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Monitoring the fetal heart for the assessment of fetal wellbeing

Systematic reviews of the evidence and the design, conduct and preliminary findings of a multi-centre randomised trial

THE ADCAR TRIAL

VALERIE SMITH

September 2010
DECLARATION

This thesis is submitted to The University of Dublin, Trinity College Dublin in fulfillment of the requirement for the higher degree by research of Doctor in Philosophy (PhD). It has not been submitted for a degree at this or any other university. I declare that the content is my own work unless otherwise acknowledged.

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Ms. Valerie Smith RGN, RM, BNS, BSc Midwifery (Hons), MSc (Research), PG Dip (Stats)
SUMMARY

The assessment of fetal wellbeing throughout pregnancy, labour and birth, is essential in achieving maternity care that optimises fetal outcomes. Monitoring of the fetal heart rate (FHR), using either intermittent auscultation (IA) (i.e. listening to the FHR at regular intervals using a Pinard stethoscope or hand-held Doppler device) or electronic fetal monitoring (EFM), (i.e. recording of the FHR by a special electronic machine) is one practice central to the assessment of fetal wellbeing.

Admission cardiotocography (ACTG), a form of EFM, is a routine screening test consisting of a twenty minute electronic recording of the FHR and uterine activity performed on women on admission to the labour ward or labour assessment room with signs of possible labour. The premise for the use of ACTG is that it may identify those babies, from the onset of possible labour, who might benefit from continuous EFM during labour.

Contemporary evidence, however, questions the efficacy of routine ACTG for all women. A meta-analysis of four existing trials comparing ACTG to IA of the FHR, reported in Chapter 3 of this thesis, found that women randomised to ACTG were at a significantly increased risk for caesarean section, continuous EFM during labour, fetal blood sampling during labour and epidural analgesia during labour. No differences in neonatal outcomes were found between babies of women receiving ACTG and babies of women receiving IA.

This thesis reports the design, conduct and preliminary findings of the ADCAR trial; a multicenter (n = 3), randomised trial comparing the effect of ACTG versus IA of the FHR in low risk women on admission to the labour ward or labour assessment room with signs of possible labour on a) caesarean section, b)
obstetric intervention and c) neonatal morbidity. Women eligible and consenting to participate in the trial are randomised to either ACTG or IA on a ratio of 1:1.

In September 2010, at the time of writing, the ADCAR trial remains ongoing. The findings provided in this preliminary report comprise an analysis of the first 1,906 women recruited to the trial for which data were extracted. These 1,906 participants represent one-third (33%) of the total sample estimated as necessary to complete the ADCAR trial (n = 5,776), and meet the requirements of the first interim analysis as detailed in the trial protocol. All reported findings are based on ‘intention to treat’ analyses.

The preliminary findings demonstrate no statistically significant difference between women randomised to IA and women randomised to ACTG in any of the twenty-nine reported maternal or neonatal outcomes, except in the obstetric intervention outcome of continuous EFM during labour. Women randomised to IA on admission to the labour ward or labour assessment room with signs of possible labour, are statistically significantly less likely to have continuous EFM during labour than women who are randomised to ACTG (675 [70.5%] versus 753 [79.0%]; RR 0.89, 95% CI 0.84-0.94).

As the ADCAR trial is ongoing and is currently underpowered to detect differences between the interventions, it is not possible to infer definitive cause and effect conclusions between the use of ACTG and IA, in low risk women. For this to occur, the ADCAR trial must continue to at least its second interim analysis (3,870 women participating) and then to full sample size recruitment (5,776 women participating) if indicated. Definitive conclusions might only be inferred when the trial is complete and the full results are known.
ACKNOWLEDGEMENTS

It is with great pleasure that I thank the many people who made this thesis and my PhD journey possible.

I am grateful first and foremost to the women, in the three study sites, who agreed to take part in the ADCAR trial. The trial’s preliminary report (as provided in this thesis) would not have been possible without their commitment to and participation in this important research study.

I wish to thank the Health Research Board, Ireland and The Department of Health and Children, Ireland for recognising the value of this important research study and for providing funding to support the conduct of the ADCAR trial.

I wish to extend my sincerest gratitude to my supervisor, Mr Declan Devane. His enthusiasm, his inspiration and his ability to explain things clearly and simply, helped make this PhD thesis an achievable reality. Throughout the three year period, a time that included huge personal tragedy for Declan, with the death of his beautiful two-year old son Cillian, he continuously provided me with encouragement, sound advice, good teaching, good discussion, and lots of good ideas. I would have been lost without him.

I wish to thank Professor Cecily Begley and Professor Mike Clarke, my co-supervisors. They equally motivate and inspire me. I thank them for their infinite knowledge, expertise, calmness, and commitment to my work, and especially thank them for the time they gave to reading drafts of this thesis.

I would like to extend a huge thank you to Judith and Elaine; two wonderful research assistants who were amazing and much valued for their help in keeping the ‘ball rolling’.

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I would like to thank the clinical staff, in the three study sites, for their enthusiasm and commitment to the ADCAR trial. I thank the midwives and doctors in the antenatal clinics for providing women with study information booklets and the midwives working on the labour wards for recruiting women to the ADCAR trial.

I extend my warmest thanks to my husband and friend, Senan; for his unwavering support, encouragement and belief in me. I especially thank him for the hours spent listening, for taking my ‘stress’ all in his stride, for turning even the most difficult days into, at the very least, ‘not so bad’ days, and for grounding me on earth anytime I was in danger of heading for space!!

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Lastly, and most importantly, I wish to thank my parents, Elizabeth and Val (deceased Feb 1997); for giving me life, raising me, teaching me, supporting me, and unconditionally loving me. To them I dedicate this thesis.
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Admission Cardiotocography (ACTG): A routine screening test consisting of a twenty minute electronic recording of the fetal heart rate and uterine activity performed on women on admission to the labour ward or labour assessment room.

Asphyxia: A condition or pathological state in which an extreme decrease in the amount of oxygen in the body tissues and organs, accompanied by an increase of carbon dioxide, leads to loss of consciousness or death.

Bias: Any influences on a study that might lead to inaccurate conclusions about a treatment or intervention, (i.e. make a treatment look better or worse than it really is). Bias can occur by chance or as a result of systematic errors in the design and execution of a study. High quality study design and conduct is required to reduce the possibility of bias.

Cardiotocograph (CTG): A paper printout, produced by a specially designed electronic monitor (the CTG machine), that graphically records the fetal heart rate and uterine contractions. The paper printout can be removed, stored and reviewed many years after the recording has taken place.

Confidence Interval (CI): A range of values that includes the true population value of a particular characteristic at a specified probability level (usually 95%).

Electronic Fetal Monitoring (EFM): Any method of electronically recording the fetal heart rate. EFM may be applied continuously throughout labour or intermittently for set periods of time.

Hypoxia: Diminished amounts of oxygen in body tissues. If a state of hypoxia persists it can lead to asphyxia.
Hypoxic Ischemic Encephalopathy (HIE): A condition caused by a deficient or decreased oxygen supply to the entire brain. HIE can be fatal. It can also lead to long-term neurological damage in the neonate; for example mental retardation, developmental delay, seizures and cerebral palsy.

Intermittent Auscultation (IA): A method of listening to (and counting) the fetal heart rate, at regular intervals, for a set period of time; usually for one full minute. IA may be performed using a hand-held device called a Pinard stethoscope, (a small trumpet-like device that is placed on a woman’s abdomen), or with a hand-held, battery operated, Doppler ultrasound device.

Likelihood Ratio: An estimate of how much a test result will change the odds of having a disease/outcome. It is the ratio of the probability of the specific test result in people who have the disease to the probability in those who do not. An LR > 1 indicates that the test result is associated with the presence of an outcome whereas an LR < 1 is associated with the absence of the outcome. The further the LRs are from 1 the stronger the evidence for the presence or absence of the disease.

Negative Predictive Value (NPV): The proportion of people with a negative test result who are correctly diagnosed as not having the disease/outcome.

Meta-Analysis: A method of data analysis in which the results from a group of individual studies, investigating the same treatment, are combined (pooled). Statistical techniques are used to synthesise the findings into a single estimate of a treatment effect.

Positive Predictive Value (PPV): The proportion of people with a positive test result who are correctly diagnosed as having the disease/outcome.
Relative Risk (RR) A summary measure which represents the ratio of the risk of a given event or outcome (e.g. caesarean section) in one group of subjects compared with another group. When the ‘risk’ of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, for example, a relative risk of 2 would indicate that those receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment.

Sensitivity: In diagnostic testing, sensitivity refers to the chance of having a positive test result when an individual has the disease or condition. A sensitivity of 100% means that all those with the disease or condition will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease or condition – this is called a ‘false positive’. To fully judge the accuracy of a test, its specificity must also be considered.

Specificity: In diagnostic testing, specificity refers to the chance of having a negative test result when an individual does not have the disease or condition. A specificity of 100% means that all those without the disease or condition will test negative, but this is not the same the other way around. An individual could have a negative test result yet still have the disease or condition – this is called a ‘false negative’. The specificity of a test is also related to its ‘positive predictive value’ (true positives) – a test with a specificity of 100% means that all those who get a positive test result definitely have the disease. To fully judge the accuracy of a test, its sensitivity must also be considered.

Statistical Heterogeneity: The variability or differences between studies, in a systematic review, in the estimates of effects. It is used to assess whether the observed variability in study results (effect sizes) is greater than that expected to occur by chance.
**Systematic Review**: A method of reviewing individual studies in which the evidence from individual studies is identified, appraised and synthesised, according to predetermined criteria.

**Thematic Analysis**: A method of data analysis that involves the identification of prominent or recurrent themes in the literature on similar topics. A synthesis of the findings of the different studies is performed using thematic headings.
Section I

Introduction
Chapter 1: Introduction

1.1 Introduction

Maternity care is unique in that care provided focuses not on one individual, but rather on two; the mother and her baby. Assessment of fetal wellbeing throughout pregnancy, labour and birth, is essential in achieving maternity care that is safe, competent and strives to optimise fetal outcomes. Monitoring of the fetal heart rate (FHR) is one practice central to the assessment of fetal wellbeing. Currently the two most common methods for monitoring the FHR are intermittent auscultation (IA) and electronic fetal monitoring (EFM) with a cardiotocograph (CTG) (Devane et al. 2005a; Alfirevic et al. 2006).

IA involves listening to the FHR at predetermined intervals using an acoustic device such as a Pinard stethoscope or a hand-held Doppler ultrasound device (Figure 1).

![Pinard Stethoscope and Doppler Ultrasound Device](http://www.medisave.co.uk and http://www.aurorabioscience.com.au)

Alternatively, a CTG provides for a continuous electronic recording and paper printout of the FHR and uterine contractions, using a specially designed electronic machine (Figure 2). The FHR may be recorded by external or internal means.

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External CTG uses ultrasound technology, where an ultrasound transducer, attached to the electronic monitor, is secured externally to a woman’s abdomen using purposively designed elastic belts. The FHR is detected using sonar waves and recorded on the paper printout. Maternal uterine contractions are recorded via a pressure transducer; a small disc, attached to the electronic monitor, and secured externally to a woman’s abdomen. Internal CTG involves attaching a small electrode (clip), internally to the fetal scalp. The membranes (amniotic sac) must have ruptured (either spontaneously or artificially) before the clip can be applied. The FHR is detected by the electrode, which is attached to the electronic monitor, and recorded on the paper printout.

Figure 2: The Electronic Fetal Monitor (CTG Machine)

‘Admission cardiotocography’ (ACTG) is a routine screening test consisting of a twenty minute (approximately) electronic recording of the FHR and uterine activity performed on women on admission to the labour ward or labour assessment room. The rationale for ACTG, considering that antenatal risk factors do not identify all babies that might die or suffer morbidity, is the identification of those babies, at the onset of labour, who might be at greater risk of intrapartum

2 Downloaded from Google images; ‘CTG machine’; http://www.gndmoh.com
fetal compromise and who might benefit from continuous EFM during labour (Arulkumaran and Jenkins, 2000, Impey et al., 2003, Alfirevic et al., 2006). Recent research however (Mires et al., 2001, Cheyne et al., 2003, Impey et al., 2003, Mitchell, 2008), highlights a lack of evidence of benefit supporting the use of ACTG in low risk pregnancy. Furthermore, and contrary to recommendations that ACTG should not be performed in low risk pregnancy (RCOG 2001; NICE 2007), a national survey on the use of intrapartum fetal heart rate monitoring found that ACTG was performed on all women by 96% (n = 21) of maternity units in the Republic of Ireland and only one unit restricted the use of ACTG for high risk pregnancy (Devane et al. 2007). Similar high rates of ACTG use (79%) were found in a survey of maternity units in England, Wales and Northern Ireland conducted by the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) in 1999-2000 (Maternal and Child Health Research Consortium 2001). This finding is reflected internationally with use ranging from 76% in Canada (Kaczorowski et al. 1998) to 84% in the USA (Curtin and Mathews 1998) to 100% in Sweden (Berglund and Nordstrom 2001; Holzmann and Nordstrom 2010). This high usage may, in part, reflect the influence of non-randomised studies that have provided conflicting evidence on the value of ACTG as a screening test for fetal compromise during labour in low risk women (Ingemarsson et al. 1986; Blix et al. 2005).

There have been repeated calls for a thorough evaluation of ACTG through adequately powered randomised trials (RCOG 2001). This evaluation would require a robust and fair assessment of ACTG compared to IA of the FHR on admission to the labour ward or labour assessment room in low risk women. The ADCAR trial (described below) will provide this evaluation and inform clinical decision-makers on the use of ACTG in low risk women.

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5 Although this national survey, performed in 2004 (published 2007), precedes the publication of the NICE (2007) recommendation, personal communication with midwifery managers and midwifery colleagues, working in different maternity units in the Republic of Ireland in 2010, has not indicated any change in the use of ACTG on all women during this time.
1.2 Aim of thesis

The aim of this thesis is to evaluate fetal heart monitoring for the assessment of fetal wellbeing.

The objectives of this thesis are:

1. To report the design, conduct and preliminary findings of the ADCAR trial; a randomised trial comparing the effect of ACTG versus IA of the FHR in low risk women on admission to the labour ward or labour assessment room with signs of possible labour on a) caesarean section, b) obstetric intervention and c) neonatal morbidity. The ADCAR trial is a two-group randomised trial. This design is the most reliable way to assess the relative effects of different interventions as it offers the best assurances that the results produced are due to the variables being studied (i.e. the interventions) and not any extraneous factors (Holmes 1988; Friedman et al. 1998).

2. Review the background literature associated with EFM use in maternity care. This will include a thorough and systematic review of the current evidence surrounding the use of ACTG

1.3 Scope of thesis

To add structure and direction, this thesis is subdivided into four distinct Sections, within which there are a total of eight chapters. Section I contains two chapters. Section I, Chapter 1, is this introductory chapter, which presents a brief background to the topic under investigation, the rationale for the current study and the aim of this thesis. Section I, Chapter 2, provides a review of the literature and presents background information specific to FHR monitoring in practice. Section II places the ADCAR trial in context with current evidence and contains two chapters. Section II, Chapter 3, presents an evaluation of ACTG for the assessment of fetal wellbeing and reports the conduct and findings of a systematic review and meta-analysis of four trials comparing ACTG to IA. Section II,
Chapter 4, presents a systematic review and thematic analysis of women’s and professional’s views of FHR monitoring in practice. Section III presents the design, conduct and preliminary findings of the ADCAR trial and contains three chapters. Section III, Chapter 5, presents the ADCAR trial’s research methodology and study methods. Section III, Chapter 6, presents the preliminary findings of the ADCAR trial (i.e. the findings of the first interim analysis conducted on the first one third of women recruited to the trial). Section III, Chapter 7, presents a discussion on the preliminary findings of the trial, acknowledging that until the full findings are analysed and presented, the final result will not be known. Section IV presents a summary of the thesis. It contains one chapter (Chapter 8). Recommendations for practice and research are offered.
Chapter 2: Fetal Heart Rate Monitoring in Practice

2.1 Introduction
This chapter, in providing the reader with background information, presents a literature review of associated aspects of FHR monitoring in clinical practice. A brief history of FHR monitoring to the development of EFM in the mid-twentieth century is provided. The physiology and features of the FHR are described and discussed with reference to EFM and the CTG trace. Cerebral palsy, obstetric litigation and their association with EFM are also discussed.

2.2 Historical background
The first written report describing audible fetal heart sounds dates back to 1650, when in a poem, French physician Philippe Le Gouste ridiculed his colleague, Marsac, for declaring that the fetal heart could be heard similar to the sound of a beating bell or mill clapper (Wrightson 2002). It was not until 1819, more than a century and a half later, that the practice of auscultation for detecting fetal heart sounds became a conceivable reality. Laennec, a physician working in Paris, invented the stethoscope in 1816 and described its use for chest auscultation in 1819 (UXL Newsmakers 2005). Kergeradec, a student of Laennec’s, using the same principles applied by Laennec for chest auscultation, used the stethoscope to detect fetal heart sounds in 1821. Kergeradec concluded that by listening to the FHR the health status of the fetus might be determined (Sureau 1996; Harrison 2004). Thus began the practice of monitoring the FHR for the assessment of fetal wellbeing.

The use of the fetal stethoscope, following refinement to the development of the Pinard stethoscope by the mid-nineteenth century (Seymour 1995), remained the prominent method of FHR auscultation up to the mid-twentieth century (Lewis and Rowe 2004a). By this time, with a decline in maternal childbirth complications and the emergence of new technologies that provided an alternative means to FHR monitoring, there was a shift in focus towards improving fetal
outcomes. The challenge of how best to listen to the FHR and what to listen for soon entered the realm of science, technology and practice (Arney 1982).

The use of electronic technology (CTG machines) that provided visual tracings of the FHR began in earnest in the 1950s and 1960s by researchers working independently in the United States (Edward Hon), Germany (Konrad Hammacher) and Uruguay (Roberto Caldeyro-Barcia) (Chester, 1998, Schmidt and McCartney, 2000). FHR patterns were, for the first time, visualised, studied and documented. Changing FHR patterns and their relationship to fetal outcomes were also studied and documented. As similar observations were made by all three researchers (and subsequently by others), the limits of FHR normality, varying FHR features, and abnormal FHR patterns were soon defined and categorised (Martin 1998; Chez et al. 2000). The first electronic fetal monitor manufactured using ultrasound technology was used clinically in the 1960s (Kennedy 1998). Mass production in light of its ease of use and assumed clinical benefit soon followed. By the 1970s, when electronic fetal monitors became commercially available, the foundations for current EFM were laid firmly. The use of EFM during labour rapidly spread and by 1998, in the United States, the CTG machine was used to monitor the FHR in 84% of all labours (Chez et al. 2000).

2.3 The fetal heart rate: control, characteristics, mechanism of decelerations, classification & interpretation
2.3.1 Control of the fetal heart rate
To ensure optimum fetal assessment and appropriate monitoring of the FHR for the assessment of fetal wellbeing during pregnancy, labour and birth, an understanding of factors that control and regulate the FHR is a requirement of all midwives. In addition, a prerequisite for monitoring the FHR in clinical practice is the ability to describe FHR characteristics, recognise FHR patterns and classify CTG traces.
Several intrinsic factors control and regulate the FHR. These include the sympathetic and parasympathetic systems of the autonomic nervous system, nerve receptors (chemoreceptors and baroreceptors) and components of the central nervous system (King and Parer 2000; Gibb and Arulkumaran 2008; Menihan and Kopel 2008). In addition, extrinsic factors such as uterine and placental blood flow and gas exchange further influence the control and regulation of the FHR.

2.3.1.1 The autonomic nervous system

The autonomic nervous system consists of the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). The PNS and SNS control the FHR by decreasing and increasing the FHR respectively, ensuring a balance that helps maintain a normal FHR. If one system is stimulated significantly beyond the other this will result in a respective decrease or increase in the FHR. The PNS when stimulated will cause a decrease in the FHR. This occurs because the vagus nerve, a component of the PNS that connects the fetal brain and heart, signals to the sinoatrial node to reduce the release of impulses responsible for initiating a heartbeat (Menihan and Kopel 2008). A reduction in these impulses will cause the FHR to decrease. Alternatively, the SNS, which has nerve endings in cardiac muscle, will, when stimulated, increase cardiac output with a resulting increase in the FHR. Factors that can stimulate the PNS include vaginal examination and fetal head compression, while abdominal palpation, vibration and stimulation of the fetal scalp, can stimulate the SNS (Menihan and Kopel 2008).

2.3.1.2 Nerve receptors

Chemoreceptors and baroreceptors are nerve receptors that cause the FHR to increase and decrease. Chemoreceptors, which are present in the aortic arch of the fetal circulatory system, respond to changes in circulating oxygen and carbon dioxide levels. If fetal blood oxygen levels decrease and/or carbon dioxide levels increase, the chemoreceptors respond by stimulating the PNS. This causes a PNS mediated slowing of the FHR (King and Parer 2000; Blackburn 2007; Menihan and Kopel 2008). Baroreceptors, which are present in the right atrium of the fetal
heart and in the aortic and carotid arteries, respond to changes in fetal blood pressure. If fetal arterial blood pressure increases, as can occur during compression of the umbilical cord (Blackburn 2007), baroreceptors respond and stimulate the PNS. The PNS responds by rapidly slowing the FHR. As arterial blood pressure falls, baroreceptor activity decreases, the PNS becomes less stimulated and there is a resulting increase in the FHR (Menihan and Kopel 2008).

2.3.1.3 Uterine-placental blood flow and gas exchange
Optimal transfer of oxygen and nutrients to the fetus and removal of waste products from the fetus are dependent on adequate maternal oxygenated blood flow through the uterine spiral arteries and into the intervillous space of the placenta (Figure 3). The transfer process, which takes place in the intervillous space, although facilitated by a number of mechanisms, primarily occurs through the processes of passive diffusion and active transfer (Menihan and Kopel 2008).

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4 Downloaded from Google Images; 'The Intervillous Space'; http://www.angelsinwaitingus.com/images/MMHE
Factors that compromise uterine-placental blood flow and the natural process of gas exchange will result in a deviation from the normal FHR. Examples of compromising factors include maternal medical disease such as cardiac disease, anaemia, and/or respiratory disease, for example, which can cause a reduction in oxygenated blood flow to the fetus. Placental abnormality or insufficiency might also result in an altered FHR pattern due to an inadequate transfer of gases, nutrients, and waste products to and from the fetus. In addition, during the uterine contraction phase there may be a decrease in the FHR due to a reduced blood flow caused by compression of the uterine and umbilical blood vessels.

2.3.2 Characteristics of the fetal heart rate

The introduction of the electronic fetal monitor in the 1960s allowed for the large-scale study of varying FHR features and FHR patterns. Since that time, a number of groups have attempted to formalise FHR monitoring with definitions of patterns, aetiology and recommendations for management (ACOG, 1995, SOGC, 1995, RCOG, 2001, NICE, 2007). In the United Kingdom (and Ireland)\(^5\) the Royal College of Obstetricians and Gynaecologists (RCOG) and the National Institute of Health and Clinical Excellence (NICE) provides guidance, to clinicians, on FHR monitoring and CTG interpretation (RCOG 2001; NICE 2007). The description of FHR features and CTG pattern interpretation in this thesis are based, therefore, on those provided by the NICE guidance unless otherwise stated.

Four key features, assessed with respect to uterine activity, characterise the FHR. These are the baseline FHR, baseline FHR variability, accelerations of the FHR

\(^5\) Currently, national guidelines for the care of women during pregnancy, labour and birth do not exist in Ireland. Members of the Institute of Obstetricians and Gynaecologists (IOG) in Ireland are, for the most part, associate members of the RCOG in England and are thus directed (but not governed) by the RCOG Green-Top and other guidelines. The IOG has established a review panel for the development of national guidelines in maternity care; however, at present maternity care in Ireland is governed by local/unit hospital policy. (Personal communication with the IOG, June 25\(^{th}\) 2010).
and decelerations of the FHR (see Table 1 for definitions). All four features are visualised on the CTG. If a Pinard or Doppler device is used for FHR auscultation the baseline FHR, accelerations of the FHR and decelerations of the FHR may be assessed. Baseline variability, a feature considered by some associated only with the CTG, cannot be assessed when performing IA (Feinstein et al. 2000). Countering this however, some clinicians argue that as individuals become skilled in the art and practice of auscultation, it is possible for them to hear and identify short-term variability; that is the moment at which the FHR significantly either speeds up or slows down between one beat and the next (California College of Midwives 1999). Using a Pinard stethoscope for IA allows for the auscultation of actual fetal heart sounds (i.e. the opening and closing of the ventricular valves) while ultrasound technology (Doppler or CTG) provides for FHR features as represented by deflected fetal heart sounds (Feinstein et al. 2000). This has significant clinical implications, because personal communication with midwifery colleagues has highlighted situations of normal CTG printouts in the presence of fetal intrauterine death (although I have not found evidence within the published literature of this). In such cases, the ultrasound technology, rather than recording the FHR, recorded the maternal pulse, possibly through deflection from the abdominal aorta blood vessel. It is important clinically, therefore, to establish the presence of the FHR with a Pinard, prior to applying ultrasound technology.

6A study conducted in Harare, Zimbabwe, compared four different methods of IA for monitoring the FHR; Intermittent EFM, IA with Doppler, IA with Pinard by a research midwife and IA with Pinard by the attending midwife. No significant differences in maternal or neonatal outcomes were found between the Doppler and Pinard groups; (Mahomed K., Nayoni R., Mulambo T., Kasule J. and Jacobus E. (1994) Randomised controlled trial of intrapartum fetal heart rate monitoring. BMJ: British Medical Journal 308, 497-500.)
Table 1: Features of the FHR

<table>
<thead>
<tr>
<th>Feature</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline FHR</td>
<td>The mean FHR level excluding accelerations &amp; decelerations. Normal rate for term fetus: 110-160 beats per minute (bpm)</td>
</tr>
<tr>
<td>Baseline Variability</td>
<td>Degree of fluctuation in the FHR baseline excluding accelerations &amp; decelerations (&gt;5bpm considered normal)</td>
</tr>
<tr>
<td>Acceleration</td>
<td>An increase in the FHR of 15bpm above the baseline for at least 15 seconds</td>
</tr>
<tr>
<td>Deceleration</td>
<td>A decrease in the FHR of 15bpm for at least 15 seconds</td>
</tr>
<tr>
<td></td>
<td>Classified as early (synchronous with contractions); late (the onset is at or following the peak of a contraction); variable (variable in shape, form and timing in relation to contractions)</td>
</tr>
</tbody>
</table>

Source: (Chandraharan and Arulkumaran 2007; Gibb and Arulkumaran 2008)

A FHR baseline between 110 and 160 beats per minute (bpm), with normal baseline variability (>5bpm) and the presence of accelerations generally indicates good fetal health and are considered reassuring features of FHR traces. Decelerations may represent reduced fetal oxygenation. If visualised on the CTG trace or heard on auscultation, FHR decelerations warrant careful review.

2.3.3 Mechanisms of fetal heart rate decelerations

A deceleration of the FHR is defined as a decrease in the FHR, from the FHR baseline, of 15bpm for at least fifteen seconds. A deceleration is described by one of three types; early, late or variable. The aetiology of each type of deceleration is different and each type is visually different on the CTG. An understanding of the mechanisms that cause decelerations is clinically important for a complete and proper assessment of fetal wellbeing.

2.3.3.1. Early decelerations

Early decelerations are typically associated with fetal head compression and generally occur at the same time as a uterine contraction, often presenting a mirror-image of the contraction on a CTG trace (Sweha et al. 1999). They more often occur in the latter first stage or in the second stage of labour where descent of the fetal head is more pronounced. As the fetal head becomes compressed,
during a uterine contraction, there is a rise in fetal intracranial pressure. This in turn may cause stimulation of the vagus nerve with a resultant slowing of the FHR (Sweha *et al.* 1999; Menihan and Kopel 2008), which resolves once the compression force of the uterine contraction begins to resolve. Early decelerations are usually considered benign and are seldom associated with fetal compromise (Sweha *et al.* 1999); however, they warrant careful review so as to differentiate them accurately from other types of decelerations.

### 2.3.3.2 Variable decelerations

Variable decelerations, often considered the most common type of deceleration associated with labour (Sweha *et al.* 1999), are thus named because they vary in shape, size and timing with respect to each other and with respect to uterine contractions. They are associated with compression of the umbilical cord (Sweha *et al.* 1999; Blackburn 2007; Gibb and Arulkumaran 2008) and are associated with reduced liquor volumes, preterm prelabour rupture of membranes and uterine contractions. The mechanism of this type of deceleration generally occurs as follows; compression of the umbilical cord occurs and the flow of blood through the umbilical vein is first interrupted; an autonomic nervous system response causes a brief rise in the FHR; as the compression persists the umbilical arteries become occluded; a baroreceptor initiated response causes a sharp and rapid fall in the FHR; as the compression begins to wane, arterial flow is first restored and there is a rise in the FHR; finally as pressure is lifted from the umbilical vein there may be a momentary acceleration of the FHR before return to normal baseline. The brief accelerations at either side of the decelerative phase are termed ‘shoulders’ and are considered a sign that the fetus is coping well with umbilical cord compression (Menihan and Kopel 2008). Variable decelerations are generally not associated with severe fetal compromise; however if the decelerations are persistent, and the depth of the deceleration is below 70bpm for longer than 60 seconds (Sweha *et al.* 1999) and/or there is a loss of ‘shoulders’ (atypical variable deceleration) then the risk of progressive hypoxia occurring increases.
2.3.3.3 Late decelerations

Late decelerations occur at or after the peak of a uterine contraction and the return of the FHR to normal baseline occurs some time after the contraction has ended. Late decelerations are considered an abnormal FHR feature and are indicative of fetal compromise and hypoxia. Late decelerations are associated with a decrease in uterine blood flow or placental dysfunction (Sweha et al. 1999) and indicate a lack of oxygenated blood reserve in the retroplacental space. In a normal healthy fetus, the fetus compensates for a reduction in oxygenated blood flow during a uterine contraction by relying on an excess supply of oxygenated blood in the retroplacental space. However, in an already compromised fetus these reserves are rapidly utilised and a late deceleration occurs. This deceleration continues beyond the contraction phase up to a time when full oxygenation has been restored. The duration of the late deceleration can vary and is largely dependent on the integrity of the blood flow to the fetus and the resilience of the fetus (Gibb and Arulkumaran 2008). Persistent late decelerations are indicative of fetal hypoxia and warrant some form of action such as, fetal scalp blood sampling to evaluate fetal blood pH and base levels and/or expedient delivery of the baby.

2.3.4 Classification of the fetal heart rate

In describing the FHR and/or the CTG trace, the four features of the FHR in addition to the presence or absence of uterine contractions must be noted. The National Institute of Health and Clinical Excellence (NICE 2007) categorises the FHR features as reassuring, non-reassuring and abnormal (see Table 2). Once all four features have been categorised, the CTG trace is then classified as normal, suspicious or pathological. A normal CTG trace is one in which all four features are considered reassuring. A suspicious CTG trace is one when a single feature is non-reassuring and the remaining features are reassuring. A pathological CTG trace is one in which two or more features are considered non-reassuring or one or more features are considered abnormal (NICE 2007). It must be noted, however, that these criteria and classifications are based on the FHR at term and caution
should be advised when classifying the CTG, using these criteria, for a fetus which is not at this gestation.

Table 2: Classification of FHR Features

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Variability</th>
<th>Decelerations</th>
<th>Accelerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reassuring</td>
<td>110-160bpm</td>
<td>≥ 5bpm</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>Non-reassuring</td>
<td>100-109bpm 161-180bpm</td>
<td>&lt;5bpm for 40-90 minutes</td>
<td>Typical variable with over 50% of contractions occurring for &gt; 90 minutes Single prolonged for up to 3 minutes</td>
<td>The absence of accelerations with an otherwise normal trace is of uncertain significance</td>
</tr>
<tr>
<td>Abnormal</td>
<td>&lt;100bpm &gt;180bpm</td>
<td>&lt;5bpm for &gt;90 minutes</td>
<td>Either atypical variables with over 50% of contractions or late decelerations, both for &gt; 30 minutes. Single prolonged for &gt; 3 minutes</td>
<td></td>
</tr>
</tbody>
</table>

Source: (NICE, 2007, p26)

In the absence of risk factors to the development of fetal compromise, IA is recommended for listening to the FHR to assess fetal wellbeing. Current guidelines (NICE, 2007) recommend performing IA of the FHR every 15 minutes, for one full minute after a contraction, during the first stage of labour and every five minutes and/or after every contraction during the second stage of labour. Criteria for conversion from IA to EFM during labour includes meconium stained liquor, abnormal FHR on IA, maternal pyrexia, fresh bleeding in labour and oxytocin use (NICE, 2007, p18). If continuous monitoring by EFM is used a comprehensive overview of the CTG (that is a review of all four features and uterine contractions) is recommended at least once every hour during labour. Following this review, the CTG is classified as normal, suspicious or pathological and a continuing plan of care is made based on this.

2.3.5 Interpretation of CTG
Accurate interpretation and classification of the CTG is fundamental to the provision of best care for women requiring EFM. Decisions for subsequent
pathways of care are often based on CTG recordings. A major concern highlighted in the literature and one that has implications for clinical practice is inconsistency in CTG interpretation and classification. In one study, for example, thirty-three CTG traces were considered by three experts (Ayres-de-Campos et al. 1999), and although the study reported an overall inter-observer agreement in classification as ‘fair-good’ ($K = 0.48$, 95% CI 0.34-0.62), poor agreement between the experts was reported for both suspicious and pathological traces ($Pa = 0.42$, 95% CI 0.34-0.50 and $Pa = 0.25$, 95% CI 0.14-0.36 respectively). A further study exploring 28 midwives’ interpretation of CTG demonstrated similar inconsistencies (Devane and Lalor 2005). This study examined both inter-observer and intra-observer agreements on three CTG traces. An overall inter-observer agreement of fair-good ($K = 0.65-0.74$) was reported with agreements highest in the classification of decelerations and lowest in the classification of baseline FHR variability ($K = 0.70$ and $K = 0.50$ respectively). The overall intra-observer agreements (with each midwife classifying the same CTG on two occasions approximately two hours apart) ranged from fair-good ($K = 0.48$) to excellent ($K = 0.92$). However, reported results demonstrated that 29% ($n = 8$) of the participating midwives changed their interpretation of the suspicious CTG between each of the two assessments. This is concerning and not only highlights the challenge of accurate CTG interpretation and agreement between clinicians but also the challenge of accurate CTG interpretation for individual clinicians themselves.

2.4 Cerebral palsy, litigation and the electronic fetal monitor

The introduction of EFM was surrounded by great excitement and a genuine belief that this new technology would result in a significant decrease in the incidence of neurological deficit in the infant and young child;

‘now that the appropriate technology is available the obstetrician may virtually eliminate intrapartum stillbirths and reduce morbidity associated with parturition....’ (Filshie 1974), p.36)
This enthusiasm lay in the perceived ability of the monitor to detect, through continuous visualisation of the FHR, any impending hypoxia or fetal compromise, thereby allowing for an expedient birth and prevention of potential subsequent neurological damage (Halligan et al., 1992, Nelson et al., 1996, Williams and Arulkumaran, 2004). Such was the faith in the fetal monitor at this time that a rapid and widespread introduction of EFM into clinical practice occurred prior to a proper evaluation of its efficacy and/or safety (Devane et al, 2005a).

Subsequent research and contemporary evidence, however, raises important doubts about the efficacy of EFM and its utility in preventing neurological damage. Since the introduction of EFM the reported incidence of cerebral palsy (CP) in the developed world has remained virtually unchanged ranging from 2 to 2.5 per one thousand live births (Rosen and Dickinson 1992; Lau and Lao 1999; Sankar and Mundkar 2005). In addition, and in parallel with the widespread use of EFM, there has been a significant increase in the incidence of caesarean section throughout Europe and worldwide (Brick and Layte 2009). In the United States, for example, the rate of caesarean section in 1996 was a reported 20.7%. By 2006, this figure had risen to 31.1%, reflecting a 50% increase over ten years (Martin et al. 2009) and representing more than double the recommended World Health Organisation rate of < 15% (World Health Organisation 1985). A recent systematic review and meta-analysis evaluating the use of continuous CTG as a form of EFM for fetal assessment during labour, highlights the associated link between EFM and caesarean section (Alfirevic et al. 2006). The findings of this review reported a significant increase in caesarean section in the CTG group when compared to a group receiving IA during labour (RR 1.66, 95% CI 1.3-2.13; 10 trials, 18,761 women). In addition, women in the continuous CTG group were

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7The incidence of CP must be viewed in the context of improved survival rates, due to medical advancement, of preterm and very low birth weight infants that previously would not have survived. These infants are at a greater risk of developing CP and as such could influence current CP prevalence and trends; (Pharoah P., Cooke T., Rosenbloom I. and Cooke R. (1987) Trends in birth prevalence of cerebral palsy. Archives of Disease in Childhood 62(4), 479-384.)
more likely to have a caesarean section for abnormal FHR pattern and/or acidosis (RR 2.37, 95% CI 1.88-3.0; 11 trials, 33,379 women). When a subgroup analysis, including low risk women only, was performed the relative risk for caesarean section for abnormal FHR pattern in the CTG group increased further (RR 2.31, 95% CI 1.49-3.59; 2 trials, 15,545 women). With respect to fetal outcomes, however, there was no significant difference in perinatal mortality between the groups (RR 0.85, 95% CI 0.59-1.23; 11 trials, 33,513 women) or in the incidence of cerebral palsy (RR 1.74, 95% CI 0.97-3.11; 2 trials, 13,252 women). The only reported beneficial effect of continuous CTG during labour for the fetus was an associated halving of the risk of neonatal seizures (RR 0.50, 95% CI 0.31-0.80; 9 trials, 32,386 women). The authors of the review, however, recommend caution, due to the absence of long-term follow up data, when interpreting the results of this outcome measure.

With respect to ACTG in particular, I identified two systematic reviews in the literature (Blix et al., 2005, Gourounti and Sandall, 2007). Both reviews compared the effect of ACTG versus IA of the FHR on labour and birth outcomes and both reviews included the same three randomised controlled trials (Mires et al., 2001, Cheyne et al., 2003, Impey et al., 2003). Blix et al (2005), in addition, included eleven observational studies in their review. The results of the meta-analysis, including all three randomised trials in Blix’s review, demonstrated that women randomised to ACTG were more likely to have epidural analgesia (RR 1.2, 95% CI 1.1-1.4; 2 trials, 2,679 women), continuous EFM during labour (RR 1.3, 95% CI 1.2-1.5; 3 trials, 11,256 women) and fetal blood sampling (RR 1.3, 95% CI 1.1-1.5; 3 trials, 11,256 women) compared to women randomised to IA. An increase in the likelihood of caesarean section and operative vaginal birth was also reported for the ACTG group, but this was not statistically significant. No significant difference in neonatal outcomes was reported between the IA and ACTG groups. Findings from the observational studies demonstrated that the prognostic value of the ACTG was generally poor for the various outcomes observed. The likelihood ratio for a positive test was above 10 for two of the
twenty-eight outcomes (caesarean section for fetal distress and Apgar score < 7 at five minutes after birth) in one included study and between 5 and 10 for four of the outcomes (operative birth for fetal distress, caesarean section for fetal distress, fetal distress, admission to the neonatal unit) in three included studies (Blix et al. 2005).

The specific aim of the 2007 review by Gourounti and Sandall was to determine whether ACTG in low risk women could improve neonatal outcomes (as reflected in Apgar score) and whether ACTG was associated with an increased incidence of instrumental birth and caesarean section (Gourounti and Sandall 2007). The meta-analysis performed in this review demonstrated that women receiving ACTG were at an increased risk for caesarean section (RR 1.2, 95% CI 1.00-1.41; 3 trials, 11,259 women) and instrumental birth (RR 1.1, 95% CI 1.00-1.18; 3 trials, 11,259 women) compared to women receiving IA; however, the relative risk for having an Apgar score of less than seven at 5 minutes post birth, although slightly higher in the ACTG group, did not reach statistical significance (RR 1.35, 95% CI 0.85-2.13; 3 trials, 11,259 women).

In summary, the advent of EFM during labour has not been associated with a reduction in the incidence of CP and neurological deficit, but has been accompanied by an increasing caesarean section rate. Current evidence, through systematic review, demonstrates more than a two-fold increase in the risk of caesarean section in women who are continuously monitored with the CTG during labour compared to women receiving IA of the FHR, with no differences in rates of CP and/or neurological deficit in the newborn being identified (Alfirevic et al, 2006). In recent decades and in parallel with the rising caesarean section rate, obstetrics and maternity care has seen an unprecedented rise in malpractice litigation. Repeatedly and consistently the most frequent factor associated with obstetric malpractice claims is abnormalities of the FHR and inaccurate interpretation of the CTG trace (Lochhead 1990; Symonds and Senior 1991;
In this sense, in maternity care, there is a strong association between the CTG, CP, and obstetric litigation.

2.4.1 CTG and cerebral palsy

CP is a generalised term for a group of disorders that affect movement and posture. It is associated with abnormalities or injury to the brain at some point during the early stages of fetal and/or neonatal development (Hall, 1989, Sankar and Mundkar, 2005, Fahey and King, 2005). An associated array of neurological and developmental disorders may, but do not always, accompany CP. These include mental retardation, epilepsy and varying degrees of visual, speech and hearing impairments (Hall 1989; Sankar and Mundkar 2005; Hutton and Pharoah 2006). CP is classified according to the number of limbs affected, e.g. hemiplegic, quadriplegic etc. and by the type of gross motor dysfunction involved, e.g. spastic, dyskinetic, ataxic and akinetic (Fahey and King 2005).

An association between CP, mental retardation and the birth process was first reported by an English surgeon, William Little, in 1862 (Hall 1989; Lau and Lao 1999; Blumenthal 2001). Since that time, however, contemporary research findings have not supported Little’s hypothesis and despite technological advances, the rate of CP has remained unchanged for over 30 years (Clark and Hankins 2003). Furthermore, since Little’s assertions, CP related to intrapartum events and the birth process is thought to occur in only 10% (approximately) of cases (MacLennan, 1999, Ross and Gala, 2002, Sankar and Mundkar, 2005). The remaining cases are associated with antenatal causes (in 80-90% of cases) and postnatal causes (MacLennan 1999; Sankar and Mundkar 2005). Causes of CP include perinatal infection, congenital malformation, placental abnormalities, prematurity, multiple births, placental abruption and fetal intracranial haemorrhage (Nelson, 2003, Jacobson and Hagberg, 2004, Fahey and King, 2005, Khalil and O'Brien, 2006).
A number of studies have attempted to explore the association between FHR patterns and a subsequent diagnosis of CP and/or adverse neonatal outcome. In one study (Nelson et al. 1996), the authors describe an association between an increased risk of CP and multiple late FHR decelerations (OR 3.9; 95% CI 1.7-9.3) and decreased FHR variability (OR 2.7; 95% CI 1.1-5.8). However, when the results were extrapolated to the entire population, only twenty-one children (representing 0.19%), of the total population who were expected to have these types of FHR patterns (n = 10,791), were subsequently diagnosed with CP. This provides an extremely high false-positive rate (99.8%) for these FHR patterns as an indicator of the development of CP. This is significant for clinical practice particularly in the absence of fetal blood sampling facilities, and in circumstances where decisional care-pathways are made on the basis of CTG findings alone. A second study (Larm a et al 2007) was performed to determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of FHR features for neonatal hypoxic ischemic encephalopathy (HIE). The results of this study, of 214 women, reported a sensitivity, specificity, PPV and NPV of 15.4%, 98.9%, 66.7%, and 89.4% respectively for bradycardia; 53.8%, 79.8%, 26.9%, and 92.6% respectively for decreased variability; 92.3%, 61.7%, 2.7%, and 82.9% respectively for a non-reactive trace; and 7.7%, 98.9%, 50.0%, and 88.6% respectively for all three abnormalities combined. These results suggest that although there is an increase in FHR abnormalities, the predictive ability of CTG to identify HIE, is low (Larm a et al. 2007). The clinical implications of these findings question the rationale for the continuing high rates of CTG use in practice. In particular, these findings have implications for the use of ACTG and provide a basis for the ADCAR trial. Considering that the rationale for ACTG is to detect those babies that might benefit from continuous EFM during labour, the findings from the above studies demonstrate a poor predictive ability of EFM (with CTG) to identify adverse neonatal outcomes even in the presence of abnormal features on the CTG.
In 1997, the Perinatal Society of Australia and New Zealand funded an international collaborative consortium called The International Cerebral Palsy Task Force. The aim of this Task Force was to bring together the current literature and examine the relationship between intrapartum events and CP. A series of conferences took place that resulted in the publication of an international consensus statement concerning CP and intrapartum events (MacLennan 1999). At the core of this statement was a set of defined criteria that provided evidence of an acute intrapartum hypoxic event suggestive of a causal link in subsequent neurological deficit (see Table 3 for criteria).

### Table 3: Table of Evidence

<table>
<thead>
<tr>
<th>Essential Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evidence of metabolic acidosis in intrapartum fetal umbilical cord blood or very early neonatal blood samples (Ph &lt; 7.00 and base deficit ≥ 12mmol/l)</td>
</tr>
<tr>
<td>• Early onset of severe or moderate neonatal encephalopathy in infants of ≥ 34 weeks’ gestation</td>
</tr>
<tr>
<td>• Cerebral Palsy of the spastic quadriplegic or dyskinetic type</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria that together suggest an intrapartum timing but by themselves are non-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A sentinel hypoxic event occurring immediately before or during labour</td>
</tr>
<tr>
<td>• A sudden rapid and sustained deterioration of the FHR pattern usually after the hypoxic sentinel event where the pattern was previously normal</td>
</tr>
<tr>
<td>• Apgar scores of 0-6 for longer than 5 minutes</td>
</tr>
<tr>
<td>• Early evidence of multi-system involvement</td>
</tr>
<tr>
<td>• Early imaging evidence of acute cerebral abnormality</td>
</tr>
</tbody>
</table>

Source: (MacLennan 1999, p. 1057).  

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8 The MacLennan (1999) statement is the latest international consensus statement on CP, however, an updated report on neonatal encephalopathy and CP was published by the ACOG in 2003 (ACOG, 2003). Neonatal encephalopathy and cerebral palsy: defining the pathogenesis and pathophysiology. Washington, D.C. ACOG). The criteria detailed in Table 3 have been modified by the ACOG in their report; however, they do not significantly change from the original consensus statement defined criteria.
In the conclusion of this paper, MacLennan refers to the consensus statement as an aid to a court of law for determining the probability of sufficient evidence to attribute the cause of CP to the labour and birthing process. However, despite the efforts of the Task Force and the consensus statement, the current system of malpractice litigation remains heavily reliant on the characteristics and expert interpretation of the CTG trace (Lochhead, 1990, Symonds and Senior, 1991, Davies, 2006).

2.4.2 CTG and obstetric litigation
In 2001, Eldon Boisseau stated that: ‘In terms of attributing liability for a child with cerebral palsy to the health care provider, no single instrument has proved a greater factor than the fetal heart monitor’ (Boisseau 2001), p.26).

This statement is supported by others in the literature (Lochhead 1990; Williams and Arulkumaran 2004; Davies 2006; Hankins et al. 2006), even though the fetal monitor communicates the FHR and does not predict or diagnose CP, a fact that is rarely considered in a medico-legal case involving a child with CP (Pateman et al. 2008). Currently in Ireland and internationally, obstetrics ranks first amongst all specialties for the number of claims and sums paid (Hepworth 2003; Greve 2008; STARSWeb 2008), with claims for a brain-damaged infant having the highest average payment (Greve 2008). Recently (April 2010) in Ireland, for example, a male child with CP, who sued the Health Service Executive through his mother, for negligence causing neurological deficit, was awarded 4.5 million euro in damages by the High Court (http://www.irishtimes.com/newspaper/Ireland/2010).

