

Personal data will be stored in the university offices in locked rooms with restricted access by swipe card to only members of the research and academic team. The data will be stored in a locked cabinet and in computers that are encrypted. Only members of the supervisory/academic team will have access to participant's data. If these data needs to be emailed the content of the email will be encrypted and the password to open such email will be sent to the recipients in different emails.

5.9.7 Ancillary and post-trial care

Participants taking part in this study will be covered by indemnity for negligent harm through the standard NHS (National Health Service) indemnity arrangements. The University of Central Lancashire will meet any insurance or indemnity issues to cover for non-negligent harm associated with the protocol in its role as sponsor.

5.9.8 Dissemination policy

The results from the pilot RCT will be published in peer-reviewed journals and by oral presentation at conferences.

5.10 Biological specimens

5.10.1 Low vaginal swabs

Lower vaginal swabs will be collected by the attending practitioner just before the first vaginal examination takes place. This will provide a baseline of the microbiological state of the vagina. The tests will be carried out for the presence and growth of: GBS, *E. coli, S. aureus and P. aeruginosa.* These pathogens have been chosen either for their clinical significance or because they are exogenous to the normal vaginal flora. Another lower vaginal swab will be taken after each examination takes place. We want to analyse the first swab and the last before she gives birth, but because it's very difficult to predict

which vaginal examination will be the last one, we will take one after each examination, but we will only analyse the first and last swab to see the difference in the presence of bacteria. Swabs will be provided and once the samples have been collected from the women, the swabs should be labeled with the initials of the participants, the Study ID, all the swabs from each women will be kept in a bag and in a refrigerator until the researcher (LRM) collects them. Full details of the methodology used to analyse these swabs and the results can be seen in chapter called Microbiology.

5.10.2 Human tissue samples to be sent to histopathology

Placentas, membranes and cords from women who have developed signs of clinical infection during the latent phase or during labour, will be sent to the pathology department. This is the standard practice at the Trust where the study is being hosted. The placentas, membranes and cord will be analysed by a pathologist to confirm or rule out chorioamnionitis. This will provide more accurate data regarding maternal infection (chorioamnionitis) as definite rates of infection will be stated, rather than suspicion based on clinical symptoms alone. The placentas will be sent in a pot (medium or large size) covered in formalin solution. The clinicians will fill out a request form stating that the participant is taking part in a study called "EXPECTANT STUDY", and for the attention of the named hystopathologist. The form will also state the following clinical details necessary to carry out the pathological examination of the placentas and their interpretation. The form will state the birth weight of the infant, gestation and the maternal symptoms that lead to the suspicion of chorioamnionitis. The pathologist will take 2 samples from the membranes, one sample from the area where the rupture happened and another sample from far away from the rupture, 4 blocks of the placental tissue and a block from the cord. The pathologist will look for signs of inflammation in the tissue. The placentas, membranes and cord will be kept for 7 weeks as per trust protocol and then will be incinerated according to local guidelines.

5.10.3 Other data to be collected

It has been estimated that in order to calculate the sample size for the main trial, 100 women would need to have routine and usual care in order to determine the current rate of definite chorioamnionitis and normal birth. It was decided that the most ethical way to be able to calculate the sample size was to ask for consent to look at the records

of 100 women that are eligible to take part on the RCT but decline to take part so participants are aware that somebody is looking at their records for research purposes and are given the right to choose to give consent for that or not.Therefore, the potential participants who are eligible to take part in the pilot RCT and decline to take part in the pilot RCT, will be then asked for permission and consent to look at their records, will be given information about what it is involved in it and then if they are happy for the researcher (LRM) to look at their records, they will be asked to sign a consent form. The notes and records of these participants will be flagged and the researcher (LRM) will commence data collection 1-4 weeks after giving birth.

Table 5.4: Map of Objectives and Outcomes for pilot RCT

Objective	Outcome	Definition of outcome	How outcome was planned to be measured	How was measured in reality
To estimate rates of recruitment	Proportion/Percentage of eligible women who agree to take part in the study	Proportion of eligible women who agree to take part in the study	Screening log, in which we will log the eligible participants that the researcher/Research midwife meets for potential enrollment and following discussion gives consent to take part.	Completed as planned
To estimate rates of adherence to intervention	Proportion/percentage of participants who stay in the allocation arm	Proportion of women who are allocated to expectant arm and do not request to be induced or vice versa, proportion of women who are allocated to the active arm and do not request to wait for longer	The clinician responsible for the care of the patient will notify researcher (LRM) and this will be logged in the CRF form, participant will be asked if she is still happy for us to use her data. Protocol deviations: Number (%) of deviations from the protocol	Adhence percentages with description
To estimate attrition rates	Proportion/percentage of participants drop out from the study	Formal request to abandon the study and request that we do not use their data	The clinician responsible for the care of the patient will notify researcher (LRM) and this will be logged in the CRF form, the data of this participant will not be used for future analysis	As planned
To test randomisation procedures	Efficiency of randomisation system	Effective randomisation process that allows participants to be randomised appropriately and in a timely manner	In the screening log there is a section in which it will be recorded how the randomisation took place (online in computer vs by text message), the time that took from the moment the participant says yes to being randomised will be logged. 4 time frames will be used :0-9-min, 10- 19min, 20-29min, more than 30min. Whether there is consistent coverage for the phone	It was done on line. No problems or delays encountered. Text/phone was not an option in the end
To test data collection and reporting forms	Efficiency and completeness of: Screening log form Registration form CRF	Forms that collect the necessary information and are easy to use	Feedback from research team (LRM/research midwives) regarding the Forms will be collected. There will be a box at the end of the CRF to ask if the form was easy to complete and addressed the necessary information (yes/no) if not provide qualitative feedback Proportion/percentage of completed questions in each form. I.e. Number of questions completed/number of questions that should have been completed	Data was collected by LRM. Forms were regularly updated
To test questionnaires out as well as the method to send them (post vs survey monkey)	Efficiency and completeness of Questionnaire Return rate of questionnaires	Questionnaires that are collect the degree of satisfaction with the interventions and are easy to complete and submit by the participants	Questionnaires are completed by women, % of returned questionnaires. The questionnaire has a box, where women are asked whether they found the questionnaire easy to complete and whether they found any of the questions difficult, and which one	All questionnaires were sent in the post online survey not appropriate for VAS scale rest as planned
To determine the acceptability of the intervention: “expectant management”	Acceptability of the intervention: Expectant management	Proportion of women who find the intervention acceptable	Taking into consideration the women that complete the questionnaire, out of them, score in the CEQ and percentage of participants who deem the intervention as acceptable.	CEQ and study specific questionnaires were analysed

Table 5.4: Map of Objectives and Outcomes for pilot RCT

Objective	**Outcome**	**Definition of outcome**	**How outcome was planned to be measured**	**How was measured in reality**
To determine the acceptability of the intervention: vaginal examinations only when necessary	Acceptability of the intervention: vaginal examinations only when necessary	Proportion of women who find the intervention acceptable	Taking into consideration the women that complete the questionnaire, out of them, score in the CEQ and percentage of participants who deem the intervention as acceptable.	CEQ and study specific questionnaire were analysed
To test the integrity of the study protocol	Study protocol	Protocol of study	Changes to the protocol: (1) Implemented during the pilot trial (2) That are needed to address outstanding practical issues or unknowns for the main trial.	The protocol was updated when needed

Table 5.5: Map of Objectives and Outcomes for main RCT

Objective	Outcome	Definition of outcome	How it was planned to be measured	How it was measured in reality
To estimate the sample size necessary for the main clinical trial.	Sample size for main RCT	Sample size that has enough statistical power to answer the main research question: "For prelabour rupture of membranes at term and an otherwise low risk pregnancy, is expectant management and reduced (only when necessary) number of vaginal examinations associated with a higher rate of physiological labour and birth and a reduced rate of chorioamnionitis (maternal infection) in comparison to active management and routine vaginal examinations?"	The eligible participants that decline to be part of the pilot RCT will be asked if they would be happy for the researcher to access their records to be able to collect data in regards to rate of definitive chorioamnionitis and normal birth to be able to calculate sample size We estimate we will need 100 participants who have routine care.	Sample size estimated with participants who took part in observational study n=32
To reduce the rate of chorioamnionitis	Definitive/confirmed chorioamnionitis (Primary outcome, in which sample size is based because the incidence of chorioamninitis is less than normal birth and therefore the study will also be powered to normal birth)	See definition, in list of definitions on page 21	Records of participants will be checked and relevant information will be extracted and logged into the CRF	As planned
To increase the rate of normal birth	Normal birth (Primary outcome 2)	See definition, in list of definitions on page 21	Records of participants will be checked and relevant information will be extracted and logged into the CRF	As planned
To obtain information regarding other secondary outcomes	Neonatal infection Other modes of birth Length of labour length of SROM VEs Pain relief EBL Neonatal pH	See definition, in list of definitions on page 21	Records of participants will be checked and relevant information will be extracted and logged into the CRF	Due to small sample size, only the outcomes reported in this thesis were deemed relevant at this stage

5.11 Disscusion

Undertaking a pilot randomized control trial prior to the main randomised control trial it is often done with the aim of ensuring the smooth running of the full-scale study (Thabane et al., 2010). It has many benefits, as it has been discussed in the background section of this chapter. There are two types of pilot studies, those conducted inside the main study, or like in this case, those conducted as a separate study prior to the commencement of the full-scale study (Lancaster et al., 2004). In the case of this particular study, it has been very useful to investigate how often prelabour rupture of membranes occur in the local population, the numbers of eligible participants and out of those, how many agree to take part, prior to the start of the full-scale study. This has provided enough insight to be able to determine the necessary sample size and how many maternity units would be required to recruit enough participants for the main study. It has also been very useful to assess the acceptability of the concept of randomization, as from the existing literature it is known that randomization can be a barrier for recruitment as not everyone is happy with not being able to choose the treatment (Kaur et al., 2012) as well as the acceptability of the intervention. In the case of this study, women appear to accept the randomization, as 51% of eligible women agreed to take part. In order to assess the acceptability of the intervention, the number of women that stayed in the allocated treatment was also assessed positively. The results from the pilot RCT are described and discussed in the next chapter.

Carrying out a pilot RCT was also very useful to determine the number of research midwives/research assistants that the full-scale study would require to cover a 24 hour on-call-rota as a large proportion of the calls to approach potential participants were received during the night, or early hours of the morning. Being able to test the questionnaires, the participant's diary and the data collection forms has also been very valuable.

It also provided very interesting and helpful insights in regards to the training of the clinicians (midwives and doctors). It provided information and some prior knowledge about how much time would be necessary to train the staff, best ways to approach the staff, where and when to deliver the training e.g. at short 10minute talk during mandatory training, staff meetings, and in essence what works and what does not work in order to engage the clinicians in the study and improve the recruitment and the

adherence to the study protocol.

During the course of the pilot study, it was also interesting to see how trust started to developed between the researcher and the clinicians and how this trust started to be manifested and how it helped the smooth running of the study. It was not anticipated to see how the development of trust and good relationships could have such a positive impact in the study. Very few studies have looked at how trust can benefit clinical trials, one of them is a recent study published by Hurd et al. (2017), looked at how trust improved the recruitment and retention of participant in cancer research. Hurd et al. (2017) agree that this an area that is under-researched, however, points out that trust, and the development of trusting relationships have been extensively studied in the business arena, and makes comparisons. Although seemingly distinct, recruitment and retention in clinical trials and business have many similitudes. They share three operational business dimensions: Marketing (trial awareness), sales (recruitment) and ongoing client care (retention). Hurd et al. (2017), explain that in addition, there are four business domains and their associated components e.g. building brand value, product marketing and planning, making the sale and maintaining engagement, all which must be equally developed for a successful trial. It is therefore important to start studying this phenomenon more in detail as its advantages are not yet well known in the field of clinical trials in maternity where on the other hand, building trusting relationships between midwives and women is known to improve birth outcomes and maternal satisfaction (Leap & Pairman, 2010).

Through the weeks and months of ongoing recruitment, this was very true, that trust played an important invisible part. The study and the researcher were at the beginning not well known by the clinicians and vice versa, but as weeks and months passed by, the trial became well known, and it was evident that trust started to emerge in the encounters and experiences between the clinicians and researcher. For example, at the beginning, the midwives appear hesitant to speak to the researcher about things outside of the study, and as time passed by, the researcher started to be asked for advice and help directly by some midwives individually, for example, preparation of expression of interest to jobs, preparation for interviews, papers for another project, and in general, there was an atmosphere of camaraderie and trust. This development of trust between the clinicians and researchers seemed to indirectly benefit the participants and the public in the future, as for example, midwives seemed more likely to identify potential participants and call the researcher or if during the course of the trial, there was any

problem, midwives felt more confident about calling to ask for advice. It is a very important area to ensure the successful running of clinical trials and more research is needed to build a conceptual framework that integrates trust in clinical trials.

5.12 Conclusion

This chapter has presented the study protocol for a randomised controlled trial with four arms for women for term prelabour rupture of membranes. The protocol was developed with the input from consultations with women and clinicians and in accordance with the SPIRIT standards (Standard Protocol Items: Recommendations for Interventional Trials) stated by Chan et al. (2013). The main outcomes were normal birth and chorioamnionitis. The aims of this pilot phase were: to pilot test the recruitment strategy, randomisation procedures, to pilot test the interventions and their acceptability and ultimately to test the integrity of the research protocol as a whole. Women who declined participation in the pilot clinical trial were offered participation in an observational study that involved routine care, if they consented to take part in the observational study, their records were reviewed and the relevant clinical outcomes were collected. The results from the observational study were used for comparison with the RCT and to aid future sample size calculations. The next chapter presents the findings and results from the pilot RCT and the observational study, as well as the results obtained from the Childbirth Experience Questionnaire (CEQ) and the 10-study-specific questions.

Chapter 6: Findings

6.1 Introduction

This chapter follows the previous chapter, in which the protocol for the pilot RCT and the observational study were explained. This chapter presents the results from the screening log that was carried out during the recruitment phase, as well as results on the fidelity to the protocol. In addition it also discusses how well the different tools that were used during the study were followed by the participants taking part in the RCT and the midwives who looked after them, such as the participant's diaries or the forms that the midwives had to follow to assess women allocated to the expectant management groups. These tools provide information to conduct the future main study successfully. This chapter also presents the clinical results from the observational study and the pilot RCT, as well as the results obtained from the questionnaires that were sent to women to assess their experience, and the acceptability of the interventions.

6.2 Background

As explained in the methods chapter, the objective for the pilot RCT was to test that the protocol and all the operations worked together as a whole. I also wanted to see if the study interventions were safe and, specifically, that there was no evidence of important differences in terms of health outcomes between the groups before embarking into the main trial. Simple descriptive statistics are presented in this chapter for the continuous and dichotomous variables. Inferential statistics are provided to check that, in the case of the demographics, there were not very big differences between the groups in the pilot RCT and the observational study. Other statistical tests have been carried out to test the analysis procedures for the main study, although due to the small sample size, the results need to be taken with caution.

6.3 Findings from recruitment

6.3.1 The host

The study was hosted in a maternity unit in the North West of England that has approximately 4,500 births per year. Women who choose to give birth at this maternity unit, have the choice to give birth at home, in a stand-alone birth centre, an alongside birth centre, or in a hospital delivery suite.

6.3.2 Duration

Recruitment took place from the 15th November 2016 until the 28th February 2018. During that time, I was available on call 24h/day for an average of 5 days a week. The process of recruitment was as follows: Women who thought that their membranes had ruptured, would call the maternity unit for advice, and they would be invited to come in and have an assessment. The midwife would then call the researcher (LRM) advising that a potential candidate was going to come to the maternity unit for assessment. The researcher would then come in, and if it was confirmed that the membranes were broken, and the potential participant was happy to speak with me, I would then discuss the study with the woman and her birth partner and would then ask the woman if she would like to take part in the study.

6.3.3 Location where women where approached

Recruitment took part in any of the places where women presented themselves with a history of possible spontaneous rupture of membranes, such as: triage, the along-side birth centre, stand-alone birth centre and delivery suite. Since one of the eligibility criteria was that women had to have healthy pregnancies, most of the women were approached at the birth centres. In total 192 phone calls/women were received, 130 (68%) were approached at the alongside birth centre, 51 (27%) women at the stand-alone birth centre, five (3%) women at triage, four (2%) women at the delivery suite and for two women (1%) , the place where they were approached was not recorded. Figure 6.1 below on page 186 illustrates this.

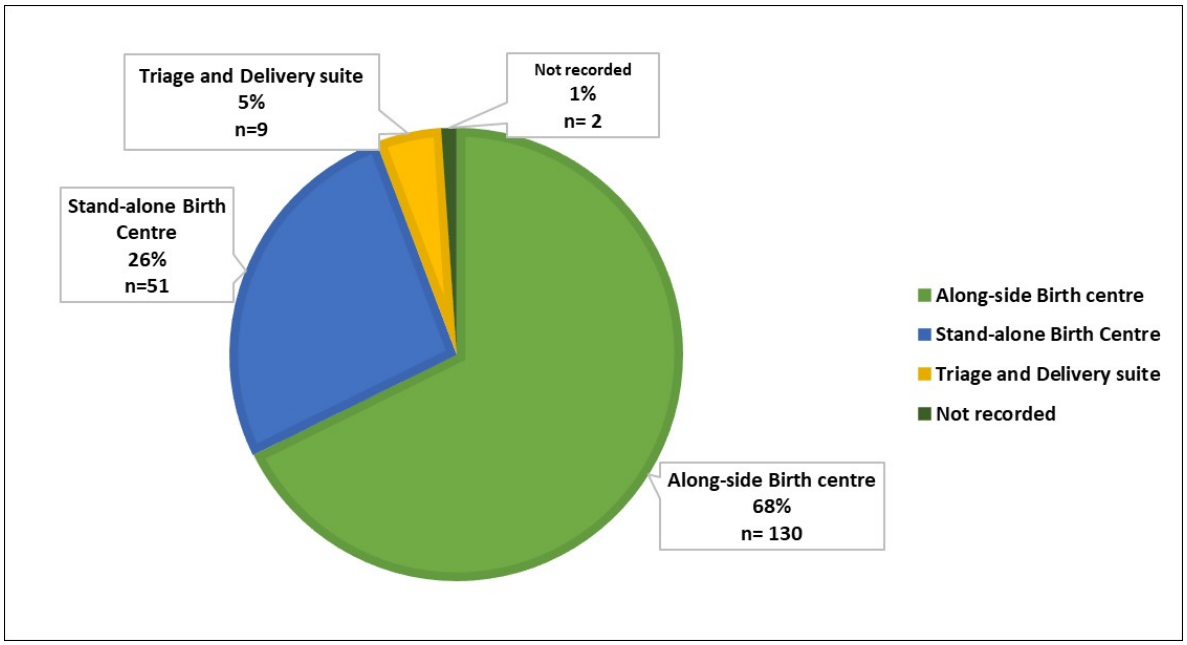


Figure 6.1: Location where women were approached

6.3.4 Results from screening log

A total of 192 calls were received from midwives alerting me that a potential participant was coming to the maternity unit for assessment and confirmation of the rupture of membranes. Of those, 46 women (24%) were approached during office hours (Monday to Friday from 9:00 to 17:00) and 146 women (76%) were approached during the rest of the week (out-of-hours). Out of those 192 phone calls, 85 women met the inclusion criteria outlined in the methods chapter and were all approached to discuss the study and were asked if they would like to participate. Therefore, 107 women did not meet the study criteria for various reasons: Amnio- test negative (n=35), contracting regularly (n=36), lived out of area (n=9), had meconium stained liquor at screening (n=6), had a current/unresolved urine infection (n=2), had current signs of infection (n=1), was known GBS (n=1), did not speak fluent English (n=4), or had other reasons (n=14) such as: decreased foetal movements (n=2), gestational diabetes (n=1), High blood pressure and proteinuria (n=1), low platelets (n=1), didn't want the placenta to be analysed, initially said yes, (n=1), gestational age more than 41+2 (n=2), maternal age less than 18 (n=1), a VE was performed before speaking to her (n=2), reason unrecorded (n=3). The reasons for not being eligible are presented graphically in figure 6.2 on page 187 ahead.

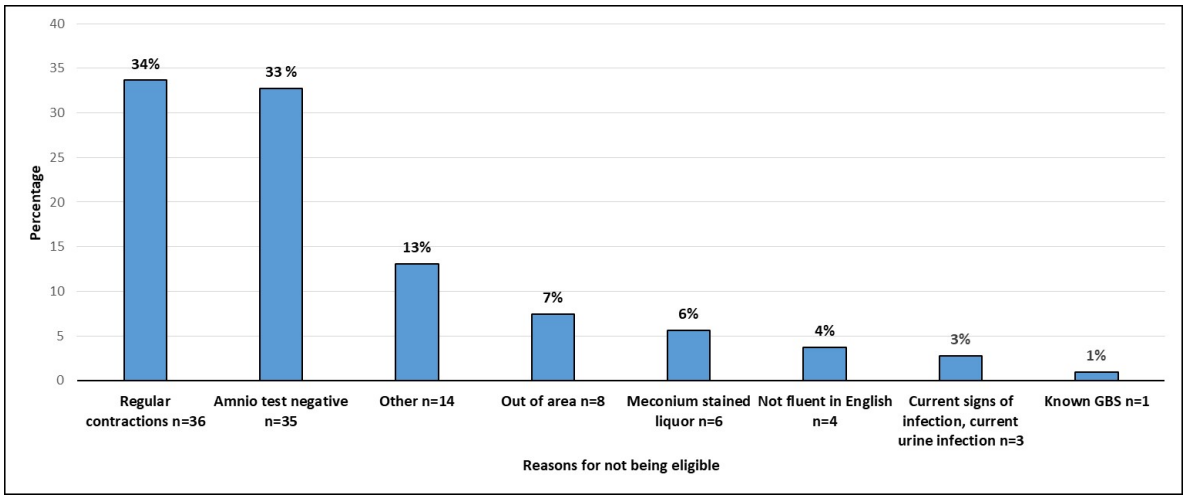


Figure 6.2: Reasons for not being eligible

All the women who met the criteria (n=85), were offered the opportunity to take part in the pilot RCT, and 43 (51%) women agreed. If they did not want to take part in the pilot RCT, they were offered to take part in the observational study. As mentioned in section 5.10.3on page 176, this involved routine care, their placenta to be sent to histopathology if there were signs of infection and permission for the researcher to look at their records and collect the relevant clinical data for this research. There were 34 women (40%) who agreed to take part in the observational study. There were eight women (9%) who did not consent to either the pilot RCT or the observational study. This is illustrated in figure 6.3 on page 188

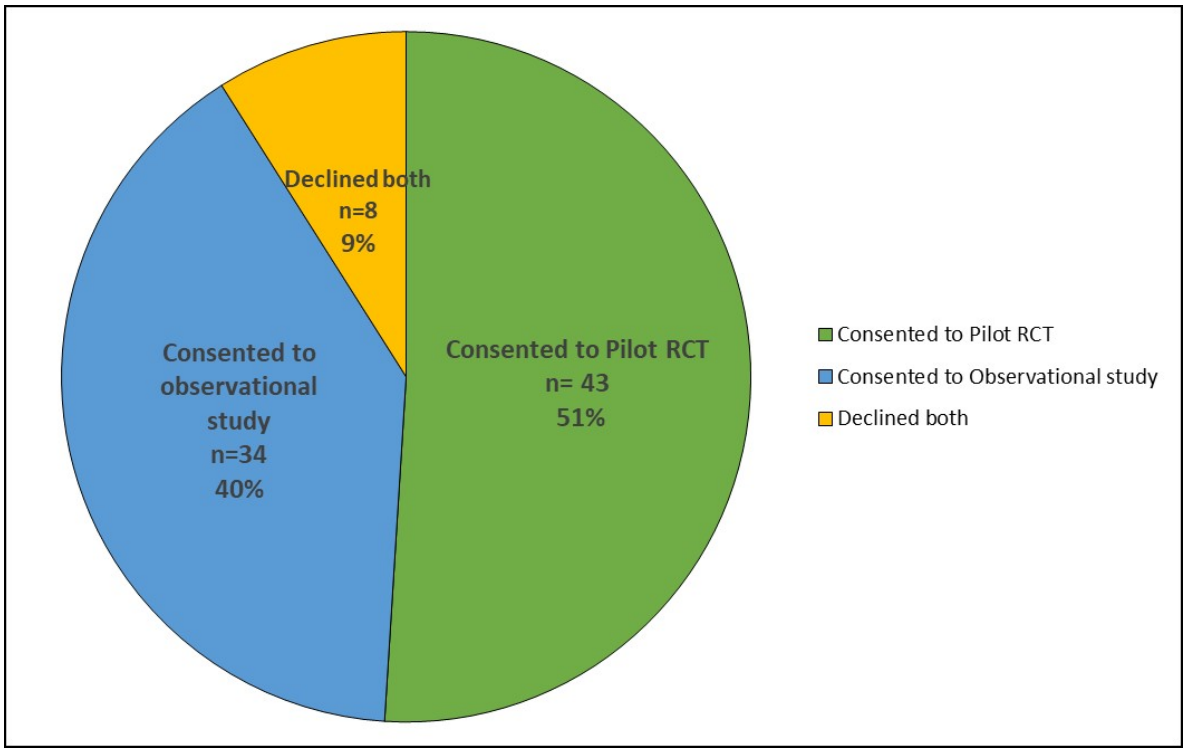


Figure 6.3: Screening log

In the pilot RCT there were 43 women who consented to take part initially. However, there were two withdrawals, one woman in the active management and minimal vaginal examinations group and another one in the active management and routine vaginal examinations group. Both decided to withdraw from the study because they did not want to have their labours induced at 24 hours. Therefore, the final sample for the pilot RCT consisted of 41 women.

In the observational study, there were initially 34 women, but here were also two withdrawals. One woman was found to carry a baby with breech presentation when the process of induction was about to start and, consequently, had a caesarean section. Since breech presentation was one of the exclusion criteria, I decided to exclude this case from the study. In another case, the midwife wrote on the consent form "withdrawal". The wishes of that woman were honoured and data were not collected. Therefore, the final sample was 32 for the observational study. Diagram 6.4 below on page 189 describes the recruitment process.

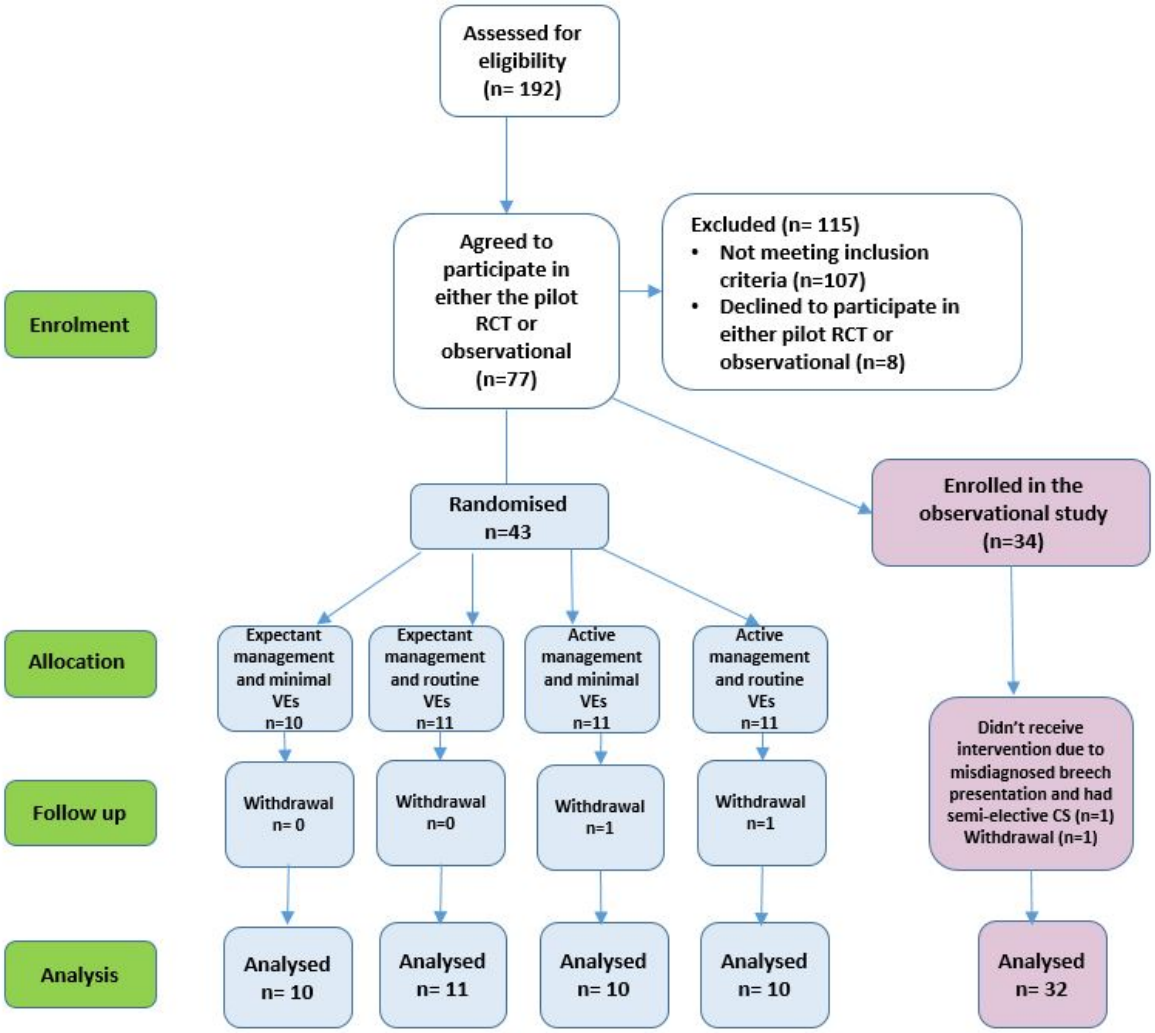


Figure 6.4: Recruitment process

6.4 Demographics

This section provides demographic data on the 73 of the women who decided to take part in either the observational study or pilot RCT. It accounts for 91% of the women who met the inclusion criteria listed in table 5.1 on page 154 . Therefore, it provides a good baseline for demographics for the future main clinical trial.

6.4.1 Rationale for choosing these demographic variables

I decided that the following demographics and baseline characteristics would be reported from the participants' clinical notes, due to their potential relationship with either the mode of birth or infection which were identified during the process of undertaking the literature review. The length of rupture of membranes at the time of consent was also recorded due to its impact on the likelihood of going into spontaneous labour within the next few hours. Tables 6.1 and 6.2 on page 190 and 191 illustrate the baseline characteristics of all participants.

Table 6.1: Demographics for pilot RCT and Observational study (Continuos variables)

	EM and minimal VEs n=10	**EM and routine VEs n=11**	**AM and minimal VEs n=10**	**AM and routine VEs n=10**	**Observational study n=32**
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age(yrs)	30.4 (6.3)	29.3 (1.7)	31.1 (3.9)	31.8 (4.7)	28.9 (5.4)
Gestational age (Decimal weeks)	39.84 (0.87)	40.06 (1.15)	39.94 (1.19)	39.41 (1.17)	39.60 (1.05)
BMI (kg/m^2)	26.9 (4.3)	24.3 (2.5)	24.7 (4.5)	22.5 (3.1)	24.8 (4.9)
Length of SROM at consent (Decimal hours)	3.8 (1.54)	3.42 (1)	4.99 (3.2)	3.14 (1.26)	4.13 (3.1)

Table 6.2: Demographics for pilot RCT and Observational study (Binary variables)

	EM minimal VEs n=10	**EM routine VEs n=11**	**AM minimal VEs n=10**	**AM routine VEs n=10**	**Observational study n=32**
Variable	n (%)	n (%)	n (%)	n (%)	n (%)
Nulliparous	7 (70%)	8 (72.7%)	7 (70%)	7 (70%)	20 (62.5%)
Multipara	3 (30%)	3 (27.2%)	3 (30%)	3 (30%)	12 (37.5%)
Smoker	0	0	2 (20%)	0	2 (6.25%)
Ethnicity (White)	8 (80%)	9 (81.8%)	9 (90%)	9 (90%)	30 (94%)
Ethnicity (Black)	0	0	0	0	0
Ethnicity (Asian)	2 (20%)	1 (9.1%)	1 (10%)	1 (10%)	2 (6%)
Ethnicity (Mix)	0	1 (9.1%)	0	0	0

Since the participants who took part in the pilot RCT were randomly assigned to each of the interventions group, it was not necessary to carry out significance tests to identify if there were any statistically significant differences in the baseline characteristics. However, I wanted to assess if the demographics from the participants in the pilot RCT were statistically significantly different from those who took part in the observational study, as there was no randomisation in the latter. Therefore, T-tests were carried out on the continuous variables and Chi-square tests on the dichotomous variables. All tests have shown that there are no statistically significant differences amongst any of the demographics between the participants who took part in the pilot RCT and those who took part in the observational study as described in tables 6.3 and 6.4 on page 192 and 193.

Table 6.3: Significance test on demographics (Continuous variables)

	Pilo RCT n=41	**Observational Study n=32**	**t-test**
Variable	Mean(SD)	Mean(SD)	P value
Age(yrs)	30.61 (4.36)	28.91 (5.36)	t=1.504, df=71, p=0.137 *NS
Gestational age (Decimal weeks)	39.82 (1.09)	39.60 (1.06)	t=0.865, df=71, p=0.390 *NS
BMI (kg/m2)	24.58 (3.85)	24.83 (4.91)	t=0.247, df=71, p=0.806 *NS
Length of SROM at consent (Decimal hours)	3.83 (1.99)	4.13 (3.1)	t=0.512, df=71, p=0.610 *NS

Age, gestational age and BMI seemed to be similar across the groups within the pilot RCT and the observational study. The study placed no restriction in regards to the BMI, and high BMI was not an exclusion criterion for inclusion in the study, because I wanted the main study to be extrapolated to all women regardless of their BMI. The average BMI in the study was below 30. This could be because one of our inclusion criteria was to have a healthy pregnancy, and a higher BMI sometimes is associated with other medical problems.

The mean length of time of SROM at consent seemed to be similar for the observational study and the four groups in the pilot RCT, which was roughly between three and five hours. This is important to consider when analysing the results and looking at the proportion of women going into spontaneous labour within the first 24 hours, as some

Table 6.4: Significance test on demographics (Dichotomous variables)

		Pilot RCT n=41	**Observational Study n=32**	**χ^2 test**
Variable		**n (%)**	**n (%)**	**P value**
Parity:	Nulliparous	29 (70.7%)	20 (62.5%)	χ^2= 0.552; df=1; p=0.798 *NS
	Multipara	12 (29.3%)	12 (37.5%)	
Smoker	Smoker	2 (4.9%)	2 (6.25%)	χ^2= 0.065; df=1; p=0.798 *NS
Ethnicity	Ethnicity: White	35 (85.4%)	30 (94%)	χ^2 = 1.585; df=2 ; p=0.453 *NS
	Ethnicity: Black	0	0	
	Ethnicity: Asian	5 (12.2%)	2 (6%)	
	Ethnicity: Mix	1 (2.4%)	0	

other previous studies have a minimum of hours with no regular contractions as one of the inclusion criteria. In this study, I wanted to see what would be the mean of length of rupture of membranes if there were no set criteria. This would help to see if for the main study, setting a minimum of hours with no regular contractions as one of the inclusion criteria would be something useful or a hindrance for recruitment. After analysing the data, and having been involved in the process of recruiting participants, I have come to the conclusion that it is better not to set a minimum number of hours with no regular contractions as part of the inclusion criteria for the main trial. This was because it could contribute to losing many potential participants and it would not add scientific value to the study because the process of recruitment would not mirror what happens in normal practice in regards to the assessment and the care plan for women who break their membranes and are not regularly contracting at the time of being assessed. What happens in normal practice is that most women call the maternity unit within an hour or so of realising that their waters might have broken, and they are then invited to come in for an assessment. Sometimes women need an hour or two to sort out transport or childcare if they have other children, so by the time they arrive, and are assessed to confirm the rupture of membranes, and the treatment options or the study are discussed, it is normally between three and five hours in most cases since the rupture of the membranes. The need for an induction is discussed at the time of the assessment, therefore, offering the study at that time is the best approach. This

is because, at that time is when women are normally booked for an induction (if they do not have regular contractions at the time), and changing their minds later on, after they have been given an appointment for induction, is more difficult.

It was also important to note that the majority of women who met the criteria and took part in either the observational or the pilot RCT were nulliparous, with a range between 63% in the observational and about 70% in the pilot RCT. This could be because prelabour rupture of membranes seems to happen more in nulliparous than in multiparous. This is consistent with previous research, Hannah et al. (1996) reported an overall proportion of 59.55% of nulliparous, and although the proportion of nulliparous women in this research is slightly higher, this could be because of the difference in the sample size. The implications of this finding for the main study can be significant in terms of recruitment. Knowing that it happens more amongst nulliparous, help us to decide where to put the effort. In order to maximise the return on the investment of time and energy in the main study, more effort should be put in telling nulliparous women about the study during pregnancy by going to places where a lot of nulliparous women go, like antenatal education, as opposed to play groups where one could find women who already have children.

Smoking at the time of delivery was recorded as a baseline characteristic due to its potential influence on infection. Most of the women who met the criteria, and agreed to take part in either the observational study or the pilot RCT were non-smokers. The rate of smoking in the observational study was 6.25% (n=2/32), whereas, in the pilot RCT the figure was similar, although slightly lower with a rate of 4.88% (n=2/41). This is lower than the national average of smoking at the time of delivery in 2015/2016 which was reported as 10.6%. The fact that the figure obtained in this study was lower than the national average for smoking could be due to many factors, but mainly that perhaps smoking is associated with other medical problems, and since one of the inclusion criteria of this study was to have a healthy pregnancy, we did not encounter as many smokers as the national average.

In terms of the demographics, and the ethnicity, most participants were white, with a few being Asians or mixed white-Asian. The lack of translators could have accounted for this. This is important to note. For the main study, it would be necessary to put strategies in place, to make sure there is enough ethnic diversity and women can be recruited across all ethnic groups, and to ensure that the RCT can be extrapolated to all

women, regardless of their ethnic background. The following strategies may be helpful to ensure that women from a wide rage of ethnic backgrounds are recruited and stay in the study. For example, making sure information leaflets are given in clinics, antenatal classes, and other community based settings where women from ethnic minorities go. It will also be important to ensure participant information leaflets, consent forms, participant's diaries are available in several languages, and that translators are available via telephone or in person 24 hours a day. Language can be a communication barrier that needs to be addressed to make sure the safety of participants is maintained.

6.5 Results from the observational study

This section outlines the results obtained from the observational study, which involved women who met the criteria for the pilot RCT, defined in table 5.1 on page 154, and declined to take part in the trial, but were happy for the researcher to look at their records. As noted in the methods chapter, the main rationale, for conducting the observational study was to have a baseline of the clinical health outcomes pertaining to women with prelabour rupture of membranes and treated under usual practice conditions, to be able to calculate the sample size for the future main study, as well as to be able to compare the results obtained in the observational study with those obtained in the pilot RCT.

As described in the methods chapter, women who took part in the observational study had routine care. Since they were not in labour at the time of screening, they were advised to return home and were given information about how to look for signs of infection every four hours during waking hours, and for signs of labour. They were advised to return at approximately 24 hours if they were not in labour or had not had the baby by then.

According to local protocols, at the beginning of the study and up to the 30th April 2017 women who had prelabour rupture of membranes were advised to return at exactly 24 hours since the rupture of membranes for the induction of labour, no matter the time of the day or night. From the 1st May 2017 women who broke their waters during the night (from midnight till 6am) they were given an appointment to come at 6am for induction of labour.

The following outcomes are outlined below: Women who went into labour within 24

hours, women who needed their labours to be induced, length of SROM, babies born after 24hours or more, number of vaginal examinations, chorioamnionitis, neonatal infection and type of birth. The rationale for choosing to report these outcomes in the observational study is described in each subsection.

6.5.1 Rates of spontaneous labour by 24 hours

The rationale for reporting the proportion of women who were in active labour within 24 hours is mainly to see the effectiveness of the current type of care. (NICE, 2017), in the intrapartum guideline claimed that 60% of women go into spontaneous labour within 24 hours. Induction of labour is recommended at approximately 24 hours, under the belief that the majority of women go into spontaneous labour within 24 hours and that therefore, not many women would need to be induced. In contrast, a smaller proportion of women were found to go into spontaneous labour within 24 hours in the observational study. Out of the 32 women who took part, 47% (n=15) of women were in spontaneous active labour within 24 hours of the rupture of membranes. One woman was in the latent phase by the time the induction of labour was scheduled and was, therefore, offered extra time in the belief that she would soon be in active labour. There were 16 women (50%) who had their labours induced. Figure 6.5 on page 197 represents graphically the percentage of women in the observational study that went into spontaneous labour and percentage that needed to have an induction under routine care.

As shown in figure 6.5 on page 197, 47% of women were in spontaneous active labour within 24 hours since the rupture of membranes. The percentage of women in spontaneous labour within 24 hours is consistent with the literature, Ottervanger et al. (1996) reported that 55% of women in their trial went into labour within 24 hours. This implies that there is still a large proportion of women, about 50%, that required induction of labour under the current protocols and this gives further justification to investigate optimal treatment options for those who do not go into labour within 24 hours. One of the implications of this finding is that the new approach under investigation offers about half of the women who experience prelabour rupture of membranes more time and therefore, a higher chance to go into spontaneous labour, if they wish.

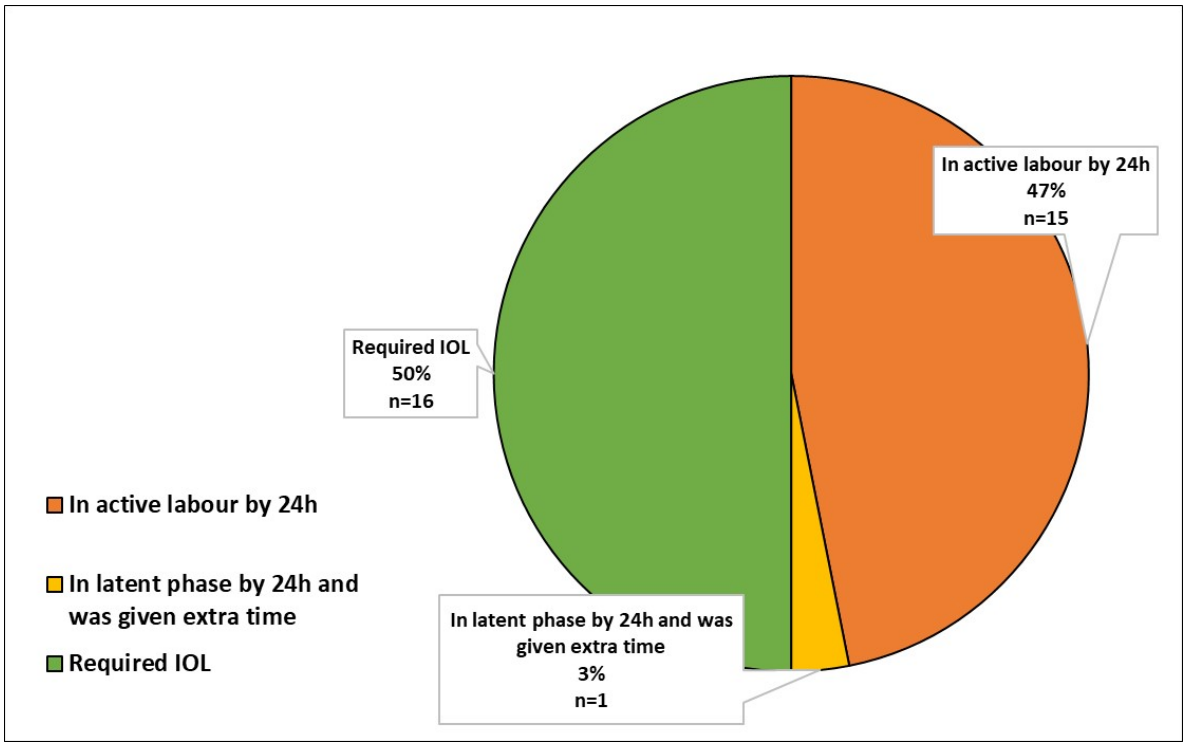


Figure 6.5: Women in active labour within 24 hours in the observational study

6.5.2 The length of rupture of membranes

The length of the rupture of membranes was reported because a length of 24 hours or more is considered a risk factor for neonatal infection according to NICE (2012). However, it has been reported in a recent systematic review carried out by Middleton et al. (2017) that there are no statistically significant differences in the rates of neonatal infection when women have active compared to expectant management. The national guidelines (NICE, 2017) on intrapartum care on page 53 state that *"induction of labour is appropriate approximately 24hours after rupture of the membrane"*. This is probably done in an attempt to reduce the risk of infection to the infant. I, therefore, wanted to see the effectiveness of the current type of care in reducing the proportion of infants born before 24 hours since the rupture of membranes. Historically, it is believed that the risk of infection to the infant is increased once the membranes have been ruptured for 24 hours or more.

The data were thus analysed to assess how many infants, were in the "at risk category", by the time were born under the normal care pathway. It was found that 20 infants (63%) had a rupture of membranes of 24 hours or more by the time they were born. The

implications of this finding is that the current type of care is not reducing the proportion of babies born "at risk of infection" as 63% is considered a high percentage and, perhaps, other options to reduce the risk of infection should be explored. This could be done in a substantial study that looks at reducing the number of vaginal examinations to reduce the risk of chorioamnionitis, and consequently, the risk of neonatal infection.

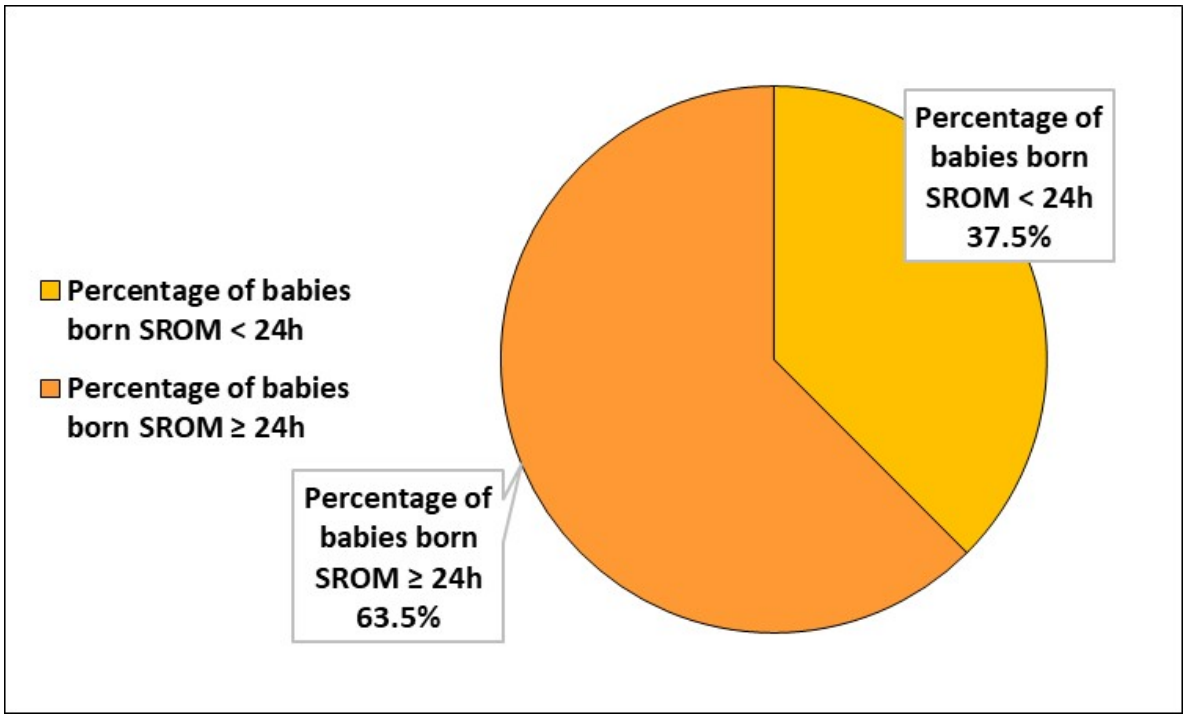


Figure 6.6: Length of SROM in babies in the observational study

6.5.3 Number of vaginal examinations

The average number of vaginal examinations was reported as there is evidence that it is one of the strongest correlators for chorioamnionitis (Seaward et al., 1997). I also wanted to be able to compare the average number of vaginal examinations for women having the standard type of care in this Trust with the results obtained in the pilot RCT.

Participants taking part in the observational study had an average number of vaginal examinations of 4.03 and the standard deviation was 2.7. According to the literature, this is above the mean number of vaginal examinations that Shepherd and Cheyne (2013) obtained. They found that the mean number of vaginal examinations was 2.9 and the SD= 1.5, although their study was also carried out in the UK, their study

was carried out in women with *"uncomplicated singleton pregnancies, admitted at term in either spontaneous or for induction of labour"* (Shepherd & Cheyne, 2013, p. 50). This difference in the mean number of vaginal examinations could be because clinicians might become more keen/anxious in making sure that women whose membranes have been ruptured give birth promptly, and they might perform more vaginal examinations to make sure they make progress steadily. The implications of this finding are that it provides a baseline for comparison with the results in the pilot RCT and for the design of the future definitive study. It also shows that plenty of training would need to be delivered during the course of the main trial, to ensure clinicians feel comfortable and competent following the study protocol on the different regimes for vaginal examinations.

6.5.4 Relationship between type of onset of labour and number of vaginal examinations

I was interested in seeing if there was an association between the type of onset of labour and the number of vaginal examinations that women had. This analysis was only possible in those participants taking part in the observational study in which there was no control or suggestions given in regards to vaginal examinations.

The results from the t-test presented in table 6.5 in page 200 show that there is an association between the number of vaginal examinations and a labour that has been induced. In the descriptive statistics table, it can be appreciated the mean number of VEs is greater in induced labours than in those that start spontaneously. Since the Levene test was not significant (p=0.271), we can assume equality of variances in the number of vaginal examinations between the 2 groups (Induced/spontaneous). As shown in table 6.5 in page 200, there is strong evidence (p=0.003) to suggest that the mean of VE is different between labours that were induced and those that started spontaneously.

The implications of this finding are crucial for this research as they show that induction of labour is associated with more vaginal examinations. Moreover, it is known that vaginal examinations are the strongest correlator for chorioamnionitis (Seaward et al., 1997). Hence, if induction of labour is associated with more vaginal examinations and the more vaginal examinations, the greater the chance of having chorioamnionitis, perhaps routenely inducing labour is not the best approach for prelabour rupture of

membranes. It implies that further research is necessary to develop types of care that give women the greatest chance of going into labour spontaneously. Also, it calls for clinicians being trained in assessing the progress of labour not only by vaginal examinations but also by using external signs of progress in order to minimise the number of vaginal examinations that women may have.

Table 6.5: Relationship between onset of labour and number of vaginal examinations

Type of onset of labour	**Number of Vaginal examinations Mean (SD)**	**Significance test (t-test)**
Spontaneous n=16	2.69 (1.95)	t=3.183; df=30; p=0.003
IOL n=16	5.38 (2.75)	

6.5.5 Length of active labour

The length of active labour was reported as it is associated with the number of vaginal examinations. The longer the labour is, the greater the potential for more vaginal examinations. In the observational study, the mean length of active labour was 4.68 hours with a SD=4.21 hours. This provides a baseline for comparison with the results obtained in the pilot RCT and future main study.
The results obtained in the observational study could act as part of a control group as they had active management and routine four hourly vaginal examinations.

It was difficult to measure the length of active labour as different clinicians diagnosed the onset of labour differently, some defined it as when the woman called saying that she wanted to come in the unit, others used the time when she was admitted, others used the time of the first vaginal examination when the cervix was found to be $\geq$3cm dilated. How crucial and sometimes difficult it is to diagnose the onset of labour has been reported previously in the literature (O'Driscoll et al., 1969; Shepherd & Cheyne, 2013). It is important to have a systematic approach to the diagnosis of labour, therefore, for the purpose of this study, active labour was defined as: Strong and regular contractions, at least 3 contractions in 10minutes, lasting at least 60 seconds each and a cervical dilation of $\geq$3cm (See definition on page 21).

6.5.6 Neonatal infection

Neonatal infection was reported as an outcome in the observational study because of the concerns that prelabour rupture of membranes is associated with a rise in the incidence of neonatal infection. I also wanted to establish the incidence of confirmed neonatal infection for women treated with the current type of care. This could also contribute to sample size calculations for the future main study and to compare it with the results obtained in the pilot RCT.

There were no confirmed cases of neonatal infection in the observational study, the definition for confirmed neonatal infection is also outlined in the list of definitions that appears on page 21. The implication of this finding is that the incidence of neonatal infection appears to be low, and it implies that if neonatal infection was to be chosen as a primary outcome in the future main clinical trial, the required sample size would need to be very large.

6.5.7 Chorioamnionitis

Chorioamnionitis was reported as this is the main outcome of the study along with normal birth. Reporting chorioamnionitis in the observational study would assist with sample size calculations for the main study.

Chorioamnionitis was confirmed following the same criteria as that for the pilot RCT (signs and symptoms of infection and confirmation by histological examination). The definition of confirmed chorioamnionitis is outlined in the list of definitions that appear on page 21. In the observational study there was one confirmed case and three suspected cases of chorioamnionitis among the 32 women who took part. In the three suspected cases the placenta was not sent to histopathology despite clinical signs of infection (for example offensive liquor, as documented in the notes). As a result, the rate of chorioamnionitis from this study is 1-4 possible cases in 32 women. These findings provide the basis for the baseline for the main study sample size calculation. It was decided to opt for a conservative approach for the sample size calculation and therefore it will based in 2 cases in 32 women. This is also consistent with the literature. Hannah et al. (1996) in the TERMPROM trial reported a rate of chorioamnionitis of 6.2% for the Active management with prostaglandins group. The rationale for choosing the active management and prostaglandins group for comparison purposes is because nowadays

the method of induction most commonly used is prostaglandins.

6.5.8 Normal birth and mode of birth

The mode of birth was reported in the observational study because normal birth is one of the primary outcomes of the pilot RCT. It will also contribute to the sample size calculation for the future main trial.