The prospect of litigation, whether that is the fear of libel action or the actual probability of such action, affects clinical practice (Symon 2000). An American survey (ACOG 2003), reported that 70% of obstetricians in the US faced litigation at some point in their career and 15% said they left the specialty because of litigation. In addition, the threat of litigation has led to what has been described as ‘defensive practice’. Defensive practice can include carrying out procedures or
ordering tests that might not necessarily be medically indicated but are performed for fear of, or protection against, possible legal action (Gilfix 1984; Bassett et al. 2000). Recent surveys provide evidence of, at least, a strong perception of defensive practice in maternity care. Symon for example, reported that 59% (n = 1,051) of midwives and 77% (n = 162) of obstetricians in his survey, thought that clinical practice was becoming more defensive (Symon 2000). A more recent UK survey, exploring midwives’ views on the rising caesarean section rate, reported that 63.7% (n = 114) of midwives felt the main reason for a rise in caesarean section rates was litigation and defensive medicine (Churchill and Francome 2009).

The first step in a medico-legal case is to establish causation. Once causation is established liability is then considered. This is generally concerned with the standard of care provided or the use of customary practice; that is care provided by a similarly qualified/competent practitioner or peer under similar practice circumstances (Gilfix 1984; Williams and Arulkumaran 2004). With respect to establishing causation in a CP case, the plaintiff’s representatives/witnesses will testify that the resultant CP was caused by hypoxia/asphyxia during labour and/or the birth process and that earlier intervention (e.g. caesarean section) might have prevented the adverse outcome. Much of causation in CP cases is based on the interpretation of the CTG trace and on the decisions that followed this (Symonds and Senior 1991; Williams and Arulkumaran 2004; Davies 2006). Data from the U.S. emphasise this point with 62.5% of possible causative factors, documented in newborn injury claims, related to a non-reassuring FHR trace (Davies 2006). Symonds and Senior report similar statistics. In their review of 110 cases of litigation for CP in the UK, 70% of claims were based on abnormalities in, and interpretation of, the CTG (Symonds and Senior 1991). Given the aforementioned difficulties with inter-observer and intra-observer agreement in classifying CTG traces (Ayres-de-Campos et al., 1999, Devane and Lalor, 2005), and the knowledge that only 10% of cases of CP are related to intrapartum events (MacLennan 1999; Sankar and Mundkar 2005), why are such a high proportion of
verdicts and payouts based on the CTG? One reason is that the CTG trace might be considered the only piece of objective documentary evidence related to the well-being of the fetus during labour, which can be examined in isolation from the clinical environment many years after the event (Bassett et al. 2000). Another suggested reason is consideration for the associated healthcare burden and healthcare costs for the parents and family of a neurologically damaged child, (Boisseau 2001; Williams and Arulkumaran 2004). A final reason relates to the high monetary awards available to plaintiff lawyers. With a lawyers’ fee ranging from 30-50% of the sum awarded to the plaintiff, CP litigation has become a lucrative business (Hankins et al. 2006).

2.5 Conclusion
This chapter has detailed important information associated with FHR monitoring in practice. It provided a brief overview of the history of FHR monitoring, from auscultation with the fetal stethoscope in 1821, to widespread use of EFM in the mid-late twentieth century. This has relevance because awareness of the history of FHR monitoring assists in setting the scene for the research study which forms a major part of this thesis: the ADCAR trial. Acknowledging this history provides an understanding for practitioners of the pathway of development in CTG technology leading to the widespread use of CTG, as a form of EFM, in contemporary maternity care.

Factors influencing the FHR, features of the FHR, characteristics and interpretation of the CTG were described in detail. This information is of paramount importance for midwives (and doctors) in clinical practice. To care appropriately for women undergoing FHR monitoring and to ensure an accurate assessment of fetal wellbeing using FHR indicators, knowledge of normal FHR characteristics, deviations from the norm and possible causation for deviations from the norm, is essential. As evidence of inconsistency and disparity in CTG interpretation was revealed, this further emphasises the requirement that midwives
understand FHR characteristics and the controlling influences on FHR features, so
that they can make an appropriate interpretation of FHR recordings.

The need for accurate CTG interpretation is evident from the discussion on
obstetric litigation. Research comparing the continuous use of CTG with IA of the
FHR provides a lack of evidence of benefit for improved neonatal outcomes in the
CTG group, yet low-risk women receiving continuous CTG during labour, are at a
greater risk of having a caesarean section than women receiving IA of the FHR. In
addition, the incidence of caesarean section is rising internationally. In parallel
with rising caesarean section rates there is a rise in obstetric litigation claims,
many of which are associated with CP. The CTG trace has become a central piece
of documentary evidence in these claims. A primary focus is inaccuracy in CTG
interpretation. This emphasises the requirement of midwives to have appropriate
knowledge and skills to ensure adequate assessment and accurate interpretation of
the FHR, in order to provide optimum maternity care.

This chapter has also described recommendations and guidance for FHR
monitoring in practice. Although NICE (2007) do not recommend ACTG for
low-risk women in any birth setting, a recent survey in Ireland reveals a
continuing, routine use of ACTG for women in all risk groups. Furthermore, due
to conflicting results from non-randomised studies and limitations in previous
trials (discussed fully in Chapter 3) there is a need to evaluate the use of ACTG
further in low risk women. The ADCAR trial is designed to meet this need. The
following Section, as a prelude to the description of the conduct and preliminary
findings of the ADCAR trial, places the ADCAR trial in the context of current
evidence. This is done through a systematic review evaluating the use of ACTG
for monitoring the FHR for the assessment of fetal wellbeing. It will ensure that a

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9 Although NICE jurisdiction does not cover Ireland, the maternity services in Ireland use the NICE
guidance for informing practice and for informing local policy, procedure and guideline
development.
comprehensive account of the most recent available evidence on ACTG is provided, prior to incorporating the findings of the ADCAR trial. To offer insight and understanding from a user’s perspective, a systematic review and thematic analysis of women’s and professionals’ views of FHR monitoring in practice is also provided.
Section II

The ADCAR trial in context
Chapter 3: Admission Cardiotocography for the Assessment of Fetal Wellbeing: A Systematic Review and Meta-analysis

3.1 Introduction

A systematic review seeks to answer a given research question by searching for, quality appraising and bringing together evidence meeting pre-specified criteria. By using methods to minimise bias, systematic reviews provide reliable evidence to help inform health care decisions. They are promoted by, among others, The Cochrane Collaboration, as an effective strategy for managing healthcare knowledge and for improving healthcare decision-making globally (www.cochrane.org).

In Chapter 2 (section 2.4), I discussed two earlier systematic reviews that examined the use of ACTG. The first of these reviews evaluated the prognostic value of the ACTG and its effectiveness compared with IA (Blix et al. 2005). Its findings demonstrated that women receiving ACTG were more likely to have epidural analgesia, continuous EFM during labour and fetal blood sampling during labour, compared to women receiving IA of the FHR on admission. No differences were identified between the groups in neonatal outcomes and the authors of the review concluded that there is no evidence of benefit to support the use of ACTG in low risk women (Blix et al. 2005). The second review sought to determine whether the ACTG in low risk women could improve neonatal outcomes (as reflected in Apgar score) and whether the ACTG was associated with an increased incidence of instrumental birth and caesarean section (Gourounti and Sandall 2007). The findings of this review report that women receiving ACTG were more likely to have a caesarean section and an instrumental birth compared with women receiving IA on admission. In addition, women with an ACTG were more likely to have an infant with an Apgar score of less than seven at five minutes, but the difference here was not statistically significant.
Since the publication of the above reviews, additional, potentially relevant studies may have been performed that might enhance the findings of the current reviews. In addition, an assessment of previous research, ideally through systematic review, on a specific topic has been recommended as the scientific and ethical justification for the conduct of a new trial as the trial can be designed, implemented and reported in the light of the current available evidence (Clarke et al. 2010). Furthermore, each of the three randomised controlled trials included in the two previous reviews have a number of limitations that warrant consideration when interpreting the generalisability of their findings, which are discussed below.

In the first of the three randomised trials, (Mires et al. 2001) the researchers performed subgroup analyses of 2,367 low risk women and concluded that ACTG, compared with IA, does not benefit neonatal outcome but leads to an increase in caesarean section and instrumental birth rates. The primary outcome in this trial was umbilical arterial acidosis defined as a cord pH < 7.20 with a base deficit of > 8.0 mmol/l, values not associated with immediate or long-term neonatal morbidity or mortality (Low et al. 1984). Concerns have also been expressed about changes that were made in relation to the design of the trial, in particular in relation to mid-trial changes in power calculations (Impey et al. 2003).

The second of the randomised trials, and the largest trial to date (Impey et al. 2003), randomised 8,580 women at low risk for ‘fetal distress’ during labour to ACTG or IA only. No differences in moderate to severe neonatal morbidity or perinatal mortality or in mode of birth were identified between the ACTG or IA groups. However, because a policy of active management of labour (AML) (that is early artificial rupture of membranes and the use of syntocinon if cervical dilatation is not progressing at 1 centimeter per hour) was practised in the study site, amniotomy was performed on women participating in the study whose membranes were intact prior to randomisation to the ACTG or IA group.
Therefore, as the researchers acknowledged, their findings are not generalisable to the majority of low-risk labours where the colour of the liquor is not known before commencing an ACTG.

In the third randomised trial (Cheyne et al. 2003), included in the two previous reviews, 312 low-risk women were randomised to ACTG or IA. The findings of this trial demonstrated no significant differences in rates of interventions or in mode of birth between the ACTG or IA groups. Significantly more women in the ACTG group received additional EFM but there was no difference between the groups in use of continuous EFM. The researchers advise caution in interpreting their findings due to erroneous recruitment assumptions on which the sample size was estimated and the small sample size.

Considering the limitations of the previous studies and the possibility of additional empirical evidence, an updated systematic review and meta-analysis evaluating the use of ACTG for assessment of fetal wellbeing, was performed.

3.2 Aim

The aim of this systematic review is two-fold:

1. To compare the effectiveness of ACTG versus IA of the FHR in women on admission to the labour ward or labour assessment room with signs of possible labour.
2. To evaluate the predictive ability of the ACTG for adverse labour and birth outcomes.

3.2.1 Criteria for considering studies for inclusion in review

3.2.1.1 Effectiveness of ACTG versus IA

All randomised trials comparing ACTG versus IA of the FHR were eligible for this review. For inclusion of randomised trials the control criterion includes a period of EFM of 20-40 minutes duration performed on women on admission to the labour ward or labour assessment room with signs of possible labour. The
intervention criterion includes auscultation of the FHR performed on women on admission to the labour ward or labour assessment room with either a Pinard stethoscope or a Doppler ultrasound device.

3.2.1.2 Predictive ability of ACTG
For evaluating the predictive ability of ACTG for adverse labour and birth outcomes, non-randomised studies were considered for inclusion in this review. For such studies to be eligible for this review, participants must have undergone a period of EFM performed on admission to the labour ward or labour assessment room with signs of possible labour lasting 20-40 minutes.

3.2.2 Types of participants
For both the effectiveness and predictive ability components of this review, participants are pregnant women at term (> 37 weeks gestation) presenting to the labour ward or labour assessment room with signs of possible labour. Both low- and high-risk women are eligible for inclusion.

3.2.3 Types of outcome measures
Outcome measures of interest for both the effectiveness and predictive ability components of this review include the incidence of caesarean section, obstetric intervention and neonatal morbidity.

Primary outcome measure
- Incidence of caesarean section

Secondary outcome measures
- Mode of birth
  o Spontaneous vaginal birth
  o Instrumental vaginal birth (Vacuum or Forceps)
  o Instrumental vaginal birth for abnormal FHR pattern
• Fetal monitoring during labour (continuous EFM; EFM ≥ 75% of time from diagnosis of labour to time of birth)
• Augmentation of labour
  o Artificial rupture of membranes
  o Use of syntocinon
• Analgesia during labour
  o Narcotic analgesia
  o Epidural analgesia
• Perinatal mortality (stillbirth or neonatal death in the first week of life)
• Apgar score ≤ 7 at 5 minutes post birth
• Metabolic acidosis (defined as arterial umbilical cord pH ≤ 7.05, BD ≥ 12mmols/l)
• Neonatal resuscitation
• Meconium stained liquor
• Admission to neonatal intensive care unit (NICU) or special care baby unit (SCBU)

3.3 Methods
3.3.1 Search and selection strategy
A combined search and selection strategy for potentially relevant papers for the effectiveness and predictive ability components of this review was performed. Computerised searches of MEDLINE (1966 – Jan 2010), CINAHL (1980 – Jan 2010), Maternity and Infant Care: MIDIRS (1980 – Jan 2010) and The Cochrane Central Registrar of Controlled Trials (CENTRAL) were conducted in January 2010 (see Table 4 below for details of computerised search and selection strategy). No restrictions were applied to any searches, however, due to the unavailability of translation services, only English language publications, where applicable, were selected for full text review. A manual search of reference lists of retrieved articles was also performed to identify any additional studies not captured by the electronic search. Contact and personal communication with
experts in the field was also performed to identify studies not previously captured and to identify unpublished or ongoing studies.

3.3.2 Data extraction and analysis

3.3.2.1 Effectiveness of ACTG versus IA

The extraction of data from the included randomised trials was performed using ‘The Cochrane Pregnancy and Childbirth Group’ Data Extraction Form (Appendix I). For each outcome measure of interest reported in the study’s findings, the number of events within each arm of the trial was entered into a data table in preparation for analysis. The analysis was based on the intention-to-treat principle. A meta-analysis was performed pooling the raw data for each outcome measure. For each outcome measure of interest, relative risks (RR) and 95% confidence intervals (95% CI) were calculated. Statistical heterogeneity was assessed using the $I^2$ statistic. Heterogeneity was regarded as substantial where $I^2$ was greater than 50%. In the absence of statistical heterogeneity, a fixed effect meta-analysis model was used. Where statistical heterogeneity was substantial, a random effects model was used (The Cochrane Pregnancy and Childbirth Group 2010). Forest plots of RRs with 95% CIs for each outcome measure from each study were produced. The computer programme RevMan (Version 5.0) was used for calculations.

3.3.2.2 Predictive ability of ACTG

For all non-randomised studies, the data for each outcome measure were extracted and entered into 2 x 2 data extraction tables. As in Blix’s review, the data extracted were classified according to the results of the ACTG and according to the presence or absence of an outcome measure in each individual study (for example instrumental birth or Apgar score ≤ seven at five minutes). For purposes of classification and report, the results of the ACTG were considered as negative or positive test results. A negative ACTG test result included the classification of the ACTG, within the individual study, as normal, reassuring or reactive. A positive ACTG test result included the classification of the ACTG, within the
individual study, as abnormal, non-reassuring, equivocal, suspicious, pathological or ominous. Likelihood ratios (LR) with 95% CIs for positive and negative test results were calculated. A LR statistic is considered clinically useful as it provides an indication of how many times more (or less) likely individuals with the condition of interest are to have a positive or negative test result compared to those individuals without the condition of interest (Deeks and Altman 2004a; Sierra et al. 2005). VassarStats (http://faculty.vassar.edu/lowry/clin1.html) was used to calculate the LRs and 95% CIs for each outcome measure of interest within each individual non-randomised study.

3.3.3 Quality assessment of included studies

3.3.3.1 Effectiveness of ACTG versus IA

The quality of all included randomised trials was assessed using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool (Effective Public Health Practice Project 2009). This tool was chosen because it provides a thorough assessment of potential sources of bias in randomised trials. Methodological components assessed within this quality assessment tool include selection bias, allocation bias, confounding, blinding, data collection methods, withdrawals and drop-outs, and analysis and intervention integrity (see Appendix II for a copy of the EPHPP Quality Assessment Tool). It should be noted, however, with respect to the assessment of blinding within the included randomised trials, that the nature of the interventions involved and the differences in the modus operandi of the ACTG and IA, make it impossible practically to blind either the clinician or the participating woman to her allocation. Therefore, a lack of blinding was not considered to undermine the quality of the included studies.

3.3.3.2 Predictive ability of ACTG

For quality assessment of all included non-randomised studies, the QUADAS tool was used (Whiting et al. 2003). This tool was designed for assessing quality specifically when reporting on diagnostic test accuracy studies. It includes a list of
fourteen questions which are answered ‘yes’, ‘no’ or ‘unclear’ for each study being assessed (see Appendix III for relevant items within the QUADAS tool).

3.4 Results

3.4.1 Description of included studies

For both the effectiveness and predictive ability component, following exclusion of duplicate papers across databases, thirty-four papers were identified for full text review. A review of the reference lists of retrieved papers identified an additional seven papers not captured by the electronic search (Ingemarsson et al. 1986; Sarno et al. 1989; Chan et al. 1994; Farrell et al. 1995; Black and Campbell 1997; Devane et al. 2005a). Personal communication with experts in the field identified one further paper (Sandhu et al. 2008) not captured by previous searches, for full text review. This resulted in the retrieval of forty-two papers for full text review (see Figure 4 for a flow chart of the search and selection strategy). Citation details for included studies are provided in Table 5 and Table 6 below; citation details for excluded studies are provided in the text following Table 4.
Table 4: Search and Selection Strategy

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</tr>
<tr>
<td></td>
<td>4</td>
<td>1 AND 2 NOT 'randomised controlled trial' [MeSH]</td>
<td>24</td>
<td>16</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>CENTRAL</td>
<td>1</td>
<td>'cardiotocography'</td>
<td>136</td>
<td>133</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>'auscultation' AND 'labor'</td>
<td>24</td>
<td>22</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>CINAHL 1980-2010</td>
<td>1</td>
<td>Tx cardiotoc*</td>
<td>168</td>
<td>162</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Tx auscultat*</td>
<td>985</td>
<td>973</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 AND 2</td>
<td>11</td>
<td>5</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>(MM 'fetal monitoring electronic +')</td>
<td>370</td>
<td>335</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>(MM 'labor') AND 2</td>
<td>10</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Tx labour admission test</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>6 AND 'randomised controlled trial'</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Following a full text review of each retrieved paper, twenty-four papers were subsequently excluded. The reasons for these exclusions were; three were systematic reviews (Blix et al., 2005, Alfirevic et al., 2006, Gourounti and Sandall, 2007) and one was a protocol for a systematic review (Devane et al. 2005a), six were narrative or descriptive reviews on FHR monitoring (Phelan, 1994, Feinstein et al., 2000, Goodwin, 2000, Wrightson, 2002, Borg, 2003, Poulaín and Mercier, 2008), five were not about ACTG (Ellison et al., 1991, Supplee and Vezeau, 1996, Black and Campbell, 1997, Blincoe, 2005, Amer-Wahlin and Dekker, 2008), three were either a letter, commentary or editorial (Rasmussen, 1998, Goddard, 2001, Alper, 2007), two were views studies (Munro et al., 2002, Blix and Ohlund, 2007), one explored influences on current practice (Lewis and Rowe 2004) and three were excluded because there was either insufficient data in the paper to construct 2 x 2 data tables (non-randomised studies only) or the study design, inclusion criteria or reported outcomes were non-comparable to included studies (Chan et al., 1994, Golditch et al., 1998, Blix et al., 2003). The remaining eighteen papers are included in this systematic review. Four of these reported on randomised trials comparing the ACTG with IA and fourteen are non-randomised studies evaluating the use of ACTG (Figure 4). The search and selection strategy led to the inclusion of one randomised trial and four non-randomised studies in this review that had not been included in the previously published similar review (Blix et al, 2005). Table 5 and Table 6 provide summary details of the included studies.
Figure 4: Search & Selection Strategy (1)
<table>
<thead>
<tr>
<th>Author &amp; Year published</th>
<th>Study setting &amp; Dates</th>
<th>Type of participants</th>
<th>No. of participants (analysis by Intention to Treat)</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impey et al (2003)</td>
<td>National Maternity Hospital, Dublin. 17/8/97-30/4/01</td>
<td>Low risk women in labour (clear liquor)</td>
<td>8628 (8580)</td>
<td>IA one full minute</td>
<td>ACTG of 20 minute duration</td>
</tr>
<tr>
<td>Mires et al (2001)</td>
<td>Obstetric Unit Dundee. Dates not provided</td>
<td>Low risk women in labour</td>
<td>3752 (3751)</td>
<td>IA with hand held Doppler device</td>
<td>ACTG of 20 minute duration</td>
</tr>
<tr>
<td>Cheyne et al (2003)</td>
<td>Midwives Birth Unit (MBU), Glasgow Royal Infirmary. Dates not provided</td>
<td>All women eligible for admission to MBU, i.e. healthy pregnant women</td>
<td>334 (312)</td>
<td>IA for a minimum of 60 seconds following a contraction</td>
<td>EFM of 20 minutes on admission to the MBU</td>
</tr>
<tr>
<td>Mitchell (2008)</td>
<td>Maternity Unit, South East England. 15/12/02-30/6/06</td>
<td>Women considered low-risk for fetal or maternal complications</td>
<td>582 (582)</td>
<td>IA in accordance with NICE guidance</td>
<td>ACTG of at least 15 minutes</td>
</tr>
</tbody>
</table>
Table 6: Summary Details of Included Non-Randomised Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study setting &amp; Dates</th>
<th>Type of study/participants</th>
<th>Number of participants</th>
<th>Classification of test (Classified by)</th>
<th>No. with positive test</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Farrell et al. 1995)</td>
<td>Ninewells Hospital Dundee, Scotland</td>
<td>Prospective; consecutive low-risk women, between 37-42 weeks gestation and no analgesia prior to ACTG</td>
<td>231 women</td>
<td>Normal, Abnormal (Clinician &amp; Independent Expert)</td>
<td>26/231 (expert)</td>
</tr>
<tr>
<td>(Ducey et al. 1990)</td>
<td>Winthrop University Hospital, New York</td>
<td>Retrospective; women presenting with singleton, cephalic presentation, ≥ 4cm dilated and birth within 24 hours</td>
<td>405 women</td>
<td>Normal, Abnormal (Unclear)</td>
<td>24/405</td>
</tr>
<tr>
<td>(Elimian et al. 2003)</td>
<td>University Hospital, Stony Brook, New York</td>
<td>Retrospective; consecutive low-risk women, between 37-42 weeks gestation, singleton and no analgesia prior to ACTG</td>
<td>426 women</td>
<td>Reassuring, Non-reassuring (Independent observer)</td>
<td>25/426</td>
</tr>
<tr>
<td>(Chua et al. 1996)</td>
<td>National University Hospital, Singapore</td>
<td>Prospective; low and high risk women, presenting with a live fetus, singleton, &gt; 37 weeks gestation and intact membranes</td>
<td>1092 women</td>
<td>Normal, Suspicious, Abnormal. (Unclear)</td>
<td>71/1092</td>
</tr>
<tr>
<td>(Sarno et al. 1990)</td>
<td>Women’s Hospital, Los Angeles</td>
<td>Retrospective; consecutive women, at term, singleton, cephalic and had internal EFM during labour</td>
<td>400 women</td>
<td>Normal, Abnormal (Independent observer)</td>
<td>90/400</td>
</tr>
<tr>
<td>(Kulkarni and Shroti 1998)</td>
<td>Sasson General Hospital, India</td>
<td>Prospective; women with high risk pregnancy, ≥ 37 weeks, ≥ 3cm dilated, cephalic</td>
<td>100 women</td>
<td>Reactive, Equivocal, Ominous. (Unclear)</td>
<td>42/100</td>
</tr>
<tr>
<td>(Sandhu et al. 2008)</td>
<td>India</td>
<td>Prospective; consecutive high-risk women presenting in active labour</td>
<td>150 women</td>
<td>Normal, Equivocal, Abnormal. (Unclear)</td>
<td>49/150</td>
</tr>
<tr>
<td>(Kushtagi and Naragoni 2002)</td>
<td>Kurstuba Medical College Hospital, Manipul</td>
<td>Prospective; consecutive low and high risk women admitted in labour</td>
<td>500 women 166 high risk 334 low risk</td>
<td>Reactive, Suspicious, Ominous. (Unclear)</td>
<td>67/500</td>
</tr>
<tr>
<td>(Blix and Oian 2001)</td>
<td>Hammerfest Hospital, Norway. 1996, 1997, 1998</td>
<td>Retrospective; low and high risk women in labour, singleton, &gt; 28 weeks gestation, birth within 24 hours</td>
<td>932 women</td>
<td>Reactive, Equivocal, Ominous. (Clinician)</td>
<td>49/932</td>
</tr>
<tr>
<td>Study</td>
<td>Hospital Location</td>
<td>Study Design</td>
<td>Participants</td>
<td>Outcome</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>-----------------------------------</td>
<td>--------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ingemarsson et al. 1986</td>
<td>Kandang Kerbau Hospital, Singapore</td>
<td>Prospective; low-risk women, &gt; 34 weeks, cephalic, birth within 24 hours of ACTG</td>
<td>1041 women</td>
<td>Reactive, Equivocal, Ominous (Independent observer)</td>
<td>59/1041</td>
</tr>
<tr>
<td>Farrell et al. 1998</td>
<td>Ninewells Hospital, Dundee, Scotland</td>
<td>Prospective; low risk women admitted in early labour, no opiate analgesia prior to fetal assessment</td>
<td>182 women</td>
<td>Normal, Abnormal (Unclear)</td>
<td>12/182</td>
</tr>
<tr>
<td>Ingemarsson et al. 1988</td>
<td>Kandang Kerbau Hospital, Singapore, 1985</td>
<td>Prospective; women, ≥ 34 weeks, cephalic, birth within 24 hours</td>
<td>766 women</td>
<td>Normal, Suspicious, Ominous (Independent Observer)</td>
<td>58/776</td>
</tr>
<tr>
<td>Sarno et al. 1989</td>
<td>Women's Hospital, Los Angeles</td>
<td>Prospective; women admitted in the latent phase of labour</td>
<td>109 women</td>
<td>Normal, Abnormal (Unclear)</td>
<td>21/109</td>
</tr>
<tr>
<td>Somerset et al. 1993</td>
<td>Princess Anne Hospital, Southampton, UK</td>
<td>Prospective; women &gt; 37 weeks gestation, singleton, cephalic, no known fetal abnormality</td>
<td>334 women</td>
<td>Normal, Suspicious, Ominous. (Unclear)</td>
<td>41/334</td>
</tr>
</tbody>
</table>
3.4.2 Quality criteria of included studies

3.4.2.1 Effectiveness of ACTG versus IA

A quality assessment was performed on each included randomised trial using the EPHPP quality assessment tool (Appendix II). An accompanying dictionary is provided to describe the components in the tool thereby assisting the reviewer to score each trial’s quality (Appendix II). Table 7 provides the results of the quality assessment. Following the quality assessment of each component, a global rating for each trial is provided as follows; ‘Strong’ indicates no ‘Weak’ ratings, ‘Moderate’ indicates one ‘Weak’ rating and ‘Weak’ indicates two or more ‘Weak’ ratings. As each included trial scored ‘Weak’ for ‘Blinding’ only, and, as discussed in full in Chapter 6 of this thesis, a lack of blinding was not considered to undermine the quality of the included studies, the global rating for each trial is ‘Strong’, indicating that all four trials were of ‘good’ methodological quality.

Table 7: Quality Assessment of Randomised Controlled Trials

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection Bias</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Allocation Bias</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Confounders</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Blinding</td>
<td>Weak</td>
<td>Weak</td>
<td>Weak</td>
<td>Weak</td>
</tr>
<tr>
<td>Data Collection Methods</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Withdrawals &amp; Drop-outs</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Analysis: Intention to Treat</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intervention Integrity: % of participants that received allocated intervention</td>
<td>80%-100%</td>
<td>80%-100%</td>
<td>80%-100%</td>
<td>60%-79%</td>
</tr>
</tbody>
</table>

3.4.2.2 Predictive ability of ACTG

The QUADAS tool was used to assess the quality of the included non-randomised studies. This tool was specifically designed to assess the quality of studies of diagnostic test accuracy (Whiting et al, 2003). Following the conduct of a four-round Delphi procedure to develop and refine the tool, the final tool consists of 14 items (Appendix III). The results of the quality assessment for
each included non-randomised study are presented in Table 8. No included non-randomised study received ‘Yes’ for all fourteen items in the tool. All studies except Somerset (1993) received either ‘No’ or ‘Unclear’ for item 14 (that is; ‘Were withdrawals from the study explained?’). Farrell (1995), Ingemarsson (1986) and Ingemarsson (1988) received the highest quality assessments, scoring ‘Yes’ to twelve (items 1-12), of the fourteen items within the tool. Blix and Oian (2001) scored the lowest receiving ‘No’ for four (items 10, 11, 13 and 14) items.
Table 8: Quality Assessment of Non-Randomised Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farrell 1995</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Ducey 1990</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Unclear</td>
</tr>
<tr>
<td>Elimian 2003</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Chua et al 1996</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
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<tr>
<td>Sarno 1990</td>
<td></td>
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<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
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<tr>
<td>Kulkarni &amp; Shrotri 1998</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Sandhu 2008</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kushtagi &amp; Naragoni 2002</td>
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<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Blix &amp; Oian 2001</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<td>Ingemarsson 1986</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>Farrell 1998</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Ingemarsson 1988</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Sarno 1989</td>
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<td>No</td>
<td>Yes</td>
<td>Unclear</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Unclear</td>
<td>Unclear</td>
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<tr>
<td>Somerset 1993</td>
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<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
</tbody>
</table>
3.4.3 Findings

3.4.3.1 Effectiveness of ACTG versus IA

Four trials with 13,225 women participating were included in the analysis of the included randomised trials, all in low-risk populations. The analysis was performed on the ‘intention to treat’ principle and included the whole population for each reported outcome measure within each individual study.

Women randomised to IA were statistically significantly less likely to have a caesarean section (RR 0.86, 95% CI 0.75-0.99; 4 trials, 13,225 women), continuous EFM during labour (RR 0.73, 95% CI 0.71-0.76; 3 trials, 12,639 women), epidural analgesia (RR 0.90, 95% CI 0.82-0.90; 2 trials, 4,063 women) and use of fetal blood sampling during labour (RR 0.81, 95% CI 0.72-0.90; 3 trials, 12,643 women). Fewer women in the IA group had an operative birth (vacuum or forceps only) but this was not significantly different to the ACTG group (RR 0.96, 95% CI 0.88-1.04; 4 trials, 13,225 women). Similarly, fewer babies born to women in the IA group had Apgar scores of ≤ 7 at 5 minutes (RR 0.96, 95% CI 0.66-1.40; 4 trials, 13,200 women), and fewer women in the IA group had their labour augmented with oxytocin infusion (RR 0.98, 95% CI 0.94-1.03; 4 trials, 13,208 women), but neither of these differences were significantly different. There was a statistically non-significant difference in the number of babies born to women in the ACTG group admitted to SCBU/NICU (RR 1.03, 95% CI 0.88-1.20; 4 trials, 13,215 women). Figure 5 provides the forest plot for the primary outcome measure; ‘Incidence of Caesarean Section’. The remaining forest plots for each reported outcome measure are provided in Appendix IV.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IA Events</th>
<th>Total</th>
<th>ACTG Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheyne 2003</td>
<td>9 164</td>
<td>11 148</td>
<td>11 148</td>
<td>2.8%</td>
<td>0.74 [0.31, 1.73]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impey 2003</td>
<td>158 4282</td>
<td>180 4298</td>
<td>43.8%</td>
<td>0.68 [0.71, 1.09]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mires 2001</td>
<td>165 1885</td>
<td>193 1866</td>
<td>47.2%</td>
<td>0.85 [0.69, 1.03]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitchell 2008</td>
<td>22 284</td>
<td>26 298</td>
<td>6.2%</td>
<td>0.89 [0.52, 1.53]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 6615 6610 100.0% 0.86 [0.75, 0.99]

Total events 354 410

Heterogeneity: Chi² = 0.21, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 2.14 (P = 0.03)

Figure 5: Incidence of Caesarean Section
3.4.3.2 Predictive ability of ACTG

Fourteen studies, including 6,668 women, were included in the analysis of the included non-randomised studies. Two studies report on high-risk populations only, (Kulkarni and Shrotri 1998; Sandhu et al. 2008), four studies report on low risk populations only (Ingemarsson et al. 1986; Farrell et al. 1995; Farrell et al. 1998; Elimian et al. 2003), and five studies report on mixed (i.e. high and low risk) populations (Ducey et al. 1990; Somerset et al. 1993; Chua et al. 1996; Blix and Oian 2001; Kushtagi and Naragoni 2002).

In the remaining three included studies (Ingemarsson et al. 1988; Sarno et al. 1989; Sarno et al. 1990) it is unclear if the populations were low risk, high risk or of mixed risk populations. The results of the analysis, for each reported outcome measure (a-h), in each included study, are presented in Table 9. The likelihood ratio and 95% CI for positive and negative ACTG tests for each reported outcome are provided.

Table 9: LRs and 95% CIs for Non-Randomised Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Positive Test: LR (95% CI)</th>
<th>Negative Test: LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Fetal Distress*</td>
<td>Elimian (2003) 5.1 (2.36-10.99) 0.8 (0.68-0.97)</td>
<td>Kulkarni &amp; Shrotri (1998) 2.6 (1.74-3.76) 0.3 (0.11-0.98)</td>
</tr>
<tr>
<td></td>
<td>Sandhu (2008) 3.7 (2.33-5.81) 0.4 (0.27-0.62)</td>
<td>Kushtagi &amp; Naragoni (2002) – Low Risk 11.4 (6.51-20.1) 0.4 (0.31-0.64)</td>
</tr>
<tr>
<td></td>
<td>Kushtagi &amp; Naragoni (2002) – High Risk 5.6 (2.94-10.78) 0.6 (0.41-0.76)</td>
<td>Blix &amp; Oian (2001) – Whole Population 3.2 (1.57-6.43) 0.9 (0.80-1.0)</td>
</tr>
<tr>
<td></td>
<td>Blix &amp; Oian (2001) – Low Risk 4.1 (1.92-8.68) 0.9 (0.75-0.99)</td>
<td>Ingemarsson (1986) – Part I 6.8 (3.55-12.93) 0.2 (0.04-1.31)</td>
</tr>
<tr>
<td></td>
<td>Ingemarsson (1986) – Part II 8.3 (4.71-14.75) 0.6 (0.44-0.88)</td>
<td>Ingemarsson (1988) 5.4 (2.93-10.0) 0.50-0.94)</td>
</tr>
<tr>
<td>b) Caesarean Section for Fetal Distress</td>
<td>Elimian (2003) 7.0 (3.30-14.64) 0.7 (0.58-0.94)</td>
<td>Ducey (1990) 35.0 (14.94-81.85) 0.4 (0.30-81.85)</td>
</tr>
<tr>
<td></td>
<td>Sarno (1990) 3.6 (2.60-4.92) 0.4 (0.20-0.66)</td>
<td>Sarno (1989) 5.4 (3.02-9.54) 0.2 (0.33-1.19)</td>
</tr>
<tr>
<td></td>
<td>Somerset (1993) 3.4 (1.68-6.90) (0.48-1.03)</td>
<td></td>
</tr>
<tr>
<td>c) Operative Birth for Fetal Distress</td>
<td>Chua (1996) 0.6 (4.01-9.90) 0.7 (0.61-0.85)</td>
<td>Kulkarni &amp; Shrotri (1998) 2.1 (1.39-3.13) 0.4 (0.13-1.0)</td>
</tr>
<tr>
<td></td>
<td>Farrell (1998) 3.5 (1.04-11.5) (0.68-1.09)</td>
<td></td>
</tr>
<tr>
<td>d) Apgar Score ≤ 7 at 5 minutes</td>
<td>Farrell (1995) - 1.1 (1.13-1.13)</td>
<td>Kulkarni &amp; Shrotri (1998) 1.8 (1.06-3.05) 0.5 (0.15-1.55)</td>
</tr>
</tbody>
</table>
Although I acknowledge that no definitively agreed definition exists for 'fetal distress' (please see section 3.5 below for further discussion) this is the term used by the individual studies, and as such, is the term used here.

The predictive ability of a positive ACTG for an adverse outcome was low for the majority of outcomes measures. Although a LR above 1 indicates that the ACTG test result is associated with the presence of the outcome measure and a LR below 1 indicates that the ACTG test result is associated with the absence of the outcome measure (Deeks and Altman 2004b), the LR should, for convincing evidence of predictive diagnostic ability, be above 10 (Blix et al. 2005).

The predictive ability of a positive ACTG was > 10 for fetal distress (LR 11.4, one study, subgroup analysis of low risk women; Kushtagi and Naragoni, 2002), caesarean section for fetal distress (LR 35.0, one study; Ducey et al., 1990), Apgar score of < 7 at five minutes (LR 19.1 and 11.0, two studies; Ducey et al 1990, Chua et al 1996, respectively) and meconium stained liquor (LR 20.2, one study; Ducey et al, 1990). For all other outcomes, the LR was below 10. In the most recent study (Sandhu et al.
which included high-risk women only, the LR for a positive ACTG test was 0.5 for Apgar score ≤ 7 at five minutes and between 3.1 and 3.7 for the other three reported outcome measures (fetal distress, admission to SCBU/NICU and perinatal mortality).

For a negative ACTG test, that is a normal ACTG, the LR values for all reported outcome measures were either 1 or less than 1, except in four outcome measures reported in five studies. For the outcome of Apgar score ≤ 7 at five minutes, four studies reported a LR of above 1 (Sarno et al. 1989; Farrell et al. 1995; Farrell et al. 1998; Sandhu et al. 2008). The LRs for this outcome reported by the four studies ranged from 1.1 to 1.2. For admission to SCBU/NICU and resuscitation at birth, Farrell et al. (1998), reported a LR for a negative ACTG test of 1.1 and 1.1 for each outcome respectively. Perinatal mortality was reported in one study with a LR of 1.3 (Sarno et al., 1990). Importantly, all the LRs for reported outcomes for a negative ACTG test are close to and only just above the level of 1 (range 1.1-1.3). As Blix et al., (2005) highlight, a LR close to 1 indicates that the negative test result is as likely present with the adverse outcome as it is in the absence of the outcome “rendering it a useless test” (Blix et al., 2005, p. 1599).

3.5 Discussion
The ACTG is a screening test consisting of a period of EFM lasting approximately twenty minutes performed on women with signs of possible labour on admission to the labour ward or labour assessment unit. The rationale for ACTG use is to identify those babies, from the onset of labour, that are at an increased risk for fetal compromise and therefore might benefit from continuous EFM during labour. In this review, no statistically significant differences were found in the meta-analysis of randomised trials between the IA and ACTG groups in any of the reported neonatal outcome measures. In contrast, women who received IA of the FHR on admission had a significantly reduced risk of caesarean section, continuous EFM during labour, epidural during labour and fetal blood sampling during labour compared with women who received ACTG. These findings demonstrate a
lack of evidence of benefit for the neonate in performing the ACTG in low risk women. In addition, these findings demonstrate that women receiving ACTG compared with women receiving IA on admission undergo increased obstetric interventions during labour.

The randomised trial is considered the 'gold-standard' in assessing the effects of interventions in healthcare research (Akobeng 2005; Silverman 2009). In conducting a systematic review that includes trials of different quality it would be usual to perform a sensitivity analysis including the findings of the 'good' quality trials only. As the overall quality of the four included trials was judged to be 'good' in this review, a sensitivity analysis based on trial quality, was not required. This increases the validity of the reported results in each individual trial.

Compared with the previous two published systematic reviews (Blix et al. 2005; Gourounti and Sandall 2007), the review includes an additional randomised trial (Mitchell 2008). The addition, in this review, of the findings from this trial support the findings of the previous two reviews; that is an increase in obstetric interventions in women receiving ACTG with no differences between the IA and ACTG groups in reported neonatal outcomes. However, as with the three previous trials, (see section 3.1), limitations associated with this additional trial require consideration. The sample size estimation for the Mitchell (2008) trial required the inclusion of 1,500 women in total. During the course of the study problems with recruitment and a reduction in research assistant hours due to a lack of funding resulted in the early termination of the study. A total of 582 women rather than the required 1,500 women were recruited to the study.

The results from the included non-randomised studies demonstrate, for the most part, a poor predictive ability of a positive ACTG test (that is an abnormal CTG trace) for adverse labour and birth outcomes. Only one study (Ducey et al. 1990), reported consistently high LRs for a positive ACTG test result in three outcome measures. In this study, the LR for a positive test for
caesarean section for fetal distress was 35.0, demonstrating that women who have an abnormal ACTG are 35 times more likely to have a caesarean section for fetal distress than women who have a normal ACTG. However, four other studies reported on this outcome measure (Sarno et al. 1989; Sarno et al. 1990; Somerset et al. 1993; Elimian et al. 2003) and none of them reported a LR of > 10. The other two outcome measures in Ducey’s study with high LRs were Apgar score ≤ 7 at 5 minutes (LR 19.1) and meconium stained liquor (LR 20.2). From the literature studied, it is unclear why the results found by Ducey et al differ so greatly from other included studies.

Reporting on the analysis of the non-randomised controlled studies, I agree with Blix et al, (2005), that interpreting the results might be problematic. The results of the outcome measure of ‘fetal distress’ for example, should be considered with caution. As there is no universally agreed definition for ‘fetal distress’, the diagnosis of fetal distress can be subjective and potentially will differ between individual clinicians and individual maternity units. Not all studies that reported on this outcome measure provided a definition for ‘fetal distress’ in their study, making me uncertain if the results presented are comparable across the included studies.

Compared to the previous review that included non-randomised studies (Blix et al, 2005), this updated review included an additional four non-randomised studies (Kulkarni and Shrotri 1998; Blix and Oian 2001; Kushtagi and Naragoni 2002; Sandhu et al. 2008). The addition of these four studies supports the findings of the previous review and provides further evidence of a poor predictive ability of abnormal ACTG for adverse labour and birth outcomes.

3.6 Conclusion
In conclusion, this systematic review and meta-analysis provides an up-dated evaluation on the use of ACTG. It provides the current state of the evidence on ACTG and supports previous findings that there is a lack of evidence of benefit for ACTG in low-risk women. This systematic review also highlights
a number of limitations associated with previous trials comparing ACTG with IA in low risk women. As a result of this, there is a need for further research evaluating the ACTG, through adequately designed randomised trials. The ADCAR trial has been designed to provide this evaluation. Section III of this thesis, reports on the methodology, conduct and preliminary findings of the ADCAR trial.
4.1 Introduction

In evaluating healthcare interventions for evidence based healthcare, the thoughts, views, perspectives and experiences of individuals directly concerned with those interventions are important. This is because exploring individual perspectives can offer insight and understanding on healthcare provision that might not be captured by traditional studies, that is experimental research, which focuses primarily on clinical outcomes. The findings of the previous chapter demonstrate that there is no evidence of benefit for ACTG compared to IA of the FHR in low risk women, yet ACTG use for low risk women, remains widespread (Kaczorowski et al. 1998; Devane et al. 2007; Holzmann and Nordstrom 2010).

Considering FHR monitoring from the perspective of the people that it affects, that is women and professionals, might prove advantageous as it may provide insight and understanding, from a user’s perspective, on the use and choice of FHR monitoring methods in practice. In addition, it may offer some explanation for continuing practices that are contrary to current evidence. For these reasons, this chapter explores FHR monitoring during labour from the view, perspective and experience of those directly involved; that is, women and professionals.

4.2 Aim

This chapter seeks to offer insight and understanding, through summary, aggregation and interpretation of findings from studies that report on women’s and professionals’ views, experiences and/or perspectives, (hereafter referred to as ‘views’ studies) on FHR monitoring during labour.
The objectives of this chapter include:

1. To explore attitudes to and preferences for FHR monitoring in clinical practice.
2. To explore reasons why EFM might remain widespread in low-risk women contrary to current recommendations.
3. To identify barriers to or facilitators for implementing evidence-based care, with respect to FHR monitoring, in clinical practice.

4.3 Methodology

As discussed in Chapter 3 (section 3.1), systematic review is a research method that compares individual research studies on similar topics and summarises their findings in one place. Traditionally, systematic reviews have focused on quantitative research studies that explore cause and effect relationships between different healthcare interventions. They are more often limited to reports of randomised and quasi-randomised trials, with pooling and statistical analysis (meta-analysis) of study results (Goldsmith et al., 2007). Increasingly, however, consideration is being given to synthesising the findings from qualitative enquiry. Although the methodology for synthesising this type of evidence remains less developed than methods for synthesis of quantitative enquiry (Dixon-Woods et al., 2001, Dixon-Woods et al., 2005, Walsh and Downe, 2005, Bondas and Hall, 2007), examples of such syntheses do exist in the literature (Garcia et al., 2002, Lucas et al., 2007a, Lakshman et al., 2009). Qualitative data synthesis, however, is not without criticism; the most significant of which is concern over its potential to destroy the integrity of individual studies (Sandelowski et al. 1997). In this sense, summarising qualitative accounts might stifle the interpretative and creative aspects of individual studies that are specific to a particular context, time and group of people (Sandelowski et al., 1997, Dixon-Woods et al., 2001, Dixon-Woods et al., 2004, Thomas and Harden, 2008). In contrast, advocates of systematic reviews of qualitative enquiry assert the more in-depth informative value, of summarising evidence on a particular topic, through qualitative data synthesis. The benefit of this type of synthesis is in the potential to identify particular views, experiences, priorities and concerns.
not identified by traditional systematic reviews which focus exclusively on clinical outcomes. This type of evidence, either on its own or incorporated into the findings of systematic reviews of intervention studies, may prove crucial to the successful implementation of interventions, new practices and may have implications for future research (Dixon-Woods et al., 2001, Dixon-Woods et al., 2006, Goldsmith et al., 2007).

In summarising evidence from ‘views’ studies, I was aware that such studies, in addition to using traditional qualitative methods such as interviews, might also use quantitative methods, such as questionnaires and surveys. A thorough review of the literature, in addition to consulting experts in the field of data synthesis, was performed to identify a framework or an established approach for summarising evidence of this type. Although the search revealed limited information on synthesising the findings from ‘views’ studies, some advances in combining evidence from qualitative and quantitative research have been made (Roberts et al. 2002; Popay and Roen 2003; Thomas et al. 2003; Goldsmith et al. 2007; Lucas et al. 2007; Lakshman et al. 2009). Of particular interest to my research into women’s and professionals’ views, was a report by Thomas et al. (2003). This report, published by the Evidence for Policy and Practice Information and Coordinating (EPPI) Centre, at the Institute of Education in London, describes the findings of two systematic reviews exploring healthy eating in young children. One of the two reviews detailed a synthesis of children’s views on healthy eating that included both qualitative and quantitative studies. The framework used by the EPPI-Centre in their review assisted, therefore, in providing a guide to my review of women’s and professionals’ views of FHR monitoring during labour.

4.3.1 Search and selection strategy
The aim of strategic searching is to locate and include all available and relevant studies in the review. In conducting a review of ‘views’ studies, Thomas & Harden (2008) argue, that it may not be necessary to locate every available study. This is because the synthesis of data depends not on the
number of studies, but rather on the range of concepts found in the studies and whether these concepts are in agreement or not. In my review however, I developed a search strategy with the aim of locating and including all available and potentially relevant studies, subject to certain constraints such as publication in English. Although contradictory to Thomas & Hardens' opinion, I believed that this search strategy would reduce bias in that the potential for missing important data would be reduced.

The electronic databases of MEDLINE (1966 - Jan 2010), CINAHL (1980 - Jan 2010), EMBASE (1974 - Jan 2010) and Maternity and Infant Care: MIDIRS (1971 - Jan 2010) were searched. A keyword search was performed using the words; 'fetal monitoring', 'labour', 'pregnancy' 'perceptions' and 'views'. These were combined using the Boolean operand 'AND'; (for example, #1 = 'fetal monitoring' AND 'views'; #2 = #1 AND 'pregnancy'). Papers were then selected for full text review based on title or on title and abstract. Reference lists of retrieved full text papers were examined to identify potentially relevant studies not captured by the electronic search. Due to the unavailability of language translators all searches were limited to English language publications. Figure 6 provides full details of the search and selection strategy.