In the observational study there were 12/32 (38%) of normal birth. The definition used in this study for normal birth it is outlined in the list of definitions that appear on page 21. Normal birth can happen in water, also called waterbirth or in land, also called normal birth in land. The different rates of normal birth in water and land are also illustrated below in figure 6.7 on page 202. It is also important to see the percentages of the other possible modes of birth as illustrated in the figure below. The definitions for each type of birth can also be seen on page 21. In regards to the different modes of birth, there were 5 caesarean sections, 6 instrumental births, 9 spontaneous vaginal deliveries, and 12 normal births (10 water births and 2 land births) in a total of 32 women. Figure 6.7 ilustrates this.

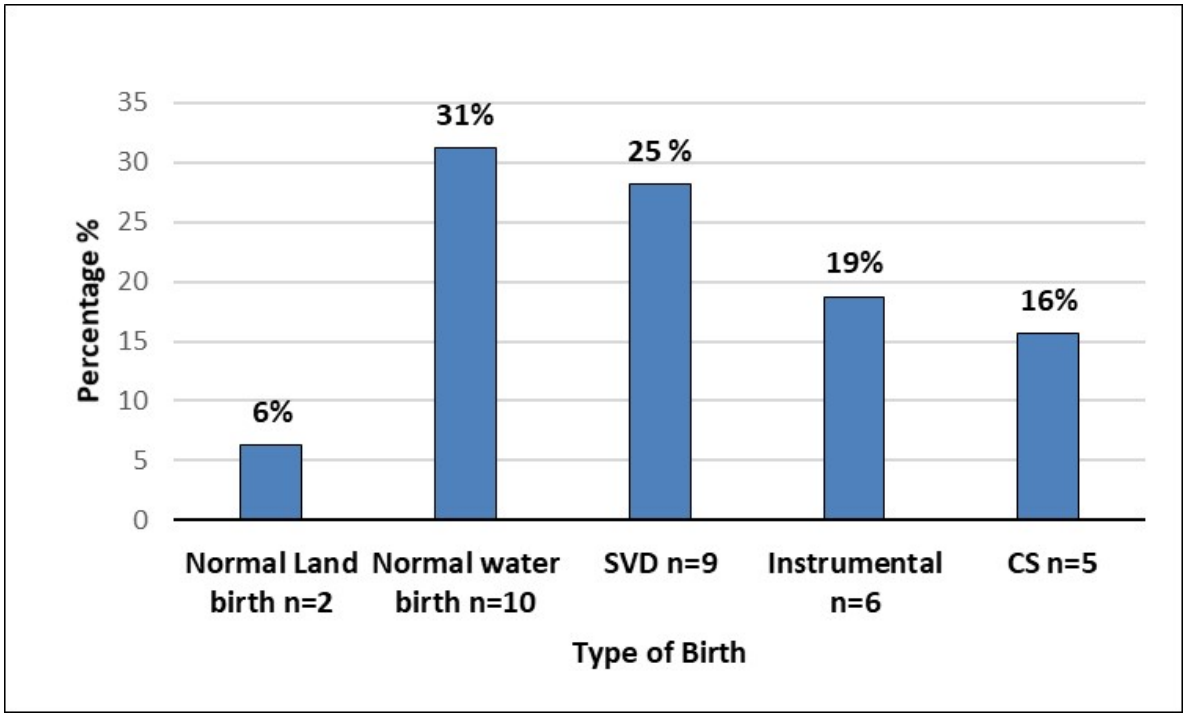


Figure 6.7: Type of birth in the observational study

As discussed earlier in the background chapter on page 28, data on normal birth, as defined in this study, are not routinely collected. Therefore, this study and the future main trial constitutes one of the first clinical trials where normal birth is one of the main outcomes. The emergency caesarean section rate was 16%. According to the statistics reported by the NHS for England and Wales, an emergency caesarean is any caesarean that was not planned antenatally (also called elective) and which reason for it rises during labour. The emergency caesarean section rate obtained in the observational study (16%) is above the national average for emergency caesarean section, which was 12.3% for women in England for 2016/2017. Therefore, it seems that women with prelabour rupture of membranes and treated with the current active management, experience a higher than the national average rate of emergency CS. There could be several reasons for this increase, but some of them could be the fear of infection amongst the clinicians and that subsequently women are not being given enough time to labour, failure of the process of induction, or that perhaps prelabour rupture of membranes is associated with malposition of the presenting part, which is not always addressed by the induction of labour. It was found that 4 out of a total of 5 (80%) women who had a caesarean section and took part in the observational study had their labours induced. The implications of this are that if women were given more time to go into spontaneous labour, the rate of emergency caesarean section could potentially decrease. The reasons for the emergency Caesarean sections in women who took part in the observational study were examined. There were five caesarean sections in the observational study, and the reasons for those sections were as follows: Failed induction (n=1), Failure to progress (n=2) and abnormal CTG (n=2) as illustrated ahead in figure 6.8 in page 204. It shows that 60% of the caesarean sections were a result of a failure of the induction process or diagnosis of slow labour. The implications of this are that if women were given more time to labour and if "slow but normal" is more widely recognised as Oladipo et al., (2018) highlights the caesarean section rate could decrease.

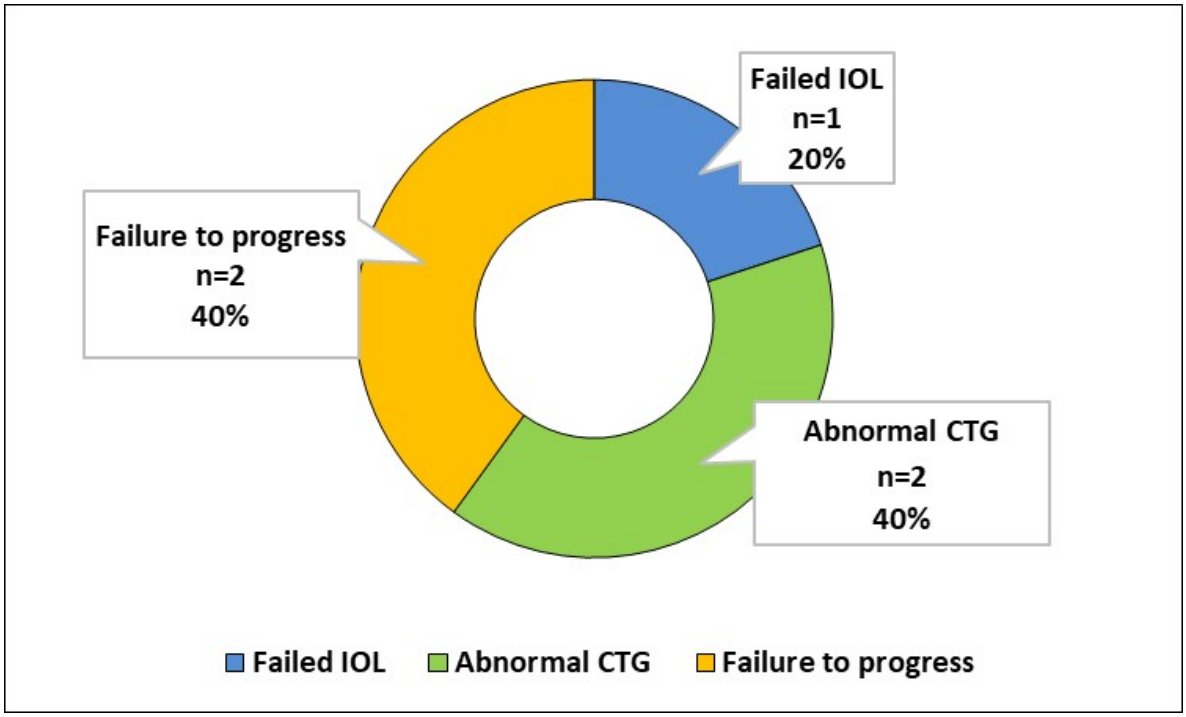


Figure 6.8: Reasons for CS in observational study

6.5.9 Sample size calculation for the future main clinical trial

Calculating the sample size for the future main clinical trials was one of the aims of conducting the observational and pilot RCT. In this section, the process to calculate the sample size for a superiority trial with four treatment groups is described. The calculation was performed with the help of a software called "N-query".

The calculation was based on the results obtained in the observational study. There were 2/32 (6.25%) cases of chorioamnionitis (maternal infection), this is also similar to the overall chorioamnionitis incidence in the TERMPROM trial (6.7%) (Hannah et al., 1996).

Therefore, the calculation was based on the following null and alternative hypotheses

$$H_0 : P_1 = P_2 = P_3 = P_4 \tag{6.1}$$

$$H_1 : P_1 \neq P_2 \neq P_3 \neq P_4 \tag{6.2}$$

For calculating the sample size, the effect size must be calculated first, and later on the sample size, the expected proportions of infected and not infected must be estimated. I have hypothesized the following:

The proportion of infected in the arms with routine VEs= 6.25% (0.0625), this is based on our observational study (2/32= 0.0625) and I hypothesize that by reducing VEs, chorioamnionitis will be reduced to 4%. The proportion of infected in the arms with minimal VEs=4% (0.04). As shown in table 6.6 the effect size is 0.003.

Figure 6.9 presents a screen shot from N-query, where the sample size calculation for a clinical trial with 4 arms is shown. This is based on a significance level α=0.05, power=0.80, and effect size=0.003 that was calculated earlier in table 6.6. The number of categories is 2 (infected/not infected).

Figure 6.9 shows that the required sample size for the future main study would be 909 per group, or 3,636 participants in total.

Table 6.6: Effect size calculation

Group	Proportion of expected infected	Proportion of expected NOT infected	SUM (must equal to 1)
Group 1: EM +minimal VE	0.04	0.96	1
Group 2: EM + routine VE	0.0625	0.9375	1
Group 3: AM + minimal VE	0.04	0.96	1
Group 4: AM + routine VE	0.0625	0.9375	1
EFFECT size	0.003		

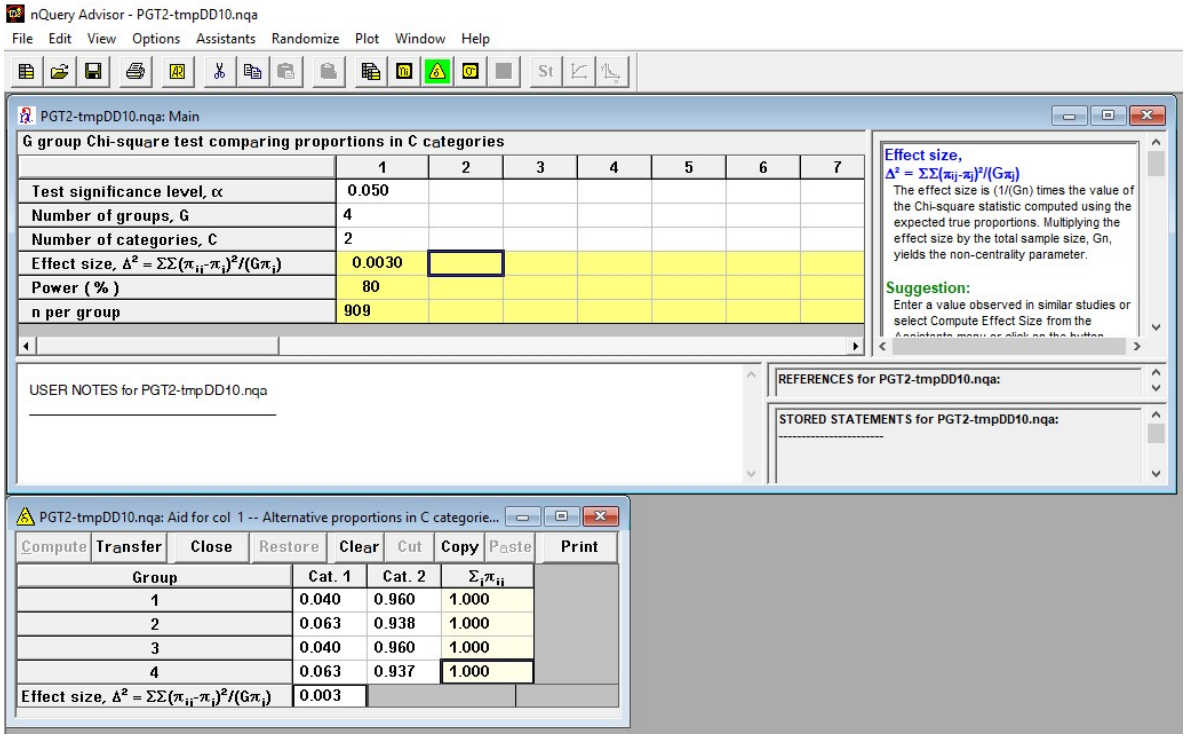


Figure 6.9: Sample size calculation with N-query

6.6 Results from the pilot RCT

This section outlines the results from the women who took part in the pilot RCT as illustrated in figure 6.4, in page 189 in this chapter. This section provides data on the fidelity to the different elements of the pilot RCT study protocol including the forms that midwives had to fill in and the diaries that participants had to complete. In the case of the health outcomes, the results from the observational study are also included, this is so the results from the pilot RCT can be compared with what happens in normal practice outside of the clinical trial. In addition, the results from the Childbirth Experience Questionnaire and study-specific questionnaire that were used to assess women's experiences and the acceptability of the interventions are also presented at the end.

6.6.1 Fidelity to the study protocol

6.6.1.1 Participants' diaries to record observations

All women taking part in the pilot RCT, no matter the group were allocated to, were advised to check their temperature, check the colour and smell of the liquor, check foetal movements, check if the uterus was painful in the absence of contractions, if there was any vaginal bleeding, if they were feeling generally well, and whether there were any other concerns. They were advised to do this every four hours while awake. All participants taking part in the pilot RCT were given a pack that contained a digital thermometer, a diary to record their observations outlined above, and ten swabs and a sheet of labels for labeling the swabs. Participants were advised to keep those packs with them, and to bring them when they came into the maternity unit, either in labour or for the induction of labour.

Overall, across all groups, most diaries n=30/41 (73.2%) were returned and all of those that were returned were completed satisfactorily. I was able to collect most diaries either while the woman was still at hospital following the birth or, in some cases where the diary was never brought in to the hospital, the women posted the diary together with the satisfaction questionnaire. As illustrated in table 6.7, in the expectant management and minimal vaginal examinations group 90% of diaries were returned and all of those were completed satisfactorily, in the expectant management and routine vaginal examinations group, 63.6% of diaries were returned and completed

satisfactorily. In the active management and minimal vaginal examinations, 60% were returned and completed satisfactorily, and in the active management and routine vaginal examinations group, 80% of the diaries were returned and completed satisfactorily. A copy of the diary can be seen in appendix 4 on page 297.

Table 6.7: Returned and completed participants' diaries

	EM minimal VEs n=10	**EM routine VEs n=11**	**AM minimal VEs n=10**	**AM routine VEs n=10**
Variable	n (%)	n (%)	n (%)	n (%)
Participants' diaries (Returned & completed)	9 (90%)	7 (63.6%)	6 (60%)	8 (80%)

The implications of these findings are that a high proportion (73.2%) of all participants completed their diaries and that it helped them to know what they were looking for. Potentially, there could have been more women who completed them but the diaries could not be found as, they would bring them with them along with the swabs in labour and these packs could get misplaced and lost easily. The returned diaries were all completed appropriately and acted upon when observations were out of the normal parameters, for example a couple of women wrote concerns with fetal movements or vaginal discharge that looked like meconium and they came to hospital for a check-up; making these diaries a good safety tool to continue to implement in the main trial. In order to avoid these diaries getting lost, perhaps for the main study, the research midwives will need to make sure that they visit all the women following birth to collect these diaries promptly.

6.6.1.2 Home visits

Women allocated to expectant management received daily home visits (approximately every 24 hours) by a community midwife. During this visit, the community midwife would review the participant's diary observations, and do a full antenatal assesment of maternal and fetal wellbeing including, a full set of maternal observations, abdominal palpation, and auscultation of the fetal heart rate. It would also be an opportunity to discuss any worries that the woman may have.

Initially, the visits could take place any time within 9.00-17.00, as long as it was around every 24 hours. However, it was decided later on that, ideally, these visits were to take

place in the morning before midday, so women were given a time-frame and also if there were any concerns, these could be addressed earlier in the day when there is more staff. A total of 21 women were allocated to the expectant management arms. Of those, 11 (52%) women needed to receive one or more home visits, while the rest did not need any due to going into labour spontaneously before the visit was due. Table 6.8 outlines the number of participants that needed visits and the total number of visits that were needed and how many of those were performed.

Table 6.8: Home visits as part of the expectant management

	EM minimal VEs n=10	**EM routine VEs n=11**	**Both EM groups together n=21**	**Total visits needed**	**Total visits performed**
Home visits needed	N of participants (%)	N of participants (%)	N of participants (%)	N visits	N visits
No visits	3 (30%)	7 (64%)	10 (48%)	0	0
One visit	4 (40%)	1 (9%)	5 (24%)	5	5
Two visits	2 (20%)	1 (9%)	3 (14%)	6	5
Three visits	1 (10%)	2 (18%)	3 (14%)	9	9
Total number of visits	N/A	N/A	N/A	20	19

As described in table 6.8, in the group "Expectant management and minimal vaginal examinations", three women did not need any visit, four women needed one visit, and one woman needed three visits. There were two women who needed two visits, although in one of these cases, she only received one and she should have received the second visit by 12pm, but didn't. A visit that should have been scheduled for 12pm, was scheduled for 4pm, but by that time, the woman came in to hospital reporting reduced fetal movements. Consequently, the study protocol was amended. This was to ensure that all visits were scheduled before midday and to ensure that women remained calm, as with the new schedule, they would know the time frame when the community midwife could come. Since the change, all visits were carried out correctly within the appropriate time frames. In order to communicate the changes effectively, a newsletter was sent and face-to-face updates were also given to individual midwives.

In the group "Expectant management and routine vaginal examinations", seven women did not need any visits, one woman needed one visit, one woman needed two visits and

two women needed three visits.

As outlined in table 6.8 on page 209, a total of 20 visits should have been carried out, (if we include the visit that was mentioned earlier that was scheduled for 4pm, but should have happened in the morning, but in the end that visit never took place, because the woman came earlier to the maternity unit), of those, 19 visits were carried out amongst all women allocated to the expectant management groups and all but one happened at home. Therefore, the adherence rate on the home visits would be 90% (18/20). The visit that did not happen at home, took place at the GP surgery as the woman already had an antenatal appointment planned with her community midwife for that day; she preferred to attend the GP surgery as planned, as she was not having any contractions. Once that woman had given birth, I asked her if she had preferred to be seen at the surgery for all her three visits during the study. She said that the first visit in her case was fine at the GP surgery, but that once she started to have some tightenings, it would have been very uncomfortable to leave the house and have to wait in a waiting room at the surgery to be seen.This insight revealed the rationale and the importance of being seen at home.

The implications of this finding are that it is important to make it clear in the protocol, when the visits need to take place, and the need to ensure that they take place before midday. It also highlighted the need for good communication between the women and midwives, if the midwife is not able to come before midday, this needs to be communicated to the woman so she is aware of the change on time-frame of the visit and does not worry unnecessarily. Furthermore, it showed that the home visits were feasible and that both women and midwives thought these were appropriate and necessary. Consequently, home visits will be implemented in the main study.

6.6.1.3 Midwives' completion of antenatal assessment forms

All participants, regardless of the group they were allocated to, were given a booklet that was enclosed in their clinical notes. This booklet outlined the group the participant was allocated to, and provided brief guidance to clinicians. In addition, from September 2017, a sticker was placed at the front of the notes of all participants to identify them easily. In the case of the participants allocated to the expectant management groups, a set of three expectant management assessment forms were part of that booklet.
I developed these forms and tested them during the developmental phase. These forms

guided midwives in the process of assessing the maternal and foetal wellbeing at home during the time between the rupture of membranes and the onset of labour.A copy of the form can be seen in appendix 6 on page 314.

Table 6.9: Midwives' completion of antenatal asessment forms

	EM minimal VEs	**EM routine VEs**	**Both EM groups together**
	Total visits performed n=10	Total visits performed n=9	Total visits performed n=19
Variable	N (%)	N (%)	N (%)
Completion of EM home assessment forms by community midwives	8 (80%)	8 (88.9%)	16 (84.2%)

The general informal feedback regarding the forms has been very positive; midwives found those forms both easy to use, and comprehensive. Although this was anecdotal data, it is reflected in the high adherence to the completion of the forms. In 84.2% of the cases the forms were used and completed appropriately. It is also important to highlight that community midwives started to use them as the only means for documentation on their own initiative. At the beginning of the study, they were documenting twice, once in the clinical notes and once in the study forms. However, as time passed by, they started to use the study forms only, and therefore, the study forms became part of the patient's clinical notes. Hence, they were not removed from the clinical records. Midwives have given me positive informal feedback about the forms. Out of 19 visits that took place, 16 visits (84.2%) were recorded appropriately in the study forms. However, in the case of 3 visits, these were recorded in the clinical notes, and not in the study forms. Consequently, since the midwives did not have the guideline that the study form offered, the respiratory rate wasn't taken or recorded, which is an important feature to consider when assessing clinical signs of infection. The implications of this finding are that the study forms were helpful to aid record keeping and to provide guidance as to what to look for, and how to assess maternal and fetal wellbeing, these forms will, therefore, be used in the main study. A copy of the form can be seen in the appendix

6.6.1.4 Adherence to the intervention: EM or AM

In this subsection, the adherence to the allocated approach (Expectant or Active management) is assessed. In particular whether the allocated time for induction was followed in the absence of any clinical contraindications. Table 6.10 on page 212 presents a summary of the results.

Table 6.10: Adherence to the intervention: EM or AM

	EM minimal VEs n=10	**EM routine VEs n=11**	**AM minimal VEs n=10**	**AM routine VEs n=10**
Variable	n (%)	n (%)	n (%)	n (%)
Adhence to intervention: EM or AM timing of the IOL	10 (100%)	9 (81.8%)	8 (80%)	8 (80%)
Notes	N/A	1 IOL delayed $\geq$ 4h 1 IOL at 57.25h due to mat request	1 IOL delayed $\geq$ 4h 1 was given extra time during IOL	1 IOL delayed $\geq$ 4h 1 woman had 1 temp of 37.7°C and after paracetamol it came back to normal and had no further temps but the IOL commenced 8h earlier

* One woman was given extra time during the process of induction, and after the prostaglandins were administered to see if IV oxytocin infusion could be avoided. Iv oxytocin started with a delay of 9 hours - She belonged to AM and minimal VEs group

As mentioned earlier there was one participant who should have been visited by 12 midday, but came to hospital at about 4pm, at 39h 15min from the rupture of membranes who belonged to the expectant management and minimal vaginal examinations reporting reduced fetal movements and was already contracting, since she was already contracting and it wasn't the first episode of reduced fetal movements in her pregnancy she was offered induction (earlier than the study protocol suggested) as her cervix was 2cm dilated, she did not require prostaglandins and was commenced on IV oxytocin about three hours since she arrived in hospital. This case was not counted as a deviation, as the principle of expectant management is to observe unless concerns arise that warrant intervention. An isolated episode of reduced fetal movements and normal CTG (Cardiotocograph trace of the fetal heart rate) is not a straight indication for induction, but in looking at the whole picture and since she had an episode of Reduced fetal movements prior to the rupture of membranes, it was a situation that needed individualised plan of care and the judgement of the clinician at the time was respected.

In the expectant management and minimal vaginal examinations, there was a participant

who noticed some vaginal discharge that looked like meconium at about 92 hours Since the rupture of membranes, and thanks to the guidance from the diary, she came to hospital, it was confirmed that it was light meconium but since she was already contracting (irregularly), and the induction was planned in a few hours, she was sent home. They sent her home because in that hospital, light meconium is seen as normal. However, in our study meconium is one of the exclusion criteria and the induction should have commenced when the meconium was noted by the clinical staff. We reviewed the protocol and found out that the reasons for induction at an earlier time was left to the clinician's judgment, so technically it was not a deviation. However as a result from this situation, I made sure that everyone was aware that meconium (light or significant) was one of the causes to have an earlier induction if the liquor turned into meconium during the course of the study.

There were five deviations in the time of induction of labour, four delays and two inductions that started earlier than suggested by the protocol. The protocol for the pilot RCT did not provide a time frame when after a specific amount of time of deviation from the scheduled time for Induction, would be classed as a breach in the protcol, but after reviewing the notes in the pilot RCT. I have decided that a deviation of 4 or more hours in the time for the induction (either earlier or later) will be classed as a violation in the main study, as any deviation of four hours or more, would interfere with the scientific value of the study. For example, in the active management groups, there were two women who were given extra time ($\geq$ 4h) and during that time, both managed to stablish labour and therefore were not induced but if the protocol had been followed, they would have been. Also, in normal practice if there is a delay of 4 hours or more in the induction time, it must be escalated, so this time frame is something that clinicians would be used to.

In the expectant and routine vaginal examination group there was one woman who came into hospital contracting with a cervical dilation of 3cm, she was told that they were not in active labour yet, and although unclear of the conversation between clinician and woman, she was offered an augmentation and was commenced on IV oxytocin, she had a CS, and did not have any signs of infection or other concerns. Although this case has not been count as induction because she came with contractions, had a cervical dilation of $\geq$ 3cm, and didn't require prostaglandins, the reason for the augmentation was not a clinical reason such as failure to progress or suspected infection. It reflects more the clinician's concerns towards the length of SROM, as it would have been unusual for

a woman with intact membranes to be offered an augmentation at 3cm and no other reason but to "speed up things". It could also reflect a maternal perception that the augmentation would end up labour faster. This case was not classed as a violation, as clinicians documented that women wanted to have the labour augmented. However, it made me reflect on the need to provide comprehensive training in how to look after women who come to hospital in early labour, to avoid unnecessary augmentations in the future main clinical trial.

6.6.1.5 Adherence to the intervention: minimal or routine VEs

The fidelity to the allocated approach for the vaginal examinations during labour was recorded and reported here due to its importance for the development of the future main trial. Table 6.11 on page 214 shows that there was an overall high fidelity 34/41(83%) to the allocated approach, with higher fidelity in the routine vaginal examinations groups 19/21(90.5%) in comparison to the minimal examinations groups 15/20 (75%). This reflects that clinicians may be more used to assessing the progress of labour by performing routine vaginal examinations on 4 four hourly intervals or less, than in assessing the progress of labour by external signs. This provides evidence that extensive training in how to assess the progress of labour holistically will need to be provided for the main clinical trial.

Table 6.11: Vaginal examinations as per study protocol

	EM minimal VEs n=10	**EM routine VEs n=11**	**AM minimal VEs n=10**	**AM routine VEs n=10**
Variable	n (%)	n (%)	n (%)	n (%)
Vaginal examinations as per study protocol	7 (70%)	9 (82%)	8* (80%)	10 (100%)

*In group (Active management and minimal VEs), apart from the 2 cases where the protocol for minimal VEs wasn't followed, there was a third case in which the woman didn't receive any VEs, although this conforms with the approach of minimal VEs, the protocol asked for an initial VE to confirm the onset of labour for the purpose of having a clear/consistent standard of when the latent phase/waiting time finished and the active labour phase begins. However, in this case it is written in the notes that the woman didn't want to have a VE, and declined it. Therefore, it has been counted

as if the protocol was followed, and making it only 2 cases where the protocol for VEs wasn't followed. However, this meant that since no VEs were performed, No swabs were taken.

6.6.1.6 Clinicians' completion of vaginal examinations forms

As mentioned earlier, all participants were given a booklet that was kept in the clinical notes, where the group that they were allocated to was outlined, and guidance to clinicians was given. As part of that booklet, a form was given where, on one side, guidance was given as to how often or when vaginal examinations could be performed and when to take the low vaginal swabs. On the other side, there was a table that asked clinicians to record the vaginal examinations and the reason for them.

This form was less successful than the one for the antenal assessments at home. Table 6.12 shows that the overall fidelity to the completion of the VE forms was 20/41 (48.7%). This is perhaps because it was asking to document something that is not "new". Although there were different regimes for the vaginal examinations, a vaginal examination is something that happens routinely in clinical practice; midwives perhaps saw this form as a duplication of what they have already recorded elsewhere. A copy of the form can be seen in appendix 6 on page 314.

Table 6.12: Clinicians' completion of vaginal examinations forms

	EM minimal VEs n=10	**EM routine VEs n=11**	**AM minimal VEs n=10**	**AM routine VEs n=10**
Variable	n (%)	n (%)	n (%)	n (%)
Clinicians' completion of VE forms	4 (40%)	6 (54.5%)	7 (70%)	3 (30%)

It was also noted that, in some cases, the vaginal examination form was completed but some vaginal examinations were missing, despite being documented in the clinical records. This meant that these forms could not be used as a case report form to ensure reliable data collection. Once I realised this, I decided not to invest energy in chasing midwives to complete these forms. Instead, I focused on ensuring that they called me when they knew of potential participants. The implications for the main study is to continue with the written instructions on when to perform the vaginal examinations and when and how to take the low vaginal swabs. However, the form where the vaginal

examinations are recorded will be removed, and clinicians will be encouraged to record the vaginal examinations clearly on the clinical records. This information will be taken directly by the research team from the clinical records instead.

6.6.1.7 Vaginal swabs

As it was briefly explained in the methods chapter on page 175, low vaginal swabs were to be taken before the first vaginal examination and after every vaginal examination from all women who took part in the pilot RCT, regardless of the group they were allocated to.

This part of the study proved to be challenging. I needed to invest a lot of time to train the midwives and doctors. In most cases, some swabs were taken, but especially at the beginning during the first few months of the study, there were sometimes problems such as: midwives using the wrong swab i.e. charcoal swabs, instead of the swab provided by the study or some clinicians forgot to take the first or last swab, which meant the swabs could not be analysed because the analysis would not be consistent or meaningful. Therefore, in this element of the study, the fidelity was lower than in other areas. There were 19 participants out of the total of 41 who had all swabs taken according to the protocol, which meant the overall adherence rate was 46.3%. The table below outlines the fidelity per group.

Table 6.13: Swabs that were taken correctly

	EM minimal VEs n=10	**EM routine VEs n=11**	**AM minimal VEs n=10**	**AM routine VEs n=10**
Variable	n (%)	n (%)	n (%)	n (%)
Swabs taken correctly	2 (20%)	5 (45.5%)	7 (70%)	5 (50%)

In terms of the protocol for the main trial, the pilot RCT demonstrated that it was possible to take the swabs, there were no women who declined or were against this part of the study and the informal feedback I got from the midwives was that somehow it helped them to become more conscious of the vaginal examinations and hence reduce the number of vaginal examinations. Given the low fidelity rate in this section, it will be important to provide enough training in the main study.

6.6.2 Clinical outcomes

6.6.2.1 Type of onset of labour

The rationale for reporting the percentage of women who were in active labour within 24 hours was mainly to see the effectiveness of the current type of care, and how many women need to have their labours induced under the different treatment types. In the case of those allocated to the expectant management, it also helped to see how many did not go into spontaneous labour within the first 24 hours and to see when they actually went into spontaneous labour. It helped to see how many inductions were avoided. Absolute numbers, percentages (%) and 95% Confidence Intervals (C.I.) using the Cooper-Pearson method are reported per group in the table below. In addition to the descriptive statistics, a Chi-square test was performed to asses if the differences between and within the groups were statistically significant. It was found that although there is a difference in the numbers who went into spontaneous labour within 24 hours since the rupture of membranes, this is not statistically significant (χ^2=2.096, df=4, p=0.718). This could be due though to the small sample.

In regards to the number of women who required induction of labour, there were two cases were women were given extra time in an attempt to avoid the induction in the active management arms. This was discussed earlier in section 6.6.1.4 on page 212. One in the active management and minimal vaginal examinations, in which the woman was given 6h 15min hours extra for labour to establish on its own, and another case,in the active and routine VEs, in which a woman was given 4 hours extra for labour to establish. Therefore, both cases did not require induction, although if the study protocol had been followed, these two women would had been induced. Absolute numbers (n), percentages (%) and 95% Confidence Intervals (C.I.) using the Cooper-Pearson method are reported per group in the table below for women requiring induction of labour. In addition to the descriptive statistics, a Chi-square test was performed to asses if the differences between and within the groups were statistically significant. It was found that although there is a difference in the numbers who required induction of labour, this is not statistically significant (χ^2=8.488, df=4, p=0.075). This could be due though to the small sample.

Table 6.14: Type of onset of labour

	EM minimal VEs n=10	**EM routine VEs n=11**	**AM minimal VEs n=10** *1 woman had 6h extra to establish labour & IOL was avoided	**AM routine VEs n=10** *1 woman had 4 h extra to establish labour & IOL was avoided	**Observational study n=32**
Variable	n (%)	n (%)	n (%)	n (%)	n (%)
	95% C.I.	95% C.I.	95% C.I.	95% C.I.	95% C.I.
Active labour by 24h	5 (50%)	5 (45.5%)	6 (60%)	7 (70%)	15 (46.9%)
	(18.7% - 81.3%)	(16.7% - 76.6%)	(26.2% - 87.8%)	(34.8% - 93.3%)	(29.1% - 65.3%)
IOL	1 (10%)	2 (18.2%)	3 (30%)	2 (20%)	16 (50%)
	(0.3% - 44.5%)	(2.3% - 51.8%)	(6.7% - 65.2%)	(2.5% - 55.6%)	(31.9% - 68.1%)
SROM $\geq$24h	6 (60%)	7 (63.6%)	5 (50%)	4 (40%)	20 (62.5%)

In the observational study, as well as those in the pilot RCT allocated to expectant management, as table 6.14 shows, the percentage of spontaneous labour within the first 24 hours remained consistent around 45-50%. This was also consistent with the literature (Ottervanger et al., 1996). However, in the case of women allocated to the active management arms there were more women being in active labour within the first 24 hours; In the active management and minimal vaginal examinations, 60% of the women were in active labour within the first 24 hours, whereas, in the active management and routine vaginal examinations group, 70% of the women went into spontaneous labour within the first 24 hours. Table 6.14 presents the results per group. Finding different percentages of women going into spontaneous labour within the first 24 hours amongst the groups in the pilot RCT could be due to chance and the small sample per group. The overall rate of women going into labour within 24 hours across all the groups is 56%, which is again consistent with the "around 50%" found in the literature. However, due to the small sample size, it meant that it affected the results in terms of type of birth and need for induction for the different allocation groups. The implications of this finding are that around 50% of women go into labour within the first 24 hours and that other options of care, apart from induction after 24 hours, should be explored and studied through a good quality RCT with enough statistical power. A frequency table that describes the percentage of women who were allocated to the expectant management and subsequently went into labour within 24, 48, 72, 96 and 104 hours is also presented in table 6.15, with the aim of understanding this phenomenon.

The breakdown of women who went into labour within different periods of time is something that women were very keen to know when discussing the different types of care during the recruitment. This will, therefore, also be presented in the main RCT, as women are demanding this evidence to be able to make informed decisions, as most women would go into labour by themselves if given enough time. It must be noted that, in the literature, it is reported that approximately 95% of women would go into labour within 96 hours (Hannah et al., 1996). However, in that study it is not clear how they defined the onset of spontaneous labour. If it was defined as having spontaneous contractions, this would also be consistent with this study, since only one woman out of 21 (5%) did not experience contractions within the allocated time (104 hours).

However, in this pilot study, there were two women who were contracting, and had their labour induced and receive prostaglandins due to reduced foetal movements and the

Table 6.15: Cumulative frequency of spontaneous labour in expectant management

		EM Minimal VEs n=10	**EM Routine VEs n=11**	**Both expectant groups together n=21**
		*1 IOL at 48h due to DFM	*1 IOL due to getting tired but was contracting She had technically started but not quite there yet *1 IOL as per protocol didn't go into labour within the time	
		Cumulative frequency	Cumulative frequency	Total cumulative frequency (%)
Spontaneous labour within	24h	5	5	10 (48%)
	48h	7	7	14 (67%)
	72h	8	7	15 (71%)
	96h	8	9	17 (81%)
	104h	9	9	18 (86%)

other one had also contractions, but decided to have her labour induced because she got tired and still needed prostaglandins because her cervix was not favourable. Since they both needed the prostaglandins, even though they were contracting, I have decided not to count them as going into spontaneous labour. Therefore, in this pilot study 18 in 21 (86%) women allocated to expectant management went into spontaneous labour. The implication of this finding is that it is important to note the definition used for the outcomes in the protocol for the future main trial, as depending on the definition used, one can obtain different figures. The issue of the definition for labour onset and for spontaneous labour is particularly important as many trials use these measures, but they are not used consistently. The implications of the lack of consistency in the definitions used in research are discussed in more depth in chapter 8 in section 8.3.6 on page 261.

6.6.2.2 Length of rupture of membranes

The length of rupture of membranes was reported due to the historical concern that the risk of infection to the infant increases as the length of the rupture of membranes increases. The mean, standard deviation (SD) and 95% Confidence Intervals (C.I.) are reported per group in table 6.16 on page 221. In addition to the descriptive statistics, a one-way ANOVA was performed to asses if the differences between and within the groups were statistically significant. It was found that although there is a difference, this is not statistically significant (F=2.304, df=4, p=0.067), although this could be due to the small sample size.

Table 6.16: Length of rupture of membranes

	Length of rupture of membranes (decimal hours)	
Group	**Mean (SD)**	**95% CI**
Group 1: EM and minimal VE n=10	41.70(32.96)	18.12 - 65.3
Group 2: EM and routine VE n=11	48.51 (40.89)	21.04 - 75.98
Group 3: AM and minimal VE n=10	26.94 (13.93)	16.98 - 36.91
Group 4: AM and routine VE n=10	20.84 (12.64)	11.80 - 29.89
Group 5: Observational study n=32	31.48 (17.50)	25.18 - 37.79

Table 6.16 shows that due to the different timings of the induction depending on the group allocation, the women allocated to the active management groups had shorter lengths of rupture of membranes than those allocated to the expectant management arms. Nevertheless, even in the expectant management groups the mean duration of the rupture of membranes stayed between 40-49 hours. There was great variety and spread of data across all groups and this is reflected in the high SD. This will naturally be amended when the main study takes place; the sample will need to be much bigger and, hence, the SD will diminish.

The number of babies that were born with a rupture of membranes of $\geq$24 hours is reported in table 6.17 because a length of SROM$\geq$24 hours is considered a risk factor for neonatal infection according to NICE (2012). Absolute numbers, percentages (%) and 95% Confidence Intervals (C.I.) using the Cooper-Pearson method are reported per

group in table 6.17 below for babies born with ruptured membranes for $\geq$ 24 hours. In addition to the descriptive statistics, a Chi-square test was performed to asses if the differences between and within the groups were statistically significant. It was found that although there is a difference in the numbers of babies with SROM$\geq$24h, this is not statistically significant (χ^2=2.006, df=4, p=0.735). This could be due though to the small sample.

Table 6.17: Babies with SROM$\geq$24h

	SROM $\geq$24 hours	
Group	**n (%)**	**95% CI**
Group 1: EM and minimal VE n=10	6 (60%)	(26.2% - 87.8%)
Group 2: EM and routine VE n=11	7 (63.6%)	(30.8% - 89.1%)
Group 3: AM and minimal VE n=10	5 (50%)	(18.7% - 81.3%)
Group 4: AM and routine VE n=10	4 (40%)	(12.2% - 73.8%)
Group 5: Observational study n=32	20 (62.5%)	(43.7% - 78.9%)

6.6.2.3 Average number of vaginal examinations

The approach to assess the progress of labour through vaginal examinations was one of the interventions in this pilot RCT. There were two approaches the experimental intervention, "minimal vaginal examinations", where the intention was to minimise the number of vaginal examinations that women received during the active phase of labour and to use other means to assess progress, and the control intervention: "routine four hourly vaginal examinations" which is what usually happens in normal practice. Therefore, the average number of vaginal examinations, together with the standard deviation, is reported in the table below as there is evidence that the number of vaginal examinations is one of the strongest correlators for chorioamnionitis. In addition to the descriptive statistics, a one-way ANOVA was performed to asses if the differences between and within the groups was statistically significant. It was found that although there is a difference, this is not statistically significant (F=1.304, df=4, p=0.278). This could be due though to the small sample.

Table 6.18: Average number of VEs

	Number of VEs	
Group	**Mean(SD)**	**95% CI**
Group 1: EM and minimal VE n=10	3.3 (2.95)	1.19 – 5.41
Group 2: EM and routine VE n=11	4.36 (2.73)	2.53 – 6.20
Group 3: AM and minimal VE n=9*/10	2.44 (1.94)	0.95 – 3.94
Group 4: AM and routine VE n=9*/10	2.56 (2)	1.01 – 4.10
Group 5: Observational study n=32	4.03 (2.7)	3.05 – 5.01

*There were two BBA (Born before arrival), in which the baby arrived at home with no care from any clinician and therefore no vaginal examinations were performed. One case belonged to the Active management and minimal VEs and the other to the active management and routine VEs, since in both cases these women received no care during labour, it seemed appropriate to exclude them from this analysis

In table 6.18 can be observed that the mean number of vaginal examinations was lower in the minimal vaginal examinations groups in comparison to the routine vaginal examinations groups when compared within the expectant or active groups. It must also be noted that some women in the active management groups had spontaneous and very quick labours which did not require many vaginal examinations. Also, due to the small sample, the average number of vaginal examinations in the active management

groups was very low or lower than average when compared with the results obtained in the observational study, which also had active management. In the observational study, the average number of vaginal examinations was 4.03and the SD= 2.7.

This difference could very well be due to chance; no definitive conclusions could be drawn due to the limitations of the small sample size. In the next subsection the length of active labour is analysed, it can be expected that a shorter labour would need fewer vaginal examinations. The implication of this finding is that it helps to see that, in general, women allocated to the minimal vaginal examinations intervention had fewer vaginal examinations when analysed within the active or expectant management groups. It is also demonstrated that the protocol was followed, although a closer analysis of the fidelity to the protocol in this regard is also presented in this chapter.

It is also important to note that, generally, a labour that is induced has the potential to be longer and also to need more vaginal examinations due to the process of having to examine the cervix, and insert the prostaglandins, which would not be required if the labour started spontaneously.

In general, the intervention in regards to the vaginal examinations was challenging as it was something new. Clinicians who were used to perform vaginal examinations only when necessary found it difficult having to change to performing vaginal examinations every four hours. And vice-versa, those used to performing vaginal examinations every four hours found it very challenging to get used to performing fewer vaginal examinations, or having to rely on other signs of progress of labour. In conclusion, extensive training will be provided for the main trial on the different interventions in regards to vaginal examinations.

6.6.2.4 Length of active labour

The length of active labour was one of the secondary outcomes to report as it has a close relationship with the number of vaginal examinations; the longer the length of active labour is, the higher the potential for more vaginal examinations. The table below outlines the mean length of labour given in hours and minutes for an easier understanding, as well as the standard deviation to have an idea of the spreadness of the data. In addition to the descriptive statistics, a one-way ANOVA was performed to asses if the differences between and within the groups was statistically significant. It was found that although there is a difference, this is not statistically significant (F=1.19, df=4, p=0.322). However, this could be due to the small sample.

Table 6.19: Length of active labour

	Length of active labour	
Group	**Mean(SD)**	**95% CI**
Group 1: EM and minimal VE n=10	6.75 (5.07)	(3.13 – 10.38)
Group 2: EM and routine VE n=11	7.22 (4.38)	(4.27 – 10.16)
Group 3: AM and minimal VE n=8*/10	4.73 (3.98)	(1.41 – 8.06)
Group 4: AM and routine VE n=9*/10	4.5 (2.06)	(2.92 – 6.09)
Group 5: Observational study n=32	4.68 (4.21)	(3.16 – 6.19)

*There were three cases excluded from the analysis of the length of active labour, the two cases of BBA (Born before arrival) mentioned earlier due to the fact that it was very difficult to calculate an accurate length of labour as they did not receive any care, and one case of failed induction in the active management and minimal vaginal examinations because she never got into active labour, she had a CS at 2cm, and in the notes appeared "unable to calculate length of labour"

As mentioned previously given the small sample and that a few women in the active management groups had spontaneous and very quick labours, this meant that the mean length of active labour was low. There were two cases of BBA (Born before arrival). In these cases, due to the fact that they received no care during labour and the potential inaccuracy of the length of labour it was decided to exclude them from the mean calculation. There was also one case of failed induction in the active and minimal vaginal examinations group, since despite the process of induction, she never got into active labour. Therefore, this case was also excluded from the mean calculation.

The implications of these findings could be that women in the active arms could have

shorter labours, although it could also be the case that women allocated to expectant management were encouraged to go to the maternity unit earlier as some of them were waiting for labour to happen and, when the contractions started, the women were very keen to come in and the clinical staff were very keen to "get on" with their labour resulting in them arriving earlier, with a cervical dilatation of 3cm or so as opposed to arriving with a very established labour with a greater cervical dilation.

On the other hand, participants allocated to active management, because it was the norm, women were encouraged to stay at home as long as possible by the clinical staff. However, all these explanations are possible hypotheses as, given the small sample, conclusions cannot be drawn. A main study with enough statistical power would help to answer these questions and, in order to ensure that women are encouraged to come to the maternity unit around the same time, the protocol will give some advice in this regard.

6.6.2.5 Neonatal infection

Although it was decided that neonatal infection would be a secondary outcome, as numerous previous studies have already shown that there is no significant difference, it was decided that, due to its clinical significance, the rates of confirmed neonatal infection would be reported. The definition for confirmed neonatal infection is outlined in the list of definitions on page 21. There were no cases of confirmed neonatal infection across any of the groups in the pilot RCT or the observational study.

The implications of these findings are positive in that we did not encounter safety issues in this area, meaning that a further main clinical trial is warranted. These findings also suggest that the sample for the main study must be big enough if we wanted to investigate if the type of management of prelabour rupture of membranes is associated with a difference in rates of confirmed neonatal infection. As mentioned before, however, this outcome has been extensively studied in the past and no significance difference has been found.

6.6.2.6 Chorioamnionitis

Confirmed chorioamnionitis is reported as it is the main/primary outcome in the pilot RCT. There was only one case of chorioamnionitis in the expectant and minimal vaginal examinations 1(10%) and none in the rest of the arms as outlined below. A significance

test was not possible as there were three groups with no cases. In the observational study, there were 4/32 (12.5%) participants who developed some signs of infection, out of those 4, one was confirmed by histological examination of the placenta, there was also another case where it was documented foul smelly liquor and clinicians took a swab from the placenta and they found *Streptococcus angionosus*. Therefore, the estimated rate of chorioamnionitis in the observational study is 2/32 (6.25%).

These findings, a rate of chorioamnionitis of 1 in 10 (10%) in Expectant and minimal VEs group or 1 in 21 (4.76%) when both expectant management groups are combined, are inline with the TermProm trial. Seaward et al. (1997) demonstrated a rate of chorioamnionitis of 7.8% in the TermProm trial for women allocated to expectant management and induction of labour with prostaglandins. These results cannot be generalised due to the small sample size but since we did not encounter any safety issues, its implications mean that a main definitive study could be done in the future.

6.6.2.7 Normal birth and other modes of birth

Normal birth is also one of the primary outcomes in this pilot RCT and future main trial. The definition for normal birth is outlined in the list of definitions on page 21. Absolute numbers, percentages (%) and 95% Confidence Intervals (C.I.) using the Cooper-Pearson method are reported per group in the table below for normal birth. In addition to the descriptive statistics, a Chi-square test was performed to asses if the differences between and within the groups were statistically significant. It was found that although there is a difference in the percentages of normal birth across the groups, this is not statistically significant (χ^2=3.826, df=4, p=0.430), which could be due to the small sample.

Table 6.20: Normal birth (Land and water together)

	Normal Birth	
Group	**n (%)**	**95% CI**
Group 1: EM and minimal VE n=10	5 (50%)	18.7% - 81.3%
Group 2: EM and routine VE n=11	4 (36.4%)	10.9% - 69.2%
Group 3: AM and minimal VE n=10	6 (60%)	26.2% - 87.8%
Group 4: AM and routine VE n=10	7 (70%)	34.8% - 93.3%
Group 5: Observational study n=32	13 (40.6%)	23.7% - 59.4%

As well as the rates of normal birth, the rates for "spontaneous vaginal deliveries", instrumental birth and caesarean sections are also presented as it is also important to see the differences in any of the other types of birth. Table 6.21 on page 229 outlines the results obtained per type of birth and per group.

The implications of these findings at this stage are mainly for safety issues, since the differences in terms of caesarean sections were not significantly different.

It was noted that women in the active management and routine vaginal examinations, which was a very similar type of management to those in the observational study, had very different outcomes to those in the observational. There were no instrumentals or Caesarian sections, however in the observational study, there was a 19% of instrumental births and 16% of caesarean sections.

Table 6.21: Mode of birth

	EM minimal VEs n=10	**EM routine VEs n=11**	**AM minimal VEs n=10**	**AM routineVEs n=10**	**Observational study n=32**
Variable	**n (%) 95% C.I.**	**n (%) 95% C.I.**	**n (%) 95% C.I.**	**n (%) 95% C.I.**	**n (%) 95% C.I.**
Normal Birth	1 (10%)	1 (9.1%)	1 (10%)	3 (30%)	3 (9%)
(Land)	0.25% - 44.5%	0.23% - 41.3%	0.25% - 44.5%	6.7% - 65.2%	2% - 25%
Normal Birth	4 (40%)	3 (27.3%)	5 (50%)	4 (40%)	10 (31%)
(Water)	12.2% - 73.8%	6.02% - 60.97%	18.7% - 81.3%	12.2% - 73.8%	16.1% - 50%
SVD	1 (10%)	1 (9.1%)	2 (20%)	3 (30%)	8 (25%)
	0.25% - 44.5%	0.23% - 41.3%	2.5% - 55.6%	6.7% - 65.2%	11.5% - 43.4%
Instrumental	3 (30%)	4 (36.4%)	1 (10%)	0	6 (19%)
	6.7% - 65.2%	10.9% - 69.2%	0.25% - 44.5%		7.2% - 36.4%
C/S	1 (10%)	2 (18.2%)	1 (10%)	0	5 (16%)
	0.25% - 44.5%	2.3% - 51.8%	0.25% - 44.5%		5.3% - 32.8%

This could be due to the well-known effect of being studied, also called the "observer effect" or being it simply random and due to the small sample. The future main study would have enough statistical power to determine what type of care is associated with higher rates of normal birth.

6.6.2.8 Safety

In this section the mayor safety outcomes in regards to the safety of participants in the pilot RCT are explored and discussed.

There was only one baby who had an apgar <7 at 5 minutes from birth in the pilot RCT, this baby needed resuscitation (inflation breaths and a set of respiration breaths) but had an apgar of 9 by 10 minutes of age, the infant did not require intubation or admission to NICU. This baby belonged to group 3 (Active management and minimal VEs), and the mother was induced at approximately 24 hours, but had a failed induction. Failed inductions and possibly fetal dystress associated with it, are expected to be a potential problem of induction of labour.

One baby in group 2 (Expectant management and routine VEs), was admitted to NICU due to a congenital and genetic condiction called hyperinsulism. This was not related to prelabour rupture of membranes or any of the study interventions.

There were two cases of maternal estimated blood loss (EBL) ≥1,000ml. in the pilot RCT. Both in relation to retained placenta, the blood loss was normal around the birth, and increased once the manual procedures to remove the placenta took place. One case belonged to group 2 (Expectant management and routine VEs) and the other belonged to group 3 (Active management and minimal VEs). Both had normal births and did not required induction or augmentation. Retained placentas are not believed to be associated with prelabour rupture of membranes.

There were no cases of definite neonatal sepsis and only one case of chorioamnionitis that belonged to group 1 (Expectant management and minimal VEs). This was in line with figures reported in the observational study that looked at the outcomes in normal clinical care, and also these were in line with the literature (Hannah et al., 1996). Overall, this pilot RCT did not raise any safety concerns.

6.6.3 Women's experiences

Women's experiences and satisfaction was assessed with the Childbirth Experience Questionnaire (CEQ), which was developed by Dencker et al. (2010), and validated in the UK by Walker et al. (2015). As well as ten specific study questions especially designed to measure the acceptability of the study interventions.

The CEQ consists of 22 questions divided into four domains: Own Capacity, Professional support, Perceived Safety and Participation. A copy of the questionnaire that was sent to pilot RCT participants can be seen in appendix 5 on page 304, where the domains and individual questions can be seen. Therefore, participants taking part in the pilot RCT were asked to complete a questionnaire with 32 questions in total at around 4-8 weeks postpartum.

6.6.3.1 Questionnaires' response and completeness rate

The response rate was high, 33/41(80.5%) of participants completed and returned their questionnaires. The completeness rate was also high 32/33 (97%), of those who completed and returned the questionnaires, only one participant left two questions un-answered on the CEQ, and even then she provided an explanation as to why she couldn't answer those questions and decided to left them blank. The questions that she left blank and the rationale that she provided, are discussed ahead on section 6.23 on page 232. The completeness rate in the study specific questionnaire was 100%, everyone who returned their questionnaire answered all the questions regarding the study. Table 6.22 on page 231 outlines the response rate obtained per allocation group.

Table 6.22: Questionnaires' response rate

	EM minimal VEs n=10	**EM routine VEs n=11**	**AM minimal VEs n=10**	**AM routine VEs n=10**
Variable	n (%)	n (%)	n (%)	n (%)
Returned questionnaires	10 (100%)	8 (72.7%)	7 (70%)	8 (80%)

6.6.3.2 Childbirth Experience Questionnaire

The Childbirth Experience Questionnaire is divided into four domains: own capacity, professional support, perceived safety and participation. The following table 6.23 outlines the results per domain and per allocation group.

The highest scores per domain were obtained in the expectant and minimal vaginal examinations group, with 2.86 in the own capacity domain, 3.86 for the professional support domain, 3.43 for the perceived safety domain, and 3.53 for the participation domain. The other groups in the pilot RCT obtained slightly lower scores for those

Table 6.23: CEQ results per domain

	EM minimal VEs n=10/10	**EM routine VEs n=8/11**	**AM minimal VEs n=7/10**	**AM routine VEs n=8/10**
CEQ Domains	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Domain 1 Own capacity	2.86 (0.72)	2.52 (0.71)	2.36 (0.67)	2.50 (0.53)
Domain 2 Professional support	3.86 (0.30)	3.75 (0.37)	3.26 (1.09)	3.70 (0.45)
Domain 3 Perceived safety	3.43 (0.59)	3.19 (0.68)	2.90 (0.82)	3.27 (0.59)
Domain 4 Participation	3.78 (0.55)	3.50 (0.40)	3.38 (0.95)	3.50 (0.59)

four domains, however the differences were not statistically significant. Scale scores were compared between groups with the Krustal wallis test. This test was chosen as the creators of this questionnaire deemed its answers to follow a non-parametric distribution and they advocated the use of Mann-Whitney-U-test (Dencker et al., 2010). However since in this case the pilot RCT has four different treatment groups, Krustal Wallis seemed more appropriate. For the domain 1 (Own capacity), the differences in scores between the groups were not statistically significant (χ^2=2.712, df=3, p=0.438), For the domain 2 (Professional support), the differences in scores between the groups were not statistically significant (χ^2=2.998, df=3, p=0.392). For the domain 3 (Perceived safety), the differences in scores between the groups were not statistically significant (χ^2=2.795, df=3, p=0.424). For the domain 4 (Participation), the differences in scores between the groups were not statistically significant (χ^2=3.999, df=3, p=0.262).