4.3.2 Inclusion/exclusion criteria

A challenge with qualitative synthesis is determining which studies are really about the same phenomenon, event or experience and thus relevant for inclusion in the review (Sandelowski et al. 1997; Dixon-Woods et al. 2001). In addition, methodological comparability, when exploring 'views' about a phenomenon or event, might pose a problem as the methods used in exploring the same phenomenon may vary greatly (as discussed in section 4.3 above). One way of overcoming this is to compare studies on broad surface parameters such as their conceptual underpinnings rather than on research design or methods (Sandelowski et al. 1997).
The inclusion criteria for this review were based on the aim of the review. All studies, irrespective of study design, whose aim was to explore and report on women’s and professionals’ views, experiences or attitudes towards any method of FHR monitoring during labour were included. A total of eighteen studies (nine on women’s views and nine on professionals’ views) were identified and selected for inclusion in this review. Table 10 and Table 11 provide summary details of the characteristics of included studies.

4.3.3 Quality assessment

In conducting systematic reviews of studies of the effects of interventions, a quality appraisal of individual studies is required to reduce the possibility of bias and a myriad of checklists are available to do this. However, in conducting a review inclusive of qualitative reports, the diversity of qualitative study designs makes quality assessment difficult. The difficulty lies in determining what ‘good’ qualitative research is or should be like (Dixon-Woods et al. 2006). For this reason, the feasibility or worth of quality appraisal when synthesising data from qualitative enquiry has been debated in the literature (Dickersin et al., 2004, Harden et al., 2004, Walsh and Downe, 2005).

In keeping with the framework used by the EPPI-Centre, I performed a quality assessment of each included study in this review. The EPPI-Centre uses twelve criteria for assessing the quality of studies in their review. These twelve criteria were adapted and used for assessing the quality of the studies included in this review of women’s and professionals’ views of FHR monitoring during labour.

4.3.4 Data extraction

Data extraction was based on the review question; that is women’s and professionals’ views of FHR monitoring during labour. It required a careful line by line review, immersion in, and a breakdown of each included study’s findings. Although labour intensive, this process was essential because the reports on the included studies varied in writing styles and publication
formats. By carefully deconstructing each study's findings, I was able to determine and retrieve the relevant data to meet the aim of the review. Data extraction tables (see Table 10 and Table 11) were designed and predetermined prior to the data extraction process. These tables allowed me present each study in a standard format and facilitated comparisons and contrast between studies, and summary aspects of the review.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Aim</th>
<th>Participants and study location</th>
<th>Key findings reported by authors</th>
<th>Key themes identified by reviewer</th>
</tr>
</thead>
</table>
| (Dulock and Herron 1976) | To investigate if monitoring during labour adversely affects the childbirth experience | 71 women > 34 weeks filled in antenatal questionnaire; 31 women who had fetal monitoring during labour were interviewed on day 2 or day 3 post birth. Moffitt Hospital, San Francisco | Postnatal Interviews, n = 31. 77% (24/31) made some positive comments; **seeing the contraction on the printout helped them anticipate a pain**, seeing the beginning of a contraction helped them control their breathing; knowing that the peak of the contraction was over. 90% (28/31) commented positively about being **able to hear the FHR — feeling of safety and security.** 70% (22/31) had some negative comments about the FM, mainly associated with the external belts — ‘**too tight**, ‘**feelings of confinement**’, ‘**lack of mobility**’. | Communication  
Reassurance |
| (Starkman 1976)   | To gain insight into the psychological effects of EFM                 | 25 women; post-birth while still in hospital. University Medical Centre, USA.                    | The Fetal Monitor as: **Protector**, Extension of Patient, Aid in **Communication**, Extension of Baby, Affecting Interactions with Husband, **A Distraction**, Aid in Mastery, Competitive Feelings, **Mechanical Monster and Producing Increased Anxiety.** | Fear  
Reassurance  
Communication  
Comfort |
| (Shields 1978)    | To explore women’s reactions to internal EFM                         | 30 women; within 48 hours of birth. USA                                                         | Positive and negative scores were tabulated; 22 women were in the positive range, 8 were in the negative range; **“too little information. ”**, **“...I was worried about brain damage because of the clamp”**. 7 women indicated that they **were reassured by the machine**, 11 had **worries** about the baby during monitoring. The most frequent complaint was **difficulty in getting comfortable.** | Anxiety  
Reassurance  
Information  
Comfort |
<table>
<thead>
<tr>
<th>(Beck 1980)</th>
<th>To investigate women’s reactions to fetal monitoring</th>
<th>Equal numbers of women had positive and negative initial responses. 74% of women had positive subsequent response ‘a safeguard’. Many women felt secure because it was <strong>reassuring to hear the heartbeat</strong>; “The monitor saved my baby’s life because the doctor knew to do a caesarean section”. The negative subsequent responses mainly centered on the <strong>discomfort caused by the belts</strong>, and the feeling of being tied down which was <strong>frightening</strong>.</th>
<th>Fear&lt;br&gt;Security&lt;br&gt;Reassurance&lt;br&gt;Comfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>(McDonough et al. 1981)</td>
<td>To understand parents reactions to the fetal monitor and to determine how best to prepare women for the procedure</td>
<td>Mother’s reported that they were <strong>not fearful of the monitor</strong>; one mother thought her baby might have <strong>died but for the monitor</strong>; some mothers were <strong>concerned that the monitor might ‘hurt’</strong> the baby. 44/50 women did not report <strong>discomfort due to the monitor</strong>, 47/50 felt <strong>less fear</strong> with the monitor, and 49/50 did not think the <strong>nurse was more interested in the monitor than in her</strong>.</td>
<td>Fear&lt;br&gt;Comfort&lt;br&gt;Communication</td>
</tr>
<tr>
<td>(Hodnett 1982)</td>
<td>To investigate the effects of two types of monitoring in labour; electronic and radiotelemetric, on ability to maintain control during labour</td>
<td>9/15 EFM did not get out of bed at all during labour; all of the 15 radiotelemetric spent some time out of bed. 28 (14 from each group) stated that the fetal monitor had an effect on their labour experiences. Negative effects included: <strong>discomfort from belts (n = 7)</strong>, <strong>interfered with movement and comfort (n=3)</strong>, <strong>made them anxious (n = 2)</strong>.</td>
<td>Comfort&lt;br&gt;Information&lt;br&gt;Protector/Safety&lt;br&gt;Reassurance</td>
</tr>
<tr>
<td>(Molfese et al. 1982)</td>
<td>To examine reactions to intrapartum fetal monitoring</td>
<td>132/180 women gave positive responses; the monitor as a <strong>protector of the baby, not as a competitor for attention</strong>; they were able to use the <strong>information from the monitor in a variety of ways</strong>, <strong>reassurance about baby’s wellbeing</strong>.</td>
<td>Communication&lt;br&gt;Information&lt;br&gt;Protector/Safety&lt;br&gt;Reassurance</td>
</tr>
<tr>
<td>Authors</td>
<td>Objective</td>
<td>Sample Size</td>
<td>Findings</td>
</tr>
<tr>
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</tr>
<tr>
<td>Garcia et al. 1985</td>
<td>To explore views related to method of FHR monitoring received</td>
<td>200 women; post-birth while still in hospital, subgroup of women who participated in large RCT, 100 allocated IAP, 100 allocated EFM</td>
<td>Women monitored by EFM felt more restricted in their movements; women who received EFM were more often left alone for short periods; EFM was not more reassuring to mothers, equal numbers of women experience some degree of anxiety.</td>
</tr>
<tr>
<td>Hindley et al. 2008</td>
<td>To ascertain women's views on intrapartum fetal monitoring techniques</td>
<td>63 women; antenatal period, 38/63 included in postnatal study. Two hospital based units, England</td>
<td>Women did not prefer one method over another; women would prefer to stay mobile; women wanted to remain in control.</td>
</tr>
<tr>
<td>Cranston 1980</td>
<td>To identify the attitudes of professionals towards fetal monitoring</td>
<td>124 nurses; 14 hospitals, St Louis, USA</td>
<td>88% felt that the fetal surveillance by the FM could not be achieved by IAP. 90% felt that the patient was more reassured by the presence of the monitor. 59% did not feel that the FM causes more patient anxiety. 98% felt that the purpose of the FM was to improve fetal outcome. EFM is one of obstetrics best inventions</td>
</tr>
<tr>
<td>Dover and Gauge 1995</td>
<td>To find out how midwives carried out intrapartum FHR monitoring and what factors influenced choice of methods</td>
<td>117 midwives of 242 (48% response rate); 3 units, England</td>
<td>Midwives felt confident to use IAP for low-risk women; midwives would benefit from education on EFM interpretation; philosophy of childbirth affected choice of method; EFM was used when staffing levels were poor.</td>
</tr>
<tr>
<td>Birch and Thompson 1997</td>
<td>To determine staff attitudes to and practice of monitoring the FHR during labour</td>
<td>96 professionals (50% response rate); Consultant Led Unit, Wirral, UK</td>
<td>EFM has improved outcomes; overall preference for IAP; disparity between midwives' and doctors' responses.</td>
</tr>
<tr>
<td>Sinclair 2001</td>
<td>To explore how midwives used the birth technology of the CTG machine</td>
<td>446 midwives of 741 (60% response rate); All labour wards, Northern Ireland</td>
<td>Dichotomy with respect to reliance on EFM and EFM as a source of anxiety; view that CTG is not required for safe birth; agreement that technology in childbirth is desirable.</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Objective</td>
<td>Sample Size and Setting</td>
<td>Findings</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>(Walker et al. 2001)</td>
<td>To explore nurses’ attitudes towards IA</td>
<td>145 nurses; 5 units, South-East Michigan, USA</td>
<td>IA should be the standard of care; staff/women ratios hinder IA use; neutral response to research on EFM and clear benefits.</td>
</tr>
<tr>
<td>(Munro et al. 2002)</td>
<td>To explore and respond to midwives’ views of different types of fetal monitoring in labour</td>
<td>20 midwives; 2 maternity units, England</td>
<td>EFM offered reassurance; increased anxiety; EFM can hinder communication; EFM reduces mobility and increased need for pain relief; trust in technology.</td>
</tr>
<tr>
<td>(Altaf et al. 2006)</td>
<td>To explore midwives’ views on the experience of using EFM</td>
<td>20 midwives; large teaching hospital, England</td>
<td>Feeling of reliance on EFM; EFM can erode and undermine professional skills; EFM deflecting attention from care.</td>
</tr>
<tr>
<td>(Hindley et al., 2006)*</td>
<td>To explore midwives’ attitudes and experiences of intrapartum fetal monitoring</td>
<td>58 midwives; 2 hospitals, Northern England</td>
<td>Midwives were motivated to use EFM to protect themselves against potential litigation; EFM may provide reassurance; IA allowed for closeness to women and freedom of movement during labour; IA facilitated a more natural approach to childbirth; danger of losing skills with over-reliance on technology; EFM used when busy.</td>
</tr>
<tr>
<td>(Blix and Ohlund 2007)</td>
<td>To explore what information the labour admission test is perceived to provide in the daily work of midwives</td>
<td>12 midwives; four maternity units, Norway</td>
<td>The core category ‘experiencing contradictions’ was explained by three sub-categories; professional identity versus technology, feeling safe versus feeling unsafe and power versus powerlessness</td>
</tr>
</tbody>
</table>

*The results of this study are reported across three publications; references for additional papers include; (Hindley and Thomson 2005, 2007).
Table 11: Methodological Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Sampling methods</th>
<th>Data collection</th>
<th>Data analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women's Views</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Dulock and Herron, 1976)</td>
<td>Non-Probability sample</td>
<td>Questionnaires and Interviews</td>
<td>Not Described</td>
</tr>
<tr>
<td>(Starkman 1976)</td>
<td>Non-Probability sample</td>
<td>Interviews</td>
<td>Descriptive, Fisher Exact Probabilities test, Students t-test</td>
</tr>
<tr>
<td>(Shields 1978)</td>
<td>Non-Probability sample</td>
<td>Interviews and ‘Moods &amp; Feelings Inventory’ to ascertain positive and negative attitudes</td>
<td>Inventory scores, Chi-square</td>
</tr>
<tr>
<td>(Beck 1980)</td>
<td>Non-Probability sample</td>
<td>Interviews</td>
<td>Descriptive, Chi-square</td>
</tr>
<tr>
<td>(McDonough et al. 1981)</td>
<td>Non-Probability sample</td>
<td>Questionnaire and interview</td>
<td>Not described</td>
</tr>
<tr>
<td>(Hodnett, 1982)</td>
<td>Random sampling</td>
<td>Questionnaire; ‘Labour Agency Scale’ and Interview</td>
<td>Students t-test, Fisher’s exact test, Chi-squared test</td>
</tr>
<tr>
<td>(Molfese et al. 1982)</td>
<td>Random sampling</td>
<td>Interviews and completed questionnaire</td>
<td>Descriptive, mean, standard deviation, Factor analysis</td>
</tr>
<tr>
<td>(Garcia et al. 1985)</td>
<td>Random sampling (sub-group of women from large RCT)</td>
<td>Semi-structured questionnaire</td>
<td>Frequencies, Chi-square, t-test</td>
</tr>
<tr>
<td>(Hindley et al. 2008)</td>
<td>Non-Probability sample</td>
<td>Questionnaire (survey research)</td>
<td>Descriptive, frequency counts, cross-tabs</td>
</tr>
<tr>
<td>Professionals' Views</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Cranston 1980)</td>
<td>Non-Probability sample</td>
<td>Questionnaire (24-item Likert scale)</td>
<td>One-way ANOVA, mean, standard deviations and frequency counts</td>
</tr>
<tr>
<td>(Dover and Gauge 1995)</td>
<td>Non-Probability sample</td>
<td>Questionnaire (20-item Likert scale)</td>
<td>ANOVA, frequencies, correlation, chi-square and t-tests</td>
</tr>
<tr>
<td>Reference</td>
<td>Sample Type</td>
<td>Methodology</td>
<td>Analysis Methods</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>(Birch and Thompson 1997)</td>
<td>Non-Probability sample</td>
<td>Questionnaire (survey research)</td>
<td>Frequencies</td>
</tr>
<tr>
<td>(Sinclair 2001)</td>
<td>Non-Probability sample</td>
<td>Questionnaire (postal survey and 25-item Likert scale)</td>
<td>Descriptive, Factor analyses</td>
</tr>
<tr>
<td>(Walker et al. 2001)</td>
<td>Non-Probability sample</td>
<td>Questionnaire (18-item Likert scale)</td>
<td>ANOVA, mean, standard deviation</td>
</tr>
<tr>
<td>(Munro et al. 2002)</td>
<td>Non-Probability sample</td>
<td>Semi-structured interviews</td>
<td>Framework analysis</td>
</tr>
<tr>
<td>(Altaf et al. 2006)</td>
<td>Non-Probability sample</td>
<td>Semi-structured interviews</td>
<td>Constant Comparative Method</td>
</tr>
<tr>
<td>(Hindley et al., 2006)*</td>
<td>Non-Probability sample</td>
<td>Semi-structured interviews</td>
<td>General thematic analysis</td>
</tr>
<tr>
<td>(Blix and Ohlund 2007)</td>
<td>Non-Probability sample</td>
<td>Interviews</td>
<td>Constant Comparative Method</td>
</tr>
</tbody>
</table>

*The results of this study are reported across three publications; references for additional papers include; Hindley & Thomson (2005) and Hindley & Thompson (2007)
4.3.5 Data analysis
The method of data analysis used in this review was a thematic analysis of each study’s findings. Thematic analysis involves the identification of prominent or recurrent themes in the literature and the synthesis of findings from studies under thematic headings. It has been described as flexible, allowing considerable latitude to reviewers, and is a means of integrating qualitative and quantitative evidence (Dixon-Woods et al. 2005). For this reason, and considering the inclusion of studies with both quantitative and qualitative research designs, a thematic analysis would appear most suited to meet the aim of the review on women’s and professionals’ views. Reviewers using thematic analysis must be mindful and considerate, however, of certain limitations associated with this method. Thematic analysis has been accused of lacking explicitness as to the process and extent of description or interpretation (Dixon-Woods et al., 2005). Merely summarising themes identified in primary studies offers little by way of theoretical advancement (Dixon-Woods et al. 2005). Thematic analysis must go beyond the content of the original studies and offer greater understanding and clarification of the concepts and patterns in the data (Bondas and Hall 2007). It must draw conclusions based on common elements across the studies and perhaps most importantly, it must fulfil an important research aim of generating evidence based on a more integrated and complete interpretation of the findings from the original studies (Bondas and Hall, 2007, Lucas et al., 2007b, Thomas and Harden, 2008).

The steps used to conduct the thematic analysis in this review on women’s and professionals’ views were adopted from Lucas et al (2007) and involved the following;

1. I extracted the data from the included studies’ findings and entered this into a table for later consideration (Table 10).
2. When ready to consider the findings of each study, I referred to the data in Table 10 and identified emergent themes from the individual studies’ findings.
3. A list of themes was produced for each study (last column of Table 10). The relevant section of the findings related to the particular identified theme was highlighted in bold to clarify the association between the findings and the list of themes (see Table 10).

4. A synthesis of the findings was performed.

It should be noted that data synthesis was iterative and involved going back and forth between the original papers and the data extraction tables. This was to ensure reliability in reporting review findings.

4.4 Results

4.4.1 Search & selection strategy

The search strategy identified 124 citations. Of these 96 were excluded on title and on title and/or abstract because they were not about women’s and/or professionals’ views of FHR monitoring during labour. This left twenty-eight citations that were selected for full text retrieval and review. Following a full-text review of retrieved papers, a further eight were excluded; one explored midwives’ perceptions of the use of technology and was not explicitly about monitoring the FHR (Sinclair and Gardner 2001), one was a narrative review on the responses of women to fetal heart rate monitoring (Syndal 1988), one was a duplicate publication (Starkman 1977), one explored women’s views on decision-making and was not explicitly about monitoring the FHR (Davey et al. 2004) and four were either non-comparable in design (for example, one study (Shalev et al., 1985) reported maternal responses to EFM as measured by blood stress-hormone levels) to the included studies or I was unable to extract themes from the data (Jackson et al. 1983; Hansen et al. 1985; Shalev et al. 1985; Killien and Shy 1989). In total, 20 papers were included in this review detailing 18 studies (see Figure 6); the findings of one study (Hindley et al. 2006) was reported across two additional publications (Hindley and Thomson 2005, 2007). Nine studies (659 participants) explored women’s views of fetal monitoring during labour. Nine studies (1,038 participants) explored professionals’ views of fetal monitoring during labour. Omitting to search a social science database is acknowledged as a limitation to the search
strategy. Social science databases might prove a useful source for studies on women’s views and should be considered as a source for potential literature retrieval in conducting a systematic review of this type in the future. Details of the included studies are provided in Table 10 and Table 11.

![Diagram of search and selection strategy]

Figure 6: Search & Selection Strategy (2)

4.4.2 Quality assessment
Table 12 details the results of the quality assessment of the studies included in this review. The assessment is based on the twelve criteria developed by the EPPI-Centre for their review on healthy eating in young children (Thomas et al. 2003). Three studies (Dover and Gauge, 1995, Sinclair, 2001, Munro et al, 2002) reported on all twelve of the EPPI-Centre’s quality assessment criteria in their papers, indicating ‘good’ quality studies. Four studies (Molfèse et al, 1982, Walker et al, 2001, Hindley et al, 2006, Blix and Ohlund), addressed eleven of the twelve criteria in their papers. Shields (1978) scored the lowest on quality assessment, addressing three of the twelve criteria and Dulock and Heron (1976), McDonough et al (1981) and Birch and Thompson (1997) addressed only four of the twelve quality assessment criteria.
Table 12: Quality Assessment of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality criteria met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulock</td>
<td>A, B, C, J</td>
</tr>
<tr>
<td>Starkman</td>
<td>A, B, C, D, E, F, H, J, K</td>
</tr>
<tr>
<td>Shields</td>
<td>A, D, E</td>
</tr>
<tr>
<td>Beck</td>
<td>B, C, D, E</td>
</tr>
<tr>
<td>McDonough</td>
<td>A, B, C, J</td>
</tr>
<tr>
<td>Hodnett</td>
<td>A, B, C, D, E, F, J, K</td>
</tr>
<tr>
<td>Molfese</td>
<td>A, B, C, D, E, F, G, H, I, J, K</td>
</tr>
<tr>
<td>Garcia</td>
<td>A, B, C, D, E, F, H, J, K</td>
</tr>
<tr>
<td>Cranston</td>
<td>A, B, C, F, H, J, K</td>
</tr>
<tr>
<td>Dover</td>
<td>A, B, C, D, E, F, G, H, I, J, K, L</td>
</tr>
<tr>
<td>Birch</td>
<td>A, C, D, J</td>
</tr>
<tr>
<td>Sinclair</td>
<td>A, B, C, D, E, F, G, H, I, J, K, L</td>
</tr>
<tr>
<td>Walker</td>
<td>A, B, C, D, E, F, G, H, I, J, K</td>
</tr>
<tr>
<td>Munro</td>
<td>A, B, C, D, E, F, G, H, I, J, K, L</td>
</tr>
<tr>
<td>Altaf</td>
<td>A, B, C, D, E, F, H, J, K</td>
</tr>
<tr>
<td>Blix</td>
<td>A, B, C, D, E, F, G, H, I, J, K</td>
</tr>
</tbody>
</table>

**Quality of study reporting**

A: Aims and objectives were clearly reported  
B: Adequate description of context of research  
C: Adequate description of the sample and sampling methods  
D: Adequate description of data collection methods  
E: Adequate description of data analysis methods  

*There was good or some attempt to establish the:*

F: Reliability of data collection tools  
G: Validity of data collection tools  
H: Reliability of data analysis  
I: Validity of data analysis  

**Quality of methods**

J: Used appropriate data collection methods to allow for expression of views  
K: Used appropriate methods for ensuring the analysis was grounded in the views  
L: Actively involved participants in the design and conduct of the study  

(Source: Thomas et al, 2003)
4.4.3 Thematic analysis

4.4.3.1 Women’s views of FHR monitoring

Thematic analysis of each included study on women’s views resulted in four themes related to their view of FHR monitoring in practice. These were; i) fear and anxiety, ii) reassurance, iii) communication, and iv) comfort.

4.4.3.1.1 Fear and anxiety

The theme of fear and anxiety emerged in seven of the nine included studies (Starkman 1976; Shields 1978; Beck 1980; McDonough et al. 1981; Hodnett 1982; Molfese et al. 1982; Garcia et al. 1985). The experience of fear was, in the main, associated with the auditory sounds emitted from the monitor. For example, women became frightened when the monitor alarmed or beeped as would happen if the transducer or internal scalp electrode became unattached (Starkman 1976; Beck 1980; McDonough et al. 1981; Molfese et al. 1982).

In addition, hearing the baby’s heart beat evoked fear and anxiety for some women particularly if the baby’s heartbeat slowed down at any point during labour (Starkman 1976; Shields 1978; Beck 1980).

EFM equipment itself evoked fear and anxiety in some women. Many were concerned that the equipment might hurt either them or their baby;

‘I thought I was going to be electrocuted. My water had broke. The cord of the machine was lying in the water.’ (Beck 1980, p. 351)

Anxiety levels appeared greatly increased in women who experienced internal EFM. More than one-quarter of the participants in Starkman’s study expressed concern that the fetal scalp electrode might injure the baby or puncture the ‘soft spot’ (Starkman 1976).

‘The head is the most important part and I was worried about brain damage because of the clip’. (Shields 1978, p. 2111)
EFM equipment malfunction also caused considerable anxiety for women. In Garcia’s study, 27% of the 100 women who had EFM said that equipment malfunctioned at some point during labour and of these, one-third experienced fear because of this (Garcia et al 1985).

4.4.3.1.2 Reassurance
In contrast to those women who experienced fear, many women were also reassured by EFM because they were able to hear the baby’s heartbeat;

‘I was happy. This way I hear myself that my baby’s heart was strong’. (Beck 1980, p. 351)

Reassurance as a prominent theme emerged in seven (Dulock and Herron 1976; Starkman 1976; Shields 1978; Beck 1980; McDonough et al. 1981; Molfese et al. 1982; Garcia et al. 1985) of the nine included studies and always related to hearing the baby’s heartbeat. For some women this confirmed to them that the baby was still alive (Starkman 1976; Beck 1980). In this sense the monitor might be considered by some women as a tool that would ensure the survival of her baby;

‘The monitor saved my baby’s life because the doctor knew to do a caesarean section’. (Beck 1980, p.351)

This view emerged also in McDonough’s (1981) study. For example, when questioned, women who had a caesarean section during their labour, felt that their baby might have died or been born seriously ill had it not been for the fetal monitor. This view was significant for women who had lost a baby in a previous pregnancy or labour (Starkman 1976) and for women of lower income when compared to women of upper income levels (Molfese et al 1982).
4.4.3.1.3 Communication

Communication as a theme emerged in eight of the included studies on women's views and was strongly associated with the provision of information. EFM and the CTG monitor were viewed as a focal point for women to initiate conversations with their doctor (Starkman 1976). In addition, for some women, the use of EFM facilitated the participation of their husbands in the process of childbirth;

'Now my husband could see when I was having a contraction and help me breathe'. (Beck 1980, p.351)

In contrast, for some women, EFM was considered a hindrance to effective communication (Starkman 1976, Shields 1978, Molfese et al 1982). In such circumstances, EFM diverted attention away from the labouring woman as clinical staff and birthing partners were perceived to become preoccupied with the monitor;

'They all came with the machine and left with the machine'. (Shields 1978, p.2112)

This opinion was also evident in Garcia's study and, although women in either group did not report feeling less supported, women in the EFM group reported being left alone more often that those women who received IA (Garcia et al 1985).

EFM was considered, by women, as a valuable source of information for midwives and doctors and this was significant for women in Molfese et al's study (1982). Women perceived that the CTG machine could tell them (and their care-giver) when a contraction was coming in situations of regional analgesia (Dulock and Herron 1976, Starkman 1976). It was also used, by both women, midwives and doctors (at times erroneously), as a diagnostic tool for labour (Starkman 1976; Shields 1978);
the monitor says your contractions are mild’. (McDonough et al 1981, p.34)

Although women in two studies (Garcia et al 1985, Hindley et al 2008) did not report a preference for one type of monitoring method over another, 94% of women in Hindley et al’s (2008) study did not report having being given a choice on method of FHR monitoring. This demonstrates a lack of communication and information on FHR monitoring methods in practice, in some circumstances.

4.4.3.1.4 Comfort

Comfort as a theme emerged in all nine included studies and was strongly associated with discomfort from EFM equipment such as the internal fetal scalp electrode or the abdominal transducer and belts (Dulock and Herron 1976, Starkman 1976, Shields 1978, Beck, 1980 Hodnett 1982, Molfese et al 1982). Mobility was often referred to in relation to comfort; or rather a reported increased discomfort resulting from enforced immobility associated with EFM (Starkman 1976, Beck 1980, Hodnett 1982, Garcia et al 1985);

‘...I felt tied down and couldn’t get out of bed. I felt like Frankenstein’s bride’. (Beck 1980, p.352)

The view that EFM restricted movement was significant in Garcia et al’s (1985) study (17 in EFM group versus 6 in IA group). In one study, (Hindley et al 2008) EFM also appeared to increase the need for analgesia. In this study all of the women who received IA during labour (n = 15/38) did not request epidural analgesia; however, all of the women who received EFM (n = 20/38) had either an epidural or narcotic analgesia.

4.4.3.2 Professionals’ views of FHR monitoring

Thematic analysis of each included study resulted in four themes related to professionals’ views on fetal monitoring in labour. These were; i) reassurance and safety, ii) technology, iii) comfort, and iv) midwife by proxy.
4.4.3.2.1 Reassurance

Reassurance emerged as a prominent theme in seven (Cranston, 1980, Birch and Thompson, 1997, Dover and Gauge, 1995, Munro et al., 2002, Altaf et al., 2006, Blix and Ohlund, 2007, Hindley and Thomson, 2007) of the nine included studies. EFM offered reassurance to midwives because they believed the CTG trace provided hard copy ‘proof’ that the baby was not compromised whilst in their care (Dover & Gauge, 1997, Munro et al, 2002, Altaf et al, 2006, Blix and Ohlund, 2007, Hindley and Thomson, 2007). When an adverse outcome occurred, this ‘proof’, not achievable through IA, was perceived as potentially minimising the exposure of clinical staff to criticism and litigation (Blix & Ohlund, 2007, Hindley & Thomson, 2007);

“The main disadvantage I can see for using intermittent auscultation is from a litigation point of view; it’s your word against theirs if there’s a problem because you’ve not got the proof...you haven’t got the CTG to look at’. (Hindley & Thomson 2007, p.236)

From the data, it appeared that a principal reason for using EFM was the perceived reassurance and protection against legal action afforded by the hard copy CTG trace (Dover & Gauge, 1997, Hindley & Thomson, 2005, Altaf et al, 2006, Blix & Ohlund, 2007, Hindley & Thomson, 2007).

Professionals’ faith in the safety of EFM in assuring improved outcomes is also evident in Cranston’s (1980) and Birch & Thompson’s (1997) studies. In these studies 96% and 63% of professionals’, respectively, believed that EFM reduced perinatal mortality and morbidity and improved maternal and neonatal outcomes. In contrast, however, a proportion of midwives did not share this view, believing instead that CTG did not necessarily ensure a good neonatal outcome. In Dover & Gauge’s (1997) study, midwives who considered childbirth as a normal life event did not agree that continuous EFM was safer than IA. In Sinclair’s (2001) study, 80% (n = 357 of 446), of midwives disagreed that a CTG was required for a safe birth. In addition, despite being reassured by the visual aspect of the CTG (Munro et al 2002),
midwives also believed that EFM can provide a false sense of security (Blix & Ohlund, 2007) with the majority (85%) in Sinclair’s study reporting that they would not always trust the CTG trace over their own observations (Sinclair, 2001).

4.4.3.2.2 Technology
Technology as a theme emerged in six (Cranston 1980, Sinclair 2001, Walker et al 2001, Altaf et al 2006, Hindley et al 2006, Blix & Ohlund 2007) of the nine included studies. EFM was considered by some as a technology offering more authoritative information than IA, but this was rejected by others. In Cranston’s (1980) study, for example, 80% of the 124 participants felt that fetal assessment achieved by EFM cannot be matched by IA and 76% believed that the fetal monitor was one of obstetrics’ best inventions. In contrast, 85% of the 446 midwives in Sinclair’s study (2001) disagreed that they would always trust the CTG over their own observations, and 74% felt that the CTG was often used unnecessarily.

Professionals also expressed concerns that EFM technology and over-reliance on the CTG was eroding traditional midwifery skills such as the use of the Pinard fetal stethoscope (Sinclair, 2001, Altaf et al, 2006, Blix & Ohlund, 2007) and detracted from normality in childbirth (Hindley et al, 2006);

'I think IA brings you closer to them, and its just more natural and normal, so its less technology that I am in favour of'. (Hindley et al 2006, p. 357)

Midwives also expressed concern that EFM technology can become the focus of care and that this might distract away from the care provided to and communication with women (Walker et al, 2001, Altaf et al, 2006, Hindley et al, 2006, Blix & Ohlund, 2007).

4.4.3.2.3 Comfort
Midwives shared the view of women (as discussed above) that EFM was more restrictive and uncomfortable than IA (Munro et al, 2002, Altaf et al,
2006, Hindley et al, 2006) and that it leads to increased requests for pain relief (Munro et al, 2002, Hindley et al, 2006);

‘I think especially with monitors, they are waiting for the next pain. The focus is on the pain’. (Hindley et al, 2006, p. 357)

Midwives expressed a preference for using IA (Hindley et al, 2006) because it facilitated freedom of movement and were equally divided (that is 40% agreed and 40% disagreed) that EFM increased a women’s anxiety during labour (Sinclair, 2001).

4.4.3.2.4 Midwife by proxy
Using EFM as a substitute for midwifery staff emerged from four of the nine included studies (Dover and Gauge, 1995, Walker et al., 2001, Munro et al., 2002, Hindley et al., 2006) and was strongly associated with poor staffing levels and busy clinical environments;

‘It can be used so you can go out and look after your fourth patient and come back in and see that the baby has been alright at the time you have gone... ’ (Munro et al 2002, p. 497)

This sentiment is quantified in Dover & Gauges’ (1995) and Walker et al’s (2002) studies where 72% and 54% of participants respectively felt that EFM was more likely to be chosen when midwife to women ratios were reduced.

4.5 Discussion
This systematic review and thematic analysis has identified themes related to women’s and professionals’ views of monitoring the FHR during labour through a synthesis of eighteen studies on this topic. Six themes were identified; two of these, reassurance and comfort were shared by both women and professionals. Other themes identified included fear and anxiety
Women’s and professionals’ views of FHR monitoring can influence and affect the routine care received by and offered to women during labour (Cranston 1980; Walker et al 2001). It can affect their experience of childbirth and consideration of both women’s and professionals’ views, perceptions towards, and experiences of FHR monitoring is important in understanding this important aspect of care. Contrary to current recommendations (RCOG, 2001, NICE, 2007) EFM as a method of monitoring the FHR in low risk women remains widespread. An insight into women’s and professionals’ views might offer some understanding as to why this might be the case.

EFM offered women reassurance because it allowed them to hear their baby’s heartbeat, although this experience was frightening for some women, especially when they could hear the baby’s heartbeat slowing down. For professionals, reassurance associated with EFM was having the hard copy ‘proof’ of an uncompromised baby. This ‘proof’ was perceived to minimise exposure to criticism and potential litigation. However, midwives also recognised the false sense of security offered by EFM and not all midwives relied on the CTG to ensure a good neonatal outcome. The view that EFM offered reassurance of an uncompromised baby appeared to change over time. The earlier studies (e.g. Cranston, 1980; Birch & Thompson, 1997) demonstrated a greater faith in EFM by professionals in assuring a good outcome than later studies (e.g. Sinclair, 2001, Blix & Ohlund, 2007). This may reflect the lack of evidence on the safety and efficacy of EFM over IA that has emerged through randomised trials during this period of time (Alfirevic et al, 2006). In addition, evidence reporting variation in inter- and intra-observer agreement in CTG interpretation has emerged (Ayres-de-Campos et al, 1999, Devane & Lalor, 2005) since the publication of the earlier studies and this may have affected the confidence of some professionals in EFM.
Both women and professionals recognised comfort as a significant experience during childbirth. Comfort was decreased when EFM was used due to discomfort from EFM equipment and reduced mobility associated with the technology. Comfort was increased when using IA due to increased mobility. For this reason professionals reported a preference for IA, yet also reported difficulty in using IA because of poor staffing levels and busy clinical environments. Although there is an absence of evidence in the literature supporting this view, it might be plausible that EFM itself might require more time than IA in practice. The time taken to maintain EFM equipment, respond to alarms and correctly interpret the CTG, could, in practice, take much longer than the time required to record the FHR by IA. Also, if EFM causes increased discomfort and this leads to an increased need for regional analgesia, then this will require increased observation by midwifery staff and ultimately more of the professional’s time. The perceived benefits of using EFM when staffing levels are low or when the clinical environment is busy should not, however, supersede best practice; that is the use of IA for low risk women during labour (NICE, 2007). In addition, professionals describe using EFM as a protector against potential litigation and as a midwife by proxy. However, applying a CTG because the midwife cannot be with a woman, implies that the midwife cannot watch the monitor, therefore reducing any protector effect potentially offered by EFM. In addition, IA allows for close proximity and engagement with women, a view highlighted by women as being very important (Garcia et al, 1985, Hindley et al, 2008). This might allow for increased communication and afford professionals a greater view of the overall clinical picture. As Shearer stated;

'intrapartum fetal death is not prevented by monitors; it is prevented by an alert doctor [midwife] at the bedside of a labouring woman'. (Shearer 1979) p. 127)
4.6 Conclusion

This systematic review and thematic analysis has identified themes related to women’s and professionals’ views of FHR monitoring in practice. It has offered insights into why EFM has such a strong foothold in the provision of care to women during childbirth. There is sufficient high quality evidence demonstrating the impact on clinical outcomes for women and their infants depending on the choice of FHR monitoring modality during labour (Alfirevic et al, 2006). Implementing evidence-based care and affecting appropriate practice change regarding FHR monitoring requires consideration of women’s and professionals’ views.

This review offers insight and understanding as it highlights some of the barriers and facilitators for the use of IA of the FHR during labour. In addition, it has identified specific areas for clinical decision-makers to consider when implementing policy and practice change. One area is the need to educate and inform women on types of FHR monitoring during labour so that they might make an informed choice on the method of FHR monitoring most suitable to them. The need to educate professionals on the most appropriate means of FHR monitoring for individual women, thereby ensuring best practice, was also identified. Recognising that women can experience fear and discomfort when EFM is applied highlights the need to inform and counsel women on the use of EFM during labour. Considering this view might also help professionals in the use of IA, for low risk women. Professionals must be knowledgeable of the current evidence on EFM. This will help by highlighting the evidence that EFM may not offer any increased reassurance over IA (RCOG, 2001, Blix et al, 2005; NICE, 2007). Regular fetal monitoring study days for all staff would provide an opportunity to discuss some of the barriers, identified in this review, for effecting evidence-based practice change (e.g. protection against and fear of litigation, poor staffing levels and busy clinical environments, increased resource requirements that can potentially result from use of EFM).
This review will be of significant benefit to policy makers as it is the first systematic review and synthesis of evidence that considers the views, perceptions and experiences of women and professionals with respect to FHR monitoring during labour. It has importance and relevance in advancing systematic review methodology, as it provides an additional example of the synthesis of evidence from qualitative and quantitative enquiry. Views, perceptions, and experiences, from a user’s perspective, that is women and professionals, must be considered when implementing care to affect best practice. Further research is required to establish how some of these views might be addressed to ensure the provision of optimum care for women (inclusive of psychological and emotional factors). In addition, further research is required to establish how professionals’ views might be considered to ensure the appropriate method of FHR monitoring is applied to individual women, so that optimum care is provided to women and their infants.
Section III

The ADCAR trial

Design, conduct and preliminary findings
Chapter 5: Research Methodology and Study Methods

5.1 Introduction
The ADCAR trial is a randomised trial comparing the use of ACTG versus IA of the FHR in low risk women on admission to the labour ward or labour assessment room with signs of possible labour. In this chapter, the research methodology and study methods for the ADCAR trial are presented. For completeness, accuracy and transparency, the CONSORT (Consolidated Standards of Reporting Trials) checklist was consulted to structure this section (Moher et al. 2010). The CONSORT statement includes a list of essential items that should be included when reporting on randomised trial research (Appendix V). The essential items included from the CONSORT are considered in reporting the methods, conduct and preliminary findings of the ADCAR trial.

In this chapter, the aim of the study is provided. The chosen methodology and the rationale for this choice are presented. Ethical issues related to the trial are discussed in detail. Issues relevant to quality in clinical trials including optimum trial design, trial conduct and trial analysis are also discussed.

5.2 Aim of study
The aim of the ADCAR trial is to evaluate the effectiveness of ACTG versus IA of the FHR in low risk women on admission to the labour ward or labour assessment room with signs of possible labour on a) caesarean section, b) obstetric intervention, and c) neonatal morbidity.

5.2.1 Background to the study
The rationale for the ADCAR trial arises from a lack of evidence of benefit supporting the use of ACTG compared to IA of the FHR in low risk pregnancy. As discussed in Chapter 3, four randomised trials evaluating the use of ACTG have been published to date (Mires et al, 2001, Cheyne et al, 2003, Impey et al 2003, Mitchell, 2008). One of these trials (Mitchell, 2008) was published after recruitment had started for the ADCAR trial. As
discussed in Chapter 3, there are a number of limitations associated with the four existing trials. These include mid-trial changes to power calculations (Cheyne et al., 2003), insufficient sample sizes, (Cheyne et al., 2003, Mitchell, 2008) and poor generalisability of study results (Impey et al., 2003). These limitations, the findings of the systematic review in this thesis (Chapter 3), a call for further research evaluating the use of ACTG (RCOG, 2001) and the widespread and routine use of ACTG in Ireland (Devane et al., 2007), provide the rationale and justification for the ADCAR trial.

5.2.2 Specific role of the research assistant
The ADCAR trial is funded by the Health Research Board (Ireland). I joined the ADCAR Trial team in October 2006 as the principal research assistant to the trial. At the time of joining the team, a proposal for funding had already been developed. This proposal outlined the major methodological tenets of the trial but lacked specific detail on how each of the tenets would be operationalized. For example, the proposal indicated that women would be randomized to control and experimental groups using a central randomisation process. I was responsible for developing the randomisation working processes (to include stratified permuted block randomisation with random sequences of block sizes of two or four and stratification by study site) and for establishing ADCAR randomisation within the ALEA service (see section 5.8.1.4.1 for further details).

Further, I had a specific role, as distinct from that of the other members of the research team, in the planning, design and implementation of the following components of the ADCAR trial:

5.2.2.1 Further development of the trial protocol
I was responsible for the development of the trial protocol that was used to register the ADCAR Trial and for the detailed protocol that would guide the conduct of the trial (see Appendix XIX for a complete copy of the trial protocol). This work involved my (i) developing the trial procedures and clinical care pathways of women following randomisation to the trial (see
section 5.8.1.5 for further details), (ii) establishing the trial’s randomisation service as above (see section 5.8.1.4.1 for further details), (iii) development of all trial support documentation including, for example, study information booklets for women, trial screening forms, study consent form, clinical care pathways, data collection booklet and trial publicity materials (see Appendices VII, XIV, XVII, XVIII, IX, VI, XVI, XXV and XXI respectively for full details), (iv) preparing applications and associated documentation for research ethical approval for The Faculty of Health Sciences, Trinity College Dublin, and for the hospital Research Ethics Committees of four proposed study sites (see section 5.4.4 for further details), (v) trial registration (see section 5.6 for further details) and (vi) development, conduct and evaluation of the pilot of the ADCAR Trial (see section 5.8.2.3 for full details).

5.2.2.2 Research ethical approval
As the research assistant to the trial, one of my primary responsibilities was to seek and obtain ethical approval to conduct the trial at the relevant study sites. This involved preparing application forms and associated documentation (including study information sheets for women, trial screening and consent forms, serious adverse report form and data collection booklet for the ethics committees and submitting these to five research ethics committees (see section 5.5 and sections 5.5.1 to 5.5.4 for full details of all ethical considerations associated with the ADCAR trial).

5.2.2.3 Preparation of study sites for implementation and launch of the trial
Preparations for implementation and launch of the trial were lengthy and ongoing throughout 2007 and 2008. I was responsible for liaising with clinical staff in preparing the clinical sites for the launch of the trial and for supporting clinical sites following trial launch. This responsibility involved organizing and facilitating study information workshops for clinical staff and arranging meetings with midwifery and obstetric managers as and when required before launch of the trial and on an ongoing basis during the trial (please see sub-sections 5.8.2.2 and 5.8.2.4 for full details).
5.2.2.4 Day to day management of the trial
I was responsible for the day to day management of the trial. This included liaising on an ongoing basis with study sites and clinical staff, preparing trial updates, arranging trial workshops and trial meetings, advertising and raising awareness of the trial at midwifery conferences and relevant study days, collecting, cleaning and managing trial data, monitoring trial recruitment and implementing strategies to optimize trial recruitment.

5.2.2.5 Data analysis
I was responsible for analyzing all data and reporting the preliminary trial results. Sections 5.8.3.1.3 and 5.8.3.2 provide full details of the data analysis procedures. Chapter 6 reports the findings of the preliminary trial analysis.

5.3 Research methodology and methods
Although closely related, research methodology and research methods are two distinct and separate components of the research process. Research methodology is the strategy chosen by the researcher that accounts for the methods used to answer the research question. Research methods concern the actual conduct of the study and include the steps taken by the researcher in collecting and analysing the data (Crotty 1998). The research question, how best to answer it, and the theoretical perspective underpinning it, informs the choice of research methodology and research methods.

5.3.1 Theoretical perspectives
An understanding of theoretical perspectives, that is ways of looking at the world and making sense of it (Crotty, 1998), is an important part of the research process as it allows one to consider an appropriate research strategy for answering a specific research question. In research, a theoretical perspective might adopt a deductive approach (that is, hypothesis testing and empirical experimentation to confirm or refute relationships) or an inductive approach (that is, identifying emergent patterns in the data that might suggest
relationships and/or construct or develop theory), although both approaches are not necessarily mutually exclusive (Gray 2009).

Epistemology is concerned with knowledge and what it means to know (Crotty, 1998). It influences a theoretical perspective in that it provides a ‘.....philosophical background for deciding what kinds of knowledge are legitimate and adequate’ (Gray, 2009, p.17). Furthermore, it is important in research as it can help to clarify issues of research design, such as how the data will be collected, from whom and from where, and how the data are going to be interpreted (Gray, 2009). Crotty (1998) describes a range of epistemologies that include objectivism and constructionism. Objectivism asserts that reality exists independent of conscious thought, whereas constructionism holds that knowledge is constructed or created through interactions with the world or the people therein (Crotty, 1998, Gray 2009).

In considering the aim of the ADCAR trial, the epistemology informing the research design is objectivism because the study seeks to identify a cause and effect relationship between the ACTG and IA of the FHR on labour and birth outcomes. A theoretical perspective closely linked to objectivism is positivism (Gray, 2009). This is because a positivist philosophy assumes a reality where all things can be studied as hard facts. The pursuit of knowledge, for the positivist, is independent of human behaviour and is derived through that which is ‘objective, discernible and measurable’ (Crossan 2003), p.47). A theoretical perspective in direct contrast to positivism is that of interpretivism (Gray, 2009), which is linked to constructionist epistemology. Interpretivism supports the creation of knowledge through observation, analysis and interpretation of the world around us.

Positivism and interpretivism support two distinct research methodologies within which there are a number of research designs. Positivists assume a quantitative methodological research approach to investigating phenomena. This is because quantitative research is concerned with outcomes that are
measurable and enumerable. Interpretivism, on the other hand, adopts a qualitative methodological research approach. Qualitative research pursues knowledge through the study of human behaviours including thoughts, perceptions and beliefs. Information accumulated during qualitative study is generally collated to inform themes or categories (Brink and Wood 1998). These themes or categories are subsequently used to explain the phenomena under investigation.

Both quantitative and qualitative research methodologies have their merits and limitations (Crossan 2003). It is important prior to undertaking a research study to consider both in the context of the research question and how best to answer it. In order to answer a research question effectively the correct study design, informed by the appropriate research methodology, which is informed by the relevant theoretical perspective, is required. The ADCAR trial, in the pursuit of objective, measurable data that might explain a cause-and-effect relationship between the use of ACTG or IA on labour and birth outcomes, is supported by objectivism, positivism and a quantitative research approach.

5.3.2 Quantitative research

Quantitative research is defined as a 'formal, objective, systematic process in which numerical data are used to obtain information about the world' (Burns and Grove 2005), p23). It is the chosen methodology when a research question aims to determine measurable phenomena or to determine relationships within or between phenomena. A well recognized quantitative research design is experimental research.

5.3.2.1 Experimental research

Experimental research studies have been described as the optimum type of studies for measuring cause and effect relationships (Knapp 1998). They are systematic and rigorous in their approach (Parahoo 2006) and generally involve one intervention and a comparison. Experimental research is conducted under strictly controlled conditions, and classically includes the features of manipulation, control and randomisation of participants to the
alternative groups. Participants in experiments are assigned to either the intervention under investigation or to a comparison or control group (often the standard treatment). Strict control of experimental conditions minimises confounding or extraneous influences. Any differences in effects between the two groups are therefore attributed to the treatment received. Experimental research may be described by two major types; quasi-experiments and true experiments.