In the case of the active management groups, active management and routine vaginal examinations obtained slightly higher scores than active management and minimal vaginal examinations. It is thought that this could be because in the group "active management and minimal vaginal examinations", there was one more induction of labour in comparison to active management and routine vaginal examinations. Although

it is only one, since the sample is small, it can make a difference. Therefore the results need to be taken with caution.

The reliability of the CEQ (Childbirth Experience Questionnaire) for the group of participants who took part in this pilot RCT, was assessed by calculating the Cronbach's alpha scores for each of the domains, and for the questionnaire as a whole. This results were also compared with the Cronbach's alpha scores reported in the original Swedish study conducted by Dencker et al. (2010). Cronbach's alpha is the statistic most widely used for assessing internal consistency and reliability (Gardner, 1995; Taber, 2017). An alpha Cronbach score of 0.70 or above is considered desirable (Taber, 2017).

The implications of these findings are positive; firstly having an overall response rate of 80% is very positive. This means that the questionnaire was easy to use and women found it feasible to complete. In addition, almost all (97%) participants who returned their questionnaires, answered all questions. Therefore, we will most likely carry on using the same questionnaire to assess the childbirth experience of women taking part in the main clinical trial. On estimating the internal consistency of the questionnaire by calculating the Cronbach's alpha scores, the questionnaire obtained high scores well above the desired 0.70. This means that the internal consistency of the questionnaire and its reliability for the group of women who completed was high, and it can be extrapolated that the CEQ questionnaire will perform well in the future main clinical trial. Since the expectant management groups scored more positively than the active management groups, and also there were no statistically significant differences amongst all the groups, this implies that the study as a whole, and the individual interventions are acceptable to women.

Table 6.24: CEQ Cronbach alpha results

Domain	**Number of items**	**Cronbach alpha**	**Cronbach alpha from original swedish study**
Domain 1: Own Capacity	8	0.883	0.82
Domain 2: Professional support	5	0.938	0.88
Domain 3: Perceived safety	6	0.868	0.78
Domain 4: Participation	3	0.8	0.62
Total scale	22	0.941	

6.6.3.3 Study specific questionnaire

The study-specific questionnaire had ten questions and it was created to assess the acceptability of the interventions in the pilot RCT, and that understandably, the childbirth experience questionnaire could not assess. The completeness rate of this questionnaire was 100%. All the participants who returned the questionnaires, completed these ten questions and none were left unanswered. The results and breakdown per group from the study specific questionnaire can be seen in appendix 9 on page 333.

In question 1: "Overall, I am satisfied with the care that I received by the midwives and doctors during the study (from the time I signed the consent form until my baby was born)". Everybody except one person who was in the active management and minimal vaginal examinations group (n=32/33), mostly or completely agree with the statement. This means that overall, 97% of all participants who completed the questionnaire, were satisfied with the care provided during the study by the midwives and doctors.

In question 2: "Overall, I felt I was in a good emotional place during the time from when my waters broke till when I went into labour or was admitted to hospital". There were 30 participants out of the 33 who completed the questionnaire that mostly or completely agree with this statement. This means that 91% of all participants who completed the questionnaire felt they were in a good emotional state. There were three participants who mostly or completely disagree with the statement and these were equally spread across all groups, with one person in each group except in the active management and routine vaginal examinations where there were none.

In question 3: "Overall, I felt mentally and emotionally capable during the time from when my waters broke till I went into labour or was admitted to hospital". This statement obtained the same results as in question two, perhaps because people associated the mental and emotional state and capability as being the same thing. There were 30 participants out of the 33 who completed the questionnaire that mostly or completely agree with the statement. There were three participants who mostly or completely disagree, and these were equally spread across all groups, with one person in each group except in the active management and routine vaginal examinations. Overall, 91% of participants who completed the questionnaire, felt mentally and emotionally capable.

In question 4: "Overall, I felt physically capable during the time from when my waters broke till when I went into labour or was admitted to hospital". This statement obtained the exact same results as in question two and three. 91% of the participants who completed the questionnaire mostly or completely agreed with the statement. The three participants who did not agree, are again equally spread across the groups in the same pattern as in questions two and three.

In question 5: "I felt I was well looked after by the midwives during the time from when my waters broke till when I went into labour or was admitted to hospital". All the participants mostly or completely agreed with this statement. This means that 100% of the participants who completed the questionnaire felt well looked after during the time from the rupture of the membranes until they went into labour or were admitted into hospital.

In question 6: "Overall, I am satisfied with the management that I had (Expectant/Active management) for my labour." Most people, 31 participants out of 33 who completed the questionnaire responded that they were satisfied with the management they were allocated to (expectant or active). However there were two participants who were allocated to active management who did not agree. This means that 94% of all participants who completed the questionnaire were satisfied with the type of care they were allocated to, and that the study in itself is acceptable to women, and that the main clinical trial would be acceptable to women.

In question 7: "I think the number of vaginal examinations that I had during my labour was appropriate". There were 25 participants out of the 33 who completed the questionnaire who mostly or completely agree with this statement. This means that 76% of women thought that the number of vaginal examinations that they received was appropriate. There were eight participants who mostly or completely disagree and these were spread across the different groups, there were five women in the minimal examinations groups and three women in the routine examinations group who mostly or completely disagreed. This means that overall, 76% of participants who completed the questionnaire were satisfied with the number of vaginal examinations that they received and that the interventions in the study were generally accepted by the women implying that a main clinical trial with these interventions would be acceptable to women.

In question 8: "I think the frequency of vaginal examinations that I had during my labour was appropriate". There were 26 out of 33 participants who completed the

questionnaire who mostly or completely agreed with this statement. However, there were seven participants who mostly or completely disagreed. These were spread across all the groups, except in the case of expectant management and minimal vaginal examinations were 100% thought that the frequency was appropriate. There were four women in the active management and minimal vaginal examinations and three in the routine vaginal examinations (one in the expectant and routine vaginal examinations and two in the active management and routine vaginal examinations). This means that overall, 79% of those who completed the questionnaire, were satisfied with the frequency of the vaginal examinations. This implies that the interventions were acceptable to women and that a future main study with these interventions would be acceptable to women.

In question 9: "I would have preferred to have more vaginal examinations". There were 26 out of 33 participants who completed the questionnaire who mostly or completely disagreed. This means that overall 79% of women were satisfied with what they got and did not prefer to have more. There were seven participants who agreed and would have preferred to have more, and these were spread across all the groups. This implies that overall, women were satisfied with the number of vaginal examinations and that the interventions were acceptable.

In question 10: "I would have preferred to have less vaginal examinations during labour". There were 26 out of 33 participants who completed the questionnaire who mostly or completely disagreed. This means that 76% of participants were satisfied with the number of vaginal examinations and this is consistent with the previous question, meaning that the same proportion of women were satisfied and did not want to have either less or more, they were satisfied with what they received. This again implies a high degree of satisfaction with the study interventions and it implies that a future main clinical study with these interventions would be acceptable for women. The table bellows outlines the results per group and per answer. Overall, there was a high degree of acceptability of the study interventions across all the groups in the study

6.7 Discussion

This chapter has discussed the results from an observational and a pilot RCT on the management of term prelabour rupture of membranes and its implications for a future definitive study. The results have been discussed one by one, and this section offers an overall discussion of the main findings. This study offers a fresh approach to how to manage prelabour rupture of membranes in women with a healthy pregnancy, and this is one of the elements of originality.

The latest Cochrane systematic review conducted by Middleton et al. (2017), revealed that several studies have looked into the management of prelabour rupture of membranes (Ayaz et al., 2008; Hannah et al., 1996; Pintucci et al., 2014). However, it is the first time that an investigation has been carried out into different ways of managing term prelabour rupture of membranes, in conjunction with an approach aimed to reduce the number of vaginal examinations, that relies on alternative ways to assess progress of labour. Also, one of the novelties is that it is the pilot phase of a clinical trial whose main outcomes were normal birth and chorioamnionitis. It is uncommon to find a clinical trial that focuses on increasing normal birth, as it is more common to find trials that focus on reducing caesarean sections or on reducing negative outcomes. Perhaps this fresh approach and change in focus is because this trial was led by a midwife with an interest in normality as opposed to pathology. Although, the focus of the main trial will be on increasing normal birth and diminishing chorioamnionitis, for the pilot phase, there was a different set of objectives. Therefore, in this chapter, other features have been the focus of attention such the rates of recruitment, the adherence to the different elements of the study protocol and the test of the tools used during the study.

It is common for clinical trials not to achieve the planned sample size, according to Walters et al. (2017), only 56% of the clinical trials achieve the planned sample size. It is true that the pilot RCT did not achieve the planned sample size (n=120). However, it is not due to a poor consent agreement proportion because in contrast to other studies in this area, such as the ARRIVE trial conducted by Grobman et al. (2018) where low proportions of the eligible women took part (27%), in the pilot RCT described in this thesis, 51% of eligible women agreed to participate.

Many reasons could account for not achieving the sample size, for example, one of the limitations of this study was that it was self-funded and it did not qualify to get into

the portfolio of studies adopted by the trust, and as a consequence, the study lacked from formal support from the research midwives for recruitment. The recruitment was therefore, carried out by only one person. It was considered if the clinical midwives could help with the recruitment, and two midwives who already had done the good clinical practice course volunteered to help, but due to the clinical pressures it meant they couldn't devote the time to talk to the potential participants and obtain consent. Women demonstrated interest in the study, not only by the proportion of eligible women who participated in the pilot RCT (51%), but also because a high proportion stayed and were committed to the procedures that the study requested.

Only 1 woman out of 21 (5%) who was allocated to the expectant management decided to have her labour induced before her induction time, because although she had started to have some contractions she was tired and according to the clinicians the woman wanted to have her labour induced earlier. As discussed in section 6.6.1.4 on page 212 there was one augmentation in a participant whose cervix was 3cm and was having 3 contractions in 10min, and clinicians offered her an augmentation, and she agreed. On the other hand, there were two women out of 22 (9.1%) who were allocated to the active management groups, but decided to come out of the study as they did not want to have their labours induced. Therefore, the rates were similar between those in the active management and expectant management.

The fidelity to the protocol was high, 73.2% of participants completed their diaries and acted upon values outside the normal range, for example women who noticed reduced fetal movements or discharge suggestive of meconium came to hospital. This would suggest that the diaries were giving autonomy and empowerment to the participants. The requirement for home visits by community midwives in the expectant management groups was something that initially triggered some resistance mainly amongst midwifery managers who were worried about workload when the study was being set up. However, as time passed by, the midwives started to see the benefits of the visits and the resistance disappeared. Midwives started to ask me if this participant would need a visit suggesting that they saw the benefits of the visits, and that they were willing and able to free up capacity to undertake them. The adherence to the home visits was high, 18/20 (90%) of visits were carried out at home as the protocol asked. The fidelity to the forms was also high, 84% of the forms to assess maternal and fetal wellbeing during the home visits were completed appropriately. The approach to the vaginal examinations had a high fidelity rate but it was lower in the minimal vaginal examinations arms (75%)

when compared to those in the routine vaginal examinations (90.5%) and this means that extensive training will need to be provided for the main clinical trial, especially for learning how to measure the progress of labour by behavioural cues. In terms of the clinical outcomes, no conclusions can be drawn due to the small sample. However, there were no big clinical or statistical differences, and no safety issues were encountered.

The high levels of acceptance towards the study in women were also seen in the high response rate of the questionnaires, 80.5% of participants completed and returned the questionnaires. Their responses, as discussed in this chapter, indicated that most women found the interventions acceptable. Satisfaction was also assessed with the CEQ (Childbirth experience questionnaire) and it was found that there were no big differences across all the groups. However, the group that had the higher satisfaction score in all the domains was "Expectant management and minimal vaginal examinations". This gives evidence that women found expectant management and minimal vaginal examinations acceptable.

In terms of the clinical outcomes, the percentage of women going into labour spontaneously within the expectant management and observational study groups, is in line with the literature. However, it was noted that more women than what the literature suggests went into spontanous labour within 24 hours in the active management groups in the pilot RCT (groups 3 and 4) 60% and 70% of women respectively went into spontaneos labour within 24 hours which is higher than usual. This could well be an artefact due to the small sample size, but it had an impact in the rest of clinical outcomes. Consequently, groups 3 and 4 also had shorter labours and more normal births. However due to the small sample size, clinical results should be taken with caution. Overall, the pilot RCT was safe, and no safety concerns were raised.

6.8 Conclusion

The recruitment analysis revealed that 85 women were found to be eligible, of those 51% agreed to take part in the pilot RCT, 40% agreed to take part in the observational study, and 9% did not take part in either. The percentage of women who agreed to take part was found to be higher than in other recent big trials, in the arrive trial, 27% of women agreed to take part (Grobman et al., 2018).

The demographics of women who took part in the observational study were compared against those who took part in the pilot RCT and the differences were not statistically significant. A great part of the analysis of the pilot RCT involved the fidelity analysis to the study protocol. In general the fidelity was found to be high. Overall, 73.2% of participants completed and returned the diary with their own observations taken during the time between the rupture of membranes and the spontaneous/induced labour. In regards to the home visits to the participants allocated to the expectant management arms, 90% happened at home as the protocol required. The fidelity to the expectant management was higher than the fidelity to the active management (85.7% vs 80%). On the contrary, the fidelity to the routine vaginal examinations approach was found to be higher than the minimal vaginal examinations approach (90.4% vs 75%). This shows that more training needs to be done in the area of the vaginal examinations and how to assess progress of labour with as few examinations as possible for the main trial.

It was found that about 45-50% of women were in spontaneous active labour within 24 hours since the rupture of membranes, this was the case for those in the expectant management arms and observational study and it is consistent with previous research (Ottervanger et al., 1996). However, in the active management arms a higher proportion of women were in spontaneous active labour in the active management groups (60-70%). Due to the small sample size no definitive conclusions can be drawn but it is something that will be monitored in the main phase. No safety issues were encountered. The engagement of participants was high and that was demonstrated with the high return of questionnaires, 80.5% of participants returned their questionnaires. The group with higher satisfaction scores was the expectant management with minimal vaginal examinations, however the differences with the other groups were not statistically significant. Study interventions seemed to be acceptable to women. The results from the low vaginal swabs are presented in the next chapter.

Chapter 7: Microbiology

7.1 Introduction

This chapter discusses the microbiological side of this program of research. I have decided to make it a separate chapter due to its complexity. Therefore, this chapter discusses the rationale for taking vaginal swabs from the participants who took part in the pilot RCT, as well as the methods followed to complete their analysis. In addition, the results from the microbiological analysis are presented at the end, followed by the implications for the main study.

7.2 Background

7.2.1 Rationale for taking the swabs

Many clinical trials collect human tissue samples alongside the interventions that are being under investigation, in particular, and within the topic of prelabour rupture of membranes, the studies conducted by Morales and Lazar (1986) and Ottervanger et al. (1996). These samples are either for the diagnosis or to gain further understanding of how a certain intervention has an impact in the human body. In the pilot RCT of this thesis, low vaginal swabs were taken to examine if non-commensal bacteria entered the vagina due to the process of vaginal examinations. Imseis et al. (1999) carried out a study in pregnant women from 34 weeks gestation, and demonstrated that the cultures taken after vaginal examinations had a higher mean of different organisms (mean=4.4) in comparison to the cultures taken before the vaginal examination (mean=2.8). This difference was found to be statistically significant ($p < 0.0001$).
However, the investigation carried out by Imseis et al. (1999) was different in that it was not a clinical trial comparing expectant vs active management nor a protocol of

routine vaginal examinations vs minimal examinations. Therefore, although the results obtained from Imseis et al. (1999) were invaluable in understanding the potential for contamination in the process of performing a vaginal examination. The pilot RCT in this thesis provides a new approach to gather new information to see if having more or less vaginal examinations would make a difference in the microorganisms found in the cultures in the main study.

7.2.2 Location where swabs were taken

Imseis et al. (1999) carried out a study to understand the microbiological effect of the vaginal examinations. They reported that in their study high vaginal swabs were taken before and after vaginal examinations in a population of pregnant women with prelabour rupture of membranes and intact membranes from 34 weeks onwards. Morales and Lazar (1986), and Ottervanger et al. (1996) also reported that high vaginal swabs were taken in their studies on the management of prelabour rupture of membranes. Therefore, in order to be consistent with previous literature, I initially had planned to take high vaginal swabs. However, high vaginal swabs need to be taken with a speculum, and during the discussion groups that were carried out during the developmental phase, prior to the pilot RCT, clinicians and women expressed resistance towards the use of speculum during active labour. This was because a speculum examination can be very uncomfortable. In view of this, it was decided that low vaginal swabs (LVS) would be taken instead, because they do not require the use of speculum. Both clinicians and women seemed to agree that low vaginal swabs would be feasible. In terms of the scientific value of the research, it was determined that if a LVS was taken before the examination and then a LVS after each vaginal examination, taking LVS instead of high vaginal swabs would be scientifically sound as the difference between before and after could be examined.

7.2.3 When the swabs were taken

Since the main purpose was to see if the vaginal examinations introduce contamination and non-commensal organisms, it was decided that the protocol would include a low vaginal swab (LVS) prior to the first vaginal examination to have a microbiological baseline. And a swab after every vaginal examination. Therefore, LVS seemed sufficient to assess the potential for contamination of the vaginal examinations. Due to lack of

financial resources, it was decided that only the low vaginal swab taken before the first vaginal examination and the low vaginal swab taken after the last vaginal examination were going to be analysed. Apart from the financial constraints that motivated this decision, this also worked from a scientific point of view because I was also interested in seeing the before and after effect and cumulative effect of the vaginal examinations. The protocol asked for a LVS (low vaginal swab) after each vaginal examination, because during childbirth we do not really know when the last examination is going to be, therefore the safest thing to do was to take a LVS before and after the first vaginal examination and after each vaginal examination and analyse the LVS before the first and the LVS after the last vaginal examination.

7.2.4 Rationale for choosing the bacteria for the study

It is important to differentiate between what constitutes the vaginal microbiota and hence the endogenous microorganisms and the exogenous microorganisms, because then it can be assessed if certain exogenous microorganisms have been introduced in the vagina through the process of vaginal examinations, or otherwise.

If microorganisms are introduced in the vagina through the process of an internal examination, that would be considered a nosocomial infection. Nosocomial infection has been defined by Benenson (1995) and Ducel, Fabry, and Nicolle (2002) as an infection acquired in a healthcare centre by a service user who was admitted for a different reason other than that infection, and the infection was not present or incubating at the time of admission. This definition covers infections contracted in the healthcare setting, but appearing after discharge, and also infections contracted by the staff working on the premises during the course of their duties.

A number of researchers have attempted to isolate potential pathogens in women and neonates with prelabour rupture of membranes, including Ottervanger et al. (1996), Morales and Lazar (1986) and Imseis et al. (1999).

Ottervanger et al. (1996) examined cervical cultures and neonatal gastric aspirates cultures at delivery. In this study several microorganims were tested as described in table 7.1 in page 245. Ottervanger et al. (1996) highlighted that cervical cultures were positive in 31/118 (26.3%), however only three women of those 31 had clinical signs of infection. In regards to the infants, there were no cases of infant morbidity.

No babies displayed symptoms of infection, however, one in the active management group had a positive culture for Group B *Streptococcus* (GBS) and seven babies had GBS identified in the gastric aspirates.

Table 7.1: Microorganisms tested by Ottervanger et al., (1996)

	Does it belong to vaginal microbiota?		
Name of microorganism	**YES**	**NO**	**If not, where do they normally live?**
Streptococcus agalactiae (GBS)	YES		
Streptococcus mitis	YES		
Enterococcus faecalis		NO	Gastro-intestinal tract
Chlamydia trachomatis	YES		
Escherichia coli		NO	Gastro-intestinal tract
Klebsiella pneumoniae		NO	Respiratory system
Proteus mirabilis		NO	Gastro-intestinal tract
Pseudomonas aeruginosa		NO	Respiratory system
Pseudomonas maltophilia		NO	Respiratory system
Ureaplasma urealyticum	YES		
Mycoplasma hominis	YES		
Gardnerella vaginalis	YES		
Candida albicans	YES		
Staphylococcus aureus		NO	Skin

Table 7.2 in page 246 outlines the microorganisms that were tested for in the clinical trial conducted by Morales and Lazar (1986).

Table 7.2: Microorganisms tested by Morales & Lazar (1986)

	Does it belong to vaginal microbiota?		
Name of microorganism	**YES**	**NO**	**If not, where do they normally live?**
Streptococcus agalactiae (GBS)	YES		
Neisseria gonorrhoea	YES		
Enterococcus spp.		NO	Gastro-intestinal tract
Escherichia coli		NO	Gastro-intestinal tract
Haemophilus influenza		NO	Respiratory system
Peptostreptococcus spp.		NO	Respiratory system
Bacteroides fragilis		NO	Gastro-intestinal tract
Staphylococcus aureus		NO	Skin

The microorganisms tested for in previous studies described in tables 7.1 and 7.2, were of importance because it helped to inform what microorganisms to test for in my study.

It was decided to test for microorganisms that are generally exogenous to the human vagina, and that its presence in the vagina could be explained by the process of the digital vaginal examination. I decided that I would test the swabs against the following bacteria: *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus agalactiae*. Table 7.3 outlines the microorganisms tested for in the study presented in this thesis. Although 18% of the female population is known to be colonised by Streptococcus agalactiae (GBS) according to Russell et al. (2017), it was also decided to be included due to its clinical significance. The prevalence of colonization of GBS can vary depending on the geographical area, ethnicity and socioeconomic status and even methodological issues, such as location where the swabs were taken (rectal vs vaginal), media for the cultures or gestation when women were offered the test. According to Russell et al. (2017), it can vary from 11%-35%.

Table 7.3: Microorganisms tested in this research study

Name of microorganism	**Where do they normally live?**
Streptococcus agalactiae (GBS)	Vagina/urinary system/gut
Escherichia coli	Gastro-intestinal tract
Pseudomonas aeruginosa	Respiratory system
Staphylococcus aureus	Skin

7.3 Objectives

1. To determine the feasibility and the women's acceptability of the vaginal swabs taken around the time of vaginal examinations
2. To determine if the bacteria that were decided to test against in the pilot phase would be appropriate for the main trial
3. To pilot test analysis procedures.

7.4 Methods

Low vaginal swabs were taken by the clinicians, they were asked to take one swab prior to the first vaginal examination and one swab after each vaginal examination. The first swab prior to the first vaginal examination and the last swab after the last

vaginal examination were analysed and compared. The swabs were tested against the microorganisms mentioned in table 7.3 on page 247.

7.4.1 Type of swab that was used

Sterilin M40 gel swabs were used in this research. This type of swab was chosen against cheaper swabs like those with charcoal, because they contain Amies media gel for the maintenance of bacterial sample during transport to the laboratory. Amies media gel has extended length of time for bacterial survival. The provider, Fisher Scientific, guarantees a minimum of 48 hours and in most cases up to 72 hours of bacterial survival. Figure 7.1 in page 248 presents a photograph of the swab.

Figure 7.1: Picture of Sterilin M40 gel swab

7.4.2 Labelling of the swab

Once the swab was taken by the clinician the swab was labelled with a sticker that helped clinicians collect only the necessary information and maintain the confidentiality of the participants. these stickers were provided as part of the participants pack, so each participant was given a set of swabs and a set of labels to take with them when they came in back to hospital. The information needed in each swab was: Participant's initials, participants' study identification number, number of swab, date and time when the swab was taken and location where the swab was taken. The swabs were numbered in relation to the number of vaginal examinations. The swab before the first vaginal examination was called "Swab 0", the swab after the first vaginal examination was called "swab 1", the swab after the second vaginal examination was called "swab 2" and so on. The numbering of the swabs was a bit confusing for some clinicians and required on-going training, but eventually most of the clinicians understood the process of the swabs.

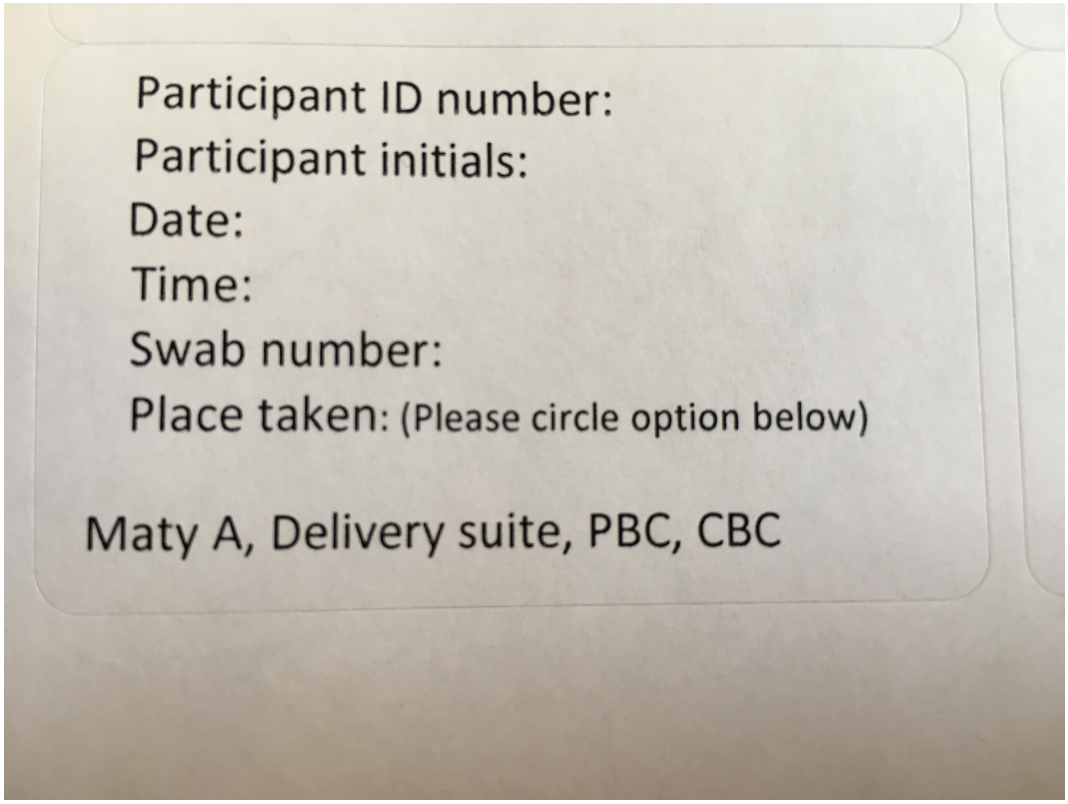


Figure 7.2: Picture of label

7.4.3 Storage of swabs

Once the swabs were taken and labeled appropriately, these were kept in the clinical fridges at the maternity unit. Once the woman had given birth, one of the midwives would notify me so I could collect the swabs and take them to the laboratory at the University. Once at the University, the swabs were initially kept in the fridge within the secured microbiology laboratory. During the course of the study I was informed that a new room for the storage of human tissue samples had been created, and since October 2017, vaginal swabs were stored in the human tissue room whilst they were being analysed. Once the analysis took place, the swabs were disposed of according to laboratory procedures.