5.3.2.1.1 Quasi-experimental research
Quasi-experiments, like true experimental research, are designed to measure causality and include manipulation of the independent variable (Knapp 1998). They differ from true experiments in that complete control is not possible because randomisation, a treatment comparison group or both is lacking. Examples of quasi-experimental research include non-equivalent comparison group studies and interrupted time series designs.

In non-equivalent comparison group studies, experimental conditions are controlled and there are comparison groups, but participants are not randomised to receive control or experimental interventions. Dependant variable measures (that is the outcomes) are obtained before and after the introduction of the treatment under investigation (the independent variable) to the treatment group (Brink and Wood 1998), and compared with the same measures in the control group. Any observed differences are subsequently attributed to the treatment. The non-random allocation of participants, however, limits this type of study because of the potential for selection bias and the threat it makes to study validity.

Interrupted time series study designs use neither randomisation nor comparison groups. In this design, a single group of participants are subjected to experimental and control conditions over a series of time intervals (Brink and Wood 1998). The effects of the treatment under investigation are inferred by comparing any outcome differences for each time interval over the lifetime of the experiment. This type of study design, although useful for
investigating cause and effect over time, is limited in a number of ways. There is an increased risk of participant attrition due to the prolonged nature of the study. Furthermore, depending on the nature of the treatment under investigation, seasonal variations, cyclical patterns and changes in data collection or record keeping procedures over time may influence measurable outcomes and threaten study validity (Burns and Grove 2005).

Quasi-experimental research is advantageous in answering causal questions when true experimental research is not feasible. However, despite attempts to control as many threats to study validity as possible, and the inference of strong links, quasi-experimental research greatly limits a researchers’ confidence in identifying definitive cause-and-effect relationships, when compared to true experimental research. For this reason, a quasi-experimental design was not considered for the ADCAR trial.

5.3.2.1.2 True experimental research

In true experimental research (more often simply referred to as experimental research) strict controls are adopted in an attempt to eliminate bias. For this to occur true experiments must incorporate manipulation, comparison groups and random allocation when interventions are being compared (Knapp 1998). Manipulation refers to the process of controlling the independent variable (the intervention) so that any effect it may have on the dependent variable (clinical outcomes) can be measured (Brink and Wood 1998). Control refers to the process of eliminating any threats to the study’s validity. It includes the use of comparison groups (that is a group receiving the intervention under investigation and a comparison group receiving the control treatment, which is often the standard treatment or no treatment at all), and the use of random (that is by chance) assignment of participants to a particular group. It also involves strict adherence to the study protocol to minimise threats to treatment fidelity (although it is recognised that the treatment for a participant can, and should, be modified if this becomes necessary because of changes in their condition or wishes). There are a number of experimental research designs used in healthcare research. The most common are the pre-test/post-
test design, the repeated measures design and the parallel group randomised trial.

The pre-test/post-test design involves the random allocation of participants to two or more different groups with participants receiving a pre-test, then their respective allocated treatment followed by a post-test. Any differences observed between the different groups are attributed to the effects of the allocated treatment received. Pre-test/post-test designs are advantageous in ascertaining the equivalence of groups prior to commencing the study. However, the pre-test component involves the collection of additional data. This can result in complicated data analysis and might incur additional study expenses (Knapp 1998).

The repeated measures (or crossover) design involves a single group of participants where each participant receives more than one randomly allocated treatment. Comparisons are then made as to the effect of the different treatments on the same individual. It is advantageous in that, like the pre-test/post-test design, it allows for determining equivalence amongst participants prior to commencing the study; however, the risk of influence from the effects of carryover on the study’s results is high. Carryover occurs when the effects of one treatment persist and influences the effects of the subsequent treatment received (Burns and Grove 2005). Suggested strategies for reducing the potential of carryover effects include; random allocation to a specific sequence of treatments, sufficient time lapse between treatments, and identical time intervals between the treatments (Burns and Grove 2005).

The parallel group randomised trial is used to measure the effects of new treatments, procedures or technology (Friedman et al. 1998). It adheres to the classic components of experimental research (that is manipulation, control and randomisation), and sets out to accept or reject a hypothesis. Participants are randomly allocated to one of the interventions being compared, and the outcomes for the groups created in this way are then compared. Considering the present study and the nature of the research question, the parallel group
randomised trial was considered the most appropriate research design for the ADCAR trial, with women allocated to either ACTG or IA.

The randomised trial has been described as the ‘gold standard’ and most reliable way to evaluate the effect of different healthcare interventions (Friedman et al., 1998, Kendall, 2003, Akobeng, 2005, Silverman, 2009). It calls for adherence to a study protocol and asserts control to ensure optimum study validity. Participants are randomly allocated to one of two or more treatment groups and to a control group (Kendall 2003; Akobeng 2005). As far as possible, all other care provided or received by participants is identical or standard. The information (outcome data) that will allow the groups to be compared is determined a priori, and is then collected and analysed. The outcome data collected are compared for the different groups with the hope that any differences observed are due to differences in the effects of the treatments received (Robertson and Torgerson 1998; Kendall 2003; Akobeng 2005). Differences that might occur due to chance or from factors other than the treatment under investigation (that is biases) are minimised by good quality trial design and strict adherence to randomisation procedures, in particular allocation concealment prior to the entry of a participant into the study (Beller et al. 2002). Achieving good quality trial design and optimising good quality randomisation procedures is discussed in detail in section 5.7.

5.4 Ethical considerations
Researchers have an ethical responsibility to ensure the rights of research participants are protected. Historical incidents of human abuse in the name of science, particularly in four experimental studies; the Nazi Medical Experiments, The Tuskegee Syphilis Study, The Willowbrook Study, and The Jewish Chronic Disease Hospital Study (Polit and Hungler 1999; Burns and Grove 2005), and the subsequent outrage, led to the development of formal guidance for medical research involving human subjects. The Declaration of Helsinki, developed by the World Medical Association (World Medical Association 1964), is one such statement that provides guidance for medical researchers. A core theme of the Declaration is maintaining ethical
standards that respect individuals and protect their health and rights. Maintaining ethical standards in the ADCAR trial, by adhering to the Declaration of Helsinki, are discussed with reference to the ethical principles of confidentiality, beneficence and justice.

5.4.1 The principle of confidentiality
Maintaining the ethical principle of confidentiality requires protecting and safeguarding all information collected on trial participants both during and after a trial is complete. A number of measures were established to ensure participant confidentiality in the ADCAR trial.

5.4.1.1 Protecting the identity of participants
Participants enrolling in the ADCAR trial were assigned a study number. This number was pre-printed on the bottom of the ADCAR trial consent form (Appendix VI) and was assigned to participants on signing the consent form prior to randomisation. The study number acted as a unique identifier, replacing the need to use individual names or dates of birth as identifiers of participants in the study. Although the research team and, where necessary, the Data Safety and Monitoring Board (see section 5.4.2.2 for further details), had access to outcome data collected, I was the only person with access to the list of study numbers linking individual participants with their outcome data. This list, and all other data and information relating to the trial was handled and stored securely to maintain confidentiality.

5.4.1.2 Storage of trial documents & data
During the trial, hard copy completed trial documents (consent forms, trial screening and register forms, audit forms etc.) were securely stored in the School of Nursing and Midwifery, Trinity College Dublin and in the School of Nursing and Midwifery, National University of Ireland Galway. All hard copy documents stored in the School of Nursing and Midwifery, Trinity College Dublin were stored in two locked filing cabinets. I was the only individual with access keys to the filing cabinets. Hard copy documents stored in the School of Nursing and Midwifery, National University of
Ireland Galway were stored in locked boxes in a locked room purposively allocated to the storage of research data. Hard copy trial data will be stored as described above for a minimum of five years following completion of the trial.

Computer held data included summary details of primary reasons for trial ineligibility, demographic details of trial participants (e.g. name, date of birth, gravida and parity) and the relevant outcome data of trial participants. These data were recorded in Excel files on a continuing basis throughout the trial and subsequently entered into SPSS version 16.0 for data analysis. All data were stored on a computer which is password protected with the password known only to me. As a precautionary measure, I ‘backed-up’ all data collected on a regular basis. I used an external hard drive for this purpose. This was stored in a locked filing cabinet, for which I was the only individual with an access key.

The ADCAR trial study information booklet for women (Appendix VII) informed potential participants that information collected during the trial would be stored for a period of five years following completion of the trial and then destroyed. Potential participants were also assured that while trial results might be published neither participants names nor personal details about them would appear in any publications. This information was provided to women before obtaining their consent to participate in the trial.

5.4.1.3 Registering as a data controller
All data were stored in accordance with the Data Protection (Amendment) Act 2003 and I registered as a data controller with the Office of the Data Protection Commissioner. Registration took place prior to commencing recruitment and was renewed on an annual basis as required. Details of this registration are available in the Public Register (Ref Number: 10166/A) held by the Office of the Data Protection Commissioner.
5.4.2 The principle of beneficence

The ethical principle of beneficence is expressed in the researcher’s responsibility to minimise risks of harm or discomfort to participants in research projects (National Health and Medical Research Council 2001). It necessitates that research is undertaken to do ‘good’ and is strongly connected to the ethical principle of non-maleficence, which requires research, above all, to ‘do no harm’ (Polit and Hungler 1999). Although no known risks were associated with the ADCAR trial a number of issues were considered in maintaining the ethical principle of beneficence throughout the trial.

5.4.2.1 Clinical equipoise

Clinical equipoise refers to a state of uncertainty regarding the comparative benefits of treatments being compared in clinical trials (Freedman 1987; Daya 2004). Although the epistemic prerequisite for conducting research, that is uncertainty regarding a clinical question (Miller and Brody 2007), ethically, clinical equipoise is the moral and practical principle justifying the conduct of a trial (Weijer et al. 2000). Without clinical equipoise, one ethical argument against randomisation is the potential for preventing half of the study population from receiving the more effective treatment. In such circumstances, a clinician or researcher knowingly recruiting a participant to a treatment, believed by them to be inferior, is in danger of compromising the welfare of that participant. Therefore, clinical equipoise, or uncertainty, is essential before enrolling a trial participant into a randomised trial.

Clinical equipoise in the ADCAR trial, that is genuine uncertainty as to whether routine ACTG is more beneficial than IA for assessing the FHR in low risk women, is demonstrated by inconclusive evidence from previous studies (Blix et al. 2005), by the findings of the systematic review in this thesis (Chapter 3), and from calls for further research evaluating the use of the ACTG (RCOG 2001).
The genuine state of uncertainty associated with clinical equipoise must exist within the collective clinical community (Weijer et al., 2000, Daya, 2004, Miller and Brody, 2007). In the ADCAR trial issues with clinical equipoise emerged at one study site. In preparation for launching the ADCAR trial, I spent a considerable amount of time meeting staff at all three clinical sites. The purpose of these meetings was to provide information on the trial (inclusive of background evidence, rationale and recruitment processes) and afford staff an opportunity to ask questions or voice concerns. During the course of such meetings it was made known to me by one midwife and two consultant obstetricians that they were unsupportive of the ADCAR trial due to their belief that the ACTG was the most appropriate method for assessing the FHR on admission in low risk women. Although individual reasons for this belief varied slightly, two prominent themes emerged. The first related to the ACTG providing a sense of security and/or assurances that the fetus was not compromised on admission. The second related to the fear of potential litigation and protection against such in the absence of not performing an ACTG. As discussed in Chapter 4, these themes are evident in the published literature. Despite discussions on current evidence and the rationale for the ADCAR trial, and assurances that the ADCAR trial was fully indemnified (see section 5.5), all three, however, remained firm in their resolve not to support the ADCAR trial. A consensus was reached that women attending the consultants’ clinics would not receive the ADCAR trial study information booklet, and would not therefore, be considered for recruitment to the study, highlighting that individual uncertainty was also necessary for recruitment to the ADCAR trial. If the professional (or a woman, whose participation was voluntary) was certain about ACTG or IA, the potential participant would not be randomised to the trial, regardless of the collective clinical community’s opinion across the trial.

5.4.2.2 Data safety and monitoring board

Data Safety and Monitoring Boards (DSMBs) were first introduced in the 1960s as a mechanism for ensuring the safety of trial participants (Slutsky and Lavery 2004; Hicks et al. 2007). The principal role of the DSMB in the
ADCAR trial is to monitor interim trial data for early evidence of significant harm or benefit with a mandate to stop the trial early if one arm of the trial demonstrates such evidence (Slutsky and Lavery, 2004, Hicks et al, 2007). Members of a DSMB should be independent of a trial so that emerging trial data might be reviewed in an unbiased manner. Members should also have sufficient collective clinical and research expertise to understand and interpret the data they review (Hicks et al. 2007). Prior to commencing the ADCAR trial, an independent DSMB was established in accordance with the terms of reference of the Medical Research Council (Medical Research Council 1998). Members of the DSMB include a Professor of Midwifery, a Professor of Obstetrics and a statistician (Appendix VIII contains the terms of reference for the DSMB for the ADCAR trial and details of its members).

The ADCAR trial DSMB will review and evaluate unblinded interim analysis, using a reduced threshold for statistical significance (alpha) for stopping the study of 0.01 (Friedlin et al. 1999) when complete data have been received on the first one-third ($n = 1,906$) and two-thirds ($n = 3,870$) of the target number of women for the main study. The DSMB will assess participant safety, rights and whether either intervention is showing a much stronger or weaker effect than expected. It will make recommendations concerning the continuation, modification or termination of the trial to the Trial Steering Committee (TSC).

5.4.2.3 Adverse events report form

As a means of further ensuring participant safety, and as a general indicator of increased adverse events occurring in one arm of the trial, a Serious Adverse Events Report Form (SAERF) (Appendix IX) was developed. Serious adverse events of significance were determined through discussion and agreement with members of the TSC.

The occurrence of a serious adverse event was highlighted either during the process of data collection or by staff members at the respective clinical site. When I became aware of a serious adverse event, I completed a SAERF. The
maternity and neonatal notes of the participant were reviewed and summary details of labour, birth, postnatal and neonatal events were documented. Copies of these documents were provided to the relevant member of the TSC (that is neonatologist, obstetrician and/or midwife) at the respective clinical site for review. In addition, the occurrence of serious adverse events was reported to the DSMB if deemed appropriate by the ADCAR team.

5.4.3 The principle of justice
In clinical research involving human participants, the ethical principle of justice refers to the fair and equitable treatment of all individuals (Polit and Hungler 1999). It aims to ensure that certain groups are protected from unfairly bearing the burden of research while concurrently protecting other groups from unfair exclusion (National Health and Medical Research Council 2001). A number of issues were considered in ensuring fairness and equity in the ADCAR trial.

5.4.3.1 Autonomy and informed consent
Autonomy and informed consent refers to an individual's right to determine participation in a study. In the ADCAR trial, it involved the provision of information that was both accurate and easy to understand. It also involved allowing sufficient time for potential participants to evaluate the information they received, ask questions about the research study and make an informed choice on their participation (Underwood et al. 2000). The ADCAR trial study information for women booklet (Appendix VII) provided potential participants with detailed information on the trial. This booklet was reviewed by the National Adult Literacy Agency (NALA) for literacy appropriateness prior to submission, for approval, to the relevant research ethics committees. Women received the information booklet during pregnancy at or any time after thirty-two weeks gestation. This provided sufficient time for them to read the information and consider taking part in the study, yet was not too lengthy to risk memory lapse. Participation in the study was voluntary and required women to sign a written consent form. Women were made aware of this in the study information booklet and were also informed that if they
decided not to participate in the study this would not compromise their care in any way.

5.4.3.2 Equitable entry to the ADCAR trial
Equitable entry to the ADCAR trial was assured by the requirement that all potential participants met pre-defined trial eligibility criteria and through the offer of voluntary participation. Excluding women with limited English proficiency or no English, although controversial and reductionist in achieving quality and fairness (Bustillos 2009) was considered necessary in the ADCAR trial. This was because midwives were uncomfortable and unwilling to obtain consent from women who were unable to communicate their consent in English. The main concern for midwives was ascertaining if such women understood the study and were in a position to provide informed consent. Midwives were happy, however, to recruit women attending with an English speaking birth partner or a translator who could communicate clearly their informed consent to participate in the trial. In such circumstances, the woman and her birth partner/translator co-signed the consent form.

5.4.4. Ethical approval for the ADCAR trial
The process of securing ethical approval to conduct the ADCAR trial was lengthy and ongoing throughout 2007 and early 2008 and involved separate applications to five Research Ethics Committees (four potential clinical study sites (Site A, Site B, Site C and Site D) and the Ethics Committee of the Faculty of Health Sciences, Trinity College Dublin).

Ethical Approval for the ADCAR trial was granted by the Ethics Committee of the Faculty of Health Sciences, Trinity College Dublin and by three of the four potential clinical sites; Site A, Site B, and Site C, subject to addressing some minor concerns (Appendix X contains relevant letters of ethical approval and Appendix XI contains concerns raised and details of how these were addressed). The Research Ethics Committee of Site D, following a review of the study at committee meetings in March and April 2007, and having discussed the study in detail at a consultant obstetricians’ meeting in
late March 2007, did not grant ethical approval for the ADCAR trial to proceed. The reason provided was that a number of consultant obstetricians ‘for a number of reasons including medico-legal concerns’ were unwilling to support the conduct of ADCAR at that time (Appendix XII).

5.5 Clinical indemnity for the ADCAR trial

Clinical indemnity refers to insurance against or compensation for any loss or damage occurring within the clinical setting. A requirement of the research ethics committee at each clinical site was a guarantee of indemnification for the ADCAR trial.

The Clinical Indemnity Scheme (CIS) as operated by the State Claims Agency provides cover for clinical trials subject to the following criteria;

- The trial has received approval from the relevant research ethics committee
- The trial is designed by an enterprise or any of its employees covered by the scheme
- Where the trial is sponsored by external organisations, the CIS cover extends to treatment only and does not cover product liability or claims arising from trial design or protocol

(www.stateclaims.ie/ClinicalIndemnityScheme.html)

The ADCAR trial is funded by an external organisation; The Health Research Board, Ireland. Therefore the ADCAR trial is indemnified by the CIS for claims arising from treatment only.

Cover for potential claims arising from trial design and/or trial protocol was provided by Trinity College Dublin’s Professional Indemnity Policy at the onset of the trial and subsequently, for the remainder of the trial, by the National University of Ireland Galway’s Professional Indemnity Scheme (see Appendix XIII for details of relevant policies). The transfer of indemnity from Dublin to Galway occurred in 2008 when the Principal Investigator for
the trial transferred employment from Trinity College Dublin to the National University of Ireland Galway.

5.6 Clinical trial registration

In 2004, The Society for Clinical Trials announced its support for legislation that would mandate registration of all clinical trials prior to enrolment of the first participant (Dickersin et al. 2004; Ghersi and Pang 2009). In that same year, the International Committee of Medical Journal Editors (ICMJE) issued a statement requiring registration of a clinical trial in a public trials registry at or before recruitment of the first participant as a condition of consideration for publication in all eleven ICMJE member journals (De Angelis et al. 2004). This call for trial registration stemmed from evidence of selective reporting of trials and the subsequent potential to distort the body of evidence available for clinical decision making (De Angelis et al., 2004, De Angelis et al., 2005, Krieza-Jeric et al., 2005).

In May 2003, the United Kingdom Clinical Controlled Trials Group formally launched a database (www.controlled-trials.com) that met the requirements of the ICMJE. A useful feature of this database is the International Standardised Randomised Controlled Trial Number (ISRCTN) whereby each registered trial is assigned a unique number to assist in tracking all publications and reports resulting from the trial.

The ADCAR trial was registered with Clinical Controlled Trials on 25th March 2008. The ISRCTN for the ADCAR trial is: ISRCTN96340041.

5.7 Quality in clinical trials

Considering the potential for randomised trials to influence clinical practice the reliability and credibility of trial evidence is paramount. This reliable and credible evidence is dependent on high standards of methodological quality, which is achieved only through appropriate trial design, conduct, and analysis.
5.7.1 Trial design
In designing the ADCAR trial a number of issues were considered to ensure optimum trial design. These included the study population, the sample size required to meet the aims of the study and the clinical sites in which ADCAR would take place. Consideration was also given to the randomisation process; specifically control within this process, to reduce any influence from confounding or bias.

5.7.1.1 Study population
Pregnant women at low risk for intrapartum fetal hypoxia at term were eligible to participate in the ADCAR trial. Women of all races and ethnic groups were eligible to participate; however, the ability to communicate consent in English was essential. For women whose first language was not English, consent could be communicated through an English speaking birth partner or language translator.

Inclusion criteria:

- Women between 37\(^0\) and 40\(^6\) completed weeks of pregnancy
- Absence of antenatal, maternal and fetal risk factors to the development of neonatal encephalopathy, cerebral palsy or perinatal death as per the Royal College of Obstetrics and Gynaecology (RCOG 2001) and as per discussion and consensus with Trial Steering Committee members (see Appendix XIV, The ADCAR Trial Screening & Register Form (TSRF), for a complete list of exclusionary factors).
- \(\geq\) 18 years of age
- \(\leq\) 40 years of age
- Ability to understand study information and willingness to give written, informed consent

Exclusion criteria:

- Any criteria that did not meet the inclusion criteria as above
5.7.1.2 Sample size assumptions and estimates

An appropriate sample size, for a clinical trial is essential for detecting any clinically important differences between the groups being compared and requires careful consideration in advance of commencing a study. Too small a sample size may lead to a failure to detect a clinically meaningful difference and a larger sample size than necessary would lead to a waste of resources (Devane et al. 2004). An appropriate sample size in clinical trials depends on three key factors; the effect size, the p-value or alpha-value and the power of the test (Friedman et al. 1998; Jones 2002; Devane et al. 2004). The effect size is a pre-determined, clinically meaningful, amount of difference between the groups. It depends on the chosen outcome under study. The p-value is the probability (ranging from zero to one) that any difference found in the study is real and not due to chance (Devane et al. 2004). The power of a test is the ability of the test to reject the null hypothesis when it should be rejected (that is avoiding a Type II error). The greater the power the less chance there is of a Type II error occurring (i.e. concluding that there is no difference between the interventions when there really is one).

In calculating sample size estimates for the ADCAR trial, a retrospective clinical audit of six hundred women was conducted in Site A and Site D in 2005. The aim of this audit was to determine the number of women meeting the eligibility criteria for ADCAR on admission to the labour ward and to determine the incidence of caesarean section in this low-risk audit sample. This audit found that 60% and 50% of women met the eligibility criteria on admission to the labour ward in Site A and Site D, respectively. Of these women, 4.7% and 5.6% respectively had a caesarean section. These figures are consistent with published figures from the United Kingdom (Steering Group of the Birth Centre Network, 2001, Cheyne et al., 2003). At the time of the audit, there were approximately 10,000 births per year in the two hospitals combined. Assuming that approximately 55% of these would be eligible and that about half would agree to take part in the ADCAR trial, it was estimated that 5,776 women could be recruited over a twenty-six month...
period allowing for a 10% attrition rate and one month contingency. This sample size (2,888 per group) would have sufficient power (at >80%) to detect a 30% reduction in the primary outcome measure of incidence of caesarean section, for example from 5.2% with ACTG to 3.6% with IA. This 30% reduction emerged from the audit data and was determined as a clinically meaningful reduction in the incidence of caesarean section through discussions with and consensus from practicing clinicians in the participating study sites. These calculations were done using SamplePower. The p-value was set at 0.05 and the test is two-tailed.

5.7.1.3 Study sites

The large sample size and optimising recruitment within a reasonable time frame necessitated multiple clinical sites for the ADCAR trial. In addition, multiple sites would allow for the inclusion of a population from different geographic regions and the ability to compare results amongst clinical sites. This would lead to an increased generalisability of study results.

The ADCAR trial took place in the maternity unit of three clinical sites in the Republic of Ireland; Site A, Site B and Site C. The process of securing multiple sites was not without difficulty and involved a considerable amount of time, delaying the anticipated start date for commencing recruitment. Initial trial proposals included two clinical sites; Site A and Site D. As discussed above, following a number of meetings and consultations, Site D declined to support the conduct of the ADCAR trial. As there were approximately four thousand births per year at Site A, an additional clinical site was required to ensure the possibility of recruiting the estimated sample size within a reasonable time frame. A lead clinician at Site B was contacted to determine the possibility of their hospital becoming a study site for ADCAR. A meeting was arranged, in May 2007, between potential TSC members, ADCAR’s Principal Investigator (PI) and me. The ADCAR trial protocol was discussed and support to conduct ADCAR at Site B was agreed, pending ethical approval.
The possibility of a third clinical site (Site C) arose early in 2008. This occurred when the PI to the study relocated to a different university. This allowed for the establishment of support links across a geographically disperse region. In addition, considering the delays already encountered in starting the ADCAR trial, the advantages of a third study site included the potential to increase recruitment rates while reducing recruitment time frames. As with Site B, a meeting was arranged with potential TSC members at Site C. This took place in May 2008. The ADCAR trial protocol was discussed and support to conduct ADCAR at Site C was agreed, pending ethical approval.

Recruitment to the ADCAR trial had started in all three study sites by April 2009. The study launched at Site A in May 2008 (incorporating the pilot phase of the study – see section 5.7.2.3). Recruitment commenced at Site B in August 2008 and at Site C in April 2009. Although launch intervals between sites were originally anticipated as being shorter, the staggered start was purposively planned so as to incorporate a pilot phase and to identify any major issues with trial design in one study site prior to launching in subsequent sites. Emerging problems identified during the pilot phase (see section 5.7.2.3) were resolved and thus avoided when ADCAR was implemented at Site B and Site C, respectively. Reasons for delayed launches at these sites included; increased time required in providing staff with information on trial processes and ensuring support at each clinical site once the trial was launched.

5.7.1.4 The reduction of bias

The reduction of bias is central to the design of a randomised trial. It not only allows for the conduct of a good quality trial; it also allows for definitive statements of cause and effect to be made and it increases the validity of trial results. When designing a randomised trial, a number of measures that will assist in minimising the introduction of bias, may be considered. These include; allocation concealment, blinding, sequence generation and an intention to treat analysis.
5.7.1.4.1 Allocation concealment

Implementing an allocation method in a randomised trial that ensures clinicians and participants remain unaware of upcoming allocations, at least until participants are assigned to their respective group, is known as allocation concealment. It is essential in minimising selection and confounding biases (Chalmers et al., 1983, Schulz and Grimes, 2002, Kendall, 2003). Awareness of upcoming allocations might result in the exclusion of potential participants because the upcoming group is undesirable to them or deemed inappropriate by the individual recruiting the potential participant to the trial (Schulz and Grimes 2002), or result in the inclusion of participants who would not have been included if the alternative intervention had been a possibility for them. Participant inclusion becomes based, therefore, not on trial eligibility but on the influence of a clinician’s desire to recruit (or not) a participant to the upcoming group. Such selection bias undermines the process of randomisation and threatens the credibility of trial results because it has the potential to lead to a miss-estimation in the effects of the treatment (Schulz and Grimes 2002). Two adequate and common methods for ensuring allocation concealment in clinical trials are sealed, consecutively numbered opaque envelopes and remote telephone or computer randomisation.

The sealed envelope method involves, in advance of the trial commencing, placing the randomly generated group allocations in consecutively numbered opaque envelopes and sealing the envelopes. When a participant has given their consent to take part in the study, the next envelope in the sequence is opened and the allocation is assigned. With telephone randomisation, the individual recruiting the participant telephones a remote randomisation service/centre, following the consent process, and is provided with the next group allocation. Telephone randomisation is often considered the preferred method of allocation concealment, particularly in large multi-centre trials where the risk of potential loss of envelopes or discarding of opened envelopes is higher (Kendall 2003).
In the ADCAR trial adequate allocation concealment was achieved via remote telephone randomisation. The randomisation service was provided by ALEA, a software package developed to support randomisation in healthcare research in Europe. ALEA is operated from the Netherlands and provides a number of randomisation modules from which researchers may choose. The module used in the ADCAR trial was the Interactive Voice Response (IVR) Module. Using this module the investigator telephones the randomisation centre. The IVR system reads the relevant questions to the caller who responds using the digits on the telephone. At the end of this process the IVR provides the caller with the group allocation (see Appendix XV for sample questions required by the IVR system).

5.7.1.4.2 Blinding
Blinding (or masking) in clinical trials refers to concealing the group allocation after it has been assigned (Daya 2006). It is necessary to minimise response bias which can result from the conscious expectation of an outcome associated with the group allocation (Day and Altman 2000). A trial may be single, double or triple blind. In a single blind trial it is usually the participants who do not know which treatment they have received. In a double blind trial, it is usual for neither the participant nor the clinician/investigator to know who has received which treatment. In triple blind trials, the data analysers, as well as the participant and the clinician/investigator might not know who has received which treatment.

In the ADCAR trial, considering that the interventions being compared involved the actual application of very different methods of FHR monitoring, it was not possible to blind either the participant or the clinician to the group allocation. The clinician needed to know the allocation so as to carry out the appropriate treatment and the participant would know the treatment she received. Although blinding is important in reducing response bias, it is considered less important in trials where outcome data are objective (Day and Altman 2000). This is because the potential for preconceived perceptions of
treatment effects influencing trial results is less than that associated with subjective data (such as measuring pain for example). As all outcome data collected in the ADCAR trial were objective, I am confident that the knowledge of treatment allocation did not have a major influence on the trial’s results.

5.7.1.4.3 Sequence generation

Sequence generation refers to the method used to ensure random allocation of the group treatments. It is important for equal distribution of group allocations and helps reduce potential bias between groups. Simple randomisation, akin to repeated coin-tossing, is the most basic form of sequence generation. It is considered the best method for ensuring unpredictability in upcoming assignments (Schulz and Grimes 2002a). A major limitation of simple randomisation, however, is the potential for unequal group sizes, although this is reduced with larger sample sizes. Block randomisation is an alternative method for ensuring equal distribution of participants to the different groups (Schulz and Grimes 2002a; Kendall 2003). Using this method the group allocations are considered in blocks containing two, four, six, eight etc. allocations randomly placed within the block. The block size may be fixed or randomly varied throughout the trial. The blocks are then randomly selected and the allocations are determined as per the group sequence within the first, second, third etc. blocks until the trial is complete (Beller et al. 2002; Akobeng 2005). Stratified randomisation is an additional method used in sequence generation. It is used to assist in reducing chance imbalances in the baseline characteristics of participants in each group (Beller et al, 2002, Akobeng, 2005, Burns and Grove, 2005). To achieve stratification the sample population are grouped according to a particular characteristic (for example, smoker or non-smoker) and then block randomisation occurs within each stratum. Stratification is considered particularly beneficial in multi-centre trials where the potential risk for imbalances is greater (Schulz and Grimes 2002a).
In the ADCAR trial, sequence generation was achieved using block randomisation and stratified randomisation by study site. Random sequences of block sizes of two or four were generated by the randomisation centre with randomisation of groups on a 1:1 ratio. Stratification by study site was achieved by establishing a separate randomisation list for each centre. As a requisite for accessing the group allocation, each centre had to enter a unique PIN identifier when telephoning the randomisation service. This allowed the ALEA system to identify which study site was telephoning the service. Group allocations per study site were identifiable on the ALEA database using the Alpha prefixes.

5.7.1.4.4 Intention to treat analysis

Intention to treat is an analysis of data based on the allocated group regardless of the treatment actually received by the participant and regardless of any subsequent withdrawal from treatment or deviation from the trial protocol (Hollis and Campbell 1999; Fergusson et al. 2002). It is considered important in clinical trials in minimising bias associated with withdrawals based on the allocated treatment and loss to follow up. An intention to treat analysis reduces the risk of a Type I error; that is rejecting the null hypothesis when the null hypothesis is actually true. Furthermore, it allows for the inclusion of all participants originally randomised thereby increasing the generalisability of the study (Fergusson et al. 2002).

The analysis of data, in the ADCAR trial, was performed based on the intention to treat principle.

5.7.1.5 Recruitment and randomisation procedures

Careful planning of recruitment and randomisation procedures is paramount to trial design to ensure effective implementation of a study. Throughout 2007 and early 2008, I spent a considerable amount of time in consultation with TSC members at all three study sites, to plan the ADCAR trial and its implementation. The purposes of these meetings were to discuss the recruitment and randomisation processes and to agree subsequent care-
pathways once women were randomised that were identical and suitable to all three study sites. When agreements were reached, the next step was to ensure that all clinical staff working in the respective areas where the study would take place were fully informed of the trial processes. This was facilitated through a series of information workshops held frequently and on an ongoing basis before the launch of the study at each clinical site. These information workshops provided an open and transparent forum to inform staff of the trial and to allow staff to raise any questions or concerns.

Consensus was reached for the ADCAR trial recruitment and randomisation procedures between the research team and TSC members at each clinical site and included the following steps (Appendix XVI contains the summary care-pathway algorithms);

- All women attending the antenatal clinics at or from thirty-six weeks gestation onwards are screened using the ADCAR trial Preliminary Trial Screening Form (Appendix XVII) to determine, at this time, their eligibility to participate in the ADCAR trial (this step was subsequently amended during the pilot phase and details are provided in section 5.7.2.3).

- Women who are eligible at this time receive the ADCAR trial study information for women booklet (Appendix VII) and a label titled ‘ADCAR study information given’ is placed on the outside of their maternity notes. Women who are ineligible do not receive the information booklet and a label titled ‘Ineligible for ADCAR’ is placed on the outside of their maternity notes.

- All women who subsequently attend the labour ward or labour assessment room with signs of possible labour are rescreened by the admitting midwife using the ADCAR trial Trial Screening & Register Form (TSRF) (Appendix XIV) to exclude those women who may have developed risk factors in the interim.

- Women who remain eligible at this time are invited to participate in the study.
Eligible women who agree to participate in the study sign a written consent form (Appendix VI) and are randomised by the admitting midwife via the telephone randomisation centre to either IA or ACTG on a ratio of 1:1. A label titled ‘IA’ or ‘ACTG’ as appropriate is placed on the outside of the participants’ maternity notes. The admitting midwife subsequently performs the care determined by the group allocation and confirms if the woman is in established labour at this time. For study purposes: IA includes abdominal palpation of uterine contractions and auscultation of the FHR for at least 60 seconds after a uterine contraction. Conversion to ACTG occurs where auscultation reveals a baseline FHR of less than 110bpm or greater than 160bpm or any decelerations in the FHR; or if any other risk factors develop, which warrant EFM, or if the clinician caring for the woman has any other cause for concern. ACTG includes a 20 minute period of EFM on admission to labour ward, followed by a review and interpretation of the ACTG by the admitting midwife. If the FHR is between 110-160bpm, baseline variability is > 5bpm, more than two accelerations are present and decelerations are absent the tracing is classified as normal, discontinued and the findings documented. The uterine contraction pattern is also assessed.

Subsequent care received by women participating in the study includes standard care; that is women who are in established labour will be transferred to the labour ward with monitoring of the FHR by IA for one full minute every fifteen minutes in the first stage of labour and every five minutes in the second stage of labour, unless otherwise indicated and conversion to EFM is required. Women who are not in established labour are admitted to the antenatal ward or discharged home (depending on their clinical status and/or proximity to the hospital), to await further signs of labour. Women randomised to IA and going home receive a twenty minute discharge CTG prior to leaving the hospital.

Women who go home and subsequently present to the hospital with further signs of possible labour are rescreened using the ADCAR
Trial Readmission Screening Form (Appendix XVIII) to ensure continuing eligibility. For women who remain eligible, monitoring of the FHR is as per the previously allocated method (that is either IA or ACTG). For women who no longer meet the eligibility criteria, an ACTG is performed, irrespective of previous group allocation, and the reason for ineligibility is documented on the readmission screening form.

5.7.2 Trial conduct
The successful conduct of a trial, following optimum trial design and ensuring measures are in place to support the trial design, is largely dependent on a number of factors including the development of a trial protocol to guide the trial, accessing study sites and ensuring support from study sites, conducting a pilot study and optimising recruitment and randomisation to the trial.

5.7.2.1 Trial protocol
In adhering to recommendations and expectations that a trial protocol is established before conducting experimental research (Burns and Grove 2005), a protocol for the ADCAR trial was developed and amended accordingly following the pilot phase of the study. The ADCAR trial protocol (Appendix XIX) provides details of Trial Steering Committee members, the rationale for the research, the aim of the study, the proposed methodology and methods, data collection and data analysis procedures and acknowledges the study’s funding sources.

5.7.2.2 Access to and support from clinical sites
Although having multiple centre in a trial might add complexity and has been associated with a reported increase in problems with recruitment when compared to single-centre studies (Puffer & Torgerson 2003, Tooher et al 2008), multicentre trials afford the advantage of allowing for an increase in potential participants, for the inclusion of geographically dispersed centers and for a comparison of results between study sites. Considering the large
sample size required to meet the aim of the ADCAR trial, multiple study sites were required to ensure sufficient recruitment within a reasonable time frame.

Accessing clinical study sites in which to conduct ADCAR began at the time of protocol development. Most of this activity was done by the PI to the study. Appropriate obstetric and midwifery clinical managers at the sites were contacted to ascertain their support for the trial. Initially, two clinical sites were approached, site A and site D. As discussed in section 5.7.1.3, site D subsequently withdrew support to conduct the ADCAR trial. A search for alternative sites began and following a series of meetings with obstetric and midwifery clinical managers (as discussed in section 5.7.1.3) and following approval from respective hospital Ethics Committees, two further sites were secured (site B and site C).

Considering the nature of the ADCAR trial and the need for twenty-four hour, seven days a week recruitment, it was recognised that support from clinical sites and the staff therein was paramount to the success of the trial. Significant in achieving this support was recognition that the ADCAR trial involved a change in clinical practice and recognition of the busy environment that clinical staff, who would recruit trial participants, were working in. It was recognised that clinical staff at each study site would require support to enable them to conduct recruitment to the trial.

Supporting staff members within each study site was facilitated by the researcher, another member of the research team, or both. It involved a series of information workshops prior to commencing the trial, and workshops as and when required (for example, during a period of staff rotation or during employment of new staff) throughout the trial. These workshops were held at a time most convenient for the clinical staff concerned. For example, at one clinical site, I held information sessions directly after morning report and at change of shift. This enabled both day and night staff to attend and allowed for discussions with a large number of staff at the same time. As the trial progressed and as staff became more familiar with the study, the information
workshops progressed towards one-to-one workshops (for example, for individual agency or new staff to the environment or individual queries from existing staff members).

Supporting clinicians also involved my visiting the clinical environment on a weekly basis throughout the trial, apart from when I was on annual leave. The purpose of these visits was to maintain and build relationships with clinical staff. They involved assisting staff through the screening, consent and randomisation process; and listening to concerns raised by staff and adopting mechanisms to facilitate recruitment that offered a minimum of disruption to their working environment. For example, at one study site clinicians experienced particular difficulty at times of heightened clinical activity, to proceed through the steps necessary to telephone the randomisation centre (Appendix XV). In an effort to reduce the time required, I discussed the option of being able to establish a ‘speed dial’ for the telephone number for the randomisation service. I discussed this with the site’s switch board who agreed to facilitate this feature. This was duly implemented and feedback showed that it made recruitment easier for staff members. Another example to facilitate easier recruitment included my assisting the randomisation process; for example, telephoning the randomisation centre for staff members when I was present on the labour ward and visiting the antenatal clinics to provide women with the study information and answer any questions women might have about the trial. Activities to support clinical staff, such as those described above, remained ongoing throughout the recruitment phase of the trial.

5.7.2.3 Pilot study

Unanticipated problems may arise when implementing a research study, which may result in the need to amend a trial protocol. It is important therefore to conduct a pilot study or trial run of the main study as a means of identifying any problems with trial design or recruitment procedures (Polit and Hungler 1999). This is especially important in experimental research because any data collected before and after changes are made might not be
combined. As Site A was in a position to commence recruitment to the ADCAR trial before the other clinical sites, a decision was made to begin the pilot study at this site. Although it has been recommended that a pilot study should be one-tenth of the size of the main study (Treece and Treece 1986), neither a time-frame nor a sample size was pre-specified for the ADCAR trial pilot study. The reason for this was a consensus among the TSC that it was more important to allow the pilot study to run for as long as was necessary to identify and resolve all emergent problems. By conducting the pilot study in this way, the risk of any further problems arising, after the main study had started, would be minimised. The pilot phase of ADCAR commenced on 23 April 2008. Within three weeks, two major problems with the trial design were identified. The first concerned the preliminary screening process and the second the provision of study information to women.

As detailed in section 5.7.1.5, the original trial design included a preliminary screening process to exclude ineligible women from thirty-six weeks gestation onwards. It was agreed that the individual (obstetrician, non-consultant hospital doctor or midwife) attending to the woman at that antenatal visit would complete the preliminary screening form and administer the information booklet as appropriate. However, in the early weeks of the pilot phase, it became apparent that women were not being screened and, therefore, many eligible women were not receiving the study information booklet. This was noted through careful review of completed screening forms, discussions with clinical staff and observing charts of women presenting to the labour ward with signs of possible labour.

Following consultation with clinical staff the main reason for non-completion of preliminary trial screening forms was that it was too time-consuming for what were already busy and demanding clinics. Staff members did not feel that it was feasible to screen all women attending the antenatal clinics. In addition, as further screening for trial eligibility would be performed on some women on admission with signs of possible labour, some staff considered the
preliminary screening as repetitive and an unnecessary duplication of workload.

Following consultation with midwifery managers, consultant obstetricians and TSC members, a decision was made to remove the formal preliminary screening process; instead all women where appropriate (that is those having no known obvious risk factor such as a previous caesarean section or serious medical problem for example) would be provided with the study information booklet. The label ‘ADCAR study information given’ would be placed on their maternity notes and these women would receive formal screening for potential participation on presenting to the labour ward with signs of possible labour.

The second main problem noted during the pilot phase related to the gestation that women received the study information. This was from thirty-six weeks gestation onwards. It soon became apparent, however, that this time frame was too short. If for some reason a woman missed her thirty-six week appointment or did not receive the information booklet at this appointment, she might present to labour ward with signs of possible labour before she was due to attend the antenatal clinic for her subsequent appointment. Having not received the study information, this woman could not be considered for participation in the study. The time frame for which women received the study information was therefore amended to include ‘at or from thirty-two weeks gestation onwards’.

Other issues that emerged during the pilot phase which required attention but did not involve a change to the trial protocol included;

- Initial problems with the ALEA package classifying some randomisations as duplicate entries when they were not. This was quickly resolved by a quality assurance check by the ALEA service providers.
- The need for more workshops to ensure all staff were familiar with the trial processes. These were increased during the launch of the trial.
at the other sites and remained available at all three sites as and when required throughout the duration of the trial

• Acknowledging that the clinical environment was extremely busy at times and that staff required support to facilitate recruitment. Clinical staff were supported by weekly visits to the clinical site by the researcher or member of the research team, throughout the duration of the trial.

Recruitment to the ADCAR trial main study commenced on 18th May 2008. As no further changes to the trial protocol or recruitment procedures were required on commencing the trial at Site B and Site C, all data on trial participants from this date onwards were collected and analysed as part of the main study analysis.

5.7.2.4 Optimising recruitment and randomisation

Recruitment to randomised trials presents a challenge and more often than not actual recruitment rates fall below expected recruitment rates (Watson and Torgerson, 2006, Sood et al., 2009, Treweek et al., 2010). Poor or slow recruitment to trials causes a number of problems for study outcomes, most important of which is a reduction in the statistical power of the study and an increased risk of a Type II error (Watson and Torgerson, 2006, Toher et al, 2008, Sood et al, 2009, Treweek et al, 2010). The clinical implication of an underpowered trial is the possibility that the study findings will erroneously conclude that there is no difference between the treatments under investigation when in reality there is a difference. This erroneous conclusion has clinical significance in that the general population may be denied a potentially more effective treatment than was previously offered. In addition, poor or slow recruitment to a trial may also require extending the trial period (Watson and Torgerson, 2006, Treweek et al, 2010). This may lead to increased costs and may have implications for future funding by the funding agency (Watson and Torgerson, 2006).
Recruitment rates were evaluated and assessed on an ongoing basis throughout the trial. In an effort to obtain optimum recruitment in the ADCAR trial, a number of strategies were considered.

5.7.2.4.1 Visits to study sites

Although a Cochrane review reported no significant increases in recruitment rates with greater contact between trial coordinator and study sites (Treweek et al, 2010), regular visits to study sites are considered important for encouraging enthusiasm and in maintaining support from clinical staff (Berger et al. 2007; Tooher et al. 2008). Prior to launching the trial, I spent a considerable amount of time meeting with staff at each site to discuss the trial processes and to allow staff to voice any questions or concerns they may have had in relation to the trial. Once the trial was launched, I or a member of the research team (this included the subsequent employment of junior research assistants\(^ {10} \) - see Appendix XX for ‘Role of Junior Research Assistant to the ADCAR Trial’) visited the study sites on a weekly basis. The purposes of these visits were to meet with staff, to support them to implement trial processes and to encourage them to facilitate ongoing recruitment. In addition, I held information sessions for existing staff, new staff, or rotating staff as and when required (see section 5.7.2.2). During these sessions, the importance of the study was highlighted and staff were encouraged to make suggestions that might facilitate easier recruitment. Time was also spent with clinical staff to ascertain recruitment skills and to offer any advice or assistance to improve these skills if deemed necessary. For example, one senior midwife had concerns over a junior midwife saying to a potential participant that... ‘I think this is a good study to join’. The senior midwife believed this was too personal an opinion that possibly might bias recruitment by potentially influencing a prospective participants’ decision to join the

\(^{10}\)Due to geographical disparity, a junior research assistant was employed, for six hours per week, to assist in supporting the trial at one study site. At a second study site, and following a meeting with TSC members six months following launch of the trial, where concerns over low recruitment rates were discussed, the clinical manager, in demonstrating support and commitment to the ADCAR trial, allocated a staff member to work for and with the trial for nine hours per week.
study. This was addressed by discussing with staff how best to support the study yet remain objective, so as to allow potential participants to make an informed but personal choice. An agreement was reached that should potential participants ask staff for their own opinion, staff members might reply that the hospital fully supports the study, that the study has been approved by the hospital Ethics Committee and that by doing this study it is hoped to improve the care provided to mothers and their babies in the future, rather than offering a personal opinion.

5.7.2.4.2 Trial updates
Ongoing trial updates for clinicians were provided throughout the trial. This was done informally and formally. Informal updates occurred during meetings with staff on site visits when the trial’s progress was discussed with them. Formal updates were provided through a series of professional meetings, posting of newsletters, use of media sources, and through conference poster and paper presentations.