7.4.4 Laboratory methods

The first and last swab were streaked into two petri dishes with horse blood Columbia agar (one petri dish for each swab), and these were incubated at 37°C for 48 hours. Following this period of incubation, axenic pure colonies were sub-cultured by choosing different colonial morphology onto Columbia horse blood agar, aiming to achieve one species of bacteria per plate. These were incubated at 37°C a further 48 hours. Once the sub-colonies were isolated and these had grown, gram-staining was performed to ascertain whether the microorganism was gram positive or gram negative. In addition, its morphology was determined under the microscope. Depending on the result obtained, further testing was performed as follows:

1. In the case of gram negative rods an API20E test was performed for the identification of *Escherichia coli* and *Pseudomonas aeruginosa*.

2. In the case of gram positive coccus in clusters, Staphytect was performed for the identification of *Staphylococcus aureus*.

3. In the case of gram positive coccus in chains, Streptococcal latex agglutination grouping kit for the identification of Group B *Streptococcus*.

4. In the case of gram negative coccus or yeasts seen under the microscope, no further testing was performed.

7.5 Results

There were 18 participants (out of 41), who had all swabs taken according to the protocol, which meant the overall adherence rate was 43.9%. Table 7.4 below outlines the adherence to the protocol per group. The fidelity to the protocol has been discussed in section 6.6.1 on page 207. However, this table is presented here for aiding the understanding of the following sections in this microbiology section. Only the swabs from the participants that were taken correctly and according to the protocol were analysed, which meant that only swabs from 18 participants were analysed.

Table 7.4: Swabs that were taken correctly

	EM minimal VEs n=10	**EM routine VEs n=11**	**AM minimal VEs n=10**	**AM routine VEs n=10**
Variable	n (%)	n (%)	n (%)	n (%)
Swabs taken correctly	2 (20%)	5 (45.5%)	7 (70%)	4 (40%)

7.5.1 Presence of *Escherichia coli*

There were two cases where *Escherichia coli* was found. One case belonged to the expectant management and minimal vaginal examinations group, and the other belonged to the active management and routine vaginal examinations.

7.5.2 Presence of *Pseudomonas aeruginosa*

No *Pseudomonas aeruginosa* were found in any of the groups in the pilot RCT.

7.5.3 Presence of *Staphylococcus aureus*

In the case of *Staphylococcus aureus*, there were two equivocal results, both found in the swabs taken after the last vaginal examination. One participant belonged to "Active management and minimal vaginal examinations" group and the other to "Active management and routine vaginal examinations" group. In these cases, the results were positive for both the test and control, and after taking advice from the provider, I was advised to report them as equivocal as further tests would be required

to give a definitive result and due to the financial limitations it was not possible to carry out further testing.

7.5.4 Presence of *Streptococcus agalactiae* (GBS)

No *Streptococcus agalactiae* were found in any of the groups in the pilot RCT.

7.5.5 Number of subcultures

The mean number of subcultures found in swab 0 (the low vaginal swab taken before the first vaginal examination) was calculated per group and compared to the mean number of subcultures found in the last swab (the swab taken after the last vaginal examination). The mean number of subcultures (different organisms) was consistently higher in the last swab across all groups. Figure 7.3 on page 253 illustrates this.

The mean number of subcultures found in the last swab (swab taken after the last vaginal examination) was consistently higher across all the groups, and this is in agreement with the literature. Imseis et al. (1999) conducted a study where cultures were taken before and after vaginal examination. Imseis et al. (1999) reported that the cultures taken before vaginal examination had a mean of 2.8 +/- 1.7 different types of organisms, and the cultures taken after digital examination demonstrated a mean of 4.4 +/- 1.5 different organisms ($p<0.001$) and that 80% (n=28) of participants had heavier growth or a greater number of different organisms in the culture after the vaginal examination than in the culture taken before the vaginal examination.

The study carried out as part of this PhD demonstrated that the mean number of subcultures was consistently higher in the last swab when compared to the swab taken before the first examination, and since this trend is also consistent with the literature, a 1 tail t-test was used. Therefore as the difference has been demonstrated to only go in one direction, a 1 tail t-test was used to see if the overall difference between the mean number of subcultures in swab 0 (mean=2.35 for all the groups together) was significantly lower than the mean number of subcultures in the last swab (mean=3.06 for all the groups together). The difference was statistically significant (t=-1.92, df=32, p=0.03). Although it is acknowledged that the sample size in this study is very small, the results are in agreement with the literature.

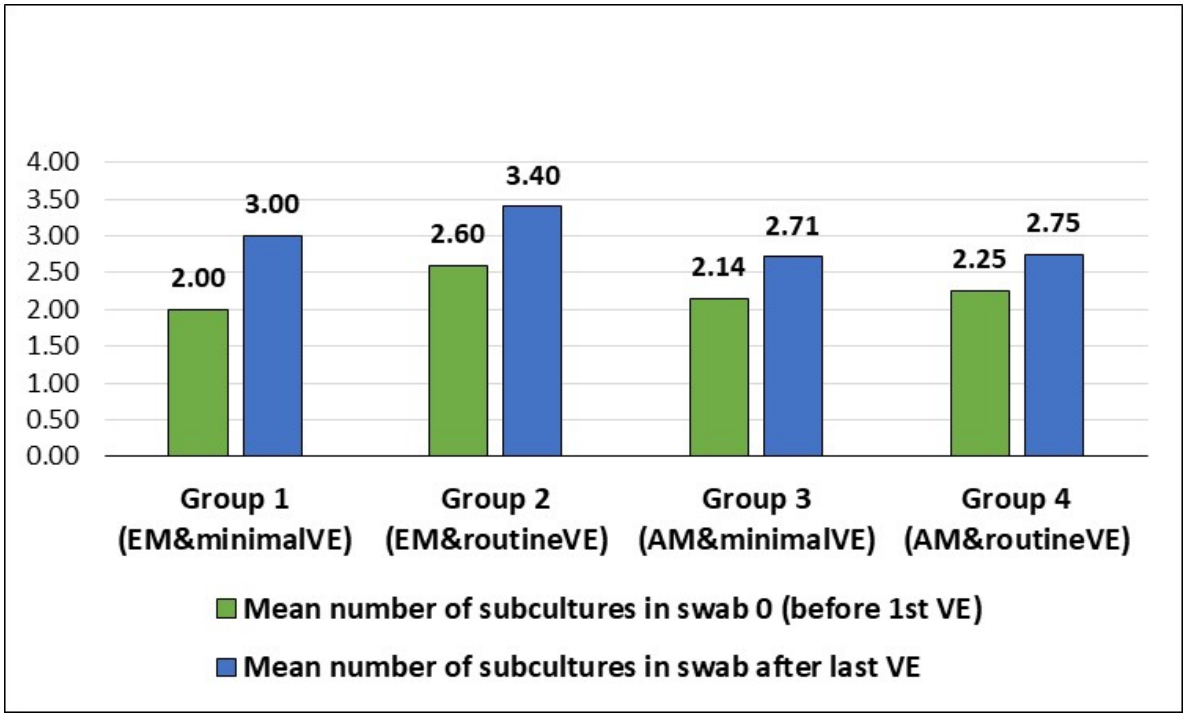


Figure 7.3: Mean number of subcultures

7.6 Discussion

This section of the study was a major learning curve for me, as microbiology is not my area of expertise and I had to learn many different and new things very quickly. The main learning points for me were in the area of interdisciplinary relationships and research to be conducted across different schools and facilities within the university.
I had to learn about different ways of working and different regulations. In particular, in regards to working within a laboratory. I had to learn basic microbiology techniques such as the streaking plate technique, preparing plates for incubation, observing and differentiating the different organisms in the plate and taking subcultures, and all the processes that the test kits for the identification of bacteria required. This section of the PhD brought many challenges that I had to face and overcome. Firstly, it was challenging to gather the funds for the purchase of the material. For that I decided to do crowdfunding, which took time to get approved, but it proved to be successful and I managed to gather a significant amount. Once I had the funds to buy the necessary material, the next challenge was to set up a budget code within the University, so I could order the material, but this was overcome. It was also challenging to learn about the regulations for human tissue and how the swabs needed to be tracked, stored and labelled.

In regards to the results obtained, the mean number of subcultures found in the last swab was higher than the mean number of subcultures found in the first swab and this difference was statistically significant. This is consistent with previous literature (Imseis et al., 1999). The possible explanations for this could be that exogenous microorganisms are introduced through the process of vaginal examinations, either from the environment or the perineal area, or that through the process of the vaginal examinations the vaginal microbiota is disrupted, allowing the proliferation of microorganisms.

No cases of GBS were found, however, two cases of *Escherichia coli* were identified. In part this was to be expected as one of the exclusion criteria to take part in this study was to be known to be colonised by GBS. However, *Escherichia coli* is equally pathogenic for the newborn and as far as I am aware, there are no routine programs testing against it during pregnancy in the UK.

The strengths and limitations of this part of the study are discussed ahead. The strengths are mainly in the demonstration of the feasibility of taking the swabs. There

were no cases of women agreeing to the study but not to the swabs, and there were no cases of participants declining the swabs during the study. However, only 18 out of 41 were taken correctly and that was more due to the clinicians. The reasons for the swabs not to be taken correctly were: clinician forgetting about, women who did not receive any vaginal examination, women who had the baby at home unexpectedly, clinician using the wrong swab, or clinician forgetting to take the last swab. The implications of this findings for the main study are that extensive training will need to be provided to the clinicians.

In regards to the analysis, since there were only 18 participants who had their swabs taken correctly, the sample size is very small so the results need to be taken with caution. Only two cases of *E. coli* were found, two potential cases of *S. aureus* but the results were unequivocal and further testing was required, but due to the financial limitations, no further testing was possible. The implications of this finding are that a wider range of bacteria should be tested for, including anaerobes (which were not tested for in this study) for example *Clostridium* spp. and the use of clinical laboratories for the testing of the swabs within the hospitals where the main study would take place would be beneficial.

Clinicians were advised to use water-based lubricants during the vaginal examination process and they were also advised to abstain from using chlorhexidine-based lubricants as this could interfere with the vaginal microbiota. Chlorhexidine-based lubricants may kill some of the bacteria, either exogenous or endogenous. This could alter the balance of the microbiome of the vagina, and the birth canal. The disruption of this balance may cause the proliferation of pathogenic bacteria leading to increased morbidity in both mother and baby. In addition, if chlorhexidine-based lubricants were used by mistake by the clinicians, this would give false results in our study as some bacteria may have died. This was not monitored during the pilot RCT, but since very few bacteria were found, it will need to be monitored during the main clinical trial to ensure reliable results.

7.7 Conclusion

Low vaginal swabs (LVS) were taken from the pilot RCT participants before and after the first vaginal examination (VE) and after every vaginal examination. The LVS taken

before the first vaginal examination was taken as a baseline of the microbiological state of the vagina. The final swab after the last vaginal examination was analysed and compared against the baseline in each participant. This was to see if new and exogenous microorganisms entered the vagina through the process of the vaginal examinations as a way to provide information on the potential for contamination of this procedure. Several studies before have examined the vaginal microbiota in the context of prelabour rupture of membranes (Imseis et al., 1999; Morales & Lazar, 1986; Ottervanger et al., 1996). However, this thesis presents the first RCT that does it within a trial that looks at not only the management of prelabour rupture of membranes but also at different regimes for vaginal examinations.

Women found the low vaginal swabs acceptable, there were no potential participants who declined taking part in the RCT because of the swabs. There were 18/41 (44%) participants who had their swabs taken correctly according to the research protocol. The main reasons for not having had the swabs taken correctly seemed to be on the clinician's side, and they include: forgetting to take the very first LVS before the first vaginal examination, or forgetting to take the last LVS after the last vaginal examination, or not using the appropriate swab. This shows that the low vaginal swabs can be done but that extensive training will need to be provided during the main RCT.

In terms of the results, the mean number of number of microorganisms found in the swabs taken before the first vaginal examination was lower than the mean number of microorganism found in the last swab taken after the last VE (2.35 vs 3.06; t=-1.92, df=32, p=0.03). This is consistent with previous literature (Imseis et al., 1999). We tested for GBS, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and we only found 2 cases of *Escherichia coli* (one on the Active management and routine VEs, and one in the expectant management and minimal VEs), and no presence of the other microorganisms. This shows that if enough resources are available a bigger and wider selection of microorganism to test against might be beneficial. Given the small sample size, conclusions cannot be drawn at this stage. The next chapter will present an overall discussion of the key findings in the light of the current literature, followed by recommendations for future practice and research and a conclusion.

Chapter 8: Discussion

8.1 Introduction

This chapter provides an overall discussion of the key findings in the light of the current literature, with the aim of answering the research question that was posed in the background chapter. It will also outline the novel aspects of this study as well as its strengths and weaknesses. In addition, it will provide recommendations for future research and will draw up a conclusion.

8.2 Research question and problem to be addressed

In the increasingly medicalised and highly interventionist philosophy that is embedded in today's maternity care around the world, a woman presenting with clinical history of prelabour rupture of membranes is often seen as being high risk, especially of maternal or neonatal infection. Infection is becoming increasingly feared, as multi-resistant strains of bacteria proliferate, and antibiotics become less effective as Wojcieszek et al. (2014) highlight. In this climate, many, if not most women who present themselves in a maternity unit in the UK with pre-labour rupture of membranes at term are informed that their labours need to be induced at around 24 hours since the rupture of membranes if they are not in established active labour or have not given birth by then (NICE, 2017). In contrast, according to the most recent Cochrane systematic review performed by Middleton et al. (2017), there are not statistically significant differences in terms of neonatal infection and there are also no statistically significant differences in the rate of chorioamnionitis when the labour is induced with prostaglandins compared to when women are given up to about 96 hours for their labours to start spontaneously (Hannah et al., 1996; Seaward et al., 1997). Therefore, this raises the question if the induction of labour should always be recommended and whether other approaches to manage

this situation should be offered to women presenting with term prelabour rupture of membranes According to the most recent published systematic review (Middleton et al., 2017), induction of labour does not appear to reduce the risk of infection, and yet, it is interfering with the process of birth, making a physiological process that could be drug-free, a drug driven process by synthetic oxytocin where other interventions such as epidural analgesia, limitation of movement during childbirth or continuous fetal monitoring may be required. Due to the process of induction other iatrogenic morbidities may appear such as an increased risk of infection due to the multiple vaginal examinations that the induction process may need as Seaward et al. (1997) and Shubeck et al. (1966) explain. Prelabour rupture of membranes is an especial situation that could be seen as a high risk situation, or as a variation of normal because normality and abnormality are not fixed concepts, they are often socially defined and they can change over time (Downe, 1996).

The current national guidelines for prelabour rupture of membranes (NICE, 2017) are mainly based on a study dated over 20 years ago (Hannah et al., 1996), and although it is the most recent and statistically powerful clinical trial to date on the subject, this topic would benefit from a new study with a fresh approach . This PhD thesis provides the study protocol for a novel clinical trial on this topic together with the demonstration of the feasibility, acceptability and pilot testing of all of its interventions, procedures and tools.

8.3 Discussion of the overall findings

8.3.1 Systematic review findings

The systematic review was crucial to be able to identify the gap in the literature that this PhD thesis would cover. Thanks to the systematic review it became clear that no studies were published before that looked into expectant management in combination with an intervention aimed to reduce the number of vaginal examinations. Although a Cochrane systematic review on the management of prelabour rupture of membranes has been published recently by Middleton et al. (2017), this systematic review did not include the intervention of vaginal examinations in their searches in combination with the management (active vs expectant). Therefore, the systematic review constitutes another element of originality of this PhD.

8.3.2 Patient and service user engagement

Patient and service user involvement in research has been demonstrated to improve the quality and acceptability of the research (Brett et al., 2014). In this study, patient and public involvement played a crucial part in the development of the research protocol. During the developmental phase, I engaged with pregnant women or women who had their babies in the past year or so, over a few discussion groups and their input was essential in the development of the recruitment strategy, and the tools used during the study. Their input contributed to have a high rate return of questionnaires (80.5%) and this is in line with what Entwistle et al. (1998) suggest.

8.3.3 Building trust in clinical trials

In addition to the work done to involve women in this research, I also wanted to involve the clinicians who worked at the maternity unit where the study took place as their input was also crucial for the development of the protocol and recruitment strategy, as they needed to contact me when a potential participant was identified.

During the developmental phase, I carried out different discussions groups with the clinicians, such as obstetricians, paediatricians, community midwives, hospital midwives, managers and even one-to-one meetings with most of the consultant obstetricians. This helped to develop the forms that were used in the study and shape the recruitment strategy with their input. Kaur et al. (2012) highlights that one of the barriers to recruitment is the lack of available support staff during the course of the trial. Therefore, as well as involving clinicians in the development of the study, it was crucial to be present and accessible in the maternity unit during the recruitment period. These two actions, helped to build trust. Although it seems obvious, little has been published in how the development of trust between researchers and clinicians can have a positive impact in recruitment rates and the smooth running of clinical trials (Hurd et al., 2017). Trust was developed as time passed and it was evident by how the resistance towards the home visits ceased and on the contrary, midwives started to share personal experiences with me or asked for help with interviews for example.

8.3.4 Key findings from the pilot RCT and observational study

The key findings from the pilot RCT were the lack of safety issues encountered during the study and that no major differences were identified between the clinical outcomes

obtained in the expectant management and minimal vaginal examination group when compared with normal practice. In addition, it was found that most women found the interventions acceptable. Assessing the acceptability of the study interventions in a pilot sample prior to undertaking the main clinical trial, is one of the main objectives of pilot studies as Lancaster et al. (2004) suggest. A pilot clinical trial that has demonstrated a good degree of acceptability of the interventions and tools such as study questionnaires and patient's diaries will have a greater chance of achiving the necessary sample size and running smoothly in its main phase.

In addition, other important findings are the high fidelity to the study protocol, as well as the ongoing engagement of clinicians and women in the study.

8.3.5 Vaginal swabs and the use of human tissue in clinical trials

It is not uncommon to find clinical trials that, as well as testing the effectiveness and efficacy of an intervention, they also collect human tissue samples to carry out certain laboratory analysis. In particular and within the topic of prelabour rupture of membranes, Morales and Lazar (1986) and Ottervanger et al. (1996) carried out a clinical trial where expectant and active management were compared, and in addition, they took vaginal swabs to test against certain bacteria. The purpose of taking swabs in this study was to see if there were any non-commensal bacteria entering the vagina due to the vaginal examinations. Imseis et al. (1999) conducted a study to understand the microbiologic effect of vaginal examinations, in a population of pregnant women from 34 weeks onwards and prelabour rupture of membranes. Therefore the results obtained by Imseis et al. (1999) were invaluable in understanding the potential for contamination in the process of performing a vaginal examination. However, this study was different to the one presented in this thesis because it was not a clinical trial comparing expectant vs active management nor a protocol of routine vaginal examinations vs minimal examinations. Although some non-commensal bacteria are harmless for either the mother or baby, I was interested in determining the potential for contamination of vaginal examinations. Since it was a pilot clinical trial, it is acknowledged that due to the small sample, no definitive conclusions can be drawn in regards to the potential for contamination of vaginal examinations. However, the main objective at the pilot stage was to determine the feasibility and the women's

acceptability of the vaginal swabs taken around the time of vaginal examinations and for testing the analysis procedures. Although only 18 participants out of 41 (44%) had their swabs taken correctly. The study shown that it was feasible and the procedure was accepted by women as no participants declined the swabs to be taken. The difficulty in obtaining the swabs was more on the side of the clinicians that sometimes would forget to take the swabs as it is not part of the routine practice.

8.3.6 Methodological issues that could be generalised to other studies

Several methodological issues have arisen from this work. It became apparent that the lack of consistency in how the onset or length of labour is defined and measured in clinical practice can bring different results in research and clinical practice. Cheyne, Dowding, and Hundley (2006) state that the diagnosis of active labour is crucial in intrapartum care. On the contrary, there seems to be a lack of consistency of what is considered active labour and how the onset of labour is defined.

A recent systematic review on the definitions of the onset of labour carried out by Hanley et al. (2016), has shown that there was a great variation on the definition for labour onset. On one hand, Incerti et al. (2011) defined active labour as at least 2 regular contractions in ten minutes and a cervical dilation of at least 2 centimetres whilst on the other hand, Ayangade (1984) defined the onset of labour as a cervical dilation of 3 centimetres or more for primiparous women and 4 centimetres or more for multiparous women. The implication of this finding is that it is important to note the definition used for the outcomes in the protocol for the future main trial, as depending on the definition used, one can obtain different figures. The issue of the definition for labour onset and for spontaneous labour is particularly important, as many trials use these measures, but they are not used consistently, resulting in different outcomes and practices that when generalised or implemented in clinical practice, do not bring the same results that the research said it would.

8.3.7 Aceptability of tools and interventions

The reliability of the CEQ (Childbirth Experience Questionnaire) for the group of participants who took part in this pilot RCT, was assessed by calculating the Cronbach's alpha scores for each of the domains, and for the questionnaire as a whole. This results

were also compared with the Cronbach's alpha scores reported in the original Swedish study conducted by Dencker et al. (2010). Cronbach's alpha is the statistic most widely used for assessing internal consistency and reliability (Gardner, 1995; Taber, 2017). An alpha Cronbach score of 0.70 or above is considered as desirable (Taber, 2017). The implications of these findings are positive; firstly having an overall response rate of 80.5% is very positive. This means that the questionnaire was easy to use and women found it feasible to complete. In addition, almost all (97%) participants who returned their questionnaires, answered all questions. On estimating the internal consistency of the questionnaire by calculating the Cronbach's alpha scores, the questionnaire obtained high scores well above the desired 0.70. This means that the internal consistency of the questionnaire and its reliability for the group of women who completed was high, and it can be extrapolated that the CEQ questionnaire will perform well in the future main clinical trial. In addition, the CEQ has been translated and validated from Swedish, its original language, to Spanish (Soriano-Vidal et al., 2016). This will become useful should the main trial becomes an international multicentre trial, as it will mean the same questionnaire could be used in at least three countries (Sweden, UK and Spain). Since there were no statistically significant differences s amongst all the groups, this implies that the study as a whole and the individual interventions in the study were acceptable to women.

8.4 Unique contribution to knowledge within the wider evidence

The study presented in this thesis makes several contributions to knowledge as discussed in the introduction chapter on page 32. In this section, however, the contribution to knowledge is restated and positioned within the wider research published in maternity up to this point.

To begin with, the importance of the research question is highly relevant in today's maternity care due to the increasingly higher induction of labour rates. The induction rate increased in England and Wales from 20.4% in 2007/2008 to 32.6% in 2017/2018 (NHS Digital, 2018). Prelabour rupture of membranes constitutes one of the main and most common reasons for induction of labour at tem, as well as "post-dates", "reduced fetal movements" and concerns about fetal growth. In the context of this high induction rate, it is worth asking if routine induction of labour at approximately 24 hours since the the rupture of membranes is always the best course of action for all women? Why is it important to look at how we look after women who break their waters but they do not go straight away into labour? Why is it worth looking at all the components of the management of prelabour rupture of membranes? In the past several studies attempted answering the question what management is best for term prelabour rupture of membranes, and looked at active management vs expectant management or at different drugs for induction of labour in the context of prelabour rupture of membranes.

If the most up to date research on prelabour rupture of membranes in the pre-term gestation (from 34 to up to 36 weeks and 6 days gestation) is reviewed, it shows that expectant management is safe and pregnancy is allowed to continue until the mother reaches 37 weeks gestation (Van der Ham et al., 2012). This means that if membranes are broken at 34 or 35 weeks gestation, the pregnancy is allowed to continue until 37 weeks, having a big latency period. Although the focus of the study presented in this thesis is the term pregnancy, it raises the question of why at term the current recomendation is to induce labour at about 24 hours (NICE, 2017) whereas before 37 weeks the current trend is to leave it until the fetus reaches 37 weeks, when potentially the fetus is more immature and perhaps more vulnerable to infection. It is hoped that the study presented in this thesis will continue into its main phase, so a

contemporaneous study can be carried out in the context of term pregnancy.

This study is also unique because, at the design stage, rather than in sub-analysis, as in some other studies in this area (Akyol et al., 1999; Hannah et al., 1996) it takes into account a critical routine practice factor that is often overlooked (frequency and number of vaginal examinations) at the design stage. In addition to the pilot RCT, this program of research included an observational study along side the RCT, where women who met the study criteria, but declined to participate in the RCT, received routine care and gave consent for their clinical records to be looked at and relevant data collected. The analysis of the number of vaginal examinations was compared in those who went into spontaneous labour in comparison to those whose labours were induced, and it was concluded that the process of induction of labour was associated with more vaginal examinations. This raises an important point about other studies of childbirth physiology and interventions - could practice factors that are seen as routine be major but overlooked influencers of outcomes?

The outcomes selected were also unique in terms of PROM trials, in that there were two, one of which reflects the concern with pathology (chorioamnionitis infection) and the other with maximising physiology (normal-physiological birth), in line with growing recognition of the need to balance these two factors in maternity care in general (Miller et al., 2016).

8.5 Strengths and limitations

The main strength of this study was the pilot testing of a bundle of interventions for term prelabour rupture of membranes in preparation for the future main clinical trial. Expectant management up to approximately 96 hours in combination with an approach that aims to reduce the number of vaginal examinations that women receive during labour has not been investigated before. This study provided novel insights into the management of prelabour rupture of membranes. Furthermore, women showed an interest in this study and in wanting to avoid the induction of labour as much as possible, this is supported by the high percentage of eligible participants who agreed to take part in the pilot RCT (51%) and further supported by the engagement of the participants during the study period with only two people out of 22 (9.1%) deciding to withdraw from the study who belonged to the active management groups. In addition, only

one-two (4.8% - 9.5%) women out of 21 who belonged to the expectant management groups decided to be induced/augmented earlier than scheduled. The high levels of interest and engagement of the women were also demonstrated with the high rate of completion of the diaries, with 30 women out of 41 (73.2%) completing their diaries, acting on the abnormal records and returning them. Another sign of high interest and engagement of women with this study was the high return rate of questionnaires, 33/41 (80.5%) of participants returned their questionnaires. This is higher than the returned rate of questionnaires in the original Swedish study conducted by Dencker et al. (2010), which was 69%. Another strength was the high completeness rate of the questionnaires, most participants (97%) answered all the questions that the CEQ and study specific questionnaire asked them to complete.

On the contrary, on examination of the limitations of the study, it was found that in terms of the systematic review, it is acknowledged that the tool used to assess the quality of the studies has been drawn upon the CASP tools (Critical Appraisal Skills Programme, 2018a; Critical Appraisal Skills Programme, 2018b; Critical Appraisal Skills Programme, 2018c), and the Cochrane risk of bias assessment tool developed by Higgins et al. (2019). It did not contain all the questions used in the Cochrane risk of bias assessment tool developed by Higgins et al. (2019), because as well as randomised clinical trials, observational studies were also included in the review. However, even though the systematic review included in this thesis did not used the Cochrane risk of bias assessment tool exclusively in the case of RCTs, the results from the systematic review presented in this thesis are in agreement with a recent cochrane systematic review published by Middleton et al. (2017) in that the quality of most studies in this topic is generally low.