Trial updates at professional (and usually multidisciplinary) meetings occurred on average every three months, at each study site, throughout the recruitment phase of the trial. This usually involved a brief overview of the trial (to inform any new staff members of the trial processes) and a graphical presentation of recruitment figures and trends to date. Time was afforded for staff to ask any questions and to provide suggestions on how recruitment might be improved. To promote ongoing interest and as a way of updating all staff on the trial, monthly or bi-monthly newsletters were posted in the clinical areas throughout the duration of the trial (Appendix XXI contains examples of these newsletters). Use of media sources, such as hospital publications, was also used to provide information on the trial, and to promote interest in it. In addition, a trial website was established (click on ADCAR at www.childbirthresearch.com). Finally, to garner further support, interest and awareness, poster and paper presentations occurred at a number of conferences and relevant events throughout the duration of the trial.
5.7.2.4.3 Regular audit

If poor recruitment rates were identified, TSC members discussed how best to improve recruitment. A decision was made to conduct an audit, which might help identify and target areas of poor recruitment. Although it was apparent that there were fewer completed screening forms per month than births at the sites, indicating that not all potentially eligible women were being approached for inclusion in the study, it was not possible to quantify this figure accurately without more work. In particular, I had no way of knowing how many eligible women were not receiving the study information or how many eligible women were not being screened for the trial. The audit procedure would allow for a quantifiable insight into this. In addition, it might allow for the identification of particular clinicians who were having difficulties recruiting potential participants. An ADCAR trial audit form was developed (Appendix XXII). The audit process involved a spot check of all postnatal charts present on the postnatal wards of the hospital on a given day and time. It was initially conducted once a week and subsequently reduced to once a month or as and when required (e.g. during a period of particularly low recruitment). Although it could not provide exact figures, the audit provided necessary insight into the quantity of women who were not receiving the information booklet and who were eligible but not screened/approached for inclusion in the trial. It also allowed for the identification of individual clinicians who might repeatedly not consider eligible women for inclusion in the trial. This latter information was kept confidential and I would approach that particular staff member individually to ascertain if he/she was experiencing particular difficulties with the trial processes and recruitment procedures. Figure 7 provides an example of the results of an accumulated audit over a series of months. The results of the audits were presented at professional on-site meetings and through trial newsletters in an effort to inform staff and encourage improved recruitment rates.
5.7.2.5 Recruitment rates

Based on sample size estimates and on the assumption that half of the women would be eligible to take part in the trial and half of those eligible would consent to take part, the target recruitment rates per month were 240 women (60 women per month from site A and site C, and 120 women from site B). This was a conservative estimate and anticipated as being reasonably achievable as it represented approximately 20% of the total birth rate at each study site. Based on recruitment rates of 240 women per month, the expected duration of the trial was two years. Recruitment rates, however, were much lower, and in spite of ongoing efforts to improve rates as described above, overall recruitment achieved just over one third of expected targets. Appendix XXIII provides a breakdown of recruitment rates per site per month, inclusive of numbers of women ineligible and numbers of women eligible versus numbers of women consenting as per completed Trial Screening & Register Forms. Appendix XXIV shows recruitment trends per site per month. (Please note: at the time of writing, recruitment to the ADCAR trial is ongoing. Data collection, for the purpose of this thesis, was completed on 31st July 2010. The findings presented in the following chapter, Chapter 6, represent the first 1,906 women recruited to the study, for which data were extracted, that is, the first of the interim analyses, as described in section 5.4.2.2).
5.7.3 Trial analysis
The analysis of a randomised trial requires consideration of data collection and data management techniques and consideration of the appropriate statistical analyses, so that differences in treatment effects may be inferred.

5.7.3.1 Data collection and management
Collection of ADCAR trial outcome data and management of trial data following collection involved careful consideration and planning both before and after commencement of recruitment to the trial. It involved collecting completed trial screening and consent forms, collecting trial outcome data and managing all collected data.

5.7.3.1.1 Trial screening and consent forms
Prior to commencing the recruitment phase, relevant trial documentation was provided to the labour ward or labour assessment room at each study site. Relevant documentation necessary for recruitment included the TSRF (Appendix XIV), the ADCAR Trial Consent Form (Appendix VI) and the ADCAR Trial Readmission Screening Form (Appendix XVIII). Filing cabinets or letters trays were provided to all relevant areas (that is where admissions with signs of labour took place) to store these documents. All completed forms were left in a drawer purposively designated for completed forms, for collection. This completed documentation was collected on an ongoing basis during site visits by me or by a member of the research team.

5.7.3.1.2 Outcome data
An important step in the development of the protocol was the defining of the outcome data of interest and relevance to the ADCAR trial. This was achieved through literature review and through discussion with TSC members and the research team. Following a period of careful consideration and re-consideration for relevance and importance, the outcome data for the trial were defined and are detailed in the trial protocol and in the ADCAR Trial Data Collection Booklet (Appendix XXV). Once defined, how best to collect the outcome data was then considered. As all three study sites used a
computerised *Maternity Information System (MIS)* to store client information, it was thought that all relevant outcome data might be collected through the MIS. Prior to launching the trial, I met with relevant staff members working in the Information Technology Department of each site to discuss the feasibility of collecting ADCAR data through this system.

These meetings identified the methods of data collection as follows: The MIS was used for data collection at site A and site B. The process of data collection at site A involved my providing the Information Technology (IT) midwife with the medical record numbers of women recruited to the study. This was done on a bi-monthly basis. The IT midwife would then provide me with an Excel spreadsheet of labour and birth outcomes for these women. A USB memory stick, designated solely to this purpose, and securely stored in a locked filing cabinet, was used. This information was subsequently removed from the USB, transferred to my personal computer and password protected. Relevant ADCAR outcome data for each woman were extracted and entered into SPSS (Version 16.0) for later analysis. The IT midwife had no knowledge of a woman’s study number or group allocation when downloading this information. Relevant ADCAR data omitted from the MIS, that is missing trial data, were obtained by retrieving and reviewing the maternity notes of the participant concerned. Maternity/neonatal records for babies admitted to the neonatal intensive care unit were also retrieved and reviewed to identify and document any significant adverse events that might have occurred.

The process of data collection at site B involved the IT midwife sending me, on a monthly basis, the labour and birth details of all women admitted in spontaneous labour who gave birth during that month. This information was provided in an Excel spreadsheet via the hospitals internal secure e-mail network (user-name and password protected). The medical record numbers only of women were provided, (i.e. no personal identifying information such as names or addresses of women were provided). I would check through these records and extract data relevant only to women randomised to
ADCAR during that month. Data were subsequently entered into SPSS for later analysis. The IT midwife had no knowledge of which women were randomised or of any group allocations. As with data from site A, any relevant ADCAR data omitted from the MIS, were obtained by retrieving and reviewing the maternity notes of the participant concerned. Maternity/neonatal records for babies admitted to the neonatal intensive care unit were also retrieved and reviewed to identify and document any significant adverse events that might have occurred.

Data collection at site C was by manual collection using the ADCAR Trial Data Collection Form (Appendix XXV). This was performed by a junior research assistant to ADCAR. The reason for manual collection at this site was that the MIS was undergoing review at the time ADCAR was launched. As a change in the system was anticipated in the year ahead, the system’s current status could not be changed to accommodate the collection of much of ADCAR’s required data. Therefore, manual collection of data was a more feasible option at this site. The junior research assistant completed the data collection form on women randomised on a bi-monthly basis without knowledge of their group allocation or study number. When I received the data collection forms, I entered the study number and group allocation for each woman. Maternity/neonatal records for babies admitted to the neonatal intensive care unit were also retrieved and reviewed by the junior research assistant to identify and document any significant adverse events that might have occurred. As with data from site A and site B, all data from site C were later entered into SPSS, Version 16.0, for data analysis.

5.7.3.1.3 Data management
As with data collection, data management was ongoing throughout recruitment to the trial. Data collected from TSRF and consent forms were managed as and when collected. Monthly Excel files were established for this purpose and relevant data from completed forms of women randomised were recorded as shown in Table 13. In addition, information was recorded on the numbers of eligible women who declined to consent, numbers of women not
receiving the study information and primary reasons for ineligibility. A separate Excel spreadsheet within each monthly Excel file was used for each study site.

Table 13: Example Summary Data Table

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Group Allocation</th>
<th>Name</th>
<th>MRN</th>
<th>DOB</th>
<th>Date Randomised</th>
<th>Additional Notes</th>
</tr>
</thead>
</table>

All relevant outcome data, once collected, were entered into SPSS Version 16.0 for data analysis. All data entered into SPSS was subsequently cleaned by cross checking each datum with the original datum for accuracy and any missing data were followed-up and retrieved where possible.

5.7.3.2 Data analysis
Advice from an expert statistician was sought for analysing the data in the ADCAR trial. Based on this advice, relative risks (RR) for an event or outcome occurring in the ACTG group versus the IA group, and the associated 95% confidence intervals (CI), were calculated. The rationale for this choice was based on the RR and 95% CI providing a measure of the size of any difference between the groups and the uncertainty around this estimate of the difference. Using SPSS Version 16.0, cross-tabulations or frequency distributions were used to calculate the number of events, for each outcome measure, in each arm of the trial. For continuous data, mean and standard deviations were calculated using the descriptive statistics function. All relevant computed data were then entered into the computer package, RevMan Version 5.0, which calculated the RRs and 95% CIs for each outcome measure. Forest plots are used to illustrate the trial results graphically.
5.8 Conclusion

This chapter presented the ADCAR trial’s methodology and associated study methods. Considering the aim of the ADCAR trial, that is evaluating the use of ACTG compared to IA of the FHR in low risk women, the randomised trial was chosen as the most appropriate method to meet the aim of the ADCAR trial. This is because the randomised trial is considered the most reliable way to evaluate the effects of different healthcare interventions. In this chapter, optimising trial design, trial conduct and trial analysis were fully discussed. However, despite numerous efforts to optimise recruitment rates, recruitment to ADCAR remained below expected targets. For this reason, the following chapter (Chapter 6) presents the preliminary findings of the ADCAR trial; that is the findings of the first interim analysis, which includes an analysis of data on the first one-third (n = 1,906) of women recruited to the trial for whom data was extracted.
Chapter 6: Findings

6.1 Introduction
This chapter presents the preliminary findings of the ADCAR trial. All reported findings are based on ‘intention to treat’ analyses. The preliminary findings comprise an analysis of the first 1,906 women recruited to the trial for which data were extracted. These 1,906 participants represent one-third (33%) of the total sample estimated as necessary to complete the ADCAR trial, which meets the requirements of the first interim analysis as detailed in the trial protocol (Appendix XIX).

6.2 Participation and participants
At the time of writing (September 2010), recruitment to the ADCAR trial is ongoing. Figure 8 provides a flow diagram of the number of women recruited to each intervention group of the trial and the number of women ineligible and not participating in the trial. This information was retrieved from completed Trial Screening and Register Forms (TSRF) (Appendix XIV) collected for each potentially eligible participant screened, in each participating study site.
Excluded (n = 7,225)
- Ineligible (n = 4,859)
- Declined to participate (n = 1,237)
- No information provided (n = 1,001)
- ACTG prior to eligibility assessment (n = 99)
- ALEA system failed to randomise (n = 29)

Assessed for Eligibility (n = 9,217)

Randomised (n = 1,992)

Allocated IA (n = 991) Allocated ACTG (n = 1,001)

Loss to follow-up (n = 3)
- Medical record number not entered correctly in ALEA and no TSRF or consent form available

Loss to follow-up (n = 4)
- Medical record number not entered correctly in ALEA and no TSRF or consent form available

(Interim Analysis 1)
First 1,906 women recruited, for whom data were extracted

Allocate IA (n = 957/991) Allocated ACTG (n = 949/1,001)

Figure 8: Screening and Recruitment Flow Chart
Approximately 27,300 women are estimated to have given birth to babies' ≥ 500g at all three study sites, from the time ADCAR was launched at that site, up to and including 31st July 2010 (based on the most recent annual report figures available publicly for each participating study site; 2006 for Site A and Site C, 2008 for Site B). The expected number of completed TSRF in each participating site was based on the number of women presenting to the labour ward or labour assessment room with signs of possible labour. Three factors influenced this figure; i) number of women presenting in spontaneous or possible labour, ii) number of women having a scheduled induction of labour, and iii) number of women having an elective caesarean section. A completed TSRF was not expected for women having a scheduled induction or elective caesarean section because they would not have presented to the hospital with signs of possible labour. These figures were considered when calculating the total number of women who should have been screened for possible inclusion in the trial.

Based on the most recent annual report figures available publicly for each participating study site (2006 for Site A and Site C, 2008 for Site B), the expected induction of labour rate and the expected caesarean section rate would be 27% and 25.4%, respectively, averaged across the three study sites. The caesarean section rate of 25.4% does not differentiate elective and emergency caesarean section; however, one participating site (Site B) provided a caesarean section rate, for women with spontaneous onset of labour at term, of 10.2% of total births. This figure was used to calculate an approximate average elective caesarean section of 15.2% (i.e. 25.4% - 10.2% = 15.2%). To calculate the expected number of completed TSRF from launch of the trial at each study site, to July 31st 2010, the induction of labour rate and elective caesarean section rate were subtracted from the total number of women giving birth (i.e. 27,300 − [7,371 + 4,149]), to give an expected 15,780 completed TSRFs (58% of women). This suggests that TSRFs were not completed for more than 6,500 women. Information on these women is therefore lost to the trial and it is not possible to know if these women would have been eligible or willing to participate in the study.
In all, 52.7% (n = 4,859) were screened ineligible to participate in ADCAR. Table 14 provides a detailed breakdown of the number of women excluded as per each documented exclusionary criterion. The most common primary reason for exclusion was post dates (defined as > 40 weeks + 6 days for trial purposes), (29.3%; n = 1,422). A previous caesarean section also excluded a significant number of women (10.7%; n = 520). The least common reason for exclusion was abnormal Doppler artery velocimetry (0.02%; n = 1) and uterine or cervical malformation (0.1%; n = 5).

Table 14: Number of Women Excluded/Exclusionary Criterion

<table>
<thead>
<tr>
<th>Exclusion Criterion</th>
<th>Number of Cases</th>
<th>% of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous caesarean section</td>
<td>520</td>
<td>10.7%</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>53</td>
<td>1.1%</td>
</tr>
<tr>
<td>Hypertension alone*</td>
<td>213</td>
<td>4.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>92</td>
<td>1.9%</td>
</tr>
<tr>
<td>Post dates (&gt; 40wks)</td>
<td>1,422</td>
<td>29.3%</td>
</tr>
<tr>
<td>Prematurity (&lt; 37 wks)</td>
<td>345</td>
<td>7.1%</td>
</tr>
<tr>
<td>Induced labour</td>
<td>529</td>
<td>10.9%</td>
</tr>
<tr>
<td>Rupture of membranes (&gt; 24 hrs)</td>
<td>167</td>
<td>3.4%</td>
</tr>
<tr>
<td>Antepartum hemorrhage (single episode at &gt; 24 wks)</td>
<td>297</td>
<td>6.1%</td>
</tr>
<tr>
<td>Infection/Pyrexia (&gt; 37.5 on admission)</td>
<td>22</td>
<td>0.5%</td>
</tr>
<tr>
<td>Uterine or cervical malformation</td>
<td>5</td>
<td>0.1%</td>
</tr>
<tr>
<td>BMI &gt; 35 at booking</td>
<td>85</td>
<td>1.8%</td>
</tr>
<tr>
<td>Maternal age &lt; 18 yrs at time of consent</td>
<td>46</td>
<td>1.0%</td>
</tr>
<tr>
<td>Maternal age &gt; 40 yrs at booking</td>
<td>27</td>
<td>0.6%</td>
</tr>
<tr>
<td>Assisted conception in this pregnancy</td>
<td>44</td>
<td>0.9%</td>
</tr>
<tr>
<td>Maternal medical disease†</td>
<td>331</td>
<td>6.8%</td>
</tr>
<tr>
<td>Previous stillbirth or neonatal death</td>
<td>43</td>
<td>0.9%</td>
</tr>
<tr>
<td>Small for Gestational Age (&lt; 10th Centile)</td>
<td>92</td>
<td>1.9%</td>
</tr>
<tr>
<td>Abnormal Liquor Volume</td>
<td>85</td>
<td>1.7%</td>
</tr>
<tr>
<td>Abnormal doppler artery velocimetry</td>
<td>1</td>
<td>0.02%</td>
</tr>
<tr>
<td>Breech/other non-cephalic/multiple pregnancy</td>
<td>38</td>
<td>0.8%</td>
</tr>
<tr>
<td>Reduced fetal movements (on more than one occasion)</td>
<td>219</td>
<td>4.5%</td>
</tr>
<tr>
<td>Meconium stained liquor</td>
<td>124</td>
<td>2.6%</td>
</tr>
<tr>
<td>Fetal congenital abnormality in this pregnancy</td>
<td>10</td>
<td>0.2%</td>
</tr>
<tr>
<td>Advanced labour (i.e. too late to randomize)</td>
<td>69</td>
<td>1.4%</td>
</tr>
<tr>
<td>No/poor english (unable to communicate consent)</td>
<td>256</td>
<td>5.3%</td>
</tr>
<tr>
<td>Other</td>
<td>110</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

*BP of 140/90 or more on at least two occasions > 24hrs apart in women previously normotensive; †Includes any of the following: cardiac/vascular disease, anaemia (Hb < 10g/l), history of thrombo-embolic disorder, thrombocytopenia (< 100 on most recent sample), hyperthyroidism, abnormal renal function, rhesus isoimmunisation, liver disease (including abnormal liver function tests), and epilepsy
Of the 9,217 completed TSRFs, 48% (n = 4,358) of women were judged to be eligible to participate in the trial. Of these, 28.4% (n = 1,237) declined to participate and 23.0% (n = 1,001) did not receive any study information prior to presenting to the hospital with signs of possible labour. In addition, randomisation was attempted for 29 (0.7%) women but the randomisation service did not provide the allocation either due to the incorrect entry of details by the admitting midwife or due to a fault in the system at the time of randomisation. In a further 2.3% of women (n = 99), an ACTG was performed prior to completing the TSRF. Documented reasons for this included; no chart available on admission with the admitting midwife proceeding with standard care (TSRF completed in retrospect when the medical chart became available), busy clinical environment at the time of admission with the admitting midwife proceeding with standard care (TSRF completed in retrospect when more time became available), or a vaginal assessment performed to confirm or rule out a diagnosis of labour prior to completing the TSRF. Therefore, 45.7% of eligible women (n = 1,992) were randomised into ADCAR with 991 women entering the IA group and 1,001 women entering the ACTG group.

Loss to follow-up includes seven women who were randomised to the study according to the ALEA database (four women randomised to ACTG and three women randomised to IA) but who cannot be traced because the medical record numbers entered on the ALEA system are not correct and the hard copy consent form or TSRF was not available for them. Therefore, it is not possible to identify these women and I am unable to extract study data relating to them. This loss to follow-up represents 0.35% of all women randomised to the study at this time.

Data extracted on the first 1,906 women, for whom data were available, was analysed. Of these 1,906 women, 50.2%, (n = 957) were allocated to IA and 49.8% (n = 949) were allocated to ACTG. This represents 95.7% of the total number of women participating in the trial on 31st July 2010 and one-third the
target recruitment for the trial as a whole. Table 15 provides baseline characteristics of participating women.

Table 15: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IA (n = 957)</th>
<th>ACTG (n = 949)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>31 years</td>
<td>31 years</td>
</tr>
<tr>
<td>Gravida = 1</td>
<td>348</td>
<td>354</td>
</tr>
<tr>
<td>Gravida &gt; 1</td>
<td>609</td>
<td>595</td>
</tr>
<tr>
<td>Parity = 0</td>
<td>439</td>
<td>409</td>
</tr>
<tr>
<td>Parity &gt; 1</td>
<td>518</td>
<td>540</td>
</tr>
<tr>
<td>Induced Labour</td>
<td>70</td>
<td>89</td>
</tr>
<tr>
<td>&gt; Term + 6</td>
<td>64</td>
<td>49</td>
</tr>
</tbody>
</table>

6.3 Primary outcome measure

6.3.1 Incidence of caesarean section

There was no statistically significant difference in total caesarean section rates between women randomised to IA and women randomised to ACTG (88 [9.2%] versus 69 [7.3%]; RR 1.26, 95% CI 0.93-1.70). Three women randomised to the IA group had an elective caesarean section (that is ‘not in labour’ caesarean section); one due to breech presentation diagnosed on vaginal examination post-randomisation, and one due to failed induction following prostaglandins. The reason for the third elective caesarean section was not documented. There was no significant difference between IA and ACTG in numbers of women requiring an emergency caesarean section for reasons other than an abnormal FHR pattern (29 [3.0%] versus 26 [2.7%]; RR 1.11, 95% CI 0.66-1.86) or emergency caesarean section for abnormal FHR pattern only (56 [5.8%] versus 43 [4.5%]; RR 1.28, 95% CI 0.87-1.89).

6.4 Secondary outcomes

6.4.1 Obstetric intervention

Women randomised to IA were statistically significantly less likely than women randomised to ACTG to have continuous EFM during labour (defined as EFM > 75% of the time from diagnosis of labour to birth of the baby), (675 [70.5%] versus 753 [79.0%]; RR 0.89, 95% CI 0.84-0.94).
There was no statistically significant difference between women randomised to IA and women randomised to ACTG in instrumental birth, other than instrumental birth for abnormal FHR pattern, (79 [8.3%] versus 84 [8.9%]; RR 0.93, 95% CI 0.70-1.25), instrumental birth for abnormal FHR pattern only (128 [13.4%] versus 111 [11.7%]; RR 1.14, 95% CI 0.90-1.45), acceleration of labour (either by artificial rupture of membranes (ARM) and/or oxytocin acceleration), (450 [47.0%] versus 456 [48.0%]; RR 0.98, 95% CI 0.89-1.08), acceleration with ARM alone (362 [37.8%] versus 374 [39.4%]; RR 0.96, 0.86-1.07), acceleration with oxytocin alone (167 [17.5%] versus 164 [17.3%]; RR 1.01, 95% CI 0.83-1.23), pethidine analgesia during labour (207 [21.6%] versus 207 [21.8%]; RR 0.99, 95% CI 0.84-1.18), epidural analgesia during labour (403 [42.1%] versus 379 [39.9%]; RR 1.05, 95% CI 0.95-1.17), fetal blood sampling during labour (67 [7.0%] versus 58 [6.1%]; RR 1.15, 95% CI 0.82-1.61), mean length (in minutes) of first (198 [standard deviation (SD) 157] versus 204 [SD 169]; mean difference (MD) -6.00, 95% CI -21.23-9.23), second (49 [SD 49] versus 50 [SD 52]; MD -1.0, 95% CI -5.71-3.71) and third stage of labour (11 [SD 48] versus 11 [SD 22]; MD; 0.0, 95% CI -3.36-3.36) or in mean length of maternal hospital stay (in days) (2.17 [SD 1.1] versus 2.15 [SD 1.2]; MD 0.02, 95% CI -0.08-0.12), (Table 16).

6.4.2 Neonatal morbidity
There was no statistically significant difference between babies of women randomised to IA and babies of women randomised to ACTG in meconium stained liquor during labour (155 [16.2%] versus 178 [18.7%]; RR 0.86, 95% CI 0.71-1.05), neonatal resuscitation at birth (274 [28.6%] versus 278 [29.3%]; RR 0.98, 95% CI 0.85-1.12), paediatric support at birth (371 [38.8%] versus 372 [39.2%]; RR 0.99, 95% CI 0.88-1.11), Apgar score of ≤ 7 at five minutes post birth (10 [1.0%] versus 6 [0.6%]; RR 1.65, 95% CI 0.60-4.53), arterial pH of ≤ 7.05 (9/714 [1.3%] versus 9/665 [1.4%]; RR 0.93, 95% CI 0.37-2.33), arterial base deficit of ≥ -12.0 (17/702 [2.4%] versus 8/648 [1.2%]; RR 1.96, 95% CI 0.85-4.51), arterial base deficit of ≥ -16.0 (2 [0.3%] versus 1 [0.2%]; RR 1.85, 95% CI 0.17-20.31), mean gestation (in weeks)
(39.91 [SD 0.86] versus 39.88 [SD 0.88]; MD 0.03, 95% CI -0.05-0.11), mean neonatal birth weight (in grams) (3528 [SD 427.9] versus 3559 [SD 443.0]; MD -31.0, 95% CI -70.14-8.14), mean length of neonatal hospital stay (in days) (2.2 [SD 1.15] versus 2.3 [SD 1.20]; MD -0.10, 95% CI -0.21-0.01), or admission to the neonatal intensive care unit/special care baby unit (NICU/SCBU) (26 [2.7%] versus 37 [3.9%]; RR 0.70, 95% CI 0.43-1.14), (Table 16). The analyses revealed a considerable amount of missing data for umbilical cord blood values. Values (arterial or venous) available for analysis was 77.8% (n = 745) in the IA group and 77.3% (n = 696) in the ACTG group.

Of those babies who required resuscitation following birth (30%, n = 552), oral/pharyngeal suctioning was the most common method of neonatal resuscitation, (IA 165/274 [60.2%] versus ACTG 175/278 [63.2%]; RR 0.96, 95% CI 0.84-1.09). Eleven babies from the IA group and ten babies from the ACTG group required intermittent positive pressure ventilation (IPPV) either by bag and mask or by endotracheal tube (11 [4.0%] versus 10 [3.6%]; RR 1.12, 95% CI 0.48-2.59). Sixty-three babies in total were admitted to NICU/SCBU, (IA 26 [2.7%] versus ACTG 37 [3.9%]; RR 0.70, 95% CI 0.43-1.14). Table 17 provides summary details of admissions to NICU/SCBU. There were no reported neonatal deaths in either the IA or ACTG group.

Table 16: Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IA (957) Event [%]/Mean [SD]</th>
<th>ACTG (949) Event [%]/Mean [SD]</th>
<th>Summary Statistic, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean section (total)</td>
<td>88 [9.2%]</td>
<td>69 [7.3%]</td>
<td>RR 1.26, 95% CI 0.93-1.70</td>
</tr>
<tr>
<td>Emergency caesarean section (other than for abnormal FHR pattern)</td>
<td>29 [3.0%]</td>
<td>26 [2.7%]</td>
<td>RR 1.11, 95% CI 0.66-1.86</td>
</tr>
<tr>
<td>Emergency caesarean section for abnormal FHR pattern (only)</td>
<td>56 [5.8%]</td>
<td>43 [4.5%]</td>
<td>RR 1.28, 95% CI 0.87-1.89</td>
</tr>
<tr>
<td>Instrumental birth (other than for abnormal FHR pattern)</td>
<td>79 [8.3%]</td>
<td>84 [8.9%]</td>
<td>RR 0.93, 95% CI 0.70-1.25</td>
</tr>
<tr>
<td>Instrumental birth for abnormal FHR pattern (only)</td>
<td>128 [13.4%]</td>
<td>111 [11.7%]</td>
<td>RR 1.14, 95% CI 0.90-1.45</td>
</tr>
<tr>
<td>Acceleration of labour (ARM and/or oxytocin)</td>
<td>450 [47.0%]</td>
<td>456 [48.0%]</td>
<td>RR 0.98, 95% CI 0.89-1.08</td>
</tr>
<tr>
<td>Acceleration of labour with ARM only</td>
<td>362 [37.8%]</td>
<td>374 [39.4%]</td>
<td>RR 0.96, 95% CI 0.86-1.07</td>
</tr>
<tr>
<td>Acceleration of labour with oxytocin only</td>
<td>167 [17.5%]</td>
<td>164 [17.3%]</td>
<td>RR 1.10, 95% CI 0.83-1.23</td>
</tr>
<tr>
<td>Pethidine analgesia during labour</td>
<td>207 [21.6%]</td>
<td>207 [21.8%]</td>
<td>RR 0.99, 95% CI 0.84-1.18</td>
</tr>
<tr>
<td>Epidural analgesia during labour</td>
<td>403 [42.1%]</td>
<td>379 [39.9%]</td>
<td>RR 1.05, 95% CI 0.95-1.17</td>
</tr>
<tr>
<td>Continuous EFM during labour</td>
<td>675 [70.5%]</td>
<td>753 [79.0%]</td>
<td>RR 0.89, 95% CI 0.84-0.94</td>
</tr>
<tr>
<td>Fetal blood sampling during labour</td>
<td>67 [7.0%]</td>
<td>58 [6.1%]</td>
<td>RR 1.15, 95% CI 0.82-1.61</td>
</tr>
<tr>
<td>Length of 1st stage of labour (mins)</td>
<td>198 [SD 157]</td>
<td>204 [169]</td>
<td>MD -6.00, 95% CI -21.23-9.23</td>
</tr>
<tr>
<td>Length of 2nd stage of labour (mins)</td>
<td>49 [SD 49]</td>
<td>50 [SD 52]</td>
<td>MD -1.00, 95% CI -5.71-3.71</td>
</tr>
<tr>
<td>Length of 3rd stage of labour (mins)</td>
<td>11 [SD 48]</td>
<td>11 [SD 22]</td>
<td>MD 0.00, 95% CI -3.36-3.36</td>
</tr>
<tr>
<td>Maternal length of hospital stay (days)</td>
<td>2.17 [SD 1.1]</td>
<td>2.15 [SD 1.2]</td>
<td>MD 0.02, 95% CI -0.08-0.12</td>
</tr>
<tr>
<td>Meconium stained liquor</td>
<td>155 [16.2%]</td>
<td>178 [18.7%]</td>
<td>RR 0.86, 95% CI 0.71-1.05</td>
</tr>
<tr>
<td>Neonatal resuscitation</td>
<td>274 [28.6%]</td>
<td>278 [29.3%]</td>
<td>RR 0.98, 95% CI 0.85-1.12</td>
</tr>
<tr>
<td>Oro/pharyngeal suction</td>
<td>165/274 [60.2%]</td>
<td>175/278 [63.2%]</td>
<td>RR 0.96, 95% CI 0.84-1.09</td>
</tr>
<tr>
<td>IPPV</td>
<td>11/274 [60.2%]</td>
<td>10/278 [3.6%]</td>
<td>RR 1.12, 95% CI 0.48-2.59</td>
</tr>
<tr>
<td>Paediatric support at birth</td>
<td>371 [38.8%]</td>
<td>372 [39.2%]</td>
<td>RR 0.99, 95% CI 0.88-1.11</td>
</tr>
<tr>
<td>Apgar score ≤ 7 at 5 minutes</td>
<td>10 [1.0%]</td>
<td>6 [0.6%]</td>
<td>RR 1.65, 95% CI 0.6-4.53</td>
</tr>
<tr>
<td>Arterial pH ≤ 7.05</td>
<td>9/714 [1.3%]</td>
<td>9/665 [1.4%]</td>
<td>RR 0.93, 95% CI 0.37-2.33</td>
</tr>
<tr>
<td>Arterial BD ≥ -12.0</td>
<td>17/702 [2.4%]</td>
<td>8/648 [1.2%]</td>
<td>RR 1.96, 95% CI 0.85-4.51</td>
</tr>
<tr>
<td>Arterial BD ≥ -16.0</td>
<td>2/702 [0.3%]</td>
<td>1/648 [0.2%]</td>
<td>RR 1.85, 95% CI 0.17-20.31</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>39.91 [SD 0.86]</td>
<td>39.88 [SD 0.88]</td>
<td>MD 0.03, 95% CI -0.05-0.11</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>3528 [SD 427.9]</td>
<td>3559 [SD 443.0]</td>
<td>MD -31.0, 95% CI -70.14-8.14</td>
</tr>
<tr>
<td>Neonatal length of hospital stay (days)</td>
<td>2.2 [SD 1.15]</td>
<td>2.3 [1.20]</td>
<td>MD -0.10, 95% CI -0.21-0.01</td>
</tr>
<tr>
<td>Admission to NICU/SCBU</td>
<td>26 [2.7%]</td>
<td>37 [3.9%]</td>
<td>RR 0.70, 95% CI 0.43-1.14</td>
</tr>
<tr>
<td>Reason</td>
<td>IA (number of cases)</td>
<td>ACTG (number of cases)</td>
<td>Diagnosis and/or Treatment</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Respiratory difficulties; e.g.</td>
<td>6</td>
<td>12</td>
<td>One baby in the IA group required CPAP ventilation support for 6 hours</td>
</tr>
<tr>
<td>Meconium Aspiration Syndrome</td>
<td>2</td>
<td>1</td>
<td>Diagnosed on x-ray</td>
</tr>
<tr>
<td>Jaundice</td>
<td>2</td>
<td>1</td>
<td>All three babies required phototherapy</td>
</tr>
<tr>
<td>Observation e.g. due to low</td>
<td>3</td>
<td>4</td>
<td>No abnormality detected (NAD)</td>
</tr>
<tr>
<td>Apgars</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIE I</td>
<td>2</td>
<td>0</td>
<td>1 baby spent 3 days and 1 baby spent 4 days in SCBU</td>
</tr>
<tr>
<td>HIE II</td>
<td>1</td>
<td>0</td>
<td>Seizure activity at 1 hrs of age. Anti-convulsive therapy by 3 doses. EEG – subclinical seizure activity on left frontal area. MRI – focal cortical lamina necrosis secondary to HIE.</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
<td>1</td>
<td>1 baby in the ACTG group developed E-Coli infection</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1</td>
<td>4</td>
<td>Baby in IA group diagnosed with tricuspid valve regurgitation; Babies in ACTG group, 1 had arterial septal defect, 1 had ventricular septal defect, 1 had tachycardia and 1 had systolic murmur.</td>
</tr>
</tbody>
</table>
6.5 Conclusion

This chapter reports the preliminary findings of the ADCAR trial. Twenty-nine outcomes are reported; three on the primary outcome measure, ‘incidence of caesarean section’, thirteen on the secondary outcome measure, ‘obstetric intervention’ and thirteen on the secondary outcome measure, ‘neonatal morbidity’. The preliminary findings demonstrate no statistically significant difference between women randomised to IA and women randomised to ACTG in any of the reported outcomes, except in the secondary, obstetric intervention outcome of continuous EFM during labour. Women randomised to IA of the FHR, on admission to the labour ward or labour assessment room with signs of possible labour, are statistically significantly less likely to have continuous EFM during labour than women who are randomised to ACTG on admission. A concerning finding was the deficit in recorded umbilical cord blood values in women participating in the trial, (IA 212, [22.2%] and ACTG 253, [22.7%]). This will have implications, due to the significant amount of missing data, for interpreting ‘neonatal morbidity’ outcomes when complete trial recruitment is achieved and the full results are known. Although these preliminary findings report on one-third only of total, expected participants’ rates, it remains reassuring that no neonatal deaths have been reported, to date, in either the IA or ACTG group.

The following chapter presents a discussion on the preliminary findings of the ADCAR trial.
Chapter 7: Discussion

7.1 Introduction
The aim of the ADCAR trial is to compare the effectiveness of ACTG versus IA of the FHR in low risk women admitted to the labour ward or labour assessment room with signs of possible labour on a) caesarean section, b) obstetric intervention and c) neonatal morbidity. This chapter, acknowledging that the ADCAR trial is ongoing, presents a discussion on the findings of the first interim analysis of the ADCAR trial’s data. This is achieved by incorporating the preliminary findings of the ADCAR trial into the meta-analysis of existing trials presented in Chapter 3 and by observing the effects of the preliminary results on the current evidence base. Limitations associated with the preliminary findings and with the ADCAR trial to date are discussed.

7.2 ADCAR and current evidence
7.2.1 Incidence of caesarean section
ADCAR’s first interim analysis found no statistically significant difference in total caesarean section rates between women randomised to IA and women randomised to ACTG. However, fewer women in the ACTG group had a caesarean section. This contrasts with the existing four studies included in the meta-analysis in Chapter 3, each of which found non-significantly fewer caesarean sections in women randomised to IA. When those studies were combined in a meta-analysis, this found an overall statistically significant reduction in caesarean section in favour of IA (see Figure 4, Chapter 3). Adding the ADCAR trial’s preliminary findings, however, would return this result to non-significant (Figure 9). This will have clinical implications as it demonstrates that use of ACTG compared to use of IA does not significantly increase the caesarean section rate in low risk women. However, with only one-third of the sample size recruited to the ADCAR trial, this interim finding might be due to chance and the overall confidence interval remains mostly on the side favouring IA (Figure 9).
One existing trial, (Impey et al, 2003), evaluating ACTG versus IA, reports on the incidence of caesarean section for abnormal FHR pattern only. The results demonstrated no statistically significant difference between women randomised to IA and women randomised to ACTG (Figure 10), although there was a slight increased risk for caesarean section for abnormal FHR pattern only, in the ACTG group. This compares favourably with ADCAR’s interim findings, which also found a non-significant difference between the groups in this outcome measure. In contrast to Impey’s study, however, ADCAR’s preliminary findings demonstrated non-significantly fewer caesarean sections for abnormal FHR pattern in the ACTG group. Pooling the results from the Impey study and ADCAR’s interim report reinforces the evidence of no significant difference in the incidence of caesarean section for abnormal FHR pattern between women randomised to IA and women randomised to ACTG (Figure 10).
### Table 1: Incidence of Caesarean Section for Abnormal FHR Pattern

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IA Events</th>
<th>ACTG Events</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCAR 2010</td>
<td>56</td>
<td>43</td>
<td>1.31 [0.87, 1.97]</td>
</tr>
<tr>
<td>Impey 2003</td>
<td>50</td>
<td>57</td>
<td>0.88 [0.60, 1.29]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>5239</td>
<td>5247</td>
<td>1.06 [0.80, 1.40]</td>
</tr>
</tbody>
</table>

- **Total events:** 106, 100
- **Heterogeneity:** Chi² = 1.95, df = 1 (P = 0.16); I² = 49%
- **Test for overall effect:** Z = 0.41 (P = 0.68)

Figure 10: Incidence of Caesarean Section for Abnormal FHR Pattern

7.2.2 Obstetric intervention

The ADCAR trial’s first interim analysis reported on thirteen secondary outcome measures associated with obstetric intervention. Five of these outcomes are reported in the meta-analysis in Chapter 3. In this section, I compare, contrast and combine ADCAR’s preliminary findings with those reported in the meta-analysis, to determine any differences in effect on the current evidence base.

In the meta-analysis in Chapter 3, no statistically significant differences in instrumental birth (vacuum or forceps only) was found between women randomised to ACTG and women randomised to IA and this is similar to ADCAR’s preliminary results. Adding ADCAR’s preliminary finding to the meta-analysis does not change the effect of this result and the evidence that there is no difference in the incidence of instrumental birth between women randomised to IA and women randomised to ACTG is reinforced (Figure 11).
The meta-analysis, in Chapter 3, demonstrated that significantly fewer women randomised to IA had epidural analgesia during labour than women randomised to ACTG. ADCAR’s preliminary results show a slight, but statistically non-significant increased rate of epidural analgesia during labour in the IA group. Adding ADCAR’s interim findings changes the effect of significance to non-significance, in this outcome (Figure 12). The clinical implication of this, acknowledging that this might change when the full results of the ADCAR trial are known, is a lack of evidence of benefit for ACTG, compared to IA, in reducing the incidence of epidural analgesia during labour, in low-risk women.
In the meta-analysis (Chapter 3), there was no statistically significant difference in acceleration of labour with oxytocin between women randomised to IA and women randomised to ACTG. This finding is similar to that of ADCAR’s preliminary finding which also demonstrated very little difference between the IA and ACTG groups. Combining the results from the meta-analysis in Chapter 3, with ADCAR’s preliminary results, has little impact on this result (Figure 13).

![Figure 13: Acceleration of Labour with Oxytocin](image)

The incidence of fetal blood sampling during labour was reported in three trials (Mires et al 2001, Cheyne et al, 2003, Impey et al, 2003) in the previous meta-analysis. Similar to ADCAR’s interim findings, one of the included trials (Cheyne et al 2003), reported a non-significant increase in fetal blood sampling during labour in the IA group. The other two included studies (Mires et al, 2001, Impey et al 2003) reported fewer women having fetal blood sampling during labour in the IA group, and in one of these studies (Impey et al, 2003), the difference was statistically significant. Pooling the results from all three studies (Chapter 3) demonstrates an overall statistically significant reduction in fetal blood sampling during labour in women randomised to IA. Adding ADCAR’s preliminary finding does not alter this effect (Figure 14), and the evidence that women randomised to ACTG are more likely to receive fetal blood sampling during labour than women randomised to IA remains constant.
The final secondary outcome measure reported in the meta-analysis in Chapter 3 is continuous EFM during labour. Three existing trials including 12,639 women, report on this outcome (Mires et al, 2001, Cheyne et al, 2003, Impey et al, 2003). All three trials report fewer women in the IA group having continuous EFM during labour and in two of these trials, (Mires et al, 2001, Impey et al, 2003) the reported difference between the groups is statistically significant. This compares favourably to ADCAR’s preliminary findings based on 1,906 women that also demonstrated statistically significantly fewer women having continuous monitoring during labour in the IA group compared to women in the ACTG group. Adding ADCAR’s preliminary findings to the previous meta-analysis does not alter the effect of this difference and women randomised to IA compared to women randomised to ACTG remain significantly less likely to have continuous EFM during labour (Figure 15).
Significant heterogeneity was noted ($I^2 = 98\%$) in this analysis. It might be argued that a meta-analysis should not be done with a value this high. However, The Cochrane Pregnancy and Childbirth Group suggest incorporating the analysis into a random effects model when substantial statistical heterogeneity exists (The Cochrane Pregnancy and Childbirth Group 2010). A subsequent sensitivity analysis, using a random effects model was therefore performed (Figure 16). This analysis assumes that the effects being estimated are not identical but follow some distribution (Higgins and Green 2008). This sensitivity analysis concurs with the previous finding, that women randomised to IA, compared to women randomised to ACTG, are significantly less likely to receive continuous EFM during labour (Figure 16).

**Figure 16: Continuous EFM during Labour**

![Figure 16: Continuous EFM during Labour - Random Effects Model](image)
The use of continuous EFM during labour was the only outcome for which a significant difference between IA and ACTG was detected. In a Cochrane review that evaluated the use of continuous EFM during labour (Alfirevic et al, 2006), a significant increase in the incidence of caesarean section was found in women receiving continuous EFM during labour compared to women receiving IA during labour (RR 1.66, 95% CI 1.30-2.13, 10 trials, 18,761 women). Considering this finding, it might be reasonable to have anticipated that the direction, in the ADCAR trial’s interim analysis, would have been toward a reduction in caesarean sections associated with IA. In contrast, there were no statistically significant differences in the incidence of caesarean section between women randomised to IA and women randomised to ACTG. This finding, although perhaps unexpected, is not unique to ADCAR’s preliminary findings. In the report on the findings of the MidU Study, a randomised trial comparing the effectiveness of midwifery led care (MLU) versus consultant led care (CLU) in the Republic of Ireland (Begley et al. 2009), no statistically significant difference in the incidence of caesarean section or in the incidence of instrumental vaginal birth between the two groups was found. Women randomised to CLU care, however, were significantly more likely to have continuous EFM during labour compared to women randomised to MLU care (RR 0.64, 95% CI 0.57-0.71). As the ADCAR trial is ongoing, and the findings reported here are based on one-third of the required sample size, it is unreasonable to infer definitive conclusions until the full results of the study are known. However, these findings do suggest some possible changes to the influential effects of type of fetal monitoring during labour, on caesarean section rates, since the publication of the Cochrane review (Alfirevic et al, 2006).

An important finding of interest, in the ADCAR trial to date, considering that all women entering the study were low risk for fetal compromise, is the high overall proportion of participating women receiving continuous EFM during labour (75%, n = 1,428). Excluding the number of women that received epidurals during labour (n = 782), the number of women who had meconium stained liquor during labour (n = 323), and accounting for the number of
women who had meconium stained liquor and an epidural \((n = 146)\), as continuous EFM is recommended in such circumstances; there remained 25% \((n = 469)\) of women who had continuous EFM during labour for no documented or clinically apparent reason. This finding contrasts with practice guidelines recommending the use of IA during labour for low-risk women (NICE, 2007). Although this practice, might be explained by some of the evidence presented in Chapter 4, it appears clear that, in the Republic of Ireland, evidence-based recommendations and guidelines have yet to be fully implemented in clinical practice.

7.2.3 Neonatal morbidity

The rationale for the ADCAR trial originates in the belief that ACTG might identify those babies that might benefit from continuous EFM during labour. It is important, therefore, to consider the findings of the primary and secondary ‘obstetric intervention’ outcomes in the context of secondary ‘neonatal morbidity’ outcomes. In this section, I compare, contrast and combine ADCAR’s preliminary findings on ‘neonatal morbidity’ with those reported in the meta-analysis (Chapter 3) to determine any differences in effect on the current evidence base.

The preliminary findings of the ADCAR trial demonstrated no statistically significant differences in any of the reported neonatal outcomes between babies of women randomised to IA and babies of women randomised to ACTG, which is not surprising given that we are only one third of the way into the sample size needed to detect important differences in these outcomes. Two of the neonatal outcomes (admission to SCBU/NICU and Apgar score \(\leq 7\) at five minutes), reported in Chapter 6, are common to the neonatal outcomes reported in the previous meta-analysis (Chapter 3). In addition, one study, (Impey et al, 2003), reported on meconium stained liquor during labour and this outcome will also be compared to the related finding in ADCAR’s interim analysis.
All four existing trials report on admissions to SCBU/NICU. In each individual study and in the overall meta-analysis (Chapter 3), no statistically significant difference was found in rates of admissions to SCBU/NICU between babies born to women randomised to IA and babies born to women randomised to ACTG. These findings are similar to ADCAR’s preliminary findings of no difference in admissions to SCBU/NICU between the ACTG and IA groups. Adding ADCAR’s preliminary findings to the previous meta-analysis does not alter the meta-analysis findings (Figure 17).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events IA</th>
<th>Events ACTG</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCAR 2010</td>
<td>26</td>
<td>37</td>
<td>10.9%</td>
<td>0.70 [0.43, 1.14]</td>
<td></td>
</tr>
<tr>
<td>Cheyne 2003</td>
<td>3</td>
<td>1</td>
<td>0.3%</td>
<td>2.71 [0.28, 25.74]</td>
<td></td>
</tr>
<tr>
<td>Impey 2003</td>
<td>197</td>
<td>203</td>
<td>59.6%</td>
<td>0.97 [0.80, 1.18]</td>
<td></td>
</tr>
<tr>
<td>Mires 2001</td>
<td>105</td>
<td>89</td>
<td>26.3%</td>
<td>1.17 [0.88, 1.54]</td>
<td></td>
</tr>
<tr>
<td>Mitchell 2008</td>
<td>7</td>
<td>10</td>
<td>2.9%</td>
<td>0.73 [0.28, 1.90]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>7565</strong></td>
<td><strong>7556</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.99 [0.86, 1.15]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>338</td>
<td>340</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 4.55, \text{df} = 4 (P = 0.34); I^2 = 12\%$

Test for overall effect: $Z = 0.08 (P = 0.94)$

**Figure 17: Admission to SCBU/NICU**

Similarly, all four existing trials report on Apgar score ≤ 7 at five minutes post birth. Overall, there was no statistically significant difference in Apgar score ≤ 7 at five minutes between babies born to women randomised to IA and babies born to women randomised to ACTG (Chapter 3). Adding ADCAR’s preliminary findings does not alter this finding and there remains no statistically significant difference between the groups in this outcome measure (Figure 18).
### Figure 18: Apgar Score ≤ 7 at 5 minutes

In the ADCAR study, to date, women randomised to IA were statistically non-significantly less likely to have meconium stained liquor during labour. This finding is similar to Impey et al’s (2003) study, which also reported a non-significant increase in the ACTG group. Pooling the results from the Impey study and ADCAR’s interim findings, demonstrates no statistically significant differences in the incidence of meconium stained liquor between women randomised to IA and women randomised to ACTG (Figure 19).

### Figure 19: Meconium Stained Liquor during Labour

The preliminary findings of the ADCAR trial and the findings of the updated meta-analysis reported here indicate a lack of evidence of benefit for ACTG compared to IA for improving neonatal outcomes in low risk women. However, due to the relatively small sample size, and the ongoing nature of the ADCAR trial, it is reasonable to assume that the findings reported in the
previous chapter (Chapter 6) and discussed in this chapter could result from chance. As no statistically significant differences in the primary outcome measure and in neonatal morbidity measures were identified, it is reasonable to continue the ADCAR trial to full participant recruitment, unless otherwise indicated by the second of the interim analyses.