The main limitation is the relatively small sample size for the pilot clinical trial. Although there is little guidance as to how large a pilot study should be (Hertzog, 2008). In a recent audit on sample sizes of feasibility and pilot studies in the UK, Billingham, Whitehead, and Julious (2013) highlighted that the median sample size per arm for pilot studies was 30 with a range (8-114). The sample size for this study was below the median described by Billingham et al. (2013).

8.6 Implications for future practice

This thesis presents many implications for practice. It became apparent that based on the most up to date evidence women should be given information and choice on the different managements (expectant vs active) for term prelabour rupture of membranes. In addition, they should be informed of the reasons why vaginal examinations should be minimised to reduce the risk of infection.

The high completion and return of the diaries provided evidence on the benefits of their use. A total of 30 women out of 41 (73.2%) completed and returned their diaries. Women also reported as anecdotal evidence that the use of a diary to record their temperatures and other observations was useful and empowering because they knew what they needed to look for whilst awaiting for the onset of labour, and it helped them to keep track of their wellbeing. This finding implies that diaries should be introduced as part of the management for term prelabour of ruptures because even if the induction is scheduled by 24 hours since the rupture of membranes, women still need to monitor their temperatures and take other observations during that time.

In regards to the vaginal examinations, the results from the study specific questionnaire from the responses from women allocated to the minimal vaginal examinations, reveled that in response to the following statement *"I would have preferred to have more vaginal examinations*", a total of 5 women out of 17 respondents (29%) responded that they mostly or totally agree, whereas 12 out of 17 respondents (71%) responded that they mostly or totally disagree. This implies that the majority of women (71%) were satisfied receiving an approach of minimal vaginal examinations. However, 29% would have preferred to have routine vaginal examinations. This findings imply that in clinical practice may be important for midwives to get to know the preferences of women in regards to how often they want the vaginal examinations. The midwife should adjust the care to these preferences. However, whilst performing regular vaginal examinations is supported and encouraged by NICE guidelines and other policies, other ways of externally monitoring the progress of labour are not as recognised and supported as much as a vaginal examination. It is hoped that this study in his main phase will provide evidence that other external means of assessing the progress of labour are as valid, reliable and helpful as vaginal examinations.

8.7 Implications for future research

This PhD thesis describes the process followed for the development of the study protocol and the feasibility, acceptability and pilot testing of complex interventions in maternity care, that are often very hard to change in clinical practice, such as a different timing for the induction of labour or when the vaginal examinations are performed. The need to carry out this preliminary work is common in randomised controlled trials, therefore this thesis provides an example for other researches. A substantial part of this thesis and preliminary work was based on "Patient and Public Involvement" (PPI) which as well as the women, it included a lot of work with clinicians. As mentioned earlier this was key for the development of trust between the clinicians and researcher and it is believed it contributed to the smooth running of the study and the high rates of adherence to the study protocol. This thesis advocates public involvement including clinicians in any future clinical trials of complex interventions.

It became apparent that the definition of onset of active labour is something that is not standardised, with different clinicians and researchers using different definitions, which contribute to obtain different results in terms of the length of latent phase and length of labour depending on the definition used. It may also lead to research that once is adopted in clinical practice it doesn't deliver the results that the research said it would. I believe it is important for future studies on induction of labour to present clearly the definition used for the onset of active labour. In addition, further research should be done to achieve an international definition of onset of active labour so results from different studies can be compared easily and later on when adopted in clinical practice, the results obtained in clinical practice are consistent with the results from the study.

The preliminary work carried out prior to a large-scale definitive clinical trial is a critical part in the development of any intervention in health care (Whitehead et al., 2014). Carrying out preliminary work prior to the main study has become a crucial part prior to applying for funding, since many large public funding bodies nowadays expect substantial work to have been done prior to the application for funding as Whitehead et al. (2014) explain. It is hoped that the work carried out during this PhD will contribute to securing the funding required to carry out with this research at large scale.

8.8 Conclusion

The rates of induction of labour (IOL) keep rising in England and Wales, from 20.4% in 2007-2008 to 32.6% in 2017-2018 (NHS Digital, 2018). This resulted in only 52.2% of women having spontaneous labours, the rest of women, had their labours induced (32.6%) or had a planned CS (15.2%) (NHS Digital, 2018). Prelabour rupture of membranes is one of the routine causes for induction of labour. Intrapartum guidelines developed by NICE (2017) recommend women to have their labours induced if they are not in active labour by 24 hours since the rupture of membranes. On the contrary, the most recent Cochrane review on the management of prelabour rupture of membranes carried out by Middleton et al. (2017) showed that there were no statistically significant differences between expectant and active management in terms of neonatal sepsis. The results from the TermProM study carried out by Hannah et al. (1996) dominate the review due to its big sample. In terms of chorioamnionitis, Hannah et al. (1996) found that the differences were not statistically significant between women who had active management in comparison to those who had expectant management when the induction was carried out with prostaglandins. Most of the women nowadays commence the process of induction with prostaglandins and not directly with IV oxytocin as it was common practice in earlier times (O'Driscoll, Stronge, & Minogue, 1973). Therefore, what happens when women are induced with prostaglandins is what is relevant to current practice.

If the rates of infection of mothers and babies are similar whether women have active or expectant management when induced with prostaglandins, it raises the question if routine induction of labour is always necessary? As induction of labour has other risk factors associated with the intervention per se (C. Duff & Sinclair, 2000). The problem of having a policy of routine induction for prelabour rupture of membranes is that it restricts women and their babies from experiencing the long term benefits of spontaneous labour and normal birth (Peters et al., 2018). The systematic review carried out as part of this program of research revealed that, to date, no RCT has been published on the management of term prelabour rupture of membranes and minimal vaginal examinations, therefore the systematic review itself and the development of the study protocol constitute the main elements of originality of this doctorate.

This program of research has used Evidence based medicine/midwifery as the framework

or the map to help the navigation. First it was identified that the most up to date evidence in regards to the management of PROM was from 1996 during my clinical practice. Then, once this PhD commenced, the systematic review helped to identify the gap in the evidence. Therefore, the developmental and pilot RCT phases of this research were conducted. The involvement of women and clinicians during the developmental phase was crucial for the design of the study and the documents associated with it. The main output from this consultations constituted the recruitment strategy, the development of the participant information sheet and diaries and how we changed from the prospect of taking high vaginal swabs to low vaginal swabs due to the women's and clinicians preference.

The involvement of clinicians was also crucial for the smooth running of this trial, and a sense of trust was developed as the study settled down and recruitment was established. Women and midwives highly engaged during the course of the study and that can be demonstrated by the high fidelity rates to the student protocol and study forms on the part of the midwives and the overall high completion rate (73.2%) of the diaries and the high return rate of the questionnaires (80.5%). No safety issues were encountered. The main limitation of this study is the small sample size. This research carried out as part of this doctorate demonstrated that it is feasible, acceptable and necessary to conduct a main clinical trial with the protocol and interventions presented in this thesis. Furthermore, women showed an interest in wanting to avoid the induction of labour that was reflected on the percentage of eligible women who agreed to take part in the pilot clinical trial (51%). The research carried out by Wada, Evans, de Vrijer, and Nisker (2018) showed that women were keen to take part in research as long as it was safe and they saw a potential benefit in it for themselves or others. Therefore more research that looks at ways to manage prelabour rupture of membranes at term that favour women achieving normal births and ways to monitor the progress of labour by behavioural cues and other external signs should be promoted as women showed an interest and commitment to it.

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Appendix 1: NHS ethics approval

North West - Greater Manchester South Research Ethics Committee
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 104 8002

07 June 2016

Miss Lucia Ramirez-Montesinos
University of Central Lancashire
College of Health and Wellbeing
Brook Building - Room BB247
PR1 2HE

Dear Miss Ramirez-Montesinos

Study title:	**"Active vs expectant management and routine vs only-when-necessary vaginal examinations during labour for prelabour rupture of membranes at term, a pilot RCT study"**
REC reference:	**16/NW/0264**
IRAS project ID:	**157230**

Thank you for your letter of 24 May 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Ms Joanne Skellern.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Kieran Hall, nrescommittee.northwest-gmsouth@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must

confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]	1.0	18 March 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
IRAS Checklist XML [Checklist_18032016]		18 March 2016
IRAS Checklist XML [Checklist_25052016]		25 May 2016
Letter from statistician [Letter from Statistician]	1.0	18 March 2016
Other [CV for S Beeton]	1.0	18 March 2016
Other [Email - Validation clarifications]		29 March 2016
Other [Letter of access]	n/a	09 May 2016
Other [Participants diary]	2.0	24 May 2016
Other [Study protocol - clean version]	2.0	24 May 2016
Other [PIS for Pilot RCT]	2.0	24 May 2016
Other [Consent form for pilot RCT - clean version]	2.0	24 May 2016
Other [PIS for observational study - checking records]	2.0	24 May 2016
Other [Consent form for observational study]	2.0	24 May 2016
Other [Questionnaire]	2.0	24 May 2016
Other [CV for Helene Thygesen]	2.0	24 May 2016
Other [Covering letter 24th May 2016]	n/a	24 May 2016
REC Application Form [REC_Form_25052016]		25 May 2016
Research protocol or project proposal [Research protocol]	1.0	18 March 2016
Summary CV for Chief Investigator (CI) [CV for L Ramirez-Montesinos]	1.0	18 March 2016
Summary CV for supervisor (student research) [CV for S Downe]	1.0	26 January 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/NW/0264	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Professor Sobhan Vinjamuri
Chair

Email: nrescommittee.northwest-gmsouth@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Mrs. Denise Forshaw

Mrs Heather Adams,
Lancashire Teaching Hospitals NHS Foundation Trust

Appendix 2: Participant information sheet (Pilot RCT)

“A Pilot RCT on the management of term prelabour rupture of membranes”

-PARTICIPANT INFORMATION SHEET-

We would like to invite you to join this study.

The study will include 120 women who have reached at least 37 weeks of pregnancy, when their waters break, but who do not go into labour straight away.

We aim to find the type of care that leads to the highest chances of having a normal labour and birth, while at the same time reducing the chance of infection for women and their babies. To do this, we will look at the differences between allowing labour to start on its own for up to approximately 24 hours (also called active management) and up to approximately 96 hours (also called expectant management). We will also look at the effect of having more or less vaginal examinations during labour.

This is a pilot study, the miniature version of a future big study, which will help us to make sure that all the parts of the research plan work well together, before we do the larger main study.

Before you decide whether to take part, it is important for you to understand why the research is being done and what it is involved. You are free to decide to participate or not. If you choose not to take part, this will not affect the care you will receive from your midwives and doctors. Please take time to read the following information and discuss it with others if you wish. If anything is not clear, or if you would like more information, please get in touch with Lucia Ramirez-Montesinos (the details are at the end of this leaflet).

Why is the study needed?

Approximately 10% (1 in 10) pregnant women will break their waters before labour starts after 37 weeks of pregnancy. When the waters do not break before labour, the risk of infection for the baby is about 0.5% (1 in 200 babies) and about 1% (1 in 100) when they do break early**.** Previous studies have shown that the rates of infection in mothers and babies are similar if labour is allowed to start on its own, compared to starting labour off with drugs or other treatments. Induction of labour is generally safe, but it has been linked to a lower chance of normal labour and birth.

Frequent vaginal examinations could contribute to the development of maternal infection, so we are looking at the effect of the vaginal examinations too.

Previously, no studies have looked at the effects of both reducing number of vaginal examinations in labour, and doing either expectant or active management, so we don't know if this improves outcomes or not.

Both methods, active and expectant management, are offered in the NHS.

Why have I been invited and am I eligible?

You can take part if your waters break before you go into labour after 37 weeks of pregnancy and meet all the following criteria:

- Healthy normal pregnancy without any medical conditions
- No current infectious diseases including (HIV, Hepatitis B, Herpes, Group B streptococcus)
- Pregnancy between 37- 41+2 (41 weeks and 2 days)
- Expecting only 1 baby
- Baby presenting by the head
- Able to understand, read and write English
- Not taking part in other clinical research currently

What happens when the waters break?

If your waters break, it is usual practice for you to call the birth centre, labour ward or community midwife. The midwife will advise you to come in for a check-up and to confirm that the waters have broken.

What do I need to do if I want to take part?

If you are one of the 1 in 10 women whose waters break before the start of labour you will be advised to go to the hospital/your birth centre for a check up. Please take this information leaflet with you and let your midwife/doctor know that you are interested in the study. The midwife/doctor will know about this study when you come. Once the midwife/doctor has confirmed that your waters have broken, you will be seen by one of the researchers, and you will have the opportunity to ask any questions you may have. If you decide to take part, you will be asked to sign a consent form.

What happens once I enroll into the study?

Once you are enrolled into the study, you will be allocated by chance to one of the 4 groups, a process also called randomization, which is like a coin toss. Randomisation means that you will have an equal chance of being allocated to any of the 4 groups (see diagram on page 4). You will not be able to choose the group or the type of care that you prefer. So before you agree to take part, it is important that you are willing to be part of any of the 4 groups that are explained below.

What does taking part in this study involve?

It is thought that in most cases, labour will start on its own if given enough time. Depending on what group you are in, you will be offered an induction of labour at around 24hours or 96 hours after your waters have broken if you are not in labour or you haven't had the baby by then. While you are waiting for labour, you will receive daily visits by your community midwife and you will need to take your temperature, check the colour and smell of your waters and check the baby's movements every 4 hours (when you are awake) and record them on a form that we will give to you.

Once you are in labour, you will either be offered vaginal examinations at least every 4 hours or the examinations will be done only when needed or when requested by you

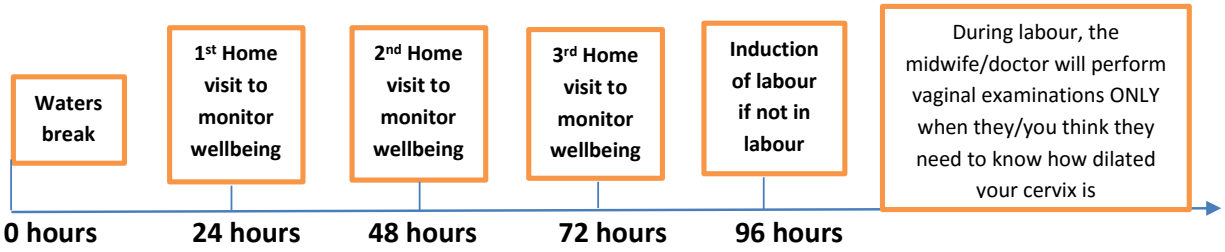
We will ask you to have a low vaginal swab taken before the first examination and another one after each vaginal examination. If you show any signs of infection, it is usual practice for your placenta to be analysed to find out if there really is an infection. We will ask you if you are happy for the laboratory to let us have those results.

So that we can make sure we have all the necessary information, we will also ask you if we can look through your medical notes and those of your baby.

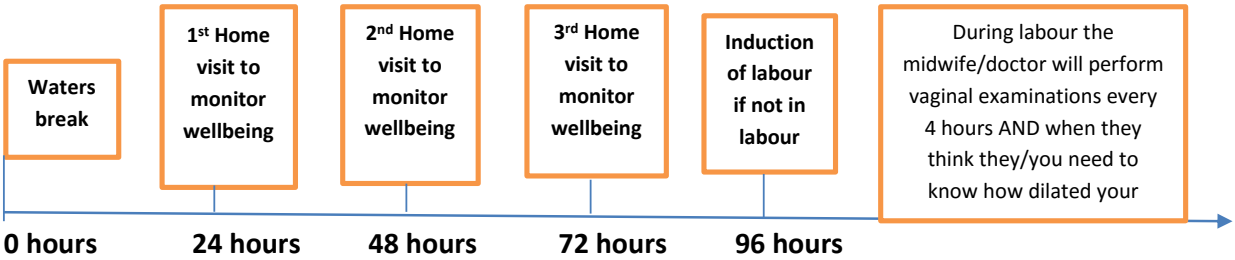
Finally, we will ask you if you could fill out a questionnaire about your experiences, between 4-6 weeks after the birth of your baby. If you agree, we will contact you at about 3-4 weeks after the birth of your baby, to see how you would prefer us to send the questionnaire to you.

Agreeing to receive a newsletter by email/post about the progress of the study (this is optional)

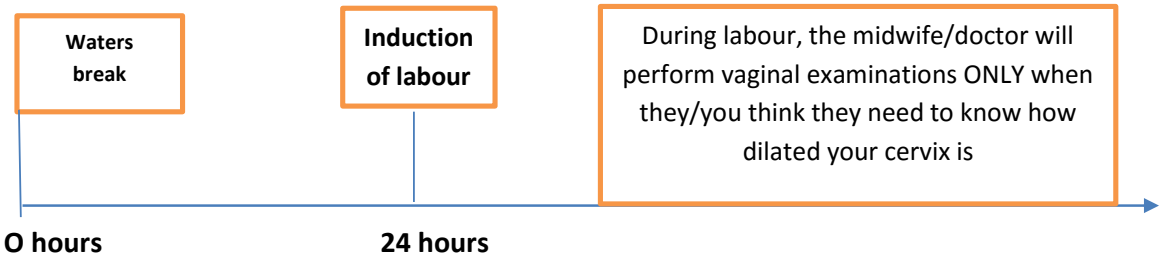
GROUP 1 = Expectant management and minimal vaginal examinations during labour



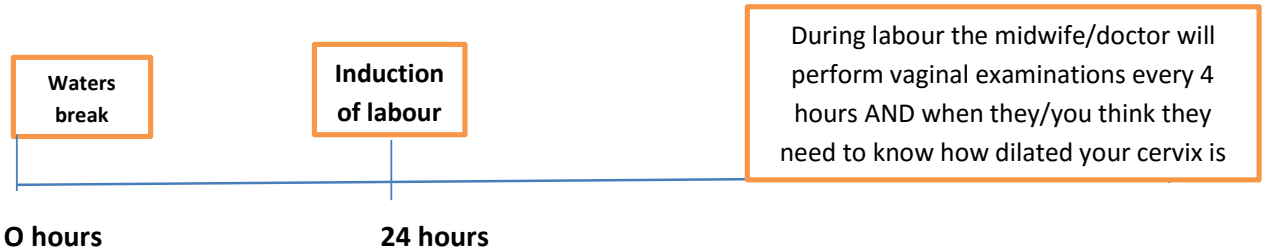
GROUP 2= Expectant management and routine vaginal examinations during labour



GROUP 3= Active management (Induction of labour at 24 hours) and minimal vaginal examinations during labour



GROUP 4 = Active management (Induction of labour at 24 hours) and routine internal examinations during labour. **This is the standard practice where you are looked after.**



What will happen if I don't want to carry on with the study?

You can leave the study at any time, without giving a reason and normal care will be resumed. Your care will not be affected.

What will happen to my samples?
They will be safely transported to the University of Central Lancashire laboratory where they will be analysed. They will be kept until the analysis has been completed (usually a week) and then will be safely disposed of. The findings will be stored anonymously. They will not be used as part of your care.

What are the possible benefits of taking part?

Taking part in this study will make a contribution to knowledge, science and women-centred maternity care.

What are the possible disadvantages and risks of taking part?

There are no extra risks for your health or that of your baby. According to the previous studies all the options for care are safe options for women and their babies as the chances of getting infected are very similar for both mother and baby when we induce labour with drugs or other treatments compared to when we wait for labour to start on its own. Regardless of the group that you are allocated to, you will be closely monitored by a team of midwives and doctors that will ensure that you feel well looked after and supported and that both, you and your baby are safe. As we do not know which approach to care is best, we cannot be sure that any of the groups you are allocated to are any better than any other of the groups. The time that it takes for you to fill out the questionnaires, and the vaginal swabs might be a disadvantage for you.

How will my information be kept confidential?

Anything that can be linked back to you, will be stored in a locked cabinet at the university and only members of the research team will have access to it for academic and research purposes. When the study results are published, all details will be anonymised. No-one will be able to identify you in any publicly available document.

Who is organising the study?

The study is undertaken as part of a doctorate research degree in Midwifery with the University of Central Lancashire.

Who has reviewed this study?

This study is being reviewed and supervised by a multidisciplinary team composed of Professor Soo Downe, Dr Steve Beeton and a statistician Dr Helene Thygesen. It has also gained ethical and governance approval from the NHS, and the University of Central Lancashire.

What can I do if I am not happy with any aspects of the study?

You can contact the University officer for ethics at officerforethics@uclan.ac.uk and your concern will be sent to the chair of the ethics committee within 2 working days and you should expect to get a response within 2 weeks.
You can also contact PALS: The patient Advice and Liaison Service (PALS) provides support for our patients, their families and carers. They can be contacted on: 01772 522972 or 01257 247280

Further information and contact details:

If you would like to gain any further information regarding this study, you can contact us. Our contact details are:

Lucia Ramirez-Montesinos (Chief investigator) **LRamirez-montesinos@uclan.ac.uk** **07897236172**

Soo Downe (Director of studies) **Sdowne@uclan.ac.uk**

Appendix 3: Consent form (Pilot RCT)

CONSENT FORM - "A Pilot RCT on the management of term prelabour rupture of membranes"

Participant ID number:

	STATEMENTS	**Please Initial this box if you agree**
1	I confirm that I have read the information sheet dated 25th October 2016 version 3.0 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand and grant permission for relevant sections of the clinical records and test results of myself and my baby to be reviewed and used by the study team	☐
4	I agree for the placenta and membranes to be analysed if it is deemed necessary by the midwives and doctors and for the results to be accessed by the research team	☐
5	I agree to have a vaginal swab taken before the first vaginal examination and after every examination and for the swabs to be analysed.	☐
6	I agree to complete the participants diary and questionnaire	☐
7	I agree to provide an email address, address and telephone contact to the research team to get in touch with me about 3-4 weeks after the birth of my baby about the questionnaire and to send me a newsletter approximately every 3-6 months	☐
8	I agree for the community midwife or lead clinician to be informed of my participation in this study	☐
8	I agree to take part in the above study	☐

Participant's print name……Signature……Date:_ _/_ _ /_ _

Name of person taking consent……Signature……Date: _ _/_ _/_ _

Appendix 4: Participants' Diary (Pilot RCT)

“A pilot RCT on the management of term prelabour rupture of membranes”

-PARTICIPANTS DIARY-

Instructions: Please complete the following diary after your waters have broken (when you started in the study) until you go into labour, OR until come to hospital to have your labour induced. If you have any questions or concerns about your health, or the wellbeing of your baby, please contact your community midwife, your birth centre, or the labour ward. If you have any questions about the study please contact Lucia Ramirez-Montesinos on 07897236172.

Please fill out the diary **every 4 hours when you are awake** whichever group you are in for the study.

	Things to look for, every 4 hours whilst you are awake	**Normal values**	**Abnormal values**	Action
1	Your temperature (taken under your tongue)	**36.0*c -37.5*c**	**35.9*c or less** **37.6*c or more**	If within normal values continue checking every 4 hours while awake. If unsure, call your midwife If abnormal values call your midwife
2	Amniotic fluid/your waters	**Colourless, pale yellow or slightly pinkish** **Slightly cloudy** **No smell**	**Green, brown** **Lumps of meconium** **Smelly**	
3	Uterus	**Contractions that come and go** **Only painful during contractions**	**Painful all the time, painful between contractions**	
4	Vaginal bleeding	**Mucosy plug – it looks like a piece of mucus (snot) or jelly, thick gelatinous mass, can be clear-yellowish or blood stained.**	**Haemorrage, bleeding, running bright red blood**	
5	Foetal movements/movements of the baby	**The normal pattern for your baby**	**No foetal movements in the past 4 hours** **Less movements than usual or change in the movements**	
6	General wellbeing	**Feeling well, your normal self**	**Feeling unwell**	

DATE & TIME	TEMPERATURE	COLOUR OF AMNIOTIC FLUID	SMELL OF AMNIOTIC FLUID	UTERUS	VAGINAL BLEEDING	FOETAL MOVEMENTS	GENERAL WELLBEING	Any other concerns?
Example *01/06/12 10.00am*	*36.1*	*clear*	*No smell*	*Not painful*	*NO*	*YES*	*Feeling well*	*NO*

DATE & TIME	TEMPERATURE	COLOUR OF AMNIOTIC FLUID	SMELL OF AMNIOTIC FLUID	UTERUS	VAGINAL BLEEDING	FOETAL MOVEMENTS	GENERAL WELLBEING	Any other concerns?

DATE & TIME	TEMPERATURE	COLOUR OF AMNIOTIC FLUID	SMELL OF AMNIOTIC FLUID	UTERUS	VAGINAL BLEEDING	FOETAL MOVEMENTS	GENERAL WELLBEING	Any other concerns?

DATE & TIME	TEMPERATURE	COLOUR OF AMNIOTIC FLUID	SMELL OF AMNIOTIC FLUID	UTERUS	VAGINAL BLEEDING	FOETAL MOVEMENTS	GENERAL WELLBEING	Any other concerns?

Thank you very much for completing this diary.

Please keep it with your maternity notes and give it to your midwife when you finish with it

Appendix 5: CEQ and Study specific questionnaire (Pilot RCT)

“A pilot RCT on the management of term prelabour rupture of membranes”

Pilot phase

-Questionnaire-

Dear new mother,

Thank you for continuing to take part in this pilot study on the management of prelabour rupture of membranes at term. We really appreciate your commitment.

One of aims of this study, is to find out how your childbirth experience was, and whether you were satisfied with the care that you received during the study or whether we need to make some changes. Therefore we would really appreciate if you could fill in the following questionnaire. If you have any extra comments or thoughts, whether positive or negative, please write them down at the end of the questionnaire in the comment boxes.

Please read the instructions at the beginning and answer the questions as best as you can. If there is any question that you don't understand, you can either contact us for further clarification, or leave it blank. We are also collecting feedback about the appropriateness and efficacy of the questionnaire itself. The final page asks you some questions about this.

Once you have finished the questionnaire, please put it into the pre-paid and self-addressed envelope and send it back to us.

Best wishes

Lucia Ramirez-Montesinos
Chief investigator, Midwife/PhD student
University of Central Lancashire
College of Health & Wellbeing
Brook Building BB247
Preston PR12HE
Tel. 07897236172

Instructions:

There are two ways to rate your experience, either by circling the option that relates best to you or by marking a line.

Examples:

Please read each statement and then indicate by circling the option that is most appropriate to you, using the scale of:

Totally disagree = 1

Mostly Disagree = 2

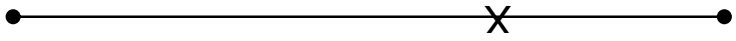
Mostly Agree = 3

Totally agree = 4

	Statement	Totally disagree	Mostly disagree	Mostly Agree	Totally agree
1.	I eat fruit every day	1	2	**3**	4

Indicate your opinion by marking on the line between the two end-points.

How much do you like apples?



Not at all My favourite fruit

Please also note that in regards to question 1, it refers to whether labour and birth went as you hoped it would go in general. For question 14, "partner" refers to your birthing partner. Your birthing partner can be anyone who spent most of the time with you during labour and birth, and could be a friend, a relative, baby's father or anyone that you chose.

The questionnaire begins on the next page.

Thank you for participating and sharing your views.