7.3 Limitations

A major limitation of the ADCAR trial, to date, is the considerable number of women (42%, n = 6,742), who were not screened on admission, with signs of possible labour, for possible inclusion in the trial. As I have no way of knowing how many of these women would have been eligible to participate in the trial or how many would have agreed to participate had they been eligible and invited to do so, it represents a considerable loss of trial data, which will impact on trial results and the completed trial report. In addition, and considering that recruitment rates as of 31st July 2010 are below targets (see Table 20) the deficit in the number of women being screened for possible inclusion in the trial has possibly (and more than likely) been a major factor in the lower than expected recruitment rates to the study.

Table 18: Expected Recruitment versus Actual Recruitment

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>Target*</th>
<th>No. of women recruited#</th>
<th>Recruitment as % of target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site A</td>
<td>1560</td>
<td>754</td>
<td>48.3%</td>
</tr>
<tr>
<td>Site B</td>
<td>2640</td>
<td>775</td>
<td>29.4%</td>
</tr>
<tr>
<td>Site C</td>
<td>900</td>
<td>463</td>
<td>51.4%</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>5100</td>
<td>1992</td>
<td>39.0%</td>
</tr>
</tbody>
</table>

*Target rates based on 60 women per month participating in Site A and Site C and 120 women participating in site B, from launch of trial to 31st July 2010, at that study site.

#Number of women recruited on 31st July 2010.

Poor or slow recruitment rates have implications for randomised trials and thus reported trial results (Watson and Torgerson 2006; Sood et al. 2009; Treweek et al. 2010). Inadequate recruitment reduces the statistical power of a study and can lead to inconclusive results or to a Type II error; that is a
reported 'no difference of significance' between the groups, when in fact there is a clinically significant difference between the interventions (Watson and Torgerson 2006; Tooher et al. 2008; Sood et al. 2009). Slow recruitment can extend the recruitment phase of the trial, which can lead to increased costs (Watson and Torgerson 2006; Tooher et al. 2008) or it may influence decisions regarding early stopping of a trial, as occurred in the Mitchell (2008) trial, due to a lack of funds and/or resources to maintain continuation of the trial for extended periods of time. In addition, slow recruitment potentially has ethical implications for the study. Delays in completing the trial can maintain a level of uncertainty surrounding the effectiveness of an intervention under study and delay a potentially more effective intervention becoming available outside the trial (Watson and Torgerson 2006).

A final limitation of the ADCAR trial, to date, is the considerable proportion of missing data for umbilical cord blood values (IA 212, [22.2%] and ACTG 253 [22.7%]). The collection of cord blood requires immediate clamping of the umbilical cord at birth and analysis of blood Ph and base deficit levels within one hour of sampling, if maintained at room temperature, or within twenty-four hours if maintained on ice (Plymouth Perinatal Research Group 2000). If for some reason, umbilical cord blood is not retrieved at birth, these data become lost to the trial. Loss of these important data can lead to an increased risk of reporting a Type II error in this outcome measure, and will impact on the full trial report, as the result of this outcome will need to be treated with caution (recommendations on ensuring that these data are more complete in the second two-thirds of the trial are reported in Chapter 9).

7.4 Conclusion

As the ADCAR trial is ongoing and is currently underpowered to detect differences between the interventions, it is not possible for me to infer definitive cause and effect conclusions between the use of ACTG and IA, in low risk women. For this to occur, the ADCAR trial must continue to at least its second interim analysis and then to full sample size recruitment if indicated. Definitive conclusions might only be inferred when the trial is
complete and the full results are known. In this chapter, I have discussed the ADCAR trials preliminary findings by comparing, contrasting and combining them with the findings of the meta-analysis presented in Chapter 3. This allows for an overview of any emerging differences in the evidence base, whilst acknowledging that these might change, following analysis of the ADCAR trials complete data or any other studies that take place.

Adding ADCAR’s preliminary findings to the meta-analysis of existing trials evaluating the use of ACTG, currently demonstrates a lack of evidence of benefit for performing ACTG compared to IA of the FHR on admission to the labour ward or labour assessment room, in low risk women. In contrast, women receiving ACTG are at an increased risk of continuous EFM during labour and fetal blood sampling during labour compared to women who have IA. The preliminary findings of the ADCAR trial support the current NICE (2007) guidance that ACTG is not recommended for low risk women, in any birth setting.

The following Section (IV) presents a summary of this thesis.
Section IV

Summary
Chapter 8: Summary of Thesis

8.1 Introduction
This chapter presents a summary of this thesis. It documents evidence that has emerged from this thesis and describes the contribution this evidence provides to original knowledge on the topic, to the ADCAR trial and to my development as a midwife researcher. Recommendations for practice, research and for the ADCAR trial are provided in addition to a final conclusion.

8.2 Summary
The primary purpose of this thesis was to report the design, conduct and preliminary findings of the ADCAR trial, a randomised trial comparing the effectiveness of the ACTG with IA in low-risk women on their admission to the labour ward or labour assessment room with signs of possible labour.

The empirical evidence evaluating the effectiveness of the ACTG and the evidence on women’s and professionals’ views, perceptions and experiences of fetal monitoring in practice, were additionally explored and documented through the conduct and reporting of two systematic reviews. The two systematic reviews, reported respectively in Chapter 3 and Chapter 4 of this thesis (and summarised in detail below), are, I believe, of particular significance to this thesis. They provide up-to-date and new evidence on the use of the ACTG for monitoring the FHR in clinical practice. They contribute original knowledge to the topic under investigation and are important in supporting the rationale for the conduct of the ADCAR trial. As the ADCAR trial remains ongoing, they provide relevant up-to-date and new information to those involved in the trial (i.e. participants, researchers and clinical staff recruiting participants to the trial). In addition, from a personal perspective, the conduct of these two systematic reviews provided me with a valuable opportunity to further develop my research skills and for advancing systematic review methodology. This will be of particular benefit to me when conducting research of this type in the future.
Chapter 3 reported the first of the systematic reviews and documents an evaluation of the effectiveness of the ACTG for assessing fetal wellbeing. This evaluation was achieved by addressing two components of ACTG use; (i) an evaluation of the effectiveness of ACTG versus IA of the FHR in low risk women and (ii) an evaluation of the predictive ability of ACTG for adverse labour and birth outcomes. Component (i) was achieved through meta-analysis of four existing trials. Component (ii) was achieved through an evaluation of likelihood ratios with 95% confidence intervals for eight labour and birth outcomes (‘fetal distress’, caesarean section for fetal distress, operative birth for fetal distress, Apgar score ≤ 7 at 5 minutes, meconium stained liquor, admission to SCBU/NICU, resuscitation at birth, and perinatal mortality) based on the findings of fourteen non-randomised studies. The results of these analyses demonstrated that low risk women receiving ACTG were significantly more likely than low risk women receiving IA to have caesarean section, epidural analgesia, continuous EFM during labour and fetal blood sampling during labour. The existing research provided no evidence of benefit for babies born to women receiving ACTG compared to babies born to women receiving IA. In addition, the ACTG, as a screening test, was found to be poorly predictive for the eight adverse labour and birth outcomes as described, in low risk, high risk and mixed risk populations.

The findings of this systematic review are important for informing clinical midwifery practice and for informing clinical decision-making on the current use of ACTG in practice. In addition, this systematic review is important and has relevance to the ADCAR trial. This importance is largely associated with a recent and, for me, highly influential correspondence paper published in the Lancet (Clarke et al 2010). In this paper the authors suggest that for a new trial to be both scientifically and ethically justified it should be considered with relevance to a complete assessment of previous research on the topic. In this sense, the design, conduct and preliminary findings of the ADCAR trial were presented in this thesis in the light of similar research on the topic and in the light of the “totality of the available evidence” (Clarke et al 2010, p. 20) on the topic. Furthermore, when the final results of the ADCAR trial are
known it will be possible to rapidly integrate these findings into this recent systematic review thereby providing clinicians with the most up-to-date evidence on the effectiveness of the ACTG compared with IA of the FHR on which to inform clinical decision-making and clinical care.

Chapter 4 provided a systematic review and thematic analysis of women’s and professionals’ views of FHR monitoring during labour. Eighteen studies were included in this systematic review; nine on women’s views and nine on professionals’ views. The decision to conduct this review emerged from discussions with clinical staff and with women on the use of ACTG and EFM in practice prior to and during launch of the ADCAR trial. Given the diversity and contradictory nature of these views, I believed it was necessary to systematically review the current empirical literature on this topic, to gain insight on the topic, and to determine the totality of the available evidence on women’s and professionals’ views on FHR monitoring in practice. The systematic review, reported in Chapter 4, involved systematically reviewing and synthesizing the evidence generated through both quantitative and qualitative research designs. Synthesizing evidence generated from such diverse designs is relatively new. As such, Chapter 4 of this thesis, in addition to providing new and original evidence on this topic, considerably advances systematic review methodology in this area.

The thematic data analysis identified six core themes; fear and anxiety (women’s views), reassurance (women’s and professionals’ views), communication (women’s views), comfort (women’s and professionals’ views), technology (professionals’ views) and midwife by proxy (professionals’ views). Of particular interest was the finding of a dichotomy in women’s views where some women felt reassured by the fetal monitor because it allowed them to hear their baby’s heart beat, while other women experienced fear and anxiety, mainly from noises emitted from the monitor. This finding has relevance to the ADCAR trial as it might, at least in part, explain some of the issues associated with low and slow recruitment to the trial. For example, of the 9,217 women assessed for trial eligibility, 1,237...
women screened eligible but declined to participate. This may reflect the view that some women feel reassured by hearing their baby’s heartbeat with the fetal monitor and therefore opted for standard care rather than participate in the trial and be randomised to the IA group. Similarly, some women may have declined to participate in the trial because of a fear or anxiety towards the fetal monitor. These women may have requested IA for evaluating their baby’s heart rate rather than participate in the trial and be allocated to the ACTG group.

An important finding from the analysis of professionals’ views was the theme of ‘reassurance’; in particular, the perceived reassurance that midwives felt in having a ‘hard copy’ trace of the FHR during labour. A major element of this theme was the reassurance against potential or actual litigation which professionals perceived that the CTG trace could offer them. This view is interesting because evidence in the literature suggests otherwise, that is, that there is a link between the use of EFM and increased obstetric litigation related in particular to inaccurate interpretation of the CTG trace (Lochhead, 1990, Symonds and Senior, 1991, Davies, 2006). This finding has relevance to the ADCAR trial because it might in part, explain why some women (n = 1,001) did not receive the study information for the trial.

A further theme of relevance to the ADCAR trial that emerged in the systematic review of women’s and professionals’ views of fetal monitoring during labour was the theme of ‘midwife by proxy’. This theme emerged from the experience of busy clinical environments and staff shortages. It informs the ADCAR trial in that at times of heightened clinical activity the ACTG may be used as a means of assessing the FHR when a midwife has to offer care to more than one woman at that time. In this sense, rather than screening for trial eligibility, standard care is implemented and an ACTG is performed as a perceived time saving measure. These themes, however, contradict the current evidence based recommendations on the use of the ACTG and will have significance for the continuation of the ADCAR trial. The findings of the systematic reviews from Chapter 3 and Chapter 4 will be
used to inform the ongoing ADCAR trial staff information workshops and the ongoing trial up-dates to ensure best efforts for improving trial recruitment rates are implemented as the trial continues into the future.

The preliminary findings of the ADCAR trial (Chapter 6) highlighted some of the challenges faced by researchers when conducting research in the clinical setting. Particular to the ADCAR trial was the lower than expected monthly recruitment rates to the trial. These lower than expected recruitment rates were, for me, perhaps the most surprising and frustrating element in conducting and managing the trial. From the outset and launch of the trial, I had anticipated recruitment rates to be much improved on the current 39% (see Table 18). Having discussed this at length with the wider research team, with experts in the field of trial research and having reviewed the literature in this area (Watson and Togerson, 2006, Sood et al, 2009, Treweek et al, 2010) it would appear that low or slow recruitment to randomised trials is not unusual. However, low or slow recruitment has significant implications for the success of the trial (e.g. an increased risk of a Type II error, extending the trial recruitment period and increased costs in maintaining the trial). It is important therefore that efforts are maintained to continue and increase recruitment to the trial. Strategies to improve recruitment that I previously implemented included increased site visits, increased information and support workshops, regular trial audit, regular trial up-dates and newsletters, presentations at multi-disciplinary meetings, voucher incentives for clinical staff, and poster and paper presentations at appropriate conferences. Increasing trial recruitment to ensure the success of the trial will pose a significant challenge for me as the trial continues into the future.

Chapter 6 reports the preliminary findings of the ADCAR trial. No statistically significant differences in any of the trial’s outcomes except the secondary outcome measure of continuous EFM during labour were found. Continuous EFM during labour was significantly increased in women receiving ACTG compared to women receiving IA. The lack of a statistically significant difference for almost all outcomes at this time is consistent with
sample size calculations for the ADCAR trial, which suggest that the number of women in the preliminary analysis presented here is one third of the total needed for the trial. Therefore, because the trial is not complete, it was not possible to infer definitive conclusions from this interim analysis. The relatively small sample size in the interim analysis can result in chance findings that might not reflect the true findings when the study is complete. However, because no significant difference was identified in the primary outcome measure, the incidence of caesarean section, and because there is no evidence of differences in adverse neonatal outcomes between babies of women receiving ACTG and babies of women receiving IA, the interim analysis is important. It indicates the need to continue the trial to at least the second interim analysis if not to the full sample size requirement in order to answer the research question effectively. The lack of any clear benefit or harm in this interim analysis reassures me, the trial team, clinicians and women involved in the trial that there is no increased risk for participants in either the IA or ACTG groups and, therefore, that there is no need to stop the trial at this time.

Although the ADCAR trial is ongoing and the full results are not yet known, the preliminary findings were discussed in the context of the current evidence base. This was achieved by comparing, contrasting and combining them with the findings of the meta-analysis presented in Chapter 3. Four outcomes in the meta-analysis in Chapter 3, that is incidence of caesarean section, epidural analgesia, fetal blood sampling during labour, and continuous EFM during labour, were statistically significantly increased in women in the ACTG group compared to women in the IA group. Adding ADCAR’s preliminary findings changed the effect estimate for two of these, that is incidence of caesarean section and epidural analgesia, to not being statistically significant. Apart from the impact on the caesarean section and epidural analgesia results, adding ADCAR’s findings had no important impact on the meta-analysis in Chapter 7. In reporting Chapter 7, I acknowledged that the results of the up-dated meta-analysis may be
reaffirmed or altered when the ADCAR trial is complete and its full results are incorporated into these analyses.

8.3 Recommendations
The following section presents recommendations for practice and research. Recommendations of relevance for the continuation of the ADCAR trial are additionally offered.

8.3.1 Recommendations for practice
1. Evidence of inconsistency in CTG interpretation was described in Chapter 2 and was highlighted as an important challenge faced by clinical practitioners using EFM technology. Midwives (and obstetricians) need to be knowledgeable of normal FHR features, deviations from the norm and possible causes for deviations from the norm. As autonomous practitioners, midwives are responsible for keeping themselves up to date with current evidence for practice and as such are responsible for educating themselves with the necessary information to care appropriately for women. With relevance to midwifery practice, it is therefore recommended that midwives keep themselves up-to-date with current evidence for FHR monitoring in practice through perusal of the literature, (independently or through, for example, journal clubs), and by attendance at relevant study days.

2. IA and CTG were highlighted as being the two most common methods for monitoring the FHR in current clinical practice. Women need to be informed of these diverse technologies, and made aware of the existing evidence and recommendations for choosing either monitoring modality. The Cochrane review evaluating continuous CTG versus IA during labour (Alfirevic et al, 2006), which was discussed briefly in Chapter 2 of this thesis, found that women receiving continuous CTG compared to women receiving IA were at a significantly increased risk of caesarean section and instrumental birth, yet no differences were identified in neonatal mortality rates or cerebral palsy rates between babies born to women in the two groups.
In contrast, however, continuous CTG during labour was associated with a reduction in neonatal seizures. Conveying this information to women is a requirement of midwives so that women may make an informed choice about fetal monitoring methods. With relevance to clinical midwifery practice it is therefore recommended that midwives should inform women of the different methods for monitoring the FHR in clinical practice including information on the current evidence base.

3. In addition to reporting the empirical evidence for monitoring the FHR during labour, this thesis identified diverse ‘views’ related to the type of FHR monitoring modality used to assess fetal wellbeing through an analysis of women’s views on FHR monitoring (Chapter 4). This further highlights the need for midwives to discuss FHR monitoring methods with women and to consider, in addition to physiological assessments, the emotional and psychological aspects of women’s care. From this finding and with relevance to clinical midwifery practice, it is recommended that midwives should consider and support the personal preferences that women might have for the type of FHR monitoring modality.

8.3.2 Recommendations for research

1. In the synthesis of nine studies exploring women’s views of FHR monitoring during labour (Chapter 4), eight of the nine studies were performed in the 1970s and 1980s, with one study performed in 2008 (Hindley et al, 2008). Since the 1980s, however, EFM use has become prolific in the developed world (Chez et al, 2000). Clinicians, therefore, have almost no contemporary evidence base on how women view FHR monitoring during labour to guide them in their care-giving. From this finding and with relevance to midwifery research, it is recommended that further research exploring women’s ‘views’ of FHR monitoring during labour be conducted.

2. As the ADCAR trial remains ongoing and with relevance to midwifery research it is recommended that midwives, in the pursuit of
evidence based practice and the provision of optimum maternity care, should support the continuation of the ADCAR trial and should offer all eligible women the opportunity to participate in the trial.

8.3.3 Recommendations relating to the ADCAR trial

From the findings of this thesis and with relevance to the ADCAR trial, it is recommended that:

1. The ADCAR trial continues to at least the second interim analysis (i.e. recruitment of two-thirds \( n = 3,870 \) of sample size estimates), or to full recruitment of sample size estimates if indicated appropriate by the second interim analysis.

2. Recruitment rates to the ADCAR trial are increased to shorten the length of time needed to complete the trial. This might be achieved by securing additional study sites for the trial. (Note: at present, the PI to the ADCAR trial is discussing this possibility with clinical managers at an alternative and potentially additional study site).

3. There should be increased screening of women who might be eligible to participate in the ADCAR trial. (Note: this recommendation is currently being implemented. During site visits (ongoing), clinical staff are reminded of the importance of screening all women presenting with signs of labour. Midwifery managers have been asked, in supporting the trial at the clinical level, to ensure new and rotating staff are aware of the trial procedures and the importance of completing the trial screening forms).

4. Umbilical cord blood values are retrieved and recorded on all participating women in the ADCAR trial in all three study sites. (Note: this recommendation is currently being implemented. During site visits (ongoing), clinical staff are reminded of the importance of obtaining and recording cord blood values on trial participants. The importance of this information as a secondary neonatal outcome measure is emphasised and reinforced. Midwifery managers have been asked, in supporting the trial at the clinical level, to ensure new
8.4 Conclusion

This thesis offers significant advancement for scholarship in maternity care. Chapter 2 collates and documents the background literature on factors associated with FHR monitoring in practice to provide a valuable, succinct source of information for clinicians that is not, at present, available in this form elsewhere. Chapter 3 and Chapter 4, through systematic review, meta-analysis and thematic analysis contribute significantly to the advancement of midwifery knowledge on the effectiveness of ACTG use and on the views of fetal monitoring in clinical practice. Chapter 3 presents an in-depth evaluation of the most up-to-date evidence on the use of ACTG and presents the design and conduct of the ADCAR trial in the light of the totality of available evidence on the topic. The systematic review and thematic analysis of women’s and professionals’ views on FHR monitoring during labour (Chapter 4) is the first such analysis of this type. It significantly contributes original evidence to the topic. It provides insight on the thoughts, perceptions and experiences from the perspective of people that are affected by FHR monitoring and discusses the barriers to and facilitators of choice of FHR monitoring methods in practice. Furthermore, Chapter 4 provides insight on some of the possible barriers to and facilitators of recruitment to the ADCAR trial and has significant relevance for informing the trial as it continues to achieve sample size estimates.

Chapter 6, in providing a preliminary report on the ADCAR trial, documents the major part of this thesis. Although the first interim analysis is not robust enough to provide conclusive evidence of any differences in major outcomes between ACTG and IA use in low risk women, the findings highlight the feasibility of the trial and the need to continue this clinically relevant and hugely important research study. Of greater importance, they indicate the lack of any clear benefit or harm, indicating no increased risk for participants.
in both the IA or ACTG group and, therefore, the continuing uncertainty which provides the scientific and ethical justification to continue offering women the opportunity to take part in the trial. The ADCAR trial seeks to determine the most appropriate method for monitoring the FHR for the assessment of fetal wellbeing on admission with signs of possible labour in low risk women. The full findings of this trial will influence the future care of tens of thousands of women accessing maternity services, who will benefit from the advances that ADCAR will bring to the evidence base, and the resulting improvements in research-based care.
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APPENDIX I

‘The Cochrane Pregnancy & Childbirth Group’ data extraction form
The Cochrane Pregnancy and Childbirth Group

Data Extraction Template

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<th>Study ID:</th>
<th>Reference ID:</th>
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<th>Year of study publication:</th>
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<table>
<thead>
<tr>
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**Study design**

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**Participants and setting**

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<th>Sub groups:</th>
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</table>
## Intervention

**Experimental intervention:**

## Comparison

**Control/Comparison intervention**

## Additional information:

## Outcomes:

**Pre-specified outcomes:**

**Reported outcomes:**

### Study methods

#### Risk of bias

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<td>Clinician:</td>
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<td></td>
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<tr>
<td>Outcome assessor:</td>
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<tr>
<td>Describe any exclusion of participants after randomisation:</td>
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<tr>
<td>Was the analysis intention to treat? If not has the data been able to be re-included?</td>
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</table>
Free of selective reporting bias
Are reports of study free of suggestions of selective reporting bias?

Free of other bias
Was the study apparently free of other problems that could put it at high risk of bias?

Describe:

Yes / Unclear / No

If the study was stopped early, explain the reasons:

Yes / Unclear / No

Describe any baseline in balance:

Describe any differential diagnosis:

Additional information requested

Notes

Outcomes for main analysis

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<td>Total no. in study =</td>
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<tr>
<td></td>
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<tr>
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</tr>
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<tr>
<td>Apgar &lt; 1 at 5 mins</td>
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<td>cord blood acidosis</td>
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<td>admission to NICU</td>
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<td>length of stay in NICU</td>
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<td>fetal blood sampling</td>
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<td>meconium</td>
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<td>Neonatal resuscitation</td>
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<tr>
<td>Mother:</td>
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<tr>
<td>caesarean section;</td>
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<td>amniotomy</td>
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<td>oxytocin during labour</td>
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General conclusions

Very brief summary of study authors main findings/conclusions:

Very brief summary of review authors conclusions:

Exclusion after data extraction

Reasons for exclusion: (study design? participants? interventions/ outcomes? attrition? bias?)

Dates:
Date entered into RevMan and by whom?
Date checked and by whom?
Date copy sent to editorial base and by whom?
APPENDIX II

EPHPP quality assessment tool
**QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES**

**COMPONENT RATINGS**

### A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

<table>
<thead>
<tr>
<th>Very Likely</th>
<th>Somewhat Likely</th>
<th>Not Likely</th>
</tr>
</thead>
</table>

(Q2) What percentage of selected individuals agreed to participate?

| 80 - 100% Agreement | 60 - 79% Agreement | Less than 60% Agreement | Not Reported | Not Applicable |

Rate this section (see dictionary) | Strong | Moderate | Weak |

### B) ALLOCATION BIAS

Indicate the study design

- RCT (go to i)
- Quasi-Experimental (go to C)
- Case-control, Before/After study, No control group, or Other: _____________________

(Score Weak and go to C)

(i) Is the method of random allocation stated? Yes No

(ii) If the method of random allocation is stated is it appropriate? Yes No

(iii) Was the method of random allocation reported as concealed? Yes No

Rate this section (see dictionary) | Strong | Moderate | Weak |

### C) CONFOUNDERS

(Q1) Prior to the intervention were there between group differences for important confounders reported in the paper?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Can't Tell</th>
<th>Not Applicable</th>
</tr>
</thead>
</table>

(Score Weak and go to D)

Please refer to your Review Group list of confounders.

Relevant Confounders reported in the study:

__________________________  _________________________  _________________________

__________________________  _________________________  _________________________

__________________________  _________________________  _________________________
(Q2) If there were differences between groups for important confounders, were they adequately managed in the analysis?

Yes  No  Not Applicable

(Q3) Were there important confounders not reported in the paper?

Yes  No

Relevant Confounders NOT reported in the study:

<table>
<thead>
<tr>
<th>Rate this section (see dictionary)</th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
<th>Not Applicable</th>
</tr>
</thead>
</table>

Note: Many studies report the results of multiple data collection tools. If you are interested in only one outcome of interest, measured by one tool, at one point in time, rate the components (validity and reliability of tool, blinding, withdrawals and drop-outs) based on that one tool. If you are collecting multiple outcomes of interest, scored by multiple tools (e.g. self-report AND assessor interview, SF-36 AND made-up questionnaire), at multiple points in time (e.g. 6-month follow-up AND 20-year follow-up) copy components of the EPHPP tool so that each data collection tool of interest is scored.

D) BLINDING

(Q1) Was (were) the outcome assessor(s) blinded to the intervention or exposure status of participants?

Yes  No  Not Reported  Not Applicable

<table>
<thead>
<tr>
<th>Rate this section (see dictionary)</th>
<th>Strong</th>
<th>Weak</th>
<th>Not Applicable</th>
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</thead>
</table>

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown or are they known to be valid?

Yes  No

Rate this section (see dictionary)  Strong  Weak  Not Applicable

(Q2) Were data collection tools shown or are they known to be reliable?

Yes  No

Rate this section (see dictionary)  Strong  Moderate  Weak  Not Applicable

F) WITHDRAWALS AND DROP-OUTS

(Q1) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).

80 -100%  60 - 79%  Less than 60%  Not Reported  Not Applicable

Rate this section (see dictionary)  Strong  Moderate  Weak  Not Applicable

Effective Public Health Practice Project Quality Assessment Tool 2003
G) ANALYSIS

(Q1) Is there a sample size calculation or power calculation?
- Yes
- Partially
- No

(Q2) Is there a statistically significant difference between groups?
- Yes
- No
- Not Reported

(Q3) Are the statistical methods appropriate?
- Yes
- No
- Not Reported

(Q4a) Indicate the unit of allocation (circle one)
- Community
- Organization/Group
- Provider
- Client
- Institution

(Q4b) Indicate the unit of analysis (circle one)
- Community
- Organization/Group
- Provider
- Client
- Institution

(Q4c) If 4a and 4b are different, was the cluster analysis done?
- Yes
- No
- Not Applicable

(Q5) Is the analysis performed by intervention allocation status (i.e., intention to treat) rather than the actual intervention received?
- Yes
- No
- Can't Tell

H) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?
- 80 - 100%
- 60 - 79%
- Less than 60%
- Not Reported
- Not Applicable

(Q2) Was the consistency of the intervention measured?
- Yes
- No
- Not reported
- Not Applicable
### SUMMARY OF COMPONENT RATINGS

Please transcribe the information from the gray boxes on pages 1-3 onto this page.

<table>
<thead>
<tr>
<th>A</th>
<th>SELECTION BIAS</th>
<th>Rate this section (see dictionary)</th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>STUDY DESIGN</td>
<td>Rate this section (see dictionary)</td>
<td>Strong</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
<tr>
<td>C</td>
<td>CONFOUNDERS</td>
<td>Rate this section (see dictionary)</td>
<td>Strong</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
<tr>
<td>D</td>
<td>BLINDING</td>
<td>Rate this section (see dictionary)</td>
<td>Strong</td>
<td>Weak</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>E</td>
<td>DATA COLLECTION METHODS</td>
<td>Rate this section (see dictionary)</td>
<td>Strong</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
<tr>
<td>F</td>
<td>WITHDRAWALS AND DROPOUTS</td>
<td>Rate this section (see dictionary)</td>
<td>Strong</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
</tbody>
</table>

**G** ANALYSIS

Comments

________________________________________________________________________
________________________________________________________________________

**H** INTERVENTION INTEGRITY

Comments

________________________________________________________________________
________________________________________________________________________

**WITH BOTH REVIEWERS DISCUSSING THE RATINGS:**

Is there a discrepancy between the two reviewers with respect to the component ratings?

No   Yes

If yes, indicate the reason for the discrepancy

1. Oversight
2. Differences in Interpretation of Criteria
3. Differences in Interpretation of Study
INTRODUCTION

The purpose of this tool is to assess the methodological quality of relevant studies since lesser quality studies may be biased and could over-estimate or under-estimate the effect of an intervention. Each of two raters will independently assess the quality of each study and complete this form. When each rater is finished, the individual ratings will be compared. A consensus must be reached on each item. In cases of disagreement even after discussion, a third person will be asked to assess the study.

*When appraising a study, it is helpful to first look at the design then assess other study methods.* It is important to read the methods section since the abstract (if present) may not be accurate. Descriptions of items and the scoring process are located in the dictionary that accompanies this tool.

The scoring process for each component is located on the last page of the dictionary.

INSTRUCTIONS FOR COMPLETION

Circle the appropriate response in each component section (A-H). Component sections (A-F) are each rated using the roadmap on the last page of the dictionary. After each individual rater has completed the form, both reviewers must compare their ratings and arrive at a consensus.

The dictionary is intended to be a guide and includes explanations of terms.

The purpose of this dictionary is to describe items in the tool thereby assisting raters to score study quality. Due to under-reporting or lack of clarity in the primary study, raters will need to make judgements about the extent that bias may be present. When making judgements about each component, raters should form their opinion based upon information contained in the study rather than making inferences about what the authors intended.

A) SELECTION BIAS

Selection bias occurs when the study sample does not represent the target population for whom the intervention is intended. Two important types of biases related to sample selection are referral filter bias and volunteer bias. For example, the results of a study of participants suffering from asthma from a teaching hospital are not likely to be generalizable to participants suffering from asthma from a general practice. In volunteer bias, people who volunteer to be participants may have outcomes that are different from those of non-volunteers. Volunteers are usually healthier than non-volunteers.

Q1 Are the individuals selected to participate in the study likely to be representative of the target population?

| The authors have done everything reasonably possible to ensure that the target population is represented (e.g.) | Very Likely |

QA Dictionary 2003
Participants may not be representative if they are referred from a source within a target population even if it is in a systematic manner (e.g. patients from a teaching hospital for adults with asthma, only inner-city schools for adolescent risk).

<table>
<thead>
<tr>
<th>Somewhat Likely</th>
</tr>
</thead>
</table>

Participants are probably not representative if they are self-referred or are volunteers (e.g. volunteer patients from a teaching hospital for adults with asthma, inner-city school children with parental consent for adolescent risk) or if you can not tell.

<table>
<thead>
<tr>
<th>Not Likely</th>
</tr>
</thead>
</table>

### Q2 What percentage of selected individuals agreed to participate?

<table>
<thead>
<tr>
<th>The % of subjects in the control and intervention groups that agreed to participate in the study before they were assigned to intervention or control groups.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no mention of how many individuals were approached to participate.</td>
<td>Not Reported</td>
</tr>
<tr>
<td>The study was directed at a group of people in a specific geographical area, city, province, broadcast audience, where the denominator is not known, e.g. mass media intervention.</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>

### B) ALLOCATION BIAS

In this section, raters assess the likelihood of bias due to the allocation process in an experimental study. For observational studies, raters assess the extent that assessments of exposure and outcome are likely to be independent. Generally, the type of design is a good indicator of the extent of bias. In stronger designs, an equivalent control group is present and the allocation process is such that the investigators are unable to predict the sequence.

### Q1 Indicate the study design.

<table>
<thead>
<tr>
<th>Investigators randomly allocate eligible people to an intervention or control group.</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort (two group pre and post)</strong> Groups are assembled according to whether or not exposure to the intervention has occurred. Exposure to the intervention may or may not be under the control of the investigators. Study groups may not be equivalent or comparable on some feature that affects the outcome.</td>
<td>Two-group Quasi-Experimental</td>
</tr>
</tbody>
</table>
Before/After Study (one group pre + post)
The same group is pretested, given an intervention, and tested immediately after the intervention. The intervention group, by means of the pretest, act as their own control group.

Case control study
A retrospective study design where the investigators gather 'cases' of people who already have the outcome of interest and 'controls' that do not. Both groups are then questioned or their records examined about whether they received the intervention exposure of interest.

No Control Group

Note: The following questions are not for rating but for additional statistics that can be incorporated in the writing of the review.

(i) If the study was reported as an RCT was the method of random allocation stated?

| The method of allocation was stated. | YES |
| The method of allocation was not stated. | NO |

(ii) Is the method of random allocation appropriate?

| The method of random allocation is appropriate if the randomization sequence allows each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next, e.g. an open list of random numbers of assignments or coin toss. | YES |
| The method of random allocation is not entirely transparent, e.g. the method of randomization is described as alternation, case record numbers, dates of birth, day of the week. | NO |

(iii) Was the method of random allocation concealed?

| The randomization allocation was concealed so that each study participant had the same chance of receiving each intervention and the investigators could not predict which group assignment was next. Examples of appropriate approaches include assignment of subjects by a central office unaware of subject characteristics, or sequentially numbered, and sealed in opaque envelopes. | YES |
| The method of random allocation was not concealed or not reported as concealed. | NO |

C) CONFOUNDERS
A confounder is a characteristic of study subjects that:
is a risk factor (determinant) for the outcome to the putative cause, or
is associated (in a statistical sense) with exposure to the putative cause
Note: Potential confounders should be discussed within the Review Group and decided a priori.

Q1 Prior to the intervention were there differences for important confounders reported in the paper?

<table>
<thead>
<tr>
<th></th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>The authors reported that the groups were balanced at baseline with respect to confounders (either in the text or a table)</td>
<td></td>
</tr>
<tr>
<td>The authors reported that the groups were not balanced at baseline with respect to confounders.</td>
<td>YES</td>
</tr>
</tbody>
</table>

Q2 Were the confounders adequately managed in the analysis?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differences between groups for important confounders were controlled in the design (by stratification or matching) or in the analysis.</td>
<td></td>
</tr>
<tr>
<td>No attempt was made to control for confounders.</td>
<td>NO</td>
</tr>
</tbody>
</table>

Q3 Were there important confounders not reported?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>All confounders discussed within the Review Group were reported.</td>
<td>NO</td>
</tr>
</tbody>
</table>

D) BLINDING

The purpose of blinding the outcome assessors (who might also be the care providers) is to protect against detection bias.

Q1 Was (were) the outcome assessor(s) blinded to the intervention or exposure status of participants?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessors were described as blinded to which participants were in the control and intervention groups.</td>
<td></td>
</tr>
<tr>
<td>Assessors were able to determine what group the participants were in.</td>
<td>NO</td>
</tr>
<tr>
<td>The data was self-reported and was collected by way of a survey, questionnaire or interview.</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>It is not possible to determine if the assessors were blinded or not.</td>
<td>Not Reported</td>
</tr>
</tbody>
</table>

E) DATA COLLECTION METHODS

Some sources from which data may be collected are:

- Self reported data includes data that is collected from participants in the study (e.g. completing a questionnaire, survey, answering questions during an interview, etc.).
- Assessment/Screening includes objective data that is retrieved by the researchers. (e.g. observations by investigators).
- Medical Records / Vital Statistics refers to the types of formal records used for the extraction of the data.
Reliability and validity can be reported in the study or in a separate study. For example, some standard assessment tools have known reliability and validity.

Q1 Were data collection tools shown or known to be valid for the outcome of interest?  
   The tools are known or were shown to measure what they were intended to measure.  YES  
   There was no attempt to show that the tools measured what they were intended to measure.  NO

Q2 Were data collection tools shown or known to be reliable for the outcome of interest?  
   The tools are known or were shown to be consistent and accurate in measuring the outcome of interest (e.g., test-retest, Cronbach's alpha, interrater reliability).  YES  
   There was no attempt to show that the tools were consistent and accurate in measuring the outcome of interest.  NO

F) WITHDRAWALS AND DROP-OUTS

Q1 Indicate the percentage of participants completing the study.  
   The percentage of participants that completed the study.  
   The study was directed at a group of people in a specific geographical area, city, province, broadcast audience, where the percentage of participants completing, withdrawing or dropping-out of the study is not known, e.g. mass media intervention.  Not Applicable  
   The authors did not report on how many participants completed, withdrew or dropped-out of the study.  Not Reported

G) ANALYSIS

If you have questions about analysis, contact your review group leader.

Q1. The components of a recognized formula are present. There's a citation for the formula used.
Q2. The appropriate statistically significant difference between groups needs to be determined by the review group before the review begins.
Q3. The review group leader needs to think about how much the study has violated the underlying assumptions of parametric analysis?
Q5. Whether intention to treat or reasonably high response rate (may need to clarify within the review group).
H) INTERVENTION INTEGRITY

Q1 What percentage of participants received the allocated intervention or exposure of interest?

<table>
<thead>
<tr>
<th>The number of participants receiving the intended intervention is noted. For example, the authors may have reported that at least 80 percent of the participants received the complete intervention.</th>
</tr>
</thead>
<tbody>
<tr>
<td>describe</td>
</tr>
<tr>
<td>describe</td>
</tr>
</tbody>
</table>

Q2 Was the consistency of the intervention measured?

The authors should describe a method of measuring if the intervention was provided to all participants the same way.

| Yes |
| No |
| Not Reported |

Q3 Is it likely that subjects received an unintended intervention (contamination or cointervention) that may influence the results?

The authors should indicate if subjects received an unintended intervention that may have influenced the outcomes. For example, co-intervention occurs when the study group receives an additional intervention (other than that intended). In this case, it is possible that the effect of the intervention may be over-estimated. Contamination refers to situations where the control group accidentally receives the study intervention. This could result in an under-estimation of the impact of the intervention.

| Yes |
| No |
| Can’t Tell |
Component Ratings for Study

A) SELECTION BIAS

Strong
Q1 = Very Likely AND Q2 = 80-100% Agreement
OR
Q1 = Very Likely AND Q2 = Not Applicable

Moderate
Q1 = Very Likely AND Q2 = 60-79% Agreement
OR
Q1 = Very Likely AND Q2 = Not Reported
OR
Q1 = Somewhat Likely AND Q2 = 80-100%
OR
Q1 = Somewhat Likely AND Q2 = 60-79% Agreement
OR
Q1 = Somewhat Likely AND Q2 = Not Applicable

Weak
Q1 = Not Likely
OR
Q2 = Less than 60% agreement
OR
Q1 = Somewhat Likely AND Q2 = Not Applicable

B) ALLOCATION BIAS

Strong
Study Design = RCT

Moderate
Study Design = Two-Group Quasi-Experimental

Weak
Study Design = Case Control, Before/After Study, No Control Group

C) CONFOUNDERS

Strong

\[
\begin{array}{ccc}
Q1 = \text{Yes} & \text{AND } Q2 = \text{Yes} & \text{AND } Q3 = \text{Yes} \\
Q1 = \text{Yes} & \text{AND } Q2 = \text{N/A} & \text{AND } Q3 = \text{No} \\
Q1 = \text{Yes} & \text{AND } Q2 = \text{N/A} & \text{AND } Q3 = \text{No} \\
\end{array}
\]

Moderate

\[
\begin{array}{ccc}
Q1 = \text{Yes} & \text{AND } Q2 = \text{Yes} & \text{AND } Q3 = \text{Yes} \\
Q1 = \text{Can't Tell} & \text{AND } Q2 = \text{No} & \text{AND } Q3 = \text{Yes} \\
Q1 = \text{Yes} & \text{AND } Q2 = \text{No} & \text{AND } Q3 = \text{Yes} \\
Q1 = \text{Yes} & \text{AND } Q2 = \text{N/A} & \text{AND } Q3 = \text{Yes} \\
Q1 = \text{No} & \text{AND } Q2 = \text{N/A} & \text{AND } Q3 = \text{No} \\
\end{array}
\]

Weak
D) BLINDING

Strong
Q1 = Yes

Weak
Q1 = No
Q1 = Not Reported

Not Applicable

E) DATA COLLECTION METHODS

Strong
Q1 = Yes AND Q2 = Yes

Moderate
Q1 = Yes AND Q2 = No

Weak
Q1 = No AND Q2 = Yes
OR
Q1 = No AND Q2 = No

F) WITHDRAWALS AND DROP-OUTS

Strong
Q1 = 80-100%

Moderate
Q1 = 60-79%

Weak
Q1 = Less than 60%
OR
Q1 = Not Reported

Not Applicable
APPENDIX III

The QUADAS tool
<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the spectrum of patients representative of the patients who will receive the test in practice?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Were selection criteria clearly described?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Did patients receive the same reference standard regardless of the index test result?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Was the execution of the index test described in sufficient detail to permit replication of the test?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Was the execution of the reference standard described in sufficient detail to permit its replication?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index test?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Were uninterpretable/ intermediate test results reported?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
<tr>
<td>Were withdrawals from the study explained?</td>
<td>(   )</td>
<td>(   )</td>
<td>(   )</td>
</tr>
</tbody>
</table>
APPENDIX IV

Chapter 3: Forest plots for remaining outcome measures
### Epidural Analgesia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IA Events</th>
<th>Total Events</th>
<th>ACTG Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheyne 2003</td>
<td>60</td>
<td>184</td>
<td>65</td>
<td>148</td>
<td>9.9%</td>
<td>0.83 [0.63, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Mires 2001</td>
<td>565</td>
<td>1885</td>
<td>617</td>
<td>1866</td>
<td>90.1%</td>
<td>0.91 [0.82, 1.00]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2049</strong></td>
<td><strong>2014</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>Total</strong></td>
<td><strong>90.0%</strong></td>
<td><strong>0.90 [0.82, 0.98]</strong></td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>625</td>
<td>6515</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 0.33, df = 1 (P = 0.56); I^2 = 0\%

Test for overall effect: \( Z = 2.33 (P = 0.02) \)

1.58 [0.81, 3.10]

1.0 Caesarean Section

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IA Events</th>
<th>Total Events</th>
<th>ACTG Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheyne 2003</td>
<td>9</td>
<td>164</td>
<td>11</td>
<td>148</td>
<td>2.8%</td>
<td>0.74 [0.31, 1.73]</td>
<td></td>
</tr>
<tr>
<td>Impey 2003</td>
<td>158</td>
<td>4282</td>
<td>180</td>
<td>4298</td>
<td>43.8%</td>
<td>0.88 [0.71, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Mires 2001</td>
<td>165</td>
<td>1885</td>
<td>193</td>
<td>1866</td>
<td>47.2%</td>
<td>0.85 [0.69, 1.03]</td>
<td></td>
</tr>
<tr>
<td>Mitchell 2008</td>
<td>22</td>
<td>284</td>
<td>26</td>
<td>298</td>
<td>6.2%</td>
<td>0.89 [0.52, 1.53]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>6615</strong></td>
<td><strong>6610</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>Total</strong></td>
<td><strong>90.0%</strong></td>
<td><strong>0.96 [0.75, 0.99]</strong></td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>354</td>
<td>932</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 0.21, df = 3 (P = 0.96); I^2 = 0\%

Test for overall effect: \( Z = 2.14 (P = 0.03) \)

2.0 Operative Birth

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IA Events</th>
<th>Total Events</th>
<th>ACTG Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheyne 2003</td>
<td>21</td>
<td>164</td>
<td>12</td>
<td>148</td>
<td>1.3%</td>
<td>1.58 [0.81, 3.10]</td>
<td></td>
</tr>
<tr>
<td>Impey 2003</td>
<td>476</td>
<td>4282</td>
<td>493</td>
<td>4298</td>
<td>50.6%</td>
<td>0.97 [0.86, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Mires 2001</td>
<td>386</td>
<td>1885</td>
<td>409</td>
<td>1866</td>
<td>42.3%</td>
<td>0.93 [0.83, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Mitchell 2008</td>
<td>49</td>
<td>284</td>
<td>50</td>
<td>298</td>
<td>5.6%</td>
<td>0.89 [0.63, 1.25]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>6615</strong></td>
<td><strong>6610</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>Total</strong></td>
<td><strong>90.0%</strong></td>
<td><strong>0.96 [0.88, 1.04]</strong></td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>932</td>
<td>932</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 2.51, df = 3 (P = 0.47); I^2 = 0\%

Test for overall effect: \( Z = 1.03 (P = 0.30) \)
### 4.0 Augmentation of labour: Oxytocin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IA Events</th>
<th>ACTG Total</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheyne 2003</td>
<td>5 164</td>
<td>7 148</td>
<td>0.2%</td>
<td>0.64 [0.21, 1.99]</td>
</tr>
<tr>
<td>Impey 2003</td>
<td>1629 4282</td>
<td>2511 4298</td>
<td>66.6%</td>
<td>0.65 [0.62, 0.68]</td>
</tr>
<tr>
<td>Mires 2001</td>
<td>1128 1882</td>
<td>1246 1865</td>
<td>33.2%</td>
<td>0.90 [0.85, 0.94]</td>
</tr>
<tr>
<td>Mitchell 2008</td>
<td>0 0</td>
<td>0 0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>6328 6311</td>
<td>100.0%</td>
<td>0.73 [0.71, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>2752 3764</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 91.42, df = 2 (P < 0.00001); I^2 = 98%$
Test for overall effect: $Z = 17.94 (P < 0.00001)$

### 5.0 Continuous EFM during labour

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IA Events</th>
<th>ACTG Total</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheyne 2003</td>
<td>2 164</td>
<td>0 148</td>
<td>1.0%</td>
<td>4.52 [0.22, 93.29]</td>
</tr>
<tr>
<td>Impey 2003</td>
<td>11 4282</td>
<td>17 4298</td>
<td>31.4%</td>
<td>0.65 [0.30, 1.38]</td>
</tr>
<tr>
<td>Mires 2001</td>
<td>34 1868</td>
<td>36 1858</td>
<td>66.7%</td>
<td>0.90 [0.59, 1.46]</td>
</tr>
<tr>
<td>Mitchell 2008</td>
<td>4 284</td>
<td>0 298</td>
<td>0.9%</td>
<td>9.44 [0.51, 174.59]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>6598 6602</td>
<td>100.0%</td>
<td>0.96 [0.68, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>51 53</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 4.39, df = 3 (P = 0.22); I^2 = 32%$
Test for overall effect: $Z = 0.21 (P = 0.83)$

### 6.0 Apgar ≤ 7 at 5 mins
Total (95% CI) 6608 6607 100.0% 1.03 [0.98, 1.20]

Total events 312 303
Heterogeneity: Chi² = 2.36, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)

7.0 Admission to NICU/SCBU

Total (95% CI) 6331 6312 100.0% 0.81 [0.72, 0.90]
Total events 534 660
Heterogeneity: Chi² = 2.13, df = 2 (P = 0.35); I² = 6%
Test for overall effect: Z = 3.86 (P = 0.0001)

8.0 Use of FBS

Total (95% CI) 5239 5247 100.0% 1.06 [0.81, 1.38]
Total events 106 100
Heterogeneity: Chi² = 1.93, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 0.41 (P = 0.68)

9.0 Caesarean Section for abnormal FHR pattern
APPENDIX V

The CONSORT statement
<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)</td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
<td></td>
</tr>
<tr>
<td>Methods</td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were actually assessed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>7a</td>
<td>How sample size was determined</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
<td></td>
</tr>
<tr>
<td>Randomisation:</td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
<td></td>
</tr>
<tr>
<td>Sequence</td>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
<td></td>
</tr>
<tr>
<td>generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation</td>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
<td></td>
</tr>
<tr>
<td>concealment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mechanism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implementation</td>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
<td></td>
</tr>
<tr>
<td>Blinding</td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those...</td>
<td></td>
</tr>
<tr>
<td>Statistical methods</td>
<td>11b</td>
<td>If relevant, description of the similarity of interventions</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>-----</td>
<td>----------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>12a</td>
<td></td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
<td></td>
</tr>
<tr>
<td>12b</td>
<td></td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
<td></td>
</tr>
</tbody>
</table>

**Results**

<table>
<thead>
<tr>
<th>Participant flow (a diagram is strongly recommended)</th>
<th>13a</th>
<th>For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>13b</td>
<td></td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
</tr>
<tr>
<td>Recruitment</td>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
</tr>
<tr>
<td>14b</td>
<td></td>
<td>Why the trial ended or was stopped</td>
</tr>
<tr>
<td>Baseline data</td>
<td>15</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
</tr>
<tr>
<td>Numbers analysed</td>
<td>16</td>
<td>For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>17a</td>
<td>For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
</tr>
<tr>
<td>17b</td>
<td></td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
</tr>
<tr>
<td>Harms</td>
<td>19</td>
<td>All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
</tr>
</tbody>
</table>

**Discussion**

| Limitations                                          | 20  | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses |
| Generalisability                                    | 21  | Generalisability (external validity, applicability) of the trial findings |
| Interpretation                                       | 22  | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence |

**Other information**

| Registration                                         | 23  | Registration number and name of trial registry |
| Protocol                                            | 24  | Where the full trial protocol can be accessed, if available |
| Funding                                             | 25  | Sources of funding and other support (such as supply of drugs), role of funders |

— We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
APPENDIX VI

The ADCAR trial consent form
The ADCAR Trial Consent Form

Title of Project
Fetal cardiotocography versus intermittent auscultation during labour ward admission; A randomised trial and qualitative follow up: The ADCAR trial.

Date: 

Woman’s Details: (Name, Address, DOB and record Number or affix addressograph)

Name of Researcher: Valerie Smith

1. I confirm that I have read, or have had read to me, and understand the study information booklet for the ADCAR study and have had the opportunity to ask questions.

2. I understand that participation in this study is voluntary and that I am free to withdraw from the study at any time, without giving any reason, without my care or legal rights being affected.

3. I understand that sections of my care records may be looked at by responsible individuals from the study organisers or from regulatory authorities where it is deemed relevant. I give permission for these individuals to have access to my records.

4. I understand that a blood sample will be taken from the umbilical cord following the birth of my baby and that this sample will be destroyed immediately after testing.

5. I agree to take part in the ADCAR trial.

My name, printed Date Signature

Midwives name, printed Date Signature

ADCAR number:
APPENDIX VII

The ADCAR trial 'study
information for women' booklet
The ADCAR Trial

Study Information for Women
Introduction
We would like to tell you about an important research study that we are doing in this hospital. This study may help to improve the health of mothers and babies. It is known as the ADCAR trial. This hospital is one of three hospitals taking part in the ADCAR trial. Although only women who are healthy and have had a normal pregnancy will be able to join the study we want to let everyone know about the study. Please read this information to see if you are able and would like to join this study.

What is the ADCAR trial?
The ADCAR trial compares two different ways of checking the baby’s heart rate when a woman comes to the hospital showing signs that labour may have started. The full name of the study is: Fetal cardiotocography versus intermittent auscultation during labour ward admission: A randomised trial and qualitative follow-up.

What does the study involve?
This type of study is known as a randomised trial. Those who take part in a randomised trial are divided by chance into different groups. Each group is given a different treatment and the results are then compared to see if one treatment is better. The two ways of checking your baby’s heart rate are:

1) Intermittent Auscultation (IA)
2) Admission Cardiotocography (CTG)

What is intermittent auscultation?
Intermittent auscultation (IA) involves listening to your baby’s heart rate, at planned times, for one full minute, using either:

a) A small hand-held device called a Pinard stethoscope which looks like a small trumpet and is placed gently on your tummy or
b) A small battery-operated machine with a built-in speaker, called a Doppler ultrasound. A small, circular part of the Doppler is placed gently on your tummy to locate your baby’s heart beat, which can then be heard through the speaker.
**What is admission cardiotocography (CTG)?**

Admission CTG is a paper printout of your baby’s heart rate and your contractions recorded by a special electronic machine called an electronic fetal monitor. The admission CTG usually lasts for about 20 minutes. The baby’s heart rate is recorded on the admission CTG by a small ultrasound disc placed gently on your tummy. Your contractions are recorded by a small disc also placed on your tummy.

**Why is this hospital taking part in the study?**

At present, every woman who comes into this hospital showing signs that labour may have started will have an admission CTG. It is thought that the admission CTG test might find those babies who might do better with more careful watching during labour. However, there is a small amount of evidence that shows that this more careful checking of the baby’s heart rate may lead to procedures that are not really needed in women who have healthy, normal pregnancies.

**What kind of procedures?**

Three studies\(^1\) that are similar to this study, but not exactly the same, showed that women who had an admission CTG were more likely to have an epidural and continuous CTG during labour (that is, checking the baby’s heart beat with the electronic fetal monitor for almost all of the time during labour) than women who had IA when they first came in to the hospital in labour. These studies showed no differences in how well the babies did whether their heart rate was checked by admission CTG or by IA.

A number of studies also looked at women who had their babies heart beat checked during labour by continuous CTG or by IA. A report\(^2\) on the results of these studies showed that fits (neonatal seizures), although rare, occurred less often in babies who had continuous CTG to check their heart rate during labour. This study, however, is

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only about this first time checking of your baby’s heart rate; it is not about how your baby’s heart rate is checked throughout your whole labour.

**Who may join this study?**

We are inviting all women who come into hospital with signs that labour may have started AND who can say ‘yes’ to the following questions, to be in this study:

- Are you at least 37 weeks pregnant?
- Are you expecting one baby (not twins or triplets)?
- Have you had a normal, healthy pregnancy without high blood pressure or diabetes or any other medical problems?
- If you were pregnant before, did you have a vaginal birth (that is, not a caesarean section)?

**What happens if I join the study?**

When you come into the hospital after 37 weeks of pregnancy with signs that labour may have started, the midwife caring for you will do a health check to make sure you are able to join the study. If you are able and wish to join the study, the midwife caring for you will ask you to sign a consent form saying that you agree to be part of the study. After this, the randomisation is done, and the midwife will tell you if your baby’s heart rate is to be checked by intermittent auscultation (IA) or by admission CTG. You have an equal chance of being placed into either group.

If you are placed into the admission CTG group, you will have a 20-minute admission CTG before the midwife confirms that you are in labour. If you are placed into the IA group, the midwife will listen to your baby’s heart for one full minute before she confirms that you are in labour.

**What happens if I am not yet in labour?**

If you are not yet in labour, you will either go to the antenatal ward or you might go home to await further signs of labour. If you decide to go home, and had IA, the midwife will do a discharge CTG (a 20-minute electronic recording of your baby’s heart beat) before you go home.

When you next come in to the hospital with signs of labour, and if everything in your pregnancy is still normal, your baby’s heart beat will be listened to in the same way
as it was the last time you came to the hospital (that is, either by IA or by admission CTG). After this, your care will proceed as is normal practice.

**Special blood test**
As part of this study, the researchers would like your permission to take a sample of blood from your baby’s cord after your baby is born. This will be done by the midwife caring for you at the time your baby is born. The sample of blood is taken from the part of the cord attached to the placenta or afterbirth once the cord has been cut. Therefore, it will not cause any harm or discomfort to your baby or to you. This sample is needed to look at the oxygen levels in your baby’s blood at the time of birth. This can tell us how well your baby coped with the labour and birth. The blood sample will be tested by a special machine on the labour ward and destroyed immediately after the test.

**Do I have to take part in this study?**
No, taking part in this study is completely up to you. If you decide not to take part in the study, you will receive the normal care offered by the hospital.

**What are the risks/benefits of taking part in this study?**
There are no known risks to taking part in this study. If you are in the IA group or in the admission CTG group and the midwife notes a possible problem in your baby’s heart rate, then you will be offered continuous monitoring by CTG throughout your labour. The benefits of taking part in this research study are that you will have helped to answer questions that could improve the health of future generations of mothers and babies.

**Can I leave the study after I have joined?**
Yes, you have the right to leave the study at any time you wish. If you decide to leave the study, you must tell the midwife on duty or contact the research assistant to the study (you will find contact details at the end of this booklet).

**Is my personal health information kept private?**
All study information is kept private. You will be given a study number so that any personal information collected during the study will not be linked to your name. All study information will be kept for five years after the study is finished and then
destroyed. The results of the study may be published; however, neither your name nor any personal details about you will appear in any publications.

Who is running the study?
The study is being carried out by the ADCAR Trial Steering Committee. The committee is made up of midwives, obstetricians, neonatologists, researchers and women who represent the women who use maternity hospital services during their pregnancy and birth. The study is coordinated by the School of Nursing and Midwifery at the National University of Ireland, Galway. Valerie Smith, a midwife researcher based in Trinity College Dublin, is responsible for the day to day management of the trial. The ADCAR trial has been funded by the Health Research Board, Trinity College Dublin and the Department of Health and Children. This study has received ethical approval from the Research Ethics Committee of the Faculty of Health Sciences, Trinity College Dublin, and from the hospital’s Research Committees.

What do I do now if I wish to be in the study?
You don’t need to do anything else right now. It is only when you go into hospital with signs of labour possibly starting that you can actually ‘sign up’ to join the study. This is when you will have the final health check to make sure that you are able to be in the study.

Where can I get more information or ask questions about the study?
The midwives and doctors in your hospital have information about the study. The ADCAR trial website (see www.childbirthresearch.com and then click on ADCAR) also has information on the study and this will be updated regularly. Finally, the research midwife, Valerie Smith, will be happy to provide you with more information. You can contact Valerie by emailing vasmith@tcd.ie or by telephoning 01-8964063.

THANK YOU FOR YOUR TIME AND FOR CONSIDERING TAKING PART IN THIS IMPORTANT RESEARCH STUDY
APPENDIX VIII

Data monitoring & safety board:

Terms of reference & members
The ADCAR Trial Data and Safety Monitoring Board (DSMB) Operating Procedures

DSMB Terms of Reference:
The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the ADCAR Trial Steering Committee (TSC). The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to:

1. Become familiar with the research protocol and the procedures for data safety and monitoring.
2. Review unblinded interim analyses of outcome data and adverse event reports.

In light of 2 above and ensuring that ethical considerations and safety are of prime importance, the DSMB will:

1. Make written recommendations to the Trial Steering Committee (TSC) concerning the continuation, modification, or termination of the trial.
2. Consider any requests for release of interim trial data and to recommend to the TSC on the advisability of this.
3. Members will review major proposed modifications to the study prior to their implementation (e.g. termination, increasing target sample size).
4. Maintain confidentiality during all phases of DSMB review and deliberations.

Membership:
The membership of the DSMB reflects the professions necessary to interpret the data from the ADCAR Trial and to evaluate participant safety fully.

Members of the DSMB are Professor Soo Downe (in the capacity of Chair and Director of Midwifery Studies Research Unit, University of Lancashire), Professor Zarko Alfirevic (Department of Obstetrics and Gynaecology, University of Liverpool), and Dr. Simon Gates (Statistician, Principal Research Fellow, Medical School, University of Warwick).

Conflict of Interest:
No member of the DSMB has direct involvement in the conduct of the study. Furthermore, no member has certain financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. At the beginning
of every DSMB meeting, the DSMB Chair will reconfirm that no conflict of interest exists for DSMB members. Interests that may create a potential conflict of interest should be disclosed to the DSMB prior to any discussion. The DSMB will determine how to handle such potential conflict. The DSMB can require that a member with a potential conflict not vote or take other means deemed appropriate.

Meetings:
During the period of recruitment to the main trial, two interim analyses (accrual rates, baseline data, data describing the compliance with the intervention and outcome data in tabular form, using an intention to treat approach, unblinded to allocation group) will be supplied by the PI and/or the researcher in consultation with the DSMB statistician and in strict confidence, to the DSMB as follows: the first after complete data have been received on the first 1906 (33%) women recruited to the main study and the second after complete data have been received on the first 3870 (67%) women recruited to the main study. Meetings will be organised by the PI and/or the researcher in consultation with the DSMB Chair to coincide with interim analyses i.e. two scheduled meetings. Meetings will be held in Dublin with a venue provided by the School of Nursing and Midwifery Studies, Trinity College. Additional meetings may be called at the request of the DSMB Chair.

An early stopping guideline of a reduced alpha of 0.01 will be used to assess whether the intervention is showing a much stronger or weaker effect on outcomes than expected. Decisions to hold ad hoc meetings will be made by the PI and/or the researcher and DSMB Chair. Face-to-face meetings are preferable but conference calls or videoconferences are acceptable alternatives with the agreement of all DSMB members and the PI and/or researcher.

Guidance notes:
The role of the DSMB is to look at the unblinded data from an ethical standpoint; the safety, rights and wellbeing of trial participants being paramount. All significant communications between the DSMB Chair and the PI and/or the researcher should, wherever possible, be in writing.
In the light of interim data, the DSMB will inform the PI within 1 week of each meeting by means of a confidential written report if, in their opinion;
- There is insufficient evidence of benefit or harm and the study can continue as originally designed;
- If it is ethical to continue randomising women when there are potential differences in treatment efficacy and/or safety;
- The data suggest that there may never be any difference in efficacy and the trial should be stopped or
- Where accrual rates are poor, whether the trial should be prematurely closed to participant entry because it is unlikely to meet its accrual objectives in a reasonable period of time or whether accrual in the trial should continue.

This recommendation should be made by formal majority vote. A recommendation to terminate the study should be transmitted to the PI as rapidly as possible, by immediate telephone and fax if sufficiently urgent. In the event of a split vote in favour of continuation, a minority report should be contained within the regular DSMB report.

DSMB members should consider the statistical early stopping guideline of a reduced alpha of 0.01 as a guideline rather than as pre-determined statistical rule. The DSMB should also take into consideration all other aspects and information relevant to the trial such as the number of women and events observed (data maturity), the length of the confidence interval for the size of the treatment difference, safety, quality of life, feasibility, information from other trials, and likelihood that the trial’s findings at the time that it is stopped early will influence future health care practice.

The PI and/or the researcher and DSMB Statistician will prepare a comprehensive report for circulation to DSMB members in advance of DSMB meetings. This report will contain information on trial accrual rates, baseline data, data describing the compliance with the intervention and outcome data in tabular form, using an intention to treat approach, unblinded to allocation group. The PI and/or the researcher may be invited by the DSMB Chair to attend part of the DSMB meetings to present the data. If this is the case, the PI and/or researcher will withdraw from the meeting after presentation of the data.

Confidentiality:
All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

**Trial Steering Committee:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Role in research</th>
<th>Occupation</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declan Devane</td>
<td>Principal Investigator</td>
<td>Lecturer in Midwifery</td>
<td>School of Nursing &amp; Midwifery, University College Galway, Galway.</td>
</tr>
<tr>
<td>Tel: 087-6596923</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-mail: <a href="mailto:Declan.devane@nuigalway.ie">Declan.devane@nuigalway.ie</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prof. Cecily Begley</td>
<td>Co-Applicant</td>
<td>Director of Nursing and Midwifery</td>
<td>School of Nursing &amp; Midwifery, Trinity College Dublin, 24 D’Olier Street, Dublin 2.</td>
</tr>
<tr>
<td>Prof. Mike Clarke</td>
<td>Co-Applicant</td>
<td>Director of UK Cochrane Centre</td>
<td>UK Cochrane Centre NHS R&amp;D Programme Middle Way Oxford OX2 7L.G England.</td>
</tr>
<tr>
<td>Valerie Smith</td>
<td>Researcher</td>
<td>Midwifery Research Assistant/PhD Student</td>
<td>School of Nursing &amp; Midwifery, Trinity College Dublin</td>
</tr>
<tr>
<td>E-mail: <a href="mailto:vasmith@tcd.ie">vasmith@tcd.ie</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ms. Dawn Staudt</td>
<td>TSC member</td>
<td>Consumer Representative</td>
<td>Kellystown, Slane, Co-Meath.</td>
</tr>
<tr>
<td>Dr Shane Higgins</td>
<td>TSC member</td>
<td>Consultant obstetrician/Clinical Director</td>
<td>Maternity unit, Our Lady of Lourdes Hospital, Drogheda, Co-Louth.</td>
</tr>
<tr>
<td>Prof Deirdre Murphy</td>
<td>TSC member</td>
<td>Consultant obstetrician</td>
<td>Coombe Women’s Hospital, Dublin.</td>
</tr>
<tr>
<td>Anne Keating</td>
<td>TSC member</td>
<td>Midwifery manager, labour ward</td>
<td>Our Lady of Lourdes Hospital, Drogheda</td>
</tr>
<tr>
<td>Susan Kelly</td>
<td>TSC member</td>
<td>Midwifery manager, labour ward</td>
<td>Coombe Women’s Hospital, Dublin.</td>
</tr>
<tr>
<td>Dr Siobhan Gormally</td>
<td>TSC member</td>
<td>Consultant Neonatologist</td>
<td>Our Lady of Lourdes Hospital, Drogheda, Co-Louth.</td>
</tr>
<tr>
<td>Dr Mike Geary</td>
<td>TSC member</td>
<td>Consultant obstetrician</td>
<td>Rotunda Hospital, Dublin.</td>
</tr>
</tbody>
</table>

The following documents were used in developing these operating procedures:

APPENDIX IX

The ADCAR trial 'serious adverse events report form'
The ADCAR Trial – Serious Adverse Event Report Form

Name of hospital: Site A □ Site B □ Site C □

Name of person completing this form: ____________________________
(use BLOCK CAPITALS please)

Date form completed: [ ]/[ ]/[ ]

Date Serious Adverse Event occurred: [ ]/[ ]/[ ]

Woman's Details: (Name, Address, DOB and record Number or affix addressograph)

Mother's study number: [ ][ ][ ][ ]

Description of Serious Adverse Event

- Stillbirth □
- Neonatal death □
- Seizures (either apparent clinically or detected by electro-encephalographic recordings) □
- Hypoxic Ischemic Encephalopathy - Grade II and III using Sarnat Staging System □
- Intracranial Haemorrhage □
- Meconium aspiration (as determined on x-ray) □
- Renal failure (defined as oliguria with a creatinine concentration of more than 120μmol/L □
- IPPV via ETT □
- External cardiac massage □
- Neonatal drug therapy (excluding narcotic antagonist e.g. naloxone) □
- Metabolic acidosis (defined as an umbilical artery pH<7.05 and a base deficit in the extracellular fluid compartment (BD) of >12.0 mmol/L) □
- Maternal death □
- Prolongation of maternal/neonatal hospital stay □
- Unusual maternal morbidity (e.g. need for blood transfusion) □
- Maternal/neonatal life-threatening event □

Comments: ______________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
APPENDIX X

Letters of ethical approval
Friday, 16 November 2007

STUDY: “Fetal cardiotocography versus intermittent auscultation during labour ward admission: a randomised trial and qualitative follow up: the adcar trial”

Dear Ms Smith

Further to a meeting of the Faculty of Health Sciences Research Ethics Committee 2007 - 2008, we are pleased to inform you that the above project has been approved without further audit.

Yours sincerely

[Signature]

Dr. Orla Sheils
Chairperson
Faculty of Health Sciences Ethics Committee

cc. Supervisor, Mr D Devane, Nursing
2nd August 2007

Ms Valerie Smith
School of Nursing & Midwifery
Trinity College Dublin
24 D'Olier Street
Dublin 2

Re/ Research Study Proposal:
"Fetal cardiotocography versus intermittent auscultation during labour ward admission: A randomised trial and qualitative follow up"
HRAC Meeting: 10th May 2007

Dear Ms Smith

I wish to acknowledge receipt of a copy of ethical approval from the Faculty of Health Sciences Ethics Committee, Trinity College, Dublin in connection with your above study.

I wish to advise that all the requirements of the Healthcare Research Advisory Committee have been met and final approval to commence your study is given.

Yours sincerely,

Dr. Declan Bedford
Chairperson
Healthcare Research Advisory Committee

Copied to/ Mr Des O'Flynn, General Manager, Louth Hospital Group, Our Lady of Lourdes Hospital, Drogheda, Co Louth
Ms Colette McCann, Nurse Manager for Women & Childrens Services, Our Lady of Lourdes Hospital, Drogheda, Co Louth
Mr Declan Devane, Lecturer in Midwifery, School of Nursing & Midwifery, Trinity College Dublin, 24 D'Olier Street, Dublin 2
Mr. Declan Devane  
Senior Lecturer  
School of Nursing & Midwifery  
National University of Ireland  
Galway.

Ref: C.A. 149 – Fetal Cardiotocography versus intermittent auscultation during labour ward admission: A randomized trial and qualitative follow up. The ADCAR trial.

Dear Mr. Devane,

The Chairman’s decision to approve the above project, was ratified at the last Clinical Research Ethics Committee meeting of Wednesday 17th September, 2008.

Yours sincerely,

Dr. Shaun T. O’Keeffe  
Chairman Clinical Research Ethics Committee.
11 February 2008

Mr Declan Devane  
Lecturer in Midwifery  
School of Nursing & Midwifery  
Trinity College  
Dublin 2

Re.: Study No. 2007 20 – The ADCAR Trial

Dear Declan

The committee has now had time to review the changes made in the protocol, including the changes made in the Patient Information Leaflet. As no objections have been raised, this study is now fully approved.

Yours sincerely

Dr Michael Carey  
Chairman
Ethical concerns raised and addressed
Reply to comments from Faculty Ethics Committee,
March 27th 2007

- Concerns regarding the taking of consent from expectant mothers as they are admitted to hospital in labour (3.1). Could this be done in any other way?

The Association for Improvements in Maternity Care and the National Childbirth Trust in their 'A Charter for Ethical Research in Maternity Care' (1997) state that;

1. Wherever possible, women should be given information well in advance of being asked for their consent to participate, and
2. Informed consent should be sought as close to randomisation/treatment as possible.

The researcher feels it is important to adhere to these guidelines and does not believe it ethical to gain consent any earlier as it is at the point of entering the study that women can only be sure then that they wish to participate. The information is provided well in advance of this point (see section 3.1) allowing them sufficient time to consider participating and allowing time for questions to be asked.

- The qualitative follow-up: It is recommended that the consent form be submitted at interview rather than being posted in. this would allow questions to be asked and answered.

Amendment made and highlighted in section 3.1

- 3.7. It is recommended that code numbers rather than pseudonyms be used.
  If there is an overwhelming need to use pseudonyms further justification is required.

Amendment made as suggested and highlighted in section 3.7

- 3.7 and 3.11 Please indicate how long details will be kept – 5 years is recommended.

Comment addressed and highlighted in section 3.7 and 3.11

- It should be made clearer on the information leaflet p.45 that the qualitative study is optional and that you can sign up for first (quantitative) part without committing to qualitative part. Please amend.

Amendment made and highlighted in the information booklet.
• Please advise whether the hospitals involved will be giving ethical approval. If so, approval from this committee will be subject to receipt of hospital approval.

I am in the process of seeking ethical approval from hospital sites. This is detailed in sections 6.1 and 6.2 of the ethical approval form. I will forward said approval immediately on receipt of same.

Reply to Hospital Ethics Committee

12 November 2007

Dear Dr

Re: Study No. 2007: 20 – Fetal cardiotocography versus intermittent auscultation during labour ward admission (The ADCAR Trial).

The above study was approved by the Hospital Ethics Committee, at the meeting dated 17th October 2007, subject to a number of conditions as detailed in your letter dated the 26th October 2007.

We are pleased to inform you that we have now addressed these conditions and enclose our response as follows for your approval:

**Condition 1:** Documentary evidence is to be supplied indicating that the hospital is indemnified by the HSE for patient treatment and by Trinity College for issues arising out of the study design and protocol.

**Response:** The Clinical Indemnity Scheme provides cover for claims arising from treatment arising from research projects carried out in its approved institutions, which include the Hospital. Documentary evidence of this can be found in the section on Research on the Department of Health and Children’s website at below link: [http://www.dohc.ie/issues/enterprise_liability/cis.html](http://www.dohc.ie/issues/enterprise_liability/cis.html)

Enclosed please find a copy of Trinity College Dublin’s Professional Indemnity. You will note that the last paragraph states that ‘The Professional Indemnity policy provides an indemnity for research projects carried out by Trinity College (excluding Clinical Trials),’ We confirm that this study is not a clinical trial that falls within neither the EU Clinical Trials Directive nor the Control of Clinical Trials Act 1987 and is therefore covered within Trinity’s Professional Indemnity policy as detailed in attached.
Condition 2: The consent form is to be amended, include a reference to previous studies done in this area, with particular reference to neonatal seizures in a similar (although not exact same) study.
Response: The study information letter and consent form have been amended as required and are enclosed for your approval. The required changes have been highlighted for your convenience.

Condition 3: The term 'low-risk' needs to be defined and some concern was expressed regarding patients who were post-dates. You would need to liaise with clinicians via the Master as to what is 'low risk'.
Response: All criteria for eligibility (i.e. low and high-risk status) will be agreed with obstetric and midwifery representatives from all participating sites, including the Coombe Women's hospital, prior to commencement of the study.

We hope the above responses meet the requirements of the hospital Ethics Committee. Thank you for considering the ADCAR trial and we very much look forward to working with the hospital on this research study.

Yours sincerely,

Valerie Smith
Midwifery Research Assistant,
School of Nursing & Midwifery
24 D'Olier Street
Dublin 2.

---

**Reply to Healthcare Research Advisory Committee**
**Meeting date May 10th 2007**

- **Appendix VI** – The committee queried the reason for obtaining a sample of blood from the baby's cord after birth.

The analysis of blood form the umbilical cord at delivery provides objective information on the acid-base status of the fetus and may provide information on the occurrence, timing and possible causes of oxygen deficiency (if any) in a baby at birth. In this study, as a secondary outcome measure, we wish to evaluate if there is any difference in neonatal morbidity between babies born in either group (i.e. babies born of mothers receiving the admission CTG or babies born of mothers receiving intermittent auscultation). Obtaining a sample of blood from the baby's cord after birth provides a measure of the cord Ph at birth. A cord Ph of less than 7.0 and a Base Deficit of more than 16mmol/l is an indicator of fetal metabolic acidaemia, and
these levels are associated with an increasing risk of neurological deficit in the baby. Therefore we believe it is essential to obtain this sample of cord blood in order to evaluate one aspect of potential differences in neonatal outcomes between babies born in either group of the trial.

- **Section 3.3.** The committee request that the following groups are included in the study

  1. adults/children with learning disabilities
  2. adults/children with communication difficulties
  3. adults/children who have a terminal illness
  4. adults/children with mental illness
  5. prisoners
  6. young offenders

The National Health and Medical Research Committee (1999) state that; "Research involving a person under the age of 18 years is usually granted on the condition that consent from the child or young person is obtained when they have the capacity to make that decision, and also that consent is obtained from a parent, or other responsible adult, or guardian".

With respect to 1, 2, 3, 4, 5 and 6 above; individuals in these groups, who meet the eligibility criteria for the study, who are deemed suitable to receive study information during the preliminary screening process from 36 weeks onwards, and who demonstrate the ability to provide informed consent, or where a parent, or other responsible adult, or guardian can provide that informed consent, will be invited to participate in the study as requested by the Healthcare Research Advisory Committee. This has been amended on the attached ethical approval form.
APPENDIX XII

Letter of correspondence
30th April, 2007.

Ms. Valerie Smith/Mr. Declan Devane,
Department of Nursing and Midwifery,
Trinity College,
Dublin 2.

Re: The ADCAR Trial

Dear Valerie and Declan,

Thank you for attending the Research Ethics Committee meeting on 19th April to discuss the randomised controlled trial comparing the effect of admission cardiotocograph versus intermittent auscultation of the fetal heart rate on low risk women.

As you know it was decided following the initial presentation of the proposed study on 8th March to obtain the views of the consultant obstetricians at the [Hospital] Hospital, under whose care the patients would be admitted. As you know the majority of the obstetricians have indicated they are not happy to proceed with the study for a number of reasons including medico-legal concerns. In view of this the Research Ethics Committee is not happy for the study to proceed at present.

I understand that you will discuss with [Master] the Master, whether it is worthwhile arranging a meeting with a group of obstetricians to see if there is any possibility of amending the study to address their concerns. I also understand that the obstetricians will be happy to meet with you again following the completion of the pilot study in Drogheda to review the situation.

Yours sincerely,
APPENDIX XIII

Clinical indemnity for the ADCAR trial
Ms. Bernadette Costello,
Director of Internal Audit & Risk Management.
National University of Ireland,
Newcastle Road,
Galway.

Dear Bernadette,

Re The ADCAR Trial.

We are insurance brokers to the National University of Ireland, Galway and confirm the undernoted policies extend, subject to policy terms & conditions, to cover Insured’s legal liability, for claims arising from trial design and protocol in relation to The ADCAR Trial.

**Employers Liability Policy No. 0747**

- **Limit of Indemnity:** €13,000,000 any one accident.
- **Insurer:** Irish Public Bodies Mutual Ins. Co. Ltd.
- **Period of Cover:** 12 months from 1st October 2007

**Public Liability Policy No. X/5675**

- **Limit of Indemnity:** €6,500,000 any one accident.
- **Insurer:** Irish Public Bodies Mutual Ins. Co. Ltd
- **Period of Cover:** 12 months from 1st October 2007

**Professional Indemnity Policy No. EX92868588**

- **Limit of Indemnity:** €2,000,000 aggregate.
- **Insurer:** Royal & Sun Alliance
- **Period of Cover:** 12 months from 1st October 2007

Trusting this is the information you require. If you have any further queries, please do not hesitate to contact us.

Yours sincerely,

JOHN LEONARD
Director, Corporate Risks

Registered in Ireland number 78812
Registered office 7-9 South Leinster Street, Dublin 2
Coyle Hamilton Willis Ltd is regulated by the Irish Financial Services Regulatory Authority as an Authorised Intermediary
APPENDIX XIV

The ADCAR trial, Trial screening

& register form (TSRF)
The ADCAR Trial Screening and Register Form

This form MUST be fully completed on admission for all women with stickers titled 'ADCAR study information given' on their chart.

Date: ____________

Woman's Details: (Name, Address, DOB and record Number or affix addressograph)

Study information
Study information received prior to attending the labour ward/admission room: Yes □ No □

Eligibility (See criteria on the back of this form)
Eligible for ADCAR Trial: Yes □ No □

If no, DO NOT PROCEED and document primary reason for ineligibility:
1. ........................................................................................................................................................................

Consent - Please go to consent Booklet (this will be N/A where a woman is ineligible for ADCAR)

ADCAR Trial Consent form signed and witnessed:
Yes □ ADCAR number: ____________
No □

If no, DO NOT PROCEED to randomisation

Randomisation - Please telephone randomisation centre for group allocation

Allocation: Admission CTG □
Intermittent Auscultation □

Signature and printed name of midwife/doctor completing this form:

Printed Name: ___________________________ Signature: ___________________________
ADCAR Trial Screening and Register Form - Eligibility Criteria

Please tick as appropriate for EACH risk factor. If 'YES' is ticked for any risk factor the woman is ineligible and should not be considered further for the ADCAR trial.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous caesarean section†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Hypertension alone†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post dates (&gt;40 + 6 weeks)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prematurity (&lt;37 + 0)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induced labour†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rupture of membranes &gt;24 hours †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antepartum Haemorrhage (single episode at &gt;24 weeks)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection/pyrexia (&gt;37.5°C on admission)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine or Cervical Malformation ‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt;35 at booking‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age &lt;18 years at time of consent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age &gt;40 years at booking‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assisted conception in this pregnancy‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal medical Disease:‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cardiac/vascular disease/anaemia (Hb&lt;10g/l)</td>
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<td></td>
</tr>
<tr>
<td>- history of thrombo-embolic disorder</td>
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<td></td>
</tr>
<tr>
<td>- thrombocytopenia (&lt;100 on most recent sample)</td>
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<tr>
<td>- hyperthyroidism</td>
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<td></td>
</tr>
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<td>- abnormal renal function</td>
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<td></td>
</tr>
<tr>
<td>- rhesus isoimmunisation</td>
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<td></td>
</tr>
<tr>
<td>- liver disease (abnormal LFT's)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- epilepsy</td>
<td></td>
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<tr>
<td>- other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stillbirth or neonatal death†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small for gestational age (&lt;10th centile)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal liquor volume†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oligohydraminosus (single pool &lt;2/AFI &lt;5cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Polyhydraminosus (single pool &gt;10cm/AFI &gt;25cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Doppler artery velocimetry†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breech/other non-cephalic/Multiple pregnancy†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced fetal movements (on more than one occasion)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meconium stained liquor†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal congenital abnormality in this pregnancy†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†adapted from NICE (2007) 'Intrapartum care: care of healthy women and their babies during childbirth'.
‡From ADCAR Trial Steering Committee members
§BP of 140/90 or more on at least 2 occasions >24hrs apart in women previously normotensive (Broughton 1981)
APPENDIX XV

The ALEA IVR system
ADCAR TRIAL-RANDOMISATION PROCEDURES

A telephone randomisation service called ‘TENALEA’ provides the group allocation (i.e. intermittent auscultation or admission CTG). The system is an interactive voice response system and asks for a number of details prior to giving the group allocation.

The following provides the steps involved in the randomisation process:

1. Ring switch board and ask to be put through to the ADCAR study number.
2. Welcome to Cheap calls – Dial 0031206173947 followed by # key.
3. Enter pin number: 9457
4. Press 1 for Study Site.
5. Enter trial number for patient; This is the 4 digit ADCAR study number located on the bottom of the ADCAR trial consent form (which the woman must have already signed).
6. Enter mother’s medical record number.
7. Is participant eligible and is consent signed
   - Press 1 for yes
   - Press 2 for no
8. Submits the form.
9. Group Allocation is given (Admission CTG or Intermittent Auscultation) – the system repeats the allocation until you hang up.
APPENDIX XVI

Summary care-pathway algorithms
The ADCAR Trial
Providing Women with Study Information

1. All women attending antenatal clinics from 32 weeks gestation onwards

2. Absence of obvious risk factors (e.g. previous cesarean section)

3. Provide women with the ADCAR study information booklet and brief overview of the study

4. Place 'ADCAR study information given' sticker on chart

5. On subsequent clinic visits ask women who have received the study information if they read it, understood it or have any questions about the study
The ADCAR Trial
Admission Algorithm

Admission with signs of labour
  Yes
  Complete Trial screening form
  Eligible for ADCAR
    Yes
    ADCAR Information Given
      Yes
      Invite to participate
        Agrees to participate
          Consent form signed
            Telephone randomisation service
              ACTG
        Declines to participate
          Standard care
    No
    Exclude
      Standard care
Randomise 1:1 ACTG
To labour ward and standard care
Li Mot in
established
established
established
labour
labour
labour
Home Antenatal ward
To labour ward and standard care
I
I
T
...........
I
...............
See Readmission Algorithm -
Labour established
Labour not established
If woman remains low-risk, this should be IA during labour
If labour has not established and woman is low-risk, this should be IA during labour
See Readmission Algorithm
To labour ward and standard care
Discharge CTG
If not going home, for reassessment at next ward round, unless clinical status changes
Home
Labour established
Labour not established
Readmitted
Home
Readmitted
CTG
To labour ward and standard care
Discharge CTG
If not going home, for reassessment at next ward round, unless clinical status changes
Home
Labour established
Labour not established
Readmitted
Home
Readmitted
CTG
To labour ward and standard care
Discharge CTG
If not going home, for reassessment at next ward round, unless clinical status changes
Home
Labour established
Labour not established
Readmitted
Home
Readmitted
CTG
To labour ward and standard care
Discharge CTG
If not going home, for reassessment at next ward round, unless clinical status changes
Home
Labour established
Labour not established
Readmitted
Home
Readmitted
CTG
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Discharge CTG
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Labour established
Labour not established
Readmitted
Home
Readmitted
CTG
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Labour established
Labour not established
Readmitted
Home
Readmitted
CTG
To labour ward and standard care
Discharge CTG
If not going home, for reassessment at next ward round, unless clinical status changes
Home
Labour established
Labour not established
Readmitted
Home
Readmitted
CTG
To labour ward and standard care
Discharge CTG
If not going home, for reassessment at next ward round, unless clinical status changes
Home
Labour established
Labour not established
Readmitted
Home
Readmitted
CTG
To labour ward and standard care
Discharge CTG
If not going home, for reassessment at next ward round, unless clinical status changes
Home
Labour established
Labour not established
Readmitted
Home
Readmitted
CTG
To labour ward and standard care
Discharge CTG
If not going home, for reassessment at next ward round, unless clinical status changes
The ADCAR Trial

Re-admission algorithm

Readmission post randomisation with signs of labour

IA

- Complete Readmission Screening Form
  - Not Eligible
    - Document on Screening Form and perform ACTG as standard practice
      - NB: Woman remains in study and data is collected: umbilical cord bloods must be done
  - Remains Eligible
    - Perform IA as previously allocated (Do not consent and randomise again)

ACTG

- Complete Readmission Screening Form
  - Not Eligible
    - Document on Screening Form and perform ACTG as standard practice
      - NB: Woman remains in study and data is collected: umbilical cord bloods must be done
  - Remains Eligible
    - Perform ACTG as previously allocated (Do not consent and randomise again)
APPENDIX XVII

Preliminary trial screening & register form
The ADCAR Trial Preliminary Trial Screening Form

This form MUST be fully completed from 36 weeks gestation onwards for all women to determine eligibility for the ADCAR Trial

Date & Time: ___/___/______ : ___ hrs

Mother's Details
(Name, DOB, record No or affix addressograph)

Eligibility (See checklist and criteria on back of this form)

Eligible for ADCAR Trial: Yes □ No □
If no, DO NOT PROCEED and document primary reason for ineligibility:
1. ........................................................................................................................................

Study Information

Study information given Yes □ (place sticker 'ADCAR study information given' on chart)
No □ (place sticker 'ineligible for ADCAR' on chart)

Signature and printed name of midwife/doctor completing this form:

Printed Name: 
Signature: 


Please tick for EACH risk factor as appropriate. If you tick 'YES' to any one risk factor the woman is ineligible and should not be considered for the ADCAR trial. A sticker titled 'ineligible for ADCAR' should be placed on the front of her chart.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous caesarean section†</td>
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</tr>
<tr>
<td>*Hypertension alone†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged rupture of membranes (&gt;24 hours)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antepartum Haemorrhage (single episode at &gt;24 weeks)†</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt;35 at booking†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age &gt;40 years at booking†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assisted conception in this pregnancy†</td>
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<td></td>
</tr>
<tr>
<td>Maternal medical Disease:†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cardiac/vascular disease</td>
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<td></td>
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<td>Fetal congenital abnormality in this pregnancy†</td>
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† adapted from NICE (2007) 'Intrapartum care: care of healthy women and their babies during childbirth'.
†From ADCAR Trial Steering Committee members
*BP of 140/90 or more on at least 2 occasions >24hrs apart in women previously normotensive (Broughton 1981)
APPENDIX XVIII

The ADCAR trial readmission screening form
The ADCAR Trial; Trial Screening Readmission Form

This form MUST be completed on readmission for all women already randomized to the ADCAR trial to determine ongoing eligibility.

Date: ___________ / ___________ / ___________

Woman's Details: (Name, Address, DOB and record Number or affix addressograph)

Eligibility (See criteria on the back of this form)

Eligible for ADCAR Trial: Yes  □  No  □

If no, DO NOT PROCEED and document primary reason for ineligibility:

1. .........................................................................................................................

Signature and printed name of midwife/doctor completing this form:

Printed Name: .................................................................  Signature: .................................................................
Please tick as appropriate for EACH risk factor. If 'YES' is ticked for any risk factor the woman is ineligible and should not be considered further for the ADCAR trial.

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††From ADCAR Trial Steering Committee members.
*BP of 140/90 or more on at least 2 occasions >24hrs apart in women previously normotensive (Broughton 1981)
APPENDIX XIX

The ADCAR trial protocol
Fetal cardiotocography versus intermittent auscultation during labour ward admission.

The ADCAR trial.

Protocol

(Update: 26-08-2009)
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Background

Intermittent auscultation, that is the practice of listening to the fetal heart rate (FHR) at predetermined intervals using either a Doppler ultrasound device or a Pinard stethoscope, and electronic fetal monitoring (EFM) by a machine that produces a paper printout called a cardiotocograph (CTG) are the two most common methods for monitoring the FHR in pregnant women.

EFM was introduced into widespread clinical practice in the 1970-80s on the premise that it would help detect abnormal FHR patterns thought to be associated with hypoxia, and thereby allow earlier intervention to prevent fetal neurological damage or death (RCOG 2001a, Nelson et al. 1996). Despite the recognised limitations of EFM, (Thacker 1997) it is now the commonest method of assessing fetal wellbeing where there is thought to be a high risk of intrapartum asphyxia (MCHRC 2001, Impey et al. 2003a).

Antenatal risk factors do not identify all fetuses that will die or suffer morbidity and so the admission CTG (ACTG) has been introduced to try and identify those at greater risk of intrapartum asphyxia (Arulkumaran and Jenkins 2000) who might benefit from continuous EFM (Impey et al. 2003a). The ACTG is a screening test consisting of a 20 minute electronic recording of the FHR and uterine activity performed on admission to the labour ward or labour assessment room (Alfirevic et al. 2006).

Although there is a lack of good evidence supporting the use of the ACTG in low-risk pregnancy and contrary to recommendations that it should not be used for these women, (RCOG 2001a) an admission CTG was performed on all women by 96% (n=21) of maternity units in the Republic of Ireland and one unit (4%) restricted the use of the admission CTG for women with risk factors. Similar high rates of admission CTG use (79%, n=189) were found in a survey of maternity units in England, Wales and Northern Ireland conducted by CESDI in 1999-2000 (MCHRC 2001). This finding is reflected internationally, with use ranging from 76% (Kaczorowski et al. 1998) to 84% (Curtain and Matthews 2000). This high usage may, in part, reflect the influence of non-randomised studies that have provided conflicting evidence on the value of the ACTG as a screening test for fetal compromise in labour in low-risk women (Blix and Oian 2001, Ingermarsson et al. 1986).

There have been repeated calls for a thorough evaluation of the ACTG through adequately powered randomised trials, (RCOG 2001a, Thacker 1997) but only four such trials have been done and these are described in brief below (Mitchell 2008, Impey et al. 2003a, Mires et al. 2001, Cheyne et al. 2003). Three of these trials (Cheyne et al. 2003, Impey et al. 2003a, Mires et al. 2001) have been included in a systematic review and meta analysis, (Blix et al. 2005) which found that women randomised to ACTG were more likely to have epidural analgesia, continuous electronic fetal monitoring and fetal blood sampling (FBS) compared with women randomised to IA on admission; indicating that there is currently no good evidence for a beneficial effect of the ACTG for low-risk women.

In the most recent randomised trial comparing ACTG with IA, Mitchell (Mitchell 2008) reports a persistent increase in operative delivery rates in the ACTG group throughout the study period, however due to the small sample size (n=582), this difference remained unproven in terms of significance.
Furthermore due to early termination of this study and a short fall in recruitment rates (582 women compared to sample size calculations of 1500), the author reports a lack of clear evidence supporting the use of ACTG over IA in low-risk women and addresses the need for further research in this area.

Mires et al (2001), in their trial, performed subgroup analyses of 2367 low risk women and concluded that ACTG, compared with IA, does not benefit neonatal outcome but leads to an increase in caesarean and instrumental delivery rates. The primary outcome in that trial was umbilical arterial acidosis defined as a cord pH <7.20 with a base deficit of >8.0mmol/l, values not associated with immediate or long-term neonatal morbidity or mortality. Concerns have also been expressed about changes that were made in relation to the design of the trial while it was ongoing (Impey et al. 2003a).

The largest trial to date, by Impey et al, (Impey et al. 2003a) randomly assigned 8580 women at low risk of ‘fetal distress’ in labour to ACTG or to IA only. They found no difference in moderate to severe neonatal morbidity or perinatal mortality, or in mode of delivery. However, because a policy of active management of labour (AML) was practised in the study site this led to amniotomy before the ACTG. Therefore, as the researchers noted, their findings are not generalisable to the majority of low-risk labours where the colour of the liquor (the fluid surrounding the fetus) is unknown before commencement of the ACTG.

Finally, Cheyne et al’s (2003) analyses of 312 low-risk women randomised to ACTG or IA found no significant difference on rates of intervention or mode of delivery. However, the researchers advise caution in interpreting their findings due to erroneous assumptions on which sample size was calculated, the relatively small sample size of the trial and the 7% loss to follow up.

In planning an assessment of the ACTG, it is important to note that standard care in most labour wards or labour assessment rooms in Ireland involves performing an ACTG before the diagnosis of the onset of labour and before artificial rupture of the membranes (ARM). Discussions with TSC members in the proposed study sites indicate this to be the case in their respective sites. A notable exception is the National Maternity Hospital where the Impey et al trial (Impey et al. 2003a) was conducted. In the other two trials, (Mires et al. 2001, Cheyne et al. 2003) women were in spontaneous labour. Therefore, the CTG under consideration in these trials was an ACTG in labour as distinct from an ACTG on the women’s admission to the labour ward, and the latter reflects standard clinical care in the majority of maternity hospitals.

The neonatal and maternal benefits and harms of the ACTG compared with IA of the fetal heart for low-risk women before assessment for diagnosis of labour and without early rupture of the membranes remain uncertain and there is a need for a robust and fair assessment of this. The ADCAR trial will provide this assessment and will also give women an opportunity to voice their views on these types of fetal monitoring. The findings of this trial will inform maternity care providers on monitoring the fetal
heart when women are admitted to labour wards and will have relevance to many thousands of women per year in Ireland alone.

**Aim**
To compare the effect of admission cardiotocography (ACTG) versus intermittent auscultation (IA) of the FHR in low-risk women on admission to the labour ward or labour assessment room on (a) caesarean section, (b) obstetric intervention, and (c) neonatal morbidity.

**Methods**

**Design**
A two group, randomised trial is proposed. This design is the most reliable way to assess the relative effects of different interventions and to provide an unbiased estimate of the relative benefits and harms (Friedman et al. 1998) of using ACTG compared to IA in low-risk women since it will lead to two groups who differ only on the basis of which technique they are randomised to receive.

**Null Hypothesis**
There is no significant difference between ACTG and IA in low risk women on admission to the labour ward or labour assessment room in (a) caesarean section (b) obstetric intervention and (c) neonatal morbidity.

**Study Sites**
The Coombe Women & infant’s University Hospital, Dublin, Ireland.
Our Lady of Lourdes Hospital, Drogheda, Ireland.
University College Hospital, Galway, Ireland.

**Interventions**
Eligible women who consent to participate will be randomised to either ‘control’ or ‘experimental’ groups. As noted, current practice in the majority of maternity units is to use an ACTG when a woman is admitted to the hospital and, generally, before assessment for diagnosis of labour and membrane rupture and knowledge of liquor amnii colour. Discussions with TSC members in the proposed study sites indicate this to be the case in their respective sites. The ADCAR trial has been designed to reflect this current practice. Furthermore, separate care pathways have been planned for women in each group depending on whether or not they have been diagnosed as being in labour.

**Control**
Women randomised to the control group will receive the current standard of care in the three hospitals: a 20 minute ACTG on admission to labour ward or labour assessment room, followed by a review and interpretation of the ACTG by the admitting midwife based on the RCOG guidelines (RCOG 2001a). If the baseline FHR is between 110-160bpm, baseline variability is >5bpm, more than two accelerations are present and decelerations are absent the tracing will be classified as normal, discontinued and the findings documented. The uterine contraction pattern will also be assessed. If,
following the ACTG, the above interpretation criteria are met, the woman’s care will be in accordance with standard care. If she is diagnosed as being in labour, monitoring of the FHR will be by IA (see below for details of interpretation criteria and auscultation frequency). If she is diagnosed as not being in labour, her care will include discharge home or admission to the antenatal ward (based on the woman’s proximity to the hospital, the clinical situation, or both). If the above interpretation criteria are not met, cardiotocography will be continued and interpretation of this tracing used to inform subsequent care of the woman (as is current practice).