QUESTIONNAIRE

	Domain: Own capacity				
	Statements:	Totally disagree	Mostly disagree	Mostly Agree	Totally agree
1.	Labour and birth went as I had expected	1	2	3	4
2.	I felt strong during labour and birth	1	2	3	4
3.	I felt capable during labour and birth	1	2	3	4
4.	I was tired during labour and birth	1	2	3	4
5.	I felt happy during labour and birth	1	2	3	4
6.	I felt that I handled the situation well	1	2	3	4
7.	As a whole, how painful did you feel childbirth was?* Here we use VAS (visual analogical scale) scale to measure pain experience, rating it from no pain in the left to worst imaginable pain in the right	No pain ●——————————●			Worst imaginable pain
8.	As a whole, how much control did you feel you had during childbirth?* Rating from no control in the left to complete control in the right	No control ●——————————●			Complete control

	Domain: Professional support				
	Statements:	Totally disagree	Mostly Disagree	Mostly Agree	Totally agree
9.	My midwife devoted enough time to me	1	2	3	4
10.	My midwife devoted enough time to my partner	1	2	3	4
11.	My midwife kept me informed about what was happening during labour and birth	1	2	3	4
12.	My midwife understood my needs	1	2	3	4
13.	I felt very well cared for by my midwife	1	2	3	4
	Domain : Perceived safety				
	Statements:	Totally disagree	Mostly Disagree	Mostly Agree	Totally agree
14.	I felt scared during labour and birth	1	2	3	4
15.	I have many positive memories from childbirth	1	2	3	4
16.	I have many negative memories from childbirth	1	2	3	4
17.	Some of my memories from childbirth make me feel depressed	1	2	3	4
18.	My impression of the team's medical skills made me feel secure	1	2	3	4
19.	As a whole, how secure did you feel during childbirth?*	Not at all secure			Completely secure

	Domain: Participation				
	Statements:	Totally disagree	Mostly Disagree	Mostly Agree	Totally agree
20.	I felt I could have a say whether I could be up and about or lie down	1	2	3	4
21.	I felt I could have a say in deciding my birthing position	1	2	3	4
22.	I felt I could have a say in the choice of pain relief	1	2	3	4

	Domain: Study specific questions				
	Statements	Totally disagree	Mostly Disagree	Mostly Agree	Totally agree
1.	Overall, I am satisfied with the care that I received by the midwives and doctors during the study (from the time I signed the consent form until my baby was born)	1	2	3	4
2.	Overall, I felt I was in a **good emotional place** during the time from when my waters broke till when I went into labour or was admitted to hospital.	1	2	3	4
3.	Overall, I felt **mentally and emotionally** capable during the time from when my waters broke till I went into labour or was admitted to hospital.	1	2	3	4
4.	Overall, I felt **physically** capable during the time from when my waters broke till when I went into labour or was admitted to hospital.	1	2	3	4
5.	I felt I was well looked after by the midwives during the time from when my waters broke till when I went into labour or was admitted to hospital.	1	2	3	4
6.	Overall, I am satisfied with the management that I had (Expectant management/Active management) for my labour.	1	2	3	4
7.	I think the **number** of vaginal examinations that I had during labour was appropriate.	1	2	3	4
8.	I think the **frequency** of vaginal examinations that I had during labour was appropriate.	1	2	3	4
9.	I would have preferred to have **more** vaginal examinations during labour	1	2	3	4
10.	I would have preferred to have **less** vaginal examinations during labour	1	2	3	4

Additional comments regarding taking part in the study

Additional comments regarding the time between when the waters broke till when I went into labour or was admitted to hospital.

Additional comments in regards to labour and birth

Please let us know what you think about this questionnaire by answering the following questions.

1) Did you understand all the questions? Yes ☐ No ☐

If no, which ones were difficult or unclear to answer?

2) Were there any questions you think should have been omitted? Yes ☐ No ☐

If yes which ones?

3) Were there any questions that should be added, to help us understand your views?

Yes ☐ No ☐

If yes what would they be?

4) Approximately how long did it take you to complete the questionnaire?

5) If you have any other comments about the questionnaire please write them here:

Thank you!
Please now send it back to us!

Appendix 6: Example of antenatal assessment and VE forms

"A pilot RCT on the management of term prelabour rupture of membranes"

EXPECTANT MANAGEMENT

&

VAGINAL EXAMINATIONS ONLY WHEN NECESSARY

Study participant ID:	

Visit 0 -At the first point of contact and as part of the routine assessment, **the midwife** will:

- Take a set of baseline observations (BP, MP, RR, Temperature)
- Assessment of the colour/smell of liquor
- Abdominal palpation: Uterine tenderness? Contractions?
- Foetal heart rate auscultation
- Book induction at 96h since the rupture of membranes.

The researcher/person taking consent will inform women of:

1. How to complete the participant's diary, signs of concern and who to contact

2. Community midwife will visit woman at home the next day, and every day up to 96h.

3. To come to their chosen place for birth when they experience regular/strong contractions (3-4:10min lasting at least 60sec) or earlier if any concerns.

Visit 1- 24 hours later, if they are not in labour, a community midwife will go to their home to carry out a full assessment again:

- Review patient's diary
- A set of baseline observations (BP, MP, RR, Temperature)
- Assessment of the colour/smell of liquor
- Abdominal palpation: Uterine tenderness? Contractions?
- Foetal heart rate auscultation.

Visit 2: (48 hours since the rupture of membranes), if they are not in labour, a community midwife will go to their home to carry out an assessment:

- Review patient's diary
- A set of baseline observations (BP, MP, RR, Temperature)
- Assessment of the colour/smell of liquor
- Abdominal palpation: Uterine tenderness? Contractions?
- Foetal heart rate auscultation.

Visit 3: (72 hours since the rupture of membranes), if they are not in labour, a community midwife will go to their home to carry out an assessment:

- Review patient's diary
- A set of baseline observations (BP, MP, RR, Temperature)
- Assessment of the colour/smell of liquor
- Abdominal palpation: Uterine tenderness? Contractions?
- Foetal heart rate auscultation.

Women who are not in labour will come to the hospital to be induced at 96 hours since the rupture of membranes. The IOL should be booked at the time of enrolment by the midwife looking after her. *If the woman shows signs of infection during latent phase or labour, remember to send placenta to histology with appropriate form and stating that is taking part in the pilot Trial.

VISIT 0 (SCREENING):

VISIT 0 (SCREENING):

PHYSICAL EXAMINATION AND VITAL SIGNS: This is to be carried out and documented in this form by midwife looking after her).

Please keep this booklet with the woman's notes.

Date of screening :……(DD/MM/YY) Time of screening: …… (HH:MM)

Date of rupture of membranes……..(DD/MM/YY) Time of rupture of membranes:……(HH:MM)

Duration of rupture of membranes up to the time of enrolment? Hours and min……

Physical examination	measurement	Units of measurement	Normal range	
Blood pressure		mmHg	Systolic (139-90mmHg) inclusive Diastolic (89-50mmHg) inclusive	
Maternal pulse		Bpm	(51-100bpm) inclusive	
Respiratory rate		Respirations/min	(9-20 resp/min) inclusive	
Temperature		Degrees Celsius	36-37.5*C (both inclusive)	
Abdominal Palpation				
1	General appearance of the uterus: For example is it soft on palpation? Or tender/painful? Please consider this when the woman is **not** having a contraction)			
2	Lie:			
3	Presentation			
4	Position			
5	Engagement: Is the presenting part engaged (Please circle answer)		YES	NO
6	Measurement:	Units of measurement	Normal range	
Fetal Heart rate auscultation		Bpm	110-160bpm (inclusive)	

Study participant ID:	

	Assessment of well being	Yes	No
1	Is the Blood pressure within normal limits?		
2	Is the maternal pulse within normal limits?		
3	Is the temperature within normal limits?		
4	Is the respiratory rate within normal limits?		
6	Is the fetal heart rate within normal limits?		
7	Is the colour of the liquor clear/light pink?		
8	Is the smell of the liquor neutral or without smell?		
9	Is the uterus soft and not painful on palpation? (when the women is not having a tightening)		
10	Does the woman report normal fetal movement?		

*If there are abnormal results prior to enrolment, the participant must not be enrolled in the study.

Does the woman report any other concerns? If any, please describe below

	YES	NO
Is she having any tightenings?		
If yes, describe:		
Is the woman feeling strong and regular contractions? At least 3:10 strong and regular lasting at least 60sec		

If no strong and regular contractions, then arrange follow up appointment in 24 hours, advise her to complete the symptoms diary and remind her about hygiene measures (hand wash, bath and shower ok, no sexual intercourse, healthy diet and adequate hydration). Also give her information about signs of concern and who to call if any worries.

If she is having strong and regular contractions before being enrolled/ransomised, this study does not apply to her and she should not enter the study.

Print name…… Signature…….

Date…….(DD/MM/YY) Time: ……(HH:MM)

Study participant ID:	

Visit 1: Approximately 24 hours since the rupture of membranes

PHYSICAL EXAMINATION AND VITAL SIGNS: This is to be carried out and documented in this form by midwife looking after her).

Please keep this booklet with the woman's notes.

Date :……(DD/MM/YY) Time: …… (HH:MM)

Date of rupture of membranes……(DD/MM/YY) Time of rupture of membranes:……(HH:MM)

Duration of SROM so far: (hours and min)…….

Have you reviewed the participant's diary?	YES	NO
Are her own observations satisfactory?	YES	NO
If no, please describe		

Physical examination	measurement	Units of measurement	Normal range	
Blood pressure		mmHg	Systolic (139-90mmHg) inclusive Diastolic (89-50mmHg) inclusive	
Maternal pulse		bpm	(51-100bpm) inclusive	
Respiratory rate		Respirations/min	(9-20 resp/min) inclusive	
Temperature		Degrees Celsius	36-37.5*C (both inclusive)	
Abdominal Palpation				
1	Describe general appearance of the ut Is it soft on palpation? Or tender/painful? Please consider this when the woman is **not** having a contraction)			
2	Lie:			
3	Presentation			
4	Position			
5	Engagement: Is the presenting part engaged? (Please circle answer)		YES	NO
6	Measurement:	Units of measurem	Normal range	
Fetal Heart rate auscultation		bpm	110-160bpm (inclusive)	

Study participant ID:	

	Assessment of well being	Yes	No
1	Is the Blood pressure within normal limits?		
2	Is the maternal pulse within normal limits?		
3	Is the temperature within normal limits?		
4	Is the respiratory rate within normal limits?		
6	Is the fetal heart rate within normal limits?		
7	Is the colour of the liquor clear/light pink?		
8	Is the smell of the liquor neutral or without smell?		
9	Is the uterus soft and not painful on palpation? (when the women is not having a tightening)		
10	Does the woman report normal fetal movement?		

*If there are abnormal results, please advise her to come to hospital for further assessment

Does the woman report any other concerns? If any, please describe below

	YES	NO
Is she having any tightenings?		
If yes, describe:		
Is the woman feeling strong and regular contractions? At least 3:10 strong and regular lasting at least 60sec		

If no strong and regular contractions, then arrange follow up appointment in 24 hours, advise her to complete the symptoms diary and remind her about hygiene measures (hand wash, bath and shower ok, no sexual intercourse, healthy diet and adequate hydration). Also give her information about signs of concern and who to call if any worries.

If she is having strong/regular contractions, that would suggest she might be in established labour, advise her to go to Hospital/Birth centre.

Print name…… Signature……..

Date…….(DD/MM/YY) Time: ……(HH:MM)

Study participant ID:	

Visit 2: Approximately 48 hours since the rupture of membranes

PHYSICAL EXAMINATION AND VITAL SIGNS: This is to be carried out and documented in this form by midwife looking after her).

Please keep this booklet with the woman's notes.

Date :……(DD/MM/YY) Time: …… (HH:MM)

Date of rupture of membranes……(DD/MM/YY) Time of rupture of membranes:……(HH:MM)

Duration of SROM so far: (hours and min)……

Have you reviewed the participant's diary?	YES	NO
Are her own observations satisfactory?	YES	NO
If no, please describe		

Physical examination	measurement	Units of measurement	Normal range
Blood pressure		mmHg	Systolic (139-90mmHg) inclusive Diastolic (89-50mmHg) inclusive
Maternal pulse		bpm	(51-100bpm) inclusive
Respiratory rate		Respirations/min	(9-20 resp/min) inclusive
Temperature		Degrees Celsius	36-37.5*C (both inclusive)
Abdominal Palpatio			
1	General appearance of the uterus: For example is it soft on palpation? Or tender/painful? Please consider this when the woman is **not** having a contraction)		
2	Lie:		
3	Presentation		
4	Position		
5	Engagement: Is the presenting part engaged? (Please circle answer)		YES / NO
6	Measurement:	Units of measurem	Normal range
Fetal Heart rate auscultation		bpm	110-160bpm (inclusive)

Study participant ID:	

	Assessment of well being	Yes	No
1	Is the Blood pressure within normal limits?		
2	Is the maternal pulse within normal limits?		
3	Is the temperature within normal limits?		
4	Is the respiratory rate within normal limits?		
6	Is the fetal heart rate within normal limits?		
7	Is the colour of the liquor clear/light pink?		
8	Is the smell of the liquor neutral or without smell?		
9	Is the uterus soft and not painful on palpation? (when the women is not having a tightening)		
10	Does the woman report normal fetal movement?		

*If there are abnormal results, please advise her to come to hospital for further assessment

Does the woman report any other concerns? If any, please describe below

	YES	NO
Is she having any tightenings?		
If yes, describe:		
Is the woman feeling strong and regular contractions? At least 3:10 strong and regular lasting at least 60sec		

If no strong and regular contractions, then arrange follow up appointment in 24 hours, advise her to complete the symptoms diary and remind her about hygiene measures (hand wash, bath and shower ok, no sexual intercourse, healthy diet and adequate hydration). Also give her information about signs of concern and who to call if any worries.

If she is having strong/regular contractions, that would suggest she might be in established labour, advise her to go to Hospital/Birth centre.

Print name…… Signature……..

Date…….(DD/MM/YY) Time: ……(HH:MM)

Study participant ID:	

Visit 3: Approximately 72 hours since the rupture of membranes

PHYSICAL EXAMINATION AND VITAL SIGNS: This is to be carried out and documented in this form by midwife looking after her).

Please keep this booklet with the woman's notes.

Date :……(DD/MM/YY) Time: …… (HH:MM)

Date of rupture of membranes……(DD/MM/YY) Time of rupture of membranes:……(HH:MM)

Duration of SROM so far: (hours and min)……

Have you reviewed the participant's diary?	YES	NO
Are her own observations satisfactory?	YES	NO
If no, please describe		

Physical examination	measurement	Units of measurement	Normal range
Blood pressure		mmHg	Systolic (139-90mmHg) inclusive Diastolic (89-50mmHg) inclusive
Maternal pulse		bpm	(51-100bpm) inclusive
Respiratory rate		Respirations/min	(9-20 resp/min) inclusive
Temperature		Degrees Celsius	36-37.5*C (both inclusive)
Abdominal Palpatio			
1	General appearance of the uterus: For example is it soft on palpation? Or tender/painful? Please consider this when the woman is **not** having a contraction)		
2	Lie:		
3	Presentation		
4	Position		
5	Engagement: Is the presenting part engaged? (Please circle answer)	YES	NO
6	Measurement:	Units of measurement	Normal range
Fetal Heart rate auscultation		bpm	110-160bpm (inclusive)

Study participant ID:	

	Assessment of well being	Yes	No
1	Is the Blood pressure within normal limits?		
2	Is the maternal pulse within normal limits?		
3	Is the temperature within normal limits?		
4	Is the respiratory rate within normal limits?		
6	Is the fetal heart rate within normal limits?		
7	Is the colour of the liquor clear/light pink?		
8	Is the smell of the liquor neutral or without smell?		
9	Is the uterus soft and not painful on palpation? (when the women is not having a tightening)		
10	Does the woman report normal fetal movement?		

*If there are abnormal results, please advise her to come to hospital for further assessment

Does the woman report any other concerns? If any, please describe below

	YES	NO
Is she having any tightenings?		
If yes, describe:		
Is the woman feeling strong and regular contractions? At least 3:10 strong and regular lasting at least 60sec		

If no strong and regular contractions, then remind her about the IOL at 96h and when to get there, advise her to complete the symptoms diary and remind her about hygiene measures (hand wash, bath and shower ok, no sexual intercourse, healthy diet and adequate hydration). Also give her information about signs of concern and who to call if any worries.

If she is having strong/regular contractions, that would suggest she might be in established labour, advise her to go to Hospital/Birth centre.

Print name…… Signature……..

Date…….(DD/MM/YY) Time: ……(HH:MM

Study participant ID:	

CARE IN REGARDS TO THE VAGINAL EXAMINATIONS

WOMEN ALLOCATED TO MINIMAL VAGINAL EXAMINATIONS/ONLY WHEN NECESSARY

A low vaginal swab should be taken prior to the first vaginal examination (including those performed during the process of IOL)

This swab should be labelled as swab 0 and with the participant ID number, date and time. Swabs should be kept in the fridge for the researcher to collect

Women will have a vaginal examination to confirm onset of active labour. Onset of active labour = Regular and strong contractions (3-4:10min, lasting at least 60 seconds and/or a cervical dilatation of at least 4cm.

A swab should be taken after each vaginal examination (including those performed during the process of IOL) and labelled as swab 1, 2, 3…

And when a vaginal examination is taken should be recorded in the form attached below

Once they are in active labour, progress of labour will be assessed using external cues (contractions that gradually increase in frequency and intensity, women reporting to feel the urge to push, woman involuntarily pushing). The aim is that women will receive as little as possible examinations. For example avoiding situations where 2 professionals repeat an examination in a short period of time. The situations that may warrant a vaginal examination, are described in the following box. This list is not exhaustive, but is given as a guide:

- Foetal heart rate abnormalities
- Hyper-contractility (5 or more contractions in 10minutues)
- Lack of regular and strong uterine activity once active labour has been diagnosed earlier that would lead to suspect failure to progress: For example contractions that don't seem to be increasing in frequency or duration, or hypo-contractility (2 or less contractions in 10minutes) or irregular contractions or contractions that don’t last at least 60 seconds
- Any other concerns: for example excessive PV bleeding, significant meconium

Study participant ID:	

Register in the box below all the vaginal examinations including the ones during the process of induction

Have you taken swab "0" prior to the first vaginal examination? Yes/No

Ve order	Date _ _/_ _	Time _ _: __	Rationale (See code list below)	Cervical dilation (cm)	Swab taken after VE YES/NO
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					

Reasons to perform a vaginal examination:

(1) To assess Bishop score

(2) To insert prostaglandins due to process of induction

(3) Because the prostaglandin has fallen off/needs relocation

(4) Because of concerns during process of induction

(5) To confirm/diagnose active phase of labour

(6) Due to concerns with **"too little"** contractions (Hypo-contractility), contractions that don't seem to be increasing in frequency or duration, irregular contractions, weak contractions (duration less than 60seconds)

(7) Due to concerns with **"too many"** contractions (Hyper-contractility, 6 or more contractions in 10min)

(8) Heart rate abnormalities

(9) Excessive PV bleeding

(10) Assess progress of labour

(11) Other – When selecting other please specify reason on the table above

If you omitted a VE or more because you used external cues to assess progress of labour, describe external cues used:

Total number of vaginal examinations: | | Total number of omitted VEs | |

Study participant ID:	

Appendix 7: PIS (Observational study)

“A Pilot RCT on the management of prelabour rupture of membranes”

Observational study –looking at records only

-PARTICIPANT INFORMATION SHEET–

Introduction:

We are asking 100 women who are eligible to take part in the pilot clinical trial on the management of prelabour rupture of membranes at term but have decided not to take part, to allow us to look at the records and tests results of themselves and their babies'. This is to help us to find out about the medical results of labour and birth after women have broken their waters. This study does not require you to actively do anything. The researchers will collect the relevant and necessary information from your records and those of your baby as well as relevant tests results. Once we have collected your information we will code it, and then your name will never be linked with your information. Before you decide whether to take part, it is important for you to understand why the research is being done and what it is involved. You are free to decide to participate or not. If you choose not to take part, this will not affect the care you will receive from your midwives and doctors. Please take time to read the following information and discuss it with others if you wish. If anything is not clear, or if you would like more information, please contact Lucia Ramirez-Montesinos (the details are at the end of this leaflet).

Why is the study needed?

Because we need to find out what the current rates of normal birth, caesarean section, average number of vaginal examinations, maternal and neonatal infection are when women break their waters but labour doesn´t start straight away when women receive usual and routine care.

What happens once I enroll into the study?

If you are happy for us to look at your records you will need to sign the consent form that it is at the end of this leaflet.

What does taking part in this study involve?

This study does not require you to actively do anything. The researchers will collect the relevant and necessary information from your records and those of your baby as well as relevant tests results. The information will be coded, and your name will be removed from the research records (anonymized). We won´t collect any personal identifiable data.

Do I have to take part?

No, it is your choice. If you decide not to take part, the care that your midwife/doctor provides to you won't be affected. And your records won´t be checked by a member of the research team.

What will happen if I don't want to carry on with the study?

Once you have agreed to take part and signed the consent form, you are free to withdraw from the study at any time, without giving a reason. You will need to tell your midwife or doctor so they can let us know.

What are the possible benefits of taking part?

Taking part in this study will make a contribution to knowledge, science and women-centred maternity care. We would be very grateful if you could help us.

What are the possible disadvantages and risks of taking part?

There are no extra risks or disadvantages for you or your baby as you will receive the care that you would normally receive. All that is involved is, that the researchers will check your records and test results and those of your baby, and will collect the necessary information.

How will my information be kept confidential?

Anything that can be linked back to you, will be stored in a locked cabinet at the university and only members of the research team will have access to it for academic and research purposes. When the study results are published, all details will be anonymised. No-one will be able to identify you in any publicly available document.

Who is organising the study?

The study is undertaken as part of a doctorate research degree in Midwifery with the University of Central Lancashire.

Who has reviewed this study?

This study is being reviewed and supervised by a multidisciplinary team composed of Professor Soo Downe, Dr. Steve Beeton and a statistician Dr Helene Thygesen. It has also gained ethical and governance approval from the NHS, and the University of Central Lancashire.

What can I do if I am not happy with any aspects of the study?

You can contact the University officer for ethics at officerforethics@uclan.ac.uk and your concern will be sent to the chair of the ethics committee within 2 working days and you should expect to get a response within 2 weeks. **You can also contact PALS:** The patient Advice and Liaison Service (PALS) provides support for our patients, their families and carers. They can be contacted on: 01772 522972 or 01257 247280

Further information and contact details:

If you would like to gain any further information regarding this study, you can contact us. Our contact details are:

Lucia Ramirez-Montesinos (Chief investigator) **LRamirez-montesinos@uclan.ac.uk** **07897236172**

Soo Downe (Director of studies) **Sdowne@uclan.ac.uk**

Appendix 8: Consent form (Observational study)

CONSENT FORM FOR Observational study – "Just checking records and tests results"

Participant ID number:

	STATEMENTS	**Please Initial this box if you agree**
1	I confirm that I have read the information sheet dated 24th May 2016 version 2.0 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand and grant permission for relevant sections of the clinical records and test results of myself and my baby to be reviewed and used by the study team	☐
4	I agree for the placenta and membranes to be analysed if it is deemed necessary by the midwives and doctors and for the results to be accessed by the research team	☐
5	I agree to take part in the above study	☐

Participant's print name……Signature…….Date:_ _/_ _ /_ _

Name of person taking consent……Signature…….Date: _ _/_ _/_ _

Appendix 9: Study specific questionnaire results

Question		Expectant management and Minimal VEs N=10/10		Expectant Management and routine VEs N=8/11		Active Management and Minimal VEs N=7/10		Active Management and routine VEs N=8/10	
		N	%	N	%	N	%	N	%
Q1	Overall, I am **satisfied** with the care that I received by the midwives and doctors during the study (from the time I signed the consent form until my baby was born)								
	Totally disagree	0	0	0	0	1	14.29	0	0
	Mostly disagree	0	0	0	0	0	0	0	0
	Mostly agree	3	30	1	12.5	1	14.29	3	37.5
	Totally agree	7	70	7	87.5	5	71.43	5	62.5
Q2	Overall, I felt I was in a **good emotional place** during the time from when my waters broke till when I went into labour or was admitted to hospital								
	Totally disagree	0	0	0	0	0	0	0	0
	Mostly disagree	1	10	1	12.5	1	14.29	0	0
	Mostly agree	2	20	4	50	1	14.29	5	62.5
	Totally agree	7	70	3	37.5	5	71.43	3	37.5
Q3	Overall, I felt **mentally and emotionally capable** during the time from when my waters broke till I went into labour or was admitted to hospital								
	Totally disagree	0	0	0	0	0	0	0	0
	Mostly disagree	1	10	1	12.5	1	14.29	0	0
	Mostly agree	1	10	4	50	2	28.57	5	62.5
	Totally agree	8	80	3	37.5	4	57.14	3	37.5
Q4	Overall, I felt **physically capable** during the time from when my waters broke till when I went into labour or was admitted to hospital.								
	Totally disagree	0	0	0	0	0	0	0	0
	Mostly disagree	1	10	1	12.5	1	14.29	0	0
	Mostly agree	2	20	4	50	2	28.57	4	50
	Totally agree	7	70	3	37.5	4	57.14	4	50
Q5	I felt I was well looked after by the midwives during the time from when my waters broke till when I went into labour or was admitted to hospital.								
	Totally disagree	0	0	0	0	0	0	0	0
	Mostly disagree	0	0	0	0	0	0	0	0
	Mostly agree	2	20	2	25	2	28.57	4	50
	Totally agree	8	80	6	50	5	71.43	4	50

Question		Expectant management and Minimal VEs N=10/10		Expectant Management and routine VEs N=8/11		Active Management and Minimal VEs N=7/10		Active Management and routine VEs N=8/10	
		N	%	N	%	N	%	N	%
Q6	**Overall, I am satisfied with the management that I had (Expectant/Active management) for my labour**.								
	Totally disagree	0	0	0	0	1	14.29	0	0
	Mostly disagree	0	0	0	0	1	14.29	0	0
	Mostly agree	2	20	1	12.5	2	28.57	3	37.5
	Totally agree	8	80	7	87.5	3	42.86	5	62.5
Q7	**I think the number of vaginal examinations that I had during my labour was appropriate.**								
	Totally disagree	1	10	0	0	3	42.86	1	12.5
	Mostly disagree	0	0	1	12.5	1	14.29	1	12.5
	Mostly agree	2	20	3	37.5	0	0	1	12.5
	Totally agree	7	70	4	50	3	42.86	5	62.5
Q8	**I think the frequency of vaginal examinations that I had during my labour was appropriate**								
	Totally disagree	0	0	0	0	3	42.86	2	25
	Mostly disagree	0	0	1	12.5	1	14.29	0	0
	Mostly agree	3	30	3	37.5	0	0	1	12.5
	Totally agree	7	70	4	50	3	42.86	5	62.5
Q9	**I would have preferred to have more vaginal examinations**								
	Totally disagree	5	50	4	50	3	42.86	6	75
	Mostly disagree	3	30	3	37.5	1	14.29	1	12.5
	Mostly agree	2	10	1	12.5	0	0	0	0
	Totally agree	0	0	0	0	3	42.86	1	12.5
Q10	**I would have preferred to have less vaginal examinations during labour**								
	Totally disagree	4	40	5	62.5	6	85.71	6	75
	Mostly disagree	3	30	1	12.5	0	0	1	12.5
	Mostly agree	3	30	2	25	0	0	0	0
	Totally agree	0	0	0	0	1	14.29	1	12.5