**Experimental**

Women randomised to the experimental group will receive IA of the fetal heart on admission with frequency, timing and interpretation based on an expansion of the RCOG guidelines (RCOG 2001a). IA on admission will be performed by the admitting midwife using a Pinard stethoscope or a hand-held Doppler ultrasound device. There is insufficient robust evidence to prefer one of these forms of intermittent auscultation over the other and this is supported by the National Institute of Clinical Excellence (NICE) Intrapartum care guidelines.(National Institute of Clinical Excellence 2001) IA includes abdominal palpation of uterine contractions and the FHR will be monitored for at least 60 seconds after a uterine contraction and documented. Conversion to EFM will happen where auscultation reveals a baseline FHR of less than 110bpm or greater than 160bpm or any decelerations in the FHR; or if any other risk factors develop, which warrant EFM, or the clinician caring for the woman has any other cause for concern. Where, following IA, the above interpretation criteria are met and the woman is diagnosed as being in labour, subsequent care during labour will be in accordance with standard care i.e. monitoring of the FHR by IA. The frequency of IA during labour will be as per RCOG guidelines (i.e. at least every 15 minutes in the first stage and at least every 5 minutes in the second stage of labour). If, following IA, the above interpretation criteria are met and the woman is diagnosed as not being in labour, her care would also follow standard care, which includes discharge home or admission to the antenatal ward (based on the woman’s proximity to the hospital, the given clinical situation or both). The future care of women in either group who are randomised and then found not to be in labour should be in accordance with that allocation (i.e. women randomised to ACTG should have an ACTG on subsequent admission to the labour ward, and women randomised to IA should have IA only, see Appendix I). Each woman’s clinical records (available on a 24/7 basis) will contain a Trial Screening and Register Form (TSRF) and a sticker titled ‘ACTG’ or ‘IA’ placed on the front cover of the woman’s clinical records following randomisation to the relevant group, therefore clinicians will know which group a woman was randomised into. If a woman’s condition changes such that continuing her care in accordance with the randomisation is contraindicated, her management will be modified accordingly and recorded in the trial documentation.

**Outcome measures**

There will be one primary and three secondary outcome measures as follows;

**Primary**

(a) Incidence of caesarean section
Secondary
(a) Obstetric intervention which will include;
   - Use of continuous EFM,
   - Use of fetal blood sampling,
   - Augmentation of labour with oxytocin,
   - Augmentation of labour with artificial rupture of membranes (ARM),
   - Labour length – 1st Stage
   - Labour length – 2nd Stage
   - Labour length – 3rd Stage,
   - Epidural analgesia,
   - Opiate analgesia
   - Mode of Birth;
     - Spontaneous vaginal
     - Ventouse
     - Forceps
     - Instrumental vaginal birth for abnormal fetal heart rate pattern and/or fetal acidosis
     - Elective caesarean section
     - Emergency caesarean section
     - Emergency caesarean section for abnormal fetal heart rate pattern and/or fetal acidosis

Baseline characteristics
   - Maternal age
   - Duration of gestation
   - Birthweight
   - Major congenital abnormality

(b) Neonatal morbidity which will include
   - Arterial and venous umbilical cord pH and base deficit
   - Metabolic acidosis (defined as an umbilical artery blood pH <7.05, and a base deficit in the extracellular fluid compartment (BD) of >12.0 mmol/L, as measured by the Siggaard-Andersen acid-base chart algorithm.(Low 1996)),
   - Hypoxic Ischaemic Encephalopathy (HIE) (severity assessed using Sarnat staging and MRI scanning with neurological follow up findings up to two years of age),
   - Seizures (either apparent clinically or detected by electro-encephalographic recordings)
   - Use of anticonvulsants – loading dose and/or maintenance dose,
   - Apgar scores at 1 and 5 minutes,
   - Admission to the neonatal intensive care unit, (NICU)
   - Length of stay in NICU (in days)
   - Neonatal death
   - Stillbirth

Draft 14: 26th August 2009
Intracranial haemorrhage (as determined by cranial ultrasound/MRI report)
Meconium aspiration (as determined on x-ray)
Renal failure (defined as oliguria with a creatinine concentration of more than 120 µmol/L)
Neonatal resuscitation;
  - Suction (oral/pharyngeal)
  - Suction & Oxygen
  - Facial oxygen only
  - Oxygen via bag and mask
  - IPPV
  - Narcotic antagonist (e.g. naloxone)

Sample size assumptions and estimates
A retrospective clinical audit of 600 women was conducted in Our Lady of Lourdes Hospital, Drogheda in 2005 and in a large Dublin maternity hospital (not the Coombe Women & Infant’s University hospital) by collaborators in this proposal to determine the number of women meeting the eligibility criteria on admission to the labour ward and the incidence of caesarean section in this low-risk audit sample. This audit found that 60% and 50% of women met the eligibility criteria on admission to the labour ward in Our Lady of Lourdes Hospital, Drogheda and in the Dublin Maternity hospital respectively. Of these women, 4.7% and 5.6% respectively had a caesarean section. These figures are consistent with published figures from the UK.(Impey et al. 2003b, Cheyne et al. 2003, 2001) There are approximately 15,000 births per year in the three hospitals combined, assuming that approximately 55% of these would be eligible and that about half would agree to take part in the ADCAR trial, we estimate that we can recruit 5,776 women over the 18 month recruitment period allowing for a 10% attrition rate and a one month contingency. We will monitor accrual on a monthly basis. This sample size (2,888 per group) will have sufficient power (at >80%) to detect a 30% reduction in the primary outcome measure of incidence of caesarean section, for example from 5.2% with ACTG to 3.6% with IA. (These calculations were done using SamplePower, alpha was set at 0.05 and the test is 2-tailed.)

Purposive sampling (women who have experienced ACTG or IA) will be used for the individual interviews and sampling will continue until data saturation is achieved. We anticipated that this will require 10-15 women from each of the two groups. If more women than the number required for data saturation express a willingness to take part in the interviews, we will draw a random sample from within each group.

Recruitment

Study population
Pregnant women at low risk of intrapartum fetal hypoxia at term are eligible to participate in the trial. Women of all races and ethnic groups are eligible to participate and the study information will be translated accordingly.
Eligibility criteria

- Women between 37^{10} and 40^{16} completed weeks of pregnancy
- Absence of antenatal, maternal and fetal risk factors to the development of neonatal encephalopathy, cerebral palsy or perinatal death as per RCOG,(RCOG 2001b) which warrant EFM (as detailed in the trial screening form).
- ≥18 years
- Ability to understand study information and willingness to give written, informed consent
- Women participating in interviews must be able to converse in English.

Enrolment procedures

A two stage process of consent will be used. Women attending the clinic at 32-40 weeks gestation (inclusive) will be given written information about the study, and asked to consider participating in the study before their admission to the hospital with signs and symptoms of possible labour. A sticker titled 'ADCAR study information given' will be placed on the front cover of their maternity notes highlighting that they have received the study information. This should allow sufficient time for most women to consider their participation. Women who are admitted to the labour ward between 37^{10} and 40^{16} weeks gestation, with signs of possible labour, will be screened for eligibility to participate in the ADCAR trial using the Trial Screening & Register Form (TSRF). Screening will be conducted by the admitting midwife. The TSRF will include the group randomised to for all women who are screened as eligible to participate, who consent to participate and who are subsequently randomised. Women who have met the eligibility criteria, received information on the study during the antenatal period and had any questions they had about the trial answered will be invited to participate in the trial and sign a study consent form. Participants will be asked to indicate, by ticking the relevant box (present only during recruitment to the qualitative component phase) on the ADCAR trial consent form (Appendix IV), if they would consider taking part in the qualitative component to be conducted during the postnatal period. All study information leaflets and consent documentation will be reviewed by the National Adult Literacy Association for literacy appropriateness and subsequently piloted (see 'Pilot Study').

Randomisation - generation and concealment of allocations

The unit of randomisation in the trial is the woman and her pregnancy. Participants will be randomised to control or experimental groups (allocation ratio of 1:1) using a telephone randomisation service. If, following randomisation, the midwife performing the assessment decides that an intervention other than that which was allocated should be performed, this is permissible and the reasons for doing so will be recorded on the data collection form. It is neither possible nor sensible to attempt to blind participants to their intervention. This is because the nature of the procedures means that women and the midwives caring for them will know which intervention they have been allocated to and any CTG done is stored in the woman’s hospital records.
Data collection
Maternity Information Systems (MIS) in each hospital will be able, with minor, permissible modifications, to capture the necessary data for the trial, defined a priori.

Umbilical cord blood sampling and analysis: Although only umbilical artery serum is required, paired serum samples from the umbilical artery and vein will be taken to establish that both vessels have been sampled. (RCOG 2001b) Written procedures for cord blood collection and analysis have been developed (Appendix VI). All cord arterial and venous samples will be read by a self-calibrating Blood Gas Analyser available in the labour wards of the study sites. All samples will be destroyed immediately after analysis. Women’s experiences will be explored through the use of individual interviews. Interviews will be held at a time and venue of the women’s choosing at 6-8 weeks after their baby is born. Interviews will be semi-structured i.e. guided based on the study purpose, existing literature and the constant comparative method (Strauss and Corbin 1998) (CCM). Findings from the interviews will provide information on this important and well recognised, but often ignored, aspect of fetal monitoring (RCOG 2001b, MIDIRS 2003)

Data analysis
Primary analyses will be by ‘intention-to-treat’. Null hypotheses will be tested using Chi-squared tests. Relative risks (with 95% CIs) will be calculated. An a priori subgroup analysis will be performed based on the primary outcome of incidence of caesarean section and using the two subgroups: ‘in-labour’ and ‘not in-labour’ (based on clinical assessment post intervention). For this sub-group analysis, the 99% CI will be used to take account of the increased number of comparisons. Quantitative data will be analysed using SPSS. Qualitative data will be organised and managed by QSR N6 and analysed using the CCM, allowing categories to emerge from the data and inform subsequent interviews. (Strauss and Corbin 1998) There is substantial expertise in the analysis of quantitative and qualitative data within the Trial Steering Committee (TSC).

Pilot study
A pilot study will be conducted over 3 weeks anticipated to begin March/April 2008. This pilot will be used to identify problems with the research design/processes; refine data collection and analysis; assess adequacy of MIS as a source of routine data; examine selection and enrolment processes; and assess the participants’ perspective on the quality of the documentation. We will not include data from the pilot period in the main analyses of the trial.

Rigour

Data Monitoring Board (DMB)
To optimize participant safety and the scientific integrity and credibility of the results of the trial, an independent DMB has been established in accordance with the terms of reference and guidelines of the Medical Research Council (MRC). (MRC 1998) Members of the DMB (see page 3) have been confirmed and include a Professor of Midwifery (SD), a Professor of Obstetrics (ZA) and a statistical expert (SG). The DMB will review and evaluate unblinded interim analyses (using a reduced alpha value for stopping study of 0.01) (Freidlin et al. 1999) when complete data have been received on the
first 33% (1906) and 67% (3870) of women recruited to the main study. The DMB will assess participant safety, rights and whether either intervention is showing a much stronger or weaker effect than expected. It will make recommendations concerning the continuation, modification, or termination of the study to the TSC.

Adverse events
All adverse events that occur after informed consent will be recorded on an Adverse Event Recording Form (AERF) (see Appendix VII) and reported to the Clinical Director within the respective hospital and to the DMB for consideration if deemed appropriate by the ADCAR team. The ADCAR team have provisionally defined an adverse event as;

- Stillbirth
- Neonatal death
- Seizures (either apparent clinically or detected by electro-encephalographic recordings)
- Hypoxic Ischemic Encephalopathy – Grade II and III using Sarnat Staging System
- Intracranial Haemorrhage
- Meconium aspiration (as determined on x-ray)
- Renal failure (defined as oliguria with a creatinine concentration of more than 120μmol/L)
- IPPV via ETT
- External cardiac massage
- Neonatal rug therapy (excluding narcotic antagonist e.g. naloxone)
- Metabolic acidosis (defined as an umbilical artery pH <7.05 and a base deficit in the extracellular fluid compartment (BD) of >12.0 mmol/L)
- Maternal death
- Prolongation of maternal/neonatal hospital stay
- Unusual maternal morbidity (e.g. need for blood transfusion)
- Maternal/neonatal life-threatening event

Data validation
Data validation will be performed every 3 months by taking a 2% random sample of maternal and neonatal data and checking against data in the MIS. Remedial strategies will be implemented if problems are identified. The central study processes (e.g. eligibility assessment, randomisation procedures etc.) will be kept under review to add to the rigour of the study.

Qualitative component
We will ensure the rigour of the qualitative component of the study by using qualitative verification procedures (Lincoln and Guba 1985) including maintenance of an audit trail, member checking and using women’s quotes to illustrate categories.

Ethical considerations
Ethical approval for the study will be sought from the Faculty of Health Sciences, Trinity College Dublin, and the Research Ethics Committees of all three study sites. A two stage process of
information and consent will be used, with informed consent being sought as close to randomisation as possible. This is in line with recommendations in 'A charter for ethical research in maternity care'. (AIMS/NCT 1997) Women will be given information antenatally at 32-40 weeks gestation (inclusive) informing them, both verbally and in writing, of the purpose, process of study entry, potential benefits and harms, data collection procedures, time commitment, voluntary participation, the right to withdraw without prejudice to care, assurance of confidentiality (including in study publication), researchers’ contact details and an offer to answer any questions. Women who are subsequently admitted to the labour ward and who meet the eligibility criteria will be invited to participate in the trial. Women agreeing to do so will be asked to sign an informed consent document, a signed copy of which will be retained by the woman, another placed in her notes and a third kept by the researcher. Participants will be asked to indicate if they would consider taking part in the qualitative component to be conducted during the postnatal period. Women who agree to participate in the interviews and who subsequently experience an adverse neonatal (e.g. congenital anomaly, prolonged neonatal hospitalisation) or maternal (e.g. prolonged hospitalisation due to any morbidity) outcome will be written to and asked if they wish to reconsider their participation in these interviews and her decision will be respected. All data will be collected, processed, and stored confidentially in accordance with the Data Protection (Amendment) Act (2003). Participants in both the intervention and the qualitative component of ADCAR will be assigned a unique number and pseudonym respectively. The master list of participants’ names with these numeric identifiers and pseudonyms will be stored securely away from all other data. Data collection booklets for all participants (containing details on study eligibility, consent, randomisation, clinical findings, outcomes, laboratory data, etc.) and interview transcripts will be retained in a secure storage facility for at least five years after the completion of the research.

**Trial Organisation and dissemination**

The success of this study, as with any research, will depend on teamwork, knowledge and confidence among all key stakeholders. The TSC is responsible for any major decisions such as changes to the protocol, monitoring and supervising the progress of the trial, and considering recommendations from the DMB. The members of the TSC have considerable expertise in the provision of clinical maternity care, randomised trial research, qualitative research and data analysis. Importantly, the TSC includes an experienced maternity services consumer representative. Success of the ADCAR trial depends on the collaboration of midwives and doctors in the participating hospitals and the efforts of the TSC. Monthly newsletters beginning three months before accrual begins to six months after study completion, electronic mailing lists and a website will be used to disseminate details. The results of the ADCAR trial will be reported first to trial participants, collaborators and clinicians in both hospitals through workshops informing clinicians of the findings and acknowledging their role in the success of the study. Findings will be disseminated by publication following the CONSORT guidance, (Moher et al. 2001) and presentations at national and international conferences. We will work with the general media, the trial website and relevant maternity care organisations to disseminate results to the public. Last, but not least, we will work with guideline producers in Ireland, the UK and more widely where
possible to facilitate the incorporation of the ADCAR findings into clinical guidelines supported by active facilitation, monitoring and evaluation.

**Training and support for study sites**

Staff at all three study sites are proficient in the use of EFM and IA. Nevertheless, monthly fetal monitoring in-service education workshops in the use and interpretation of EFM and IA will start three months before formal study launch will continue throughout the study and will be open to all staff involved in the provision of intrapartum care. There will be workshops three months before enrolment begins to the pilot study and four months before the main study. A member of the TSC (DD) who has extensive expertise in providing this training will provide these workshops. These workshops will take place on a monthly basis commencing January 2008 until launch of recruitment to main study and then bi-monthly until completion of recruitment.

Information workshops will be provided for all staff about the background, purpose and methods of the study by the research assistant (VS). These workshops will take place fortnightly initially, until launch of the pilot study and then monthly after the completion of the pilot.

**Conclusion**

The use of EFM and routine ACTGs on low-risk pregnant women remains high in current clinical maternity care contrary to recommendations that they should not be used for this population of women. The ADCAR trial is a randomised controlled trial which will compare the effect of ACTG versus IA of the FHR in low-risk pregnant women on admission to the labour ward on (a) caesarean section, (b) obstetric intervention, and (c) neonatal morbidity. This trial will also provide women the opportunity to voice their views on these methods of fetal monitoring. The findings of this trial will be of great clinical importance in informing maternity care providers on monitoring the FHR for women admitted to labour wards and will have relevance to many thousands of women per year in Ireland alone.

**Funding/Financial Implications**

The ADCAR trial is funded by the Health Research Board (Ireland) and the Department of Health & Children.

**References**


APPENDIX XX

Role of junior research assistant
Title of Post: Junior Research Assistant to the ADCAR Trial
Location: The Coombe Women & Infant’s University Hospital (CWIUH)
Reports to: Research Assistant to the ADCAR Trial – Valerie Smith
Role: To encourage and act as a resource for the ADCAR Trial in the CWIUH

Specifics of the role include:

1. Supporting and encouraging staff to recruit to ADCAR.

2. Ensuring all women (where appropriate) receive the study information during the antenatal period (weekly audit required). This will include:
   a. Providing midwives at all clinics (i.e. Public, Semi-Private, Private, Midwives and Community Midwives clinics) with ADCAR protocol information to facilitate them administering the study information booklet to women attending clinics;
   b. Enabling midwives to provide a brief synopsis of the trial to women and to encourage women to read the study information booklet;
   c. Encouraging midwives and doctors to ask women on subsequent visits whether they have read the study information, did they understand it and/or have they any questions regarding the study.
   d. Encouraging secretaries to private consultants (except for M. O’Connell) to provide women with the study information booklet. Secretaries are not expected to answer questions on the trial but may refer women to either Valerie or their consultant with their queries.

3. Ensuring trial screening forms are completed in all areas for all women who present to the hospital with signs of possible labour (weekly audit required)

4. Ensuring that all women who are eligible and wish to take part in ADCAR are recruited to the trial

5. Ensuring confidentiality and copy-right issues are respected;
6. Supporting regular contact with appointed research assistant

7. Supporting the research time frame and liaison with clinical colleagues related to role responsibilities

8. Highlighting any issues militating against items 1-4 above, or any other concern, to Valerie Smith.
APPENDIX XXI

Example newsletters
Thank You to all Staff for continuing to support the ADCAR Trial

**Recruitment**

<table>
<thead>
<tr>
<th>Week</th>
<th>Site B Number recruited</th>
<th>Site A Number recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Target per week 26</td>
<td>Target per week = 12</td>
</tr>
<tr>
<td>1st-7th Dec</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>8th-14th Dec</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>15th-21st Dec</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>22nd-28th Dec</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>29th-4th Jan</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>5th-11th Jan</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>12th-18th Jan</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19th-25th Jan</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**Results of Audit 7th-15th Jan (all women screened)**

- Total births = 193
- Total trial screening forms completed = 139
- 60 = No information given
- 21 Eligible (6 randomized; 13 declined; 2 CTG in error)
- 58 Ineligible

Please ensure, where appropriate, that all women receive the ADCAR study information. Encourage women to read this information. Please ensure that all women who have received the information are screened for eligibility to participate in the ADCAR trial when they present to labour ward with signs of labour. Women should be informed that this study is about listening to the fetal heart on admission with signs of labour only and not about how their baby’s heart beat might be listened to throughout their labour. The HSE Ethics Committee has approved this study and therefore consider it an important and worthwhile research study. Women may be informed of this so as to promote the ADCAR trial in a positive manner.

Research Assistant: Valerie Smith (vasmith@tcd.ie; 087-1352102)
WELL DONE AND THANK YOU TO ALL STAFF FOR SUPPORTING THE ADCAR TRIAL!

Based on the birth rate per month, expected recruitment is 28-35 women per week. This allows for 50% of women being ineligible and 50% of those eligible not wishing to take part.

<table>
<thead>
<tr>
<th>Week</th>
<th>Number of women recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th-10th August</td>
<td>-</td>
</tr>
<tr>
<td>11th-17th August</td>
<td>1</td>
</tr>
<tr>
<td>18th-24th August</td>
<td>2</td>
</tr>
<tr>
<td>25th-31st August</td>
<td>9</td>
</tr>
<tr>
<td>1st-7th September</td>
<td>4</td>
</tr>
<tr>
<td>8th-14th September</td>
<td>6</td>
</tr>
<tr>
<td>15th-21st September</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
</tr>
</tbody>
</table>

An audit of 80 postnatal charts was conducted on the 18th September 2008. This audit revealed that 25% of women who had received the ADCAR study information, were not screened for potential participation in the ADCAR trial, when they were eligible to be screened. We need your continued help and would ask that staff consider the ADCAR Trial before doing an Admission CTG on all women >37 weeks gestation.

As a small token of our appreciation for supporting the ADCAR trial, monthly staff prize raffles will be held. All staff who randomize a woman during the previous month will be included in the raffle (1st raffle to include all staff who have randomized a woman to date).

Two €50 will be awarded each month for the duration of the trial.

FIRST MONTHLY STAFF RAFFLE TO BE HELD 1ST WEEK OF NOVEMBER
WELL DONE AND THANK YOU TO ALL STAFF FOR SUPPORTING THE ADCAR TRIAL!

Based on the birth rate per month, expected recruitment is approx 60 women per month. This allows for 50% of women being ineligible and 50% of those eligible not wishing to take part.

<table>
<thead>
<tr>
<th>MONTH</th>
<th>NUMBER OF WOMEN RECRUITMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>May</td>
<td>18</td>
</tr>
<tr>
<td>June</td>
<td>27</td>
</tr>
<tr>
<td>July</td>
<td>16</td>
</tr>
<tr>
<td>August</td>
<td>18</td>
</tr>
<tr>
<td>September</td>
<td>18 (as of 5pm 29th Sept)</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
</tr>
</tbody>
</table>

An audit of 77 postnatal charts was conducted on the 20th September 2008. This audit revealed that 40% of women did not receive the ADCAR study information when they appeared suitable to receive it and 10% of those that received the information were not screened for potential participation in the ADCAR trial, when they were eligible to be screened. We need your continued help and would ask that all staff consider and support the ADCAR Trial.

As a small token of our appreciation for supporting the ADCAR trial, monthly staff prize raffles will be held. All staff who randomize a woman during the previous month will be included in the raffle (1st raffle to include all staff who have randomized a woman to date). Two €50 vouchers will be awarded each month for the duration of the trial.

FIRST MONTHLY STAFF RAFFLE TO BE HELD 1ST WEEK OF NOVEMBER
APPENDIX XXII

The ADCAR trial audit form
The ADCAR Trial Audit Form

Review of all postnatal charts present on wards: completed once weekly

<table>
<thead>
<tr>
<th>Date of Audit:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

Clinical Site.............................................................................................................

Clinic: (please tick one)  public □ private □ semi-private □ midwives □

Woman's hospital number: ......................................................................................

Date of Admission to labour ward: .................................................................

Time of Admission (24hr clock): .................................................................

Admitting Midwife (Name)..................................................................................

Please tick as appropriate

<table>
<thead>
<tr>
<th>Admitted with signs of labour</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>(to mean any indicator (contractions, show, SROM) for which an assessment of labour was made)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADCAR Trial Study Information Given

ADCAR Trial Screening form completed

Eligible for ADCAR

Randomised to ADCAR

Randomised

Cord Bloods Taken

(Arterial and Venous Ph & BE)

If no cord bloods taken, name of birth attendant responsible:
APPENDIX XXIII

Monthly screening & recruitment statistics
The ADCAR trial

Monthly recruitment analysis

Minimum target recruitment per month:

Drogheda: 60
Coombe: 120
Galway: 60

Footnotes (for all tables):

1 As per completed Trial Screening Forms
2 As % of total number of Trial Screening Forms completed
3 Number of women randomised not meeting eligibility criteria
4 Number of women not randomised due to randomisation system/equipment failure

Month 1: May 2008

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible(^1)</th>
<th>No. of women ineligible(^1)</th>
<th>Eligibility as %(^2)</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations(^3)</th>
<th>System failures(^4)</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>32</td>
<td>30</td>
<td>52%</td>
<td>30</td>
<td>90%</td>
<td>8</td>
<td>14</td>
<td>2</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>B</td>
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<td>-</td>
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</tr>
<tr>
<td><strong>Totals (all sites)</strong></td>
<td><strong>32</strong></td>
<td><strong>30</strong></td>
<td><strong>52%</strong></td>
<td><strong>30</strong></td>
<td><strong>90%</strong></td>
<td><strong>8</strong></td>
<td><strong>14</strong></td>
<td><strong>2</strong></td>
<td><strong>3</strong></td>
<td><strong>22</strong></td>
</tr>
</tbody>
</table>

\(^1\) Includes 7 women consented (but not randomised)
## Month 2: June 2008

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>40</td>
<td>30</td>
<td>57%</td>
<td>29</td>
<td>73%</td>
<td>14</td>
<td>12</td>
<td>1</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>B</td>
<td>-</td>
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</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>40</strong></td>
<td><strong>30</strong></td>
<td><strong>57%</strong></td>
<td><strong>29</strong></td>
<td><strong>73%</strong></td>
<td><strong>14</strong></td>
<td><strong>12</strong></td>
<td><strong>1</strong></td>
<td><strong>3</strong></td>
<td><strong>26</strong></td>
</tr>
</tbody>
</table>

*Includes 3 women consented (but not randomised)

## Month 3: July 2008

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>33</td>
<td>40</td>
<td>45%</td>
<td>18</td>
<td>55%</td>
<td>8</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>17</td>
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<tr>
<td>B</td>
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<td>-</td>
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<td>-</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>33</strong></td>
<td><strong>40</strong></td>
<td><strong>45%</strong></td>
<td><strong>18</strong></td>
<td><strong>55%</strong></td>
<td><strong>8</strong></td>
<td><strong>9</strong></td>
<td><strong>1</strong></td>
<td><strong>0</strong></td>
<td><strong>17</strong></td>
</tr>
</tbody>
</table>

*Includes 1 women consented (but not randomised)
### Month 4: August 2008

<table>
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<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>49</td>
<td>57</td>
<td>46%</td>
<td>21</td>
<td>43%</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>B</td>
<td>26</td>
<td>55</td>
<td>32%</td>
<td>13</td>
<td>50%</td>
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<td>-</td>
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</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>75</strong></td>
<td><strong>112</strong></td>
<td><strong>39%</strong></td>
<td><strong>34</strong></td>
<td><strong>46%</strong></td>
<td><strong>15</strong></td>
<td><strong>16</strong></td>
<td><strong>1</strong></td>
<td><strong>2</strong></td>
<td><strong>31</strong></td>
</tr>
</tbody>
</table>

* Includes 3 women consented (but not randomised)

### Month 5: September 2008

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>39</td>
<td>36</td>
<td>52%</td>
<td>22</td>
<td>51%</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>56</td>
<td>108</td>
<td>34%</td>
<td>23</td>
<td>41%</td>
<td>10</td>
<td>9</td>
<td>0</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>C</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>95</strong></td>
<td><strong>144</strong></td>
<td><strong>43%</strong></td>
<td><strong>45</strong></td>
<td><strong>46%</strong></td>
<td><strong>21</strong></td>
<td><strong>18</strong></td>
<td><strong>0</strong></td>
<td><strong>5</strong></td>
<td><strong>39</strong></td>
</tr>
</tbody>
</table>

* Includes 6 women consented (but not randomised)
### Month 6: October 2008

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>47</td>
<td>52</td>
<td>47%</td>
<td>27</td>
<td>57%</td>
<td>11</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>B</td>
<td>67</td>
<td>104</td>
<td>39%</td>
<td>31</td>
<td>46%</td>
<td>15</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>C</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>114</strong></td>
<td><strong>156</strong></td>
<td><strong>43%</strong></td>
<td><strong>58</strong></td>
<td><strong>51%</strong></td>
<td><strong>26</strong></td>
<td><strong>27</strong></td>
<td><strong>1</strong></td>
<td><strong>1</strong></td>
<td><strong>53</strong></td>
</tr>
</tbody>
</table>

* Includes 5 women consented (but not randomised)

### Month 7: November 2008

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>47</td>
<td>41</td>
<td>53%</td>
<td>30</td>
<td>64%</td>
<td>16</td>
<td>14</td>
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<td>30</td>
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<tr>
<td>B</td>
<td>39</td>
<td>89</td>
<td>31%</td>
<td>14</td>
<td>36%</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>C</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>86</strong></td>
<td><strong>130</strong></td>
<td><strong>42%</strong></td>
<td><strong>44</strong></td>
<td><strong>50%</strong></td>
<td><strong>23</strong></td>
<td><strong>20</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>43</strong></td>
</tr>
</tbody>
</table>

* Includes 1 woman consented (but not randomised)
Month 8: December 2008

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>43</td>
<td>30</td>
<td>60%</td>
<td>30</td>
<td>67%</td>
<td>15</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>B</td>
<td>51</td>
<td>64</td>
<td>44%</td>
<td>16</td>
<td>29%</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>C</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>94</td>
<td>94</td>
<td>52%</td>
<td>46</td>
<td>48%</td>
<td>23</td>
<td>23</td>
<td>1</td>
<td>0</td>
<td>46</td>
</tr>
</tbody>
</table>

* includes 1 woman consented (but not randomised)

Month 9: January 2009

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>32</td>
<td>33</td>
<td>50%</td>
<td>20</td>
<td>62%</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>67</td>
<td>131</td>
<td>34%</td>
<td>21</td>
<td>31%</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>C</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>99</td>
<td>164</td>
<td>42%</td>
<td>41*</td>
<td>47%</td>
<td>20</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>40</td>
</tr>
</tbody>
</table>

* includes 1 woman consented (but not randomised)
### Month 10: February 2009

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>32</td>
<td>31</td>
<td>52%</td>
<td>24</td>
<td>72%</td>
<td>11</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>B</td>
<td>50</td>
<td>92</td>
<td>35%</td>
<td>20</td>
<td>48%</td>
<td>9</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>C</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>82</td>
<td>123</td>
<td>49%</td>
<td>44*</td>
<td>60%</td>
<td>20</td>
<td>20</td>
<td>1</td>
<td>5</td>
<td>40</td>
</tr>
</tbody>
</table>

* includes 5 women consented (but not randomised)

### Month 11: March 2009

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>51</td>
<td>43</td>
<td>54%</td>
<td>24</td>
<td>45%</td>
<td>13</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>B</td>
<td>123</td>
<td>181</td>
<td>60%</td>
<td>31</td>
<td>24%</td>
<td>14</td>
<td>15</td>
<td>0</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>14</td>
<td>18%</td>
<td>3</td>
<td>100%</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>177</td>
<td>238</td>
<td>44%</td>
<td>58*</td>
<td>56%</td>
<td>29</td>
<td>27</td>
<td>2</td>
<td>3</td>
<td>56</td>
</tr>
</tbody>
</table>

* includes 4 women consented (but not randomised)
### Month 12: April 2009

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>55</td>
<td>41</td>
<td>57%</td>
<td>25</td>
<td>61%</td>
<td>12</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>B</td>
<td>86</td>
<td>161</td>
<td>53%</td>
<td>29</td>
<td>34%</td>
<td>15</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>C</td>
<td>33</td>
<td>57</td>
<td>36%</td>
<td>22</td>
<td>66%</td>
<td>11</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td><strong>Totals (all sites)</strong></td>
<td><strong>174</strong></td>
<td><strong>259</strong></td>
<td><strong>45%</strong></td>
<td><strong>76</strong></td>
<td><strong>53%</strong></td>
<td><strong>38</strong></td>
<td><strong>38</strong></td>
<td><strong>1</strong></td>
<td><strong>0</strong></td>
<td><strong>76</strong></td>
</tr>
</tbody>
</table>

* includes 2 women consented (but not randomised)

### Month 13: May 2009

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>66</td>
<td>55</td>
<td>59%</td>
<td>45</td>
<td>68%</td>
<td>21</td>
<td>23</td>
<td>1</td>
<td>1</td>
<td>44</td>
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<tr>
<td>B</td>
<td>186</td>
<td>239</td>
<td>44%</td>
<td>66</td>
<td>36%</td>
<td>32</td>
<td>33</td>
<td>0</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>C</td>
<td>58</td>
<td>97</td>
<td>37%</td>
<td>17</td>
<td>29%</td>
<td>8</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td><strong>Totals (all sites)</strong></td>
<td><strong>310</strong></td>
<td><strong>391</strong></td>
<td><strong>47%</strong></td>
<td><strong>128</strong></td>
<td><strong>44%</strong></td>
<td><strong>61</strong></td>
<td><strong>65</strong></td>
<td><strong>1</strong></td>
<td><strong>2</strong></td>
<td><strong>126</strong></td>
</tr>
</tbody>
</table>

* includes 2 women consented (but not randomised)
### Month 14: June 2009

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>60</td>
<td>85</td>
<td>41%</td>
<td>35</td>
<td>60%</td>
<td>18</td>
<td>16</td>
<td>0</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>B</td>
<td>154</td>
<td>210</td>
<td>42%</td>
<td>55</td>
<td>36%</td>
<td>25</td>
<td>30</td>
<td>1</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>C</td>
<td>79</td>
<td>109</td>
<td>42%</td>
<td>27</td>
<td>34%</td>
<td>13</td>
<td>14</td>
<td>1</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>293</strong></td>
<td><strong>404</strong></td>
<td><strong>42%</strong></td>
<td><strong>117</strong></td>
<td><strong>43%</strong></td>
<td><strong>56</strong></td>
<td><strong>60</strong></td>
<td><strong>2</strong></td>
<td><strong>1</strong></td>
<td><strong>116</strong></td>
</tr>
</tbody>
</table>

### Month 15: July 2009

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>48</td>
<td>53</td>
<td>48%</td>
<td>27</td>
<td>56%</td>
<td>12</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>B</td>
<td>121</td>
<td>172</td>
<td>41%</td>
<td>49</td>
<td>40%</td>
<td>24</td>
<td>25</td>
<td>1</td>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>C</td>
<td>75</td>
<td>95</td>
<td>44%</td>
<td>37</td>
<td>48%</td>
<td>15</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>244</strong></td>
<td><strong>320</strong></td>
<td><strong>43%</strong></td>
<td><strong>113</strong></td>
<td><strong>46%</strong></td>
<td><strong>51</strong></td>
<td><strong>57</strong></td>
<td><strong>2</strong></td>
<td><strong>1</strong></td>
<td><strong>108</strong></td>
</tr>
</tbody>
</table>
### Month 16: August 2009

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible¹</th>
<th>No. of women ineligible¹</th>
<th>Eligibility as %²</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations³</th>
<th>Randomisation system failures⁴</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>52</td>
<td>49</td>
<td>51%</td>
<td>33</td>
<td>63%</td>
<td>16</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>B</td>
<td>126</td>
<td>169</td>
<td>43%</td>
<td>62</td>
<td>49%</td>
<td>30</td>
<td>31</td>
<td>0</td>
<td>1</td>
<td>61</td>
</tr>
<tr>
<td>C</td>
<td>103</td>
<td>66</td>
<td>61%</td>
<td>48</td>
<td>47%</td>
<td>23</td>
<td>22</td>
<td>1</td>
<td>3</td>
<td>45</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>281</td>
<td>284</td>
<td>50%</td>
<td>143*</td>
<td>51%</td>
<td>69</td>
<td>69</td>
<td>2</td>
<td>5</td>
<td>138</td>
</tr>
</tbody>
</table>

* includes 2 women consented (but not randomised)

### Month 17: September 2009

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible¹</th>
<th>No. of women ineligible¹</th>
<th>Eligibility as %²</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations³</th>
<th>Randomisation system failures⁴</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>55</td>
<td>48</td>
<td>53%</td>
<td>31</td>
<td>56%</td>
<td>15</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>B</td>
<td>98</td>
<td>114</td>
<td>46%</td>
<td>41</td>
<td>42%</td>
<td>20</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>C</td>
<td>65</td>
<td>50</td>
<td>56%</td>
<td>40</td>
<td>61%</td>
<td>19</td>
<td>19</td>
<td>0</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>218</td>
<td>212</td>
<td>51%</td>
<td>112*</td>
<td>51%</td>
<td>54</td>
<td>55</td>
<td>0</td>
<td>2</td>
<td>109</td>
</tr>
</tbody>
</table>

* includes 3 women consented (but not randomised)
### Month 18: October 2009

<table>
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<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>47</td>
<td>46</td>
<td>50%</td>
<td>21</td>
<td>45%</td>
<td>10</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>21</td>
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<tr>
<td>B</td>
<td>86</td>
<td>145</td>
<td>37%</td>
<td>28</td>
<td>32%</td>
<td>15</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>C</td>
<td>55</td>
<td>40</td>
<td>58%</td>
<td>34</td>
<td>62%</td>
<td>16</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>188</strong></td>
<td><strong>231</strong></td>
<td><strong>45%</strong></td>
<td><strong>83</strong></td>
<td><strong>44%</strong></td>
<td><strong>41</strong></td>
<td><strong>42</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>83</strong></td>
</tr>
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</table>

### Month 19: November 2009

<table>
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<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>55</td>
<td>38</td>
<td>55%</td>
<td>35</td>
<td>64%</td>
<td>18</td>
<td>16</td>
<td>0</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>B</td>
<td>79</td>
<td>117</td>
<td>40%</td>
<td>29</td>
<td>37%</td>
<td>14</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>C</td>
<td>73</td>
<td>50</td>
<td>59%</td>
<td>37</td>
<td>51%</td>
<td>20</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>207</strong></td>
<td><strong>205</strong></td>
<td><strong>50%</strong></td>
<td><strong>101</strong></td>
<td><strong>49%</strong></td>
<td><strong>52</strong></td>
<td><strong>48</strong></td>
<td><strong>0</strong></td>
<td><strong>1</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
### Month 20: December 2009

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %²</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations³</th>
<th>Randomisation system failures¹</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>45</td>
<td>45</td>
<td>50%</td>
<td>24</td>
<td>53%</td>
<td>11</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>B</td>
<td>59</td>
<td>92</td>
<td>61%</td>
<td>14</td>
<td>24%</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>C</td>
<td>72</td>
<td>47</td>
<td>60%</td>
<td>41*</td>
<td>55%</td>
<td>18</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>176</td>
<td>184</td>
<td>49%</td>
<td>79*</td>
<td>45%</td>
<td>36</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>76</td>
</tr>
</tbody>
</table>

*(Includes 4 women consented not randomised)

### Month 21: January 2010

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %²</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations³</th>
<th>Randomisation system failures¹</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>56</td>
<td>73</td>
<td>43%</td>
<td>30</td>
<td>54%</td>
<td>15</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>B</td>
<td>80</td>
<td>68</td>
<td>54%</td>
<td>23</td>
<td>29%</td>
<td>11</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>C</td>
<td>32</td>
<td>51</td>
<td>38%</td>
<td>27*</td>
<td>84%</td>
<td>13</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>168</td>
<td>192</td>
<td>47%</td>
<td>80*</td>
<td>48%</td>
<td>39</td>
<td>39</td>
<td>0</td>
<td>1</td>
<td>78</td>
</tr>
</tbody>
</table>

*(Includes 1 women consented not randomised)
Month 22: February 2010

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>53</td>
<td>72</td>
<td>42%</td>
<td>35</td>
<td>66%</td>
<td>17</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>B</td>
<td>84</td>
<td>90</td>
<td>48%</td>
<td>36</td>
<td>43%</td>
<td>18</td>
<td>17</td>
<td>0</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>C</td>
<td>43</td>
<td>30</td>
<td>60%</td>
<td>23</td>
<td>53%</td>
<td>12</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>180</td>
<td>192</td>
<td>48%</td>
<td>94*</td>
<td>52%</td>
<td>47</td>
<td>43</td>
<td>1</td>
<td>2</td>
<td>90</td>
</tr>
</tbody>
</table>

*(Includes 1 woman consented not randomised)*

Month 23: March 2010

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible</th>
<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>53</td>
<td>62</td>
<td>46%</td>
<td>35</td>
<td>66%</td>
<td>17</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>B</td>
<td>70</td>
<td>86</td>
<td>45%</td>
<td>33</td>
<td>47%</td>
<td>16</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>C</td>
<td>60</td>
<td>29</td>
<td>67%</td>
<td>31</td>
<td>51%</td>
<td>16</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>Totals (all sites)</td>
<td>183</td>
<td>177</td>
<td>51%</td>
<td>99</td>
<td>54%</td>
<td>49</td>
<td>48</td>
<td>0</td>
<td>0</td>
<td>97</td>
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### Month 24: April 2010

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible&lt;sup&gt;1&lt;/sup&gt;</th>
<th>No. of women ineligible&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Eligibility as %&lt;sup&gt;2&lt;/sup&gt;</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Randomisation system failures&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>44</td>
<td>60</td>
<td>42%</td>
<td>29</td>
<td>66%</td>
<td>15</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>B</td>
<td>49</td>
<td>57</td>
<td>46%</td>
<td>21</td>
<td>43%</td>
<td>10</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>C</td>
<td>48</td>
<td>15</td>
<td>76%</td>
<td>19&lt;sup&gt;+&lt;/sup&gt;</td>
<td>39%</td>
<td>8</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>141</strong></td>
<td><strong>132</strong></td>
<td><strong>52%</strong></td>
<td><strong>69&lt;sup&gt;+&lt;/sup&gt;</strong></td>
<td><strong>49%</strong></td>
<td><strong>33</strong></td>
<td><strong>34</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>67</strong></td>
</tr>
</tbody>
</table>

<sup>1</sup>Includes 1 woman consented not randomised

### Month 25: May 2010

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>No. of women eligible&lt;sup&gt;1&lt;/sup&gt;</th>
<th>No. of women ineligible&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Eligibility as %&lt;sup&gt;2&lt;/sup&gt;</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Randomisation system failures&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>62</td>
<td>72</td>
<td>46%</td>
<td>42</td>
<td>68%</td>
<td>21</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>B</td>
<td>108</td>
<td>172</td>
<td>39%</td>
<td>23</td>
<td>21%</td>
<td>12</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>C</td>
<td>49</td>
<td>33</td>
<td>60%</td>
<td>23</td>
<td>47%</td>
<td>11</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
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<td><strong>277</strong></td>
<td><strong>44%</strong></td>
<td><strong>88</strong></td>
<td><strong>40%</strong></td>
<td><strong>44</strong></td>
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<td><strong>1</strong></td>
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</table>
### Month 26: June 2010

<table>
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<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>42</td>
<td>69</td>
<td>38%</td>
<td>34</td>
<td>81%</td>
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<td>0</td>
<td>34</td>
</tr>
<tr>
<td>B</td>
<td>176</td>
<td>358</td>
<td>33%</td>
<td>67</td>
<td>38%</td>
<td>34</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>67</td>
</tr>
<tr>
<td>C</td>
<td>37</td>
<td>17</td>
<td>69%</td>
<td>26*</td>
<td>70%</td>
<td>11</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
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<td><strong>444</strong></td>
<td><strong>36%</strong></td>
<td><strong>127</strong></td>
<td><strong>50%</strong></td>
<td><strong>62</strong></td>
<td><strong>63</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>125</strong></td>
</tr>
</tbody>
</table>

*(Includes 2 women consented not randomised)*

### Month 27: July 2010

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<th>No. of women ineligible</th>
<th>Eligibility as %</th>
<th>No. of women consented</th>
<th>Consent as % of eligibility</th>
<th>Randomised IA</th>
<th>Randomised ACTG</th>
<th>Incorrect randomisations</th>
<th>Randomisation system failures</th>
<th>Total in ADCAR Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>43</td>
<td>66</td>
<td>39%</td>
<td>26</td>
<td>60%</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>B</td>
<td>172</td>
<td>288</td>
<td>37%</td>
<td>49</td>
<td>28%</td>
<td>24</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>49</td>
</tr>
<tr>
<td>C</td>
<td>67</td>
<td>37</td>
<td>64%</td>
<td>28</td>
<td>42%</td>
<td>15</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>282</strong></td>
<td><strong>391</strong></td>
<td><strong>42%</strong></td>
<td><strong>103</strong></td>
<td><strong>37%</strong></td>
<td><strong>52</strong></td>
<td><strong>51</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>103</strong></td>
</tr>
</tbody>
</table>
APPENDIX XXIV

Graphical presentation of monthly recruitment trends
Recruitment 2008

<table>
<thead>
<tr>
<th>Month</th>
<th>Site A</th>
<th>Site B</th>
</tr>
</thead>
<tbody>
<tr>
<td>May</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Jun</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Jul</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Aug</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Sept</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Oct</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Nov</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Dec</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>
APPENDIX XXV

The ADCAR trial data collection booklet
ADCAR Trial

Data Collection Booklet

Confidential

Edition 1 2009
**Woman’s details**

1. Woman’s study number: 
2. Randomised: 

(Note: An addressograph label may be placed over questions 3, 4, 5 & 6 if available)

3. Woman’s first Name: 
   (use BLOCK CAPITALS please) 
4. Woman’s second Name: 
   (use BLOCK CAPITALS please) 
5. Woman’s record number: 
6. Woman’s date of birth: day month year 
7. Date of randomisation: day month year 

**Woman’s baseline characteristics**

8. Gravida: 
   (number of times a woman has been pregnant irrespective of outcome): 
   *Using above definition means that ‘+’ must NOT be used*

9. Parity: 
   (number of previous live births) 

10. Woman’s agreed EDD: day month year 

**Antenatal**

A1. Antenatal transfer from IA to ACTG post randomisation and prior to the diagnosis of labour: 

   (a) Antenatal transfer required 
      Yes 1  No 0  N/A 2

      (i) Reason for transfer

      ........................................................................................................

      ........................................................................................................
L7. Mode of birth: (please tick one box only)
(a) Spontaneous vaginal 1
(b) Ventouse 2
(c) Forceps 3
(d) Instrument for abnormal FHR pattern 4
(e) Elective Caesarean section 5
(f) Emergency Caesarean section 6
(g) Emergency Caesarean section for abnormal FHR pattern 7

L8. Position for birth: (please tick one box only)
(a) Lateral (Sim's) position 1
(b) Lithotomy 2
(c) Knee-elbow (all fours) position 3
(d) Semi-recumbent (trunk tilted backwards 30° to the vertical) 4
(e) Theatre table (for LSCS or instrumental delivery in theatre) 5
(f) Other 6
(g) Not stated 7

Postpartum

P1. Length of mother's postnatal hospital
(in days* from time of birth to discharge from hospital

*Days documented as 1 day = 24hrs as follows:
0-23hrs = 1 day, 24-47hrs = 2 days, Etc

Neonatal

N1. Infant's date of birth:

N2. Infant's time of birth:
(Please use 24hr clock)

N3. Paediatrician/Neonatologist present at delivery
Yes 1 No 0

N4. Apgar Scores:
(a) Apgar score at 1 minute

(b) Apgar score at 5 minutes
N11. **Type of Complication** *(give full details; reason for admission to NICU/SCBU, Treatment, Diagnosis)*

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________________________________________________________________________________________________________

________________________________________________________________________________________________________

N12. **Length of neonatal hospital stay:**
*(in days from birth to discharge)*

*Days documented as 1 day = 24hrs as follows:
0-23hrs = 1 day, 24-47hrs = 2 days
Etc*

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