

Study Protocol

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality - a stepped wedge cluster randomised trial?

AFFIRM

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PROTOCOL APPROVAL

Does promoting increased awareness of decreased fetal movements reduce stillbirth, a stepped wedge cluster randomised trial?

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LIST OF ABBREVIATIONS

GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
RFM	Reduced Fetal Movements
TMF	Trial Master File
SOP	Standard Operating Procedure
CRF	Case Report Form
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian

SUMMARY

Rates of stillbirth in Scotland are amongst the highest in resource rich countries. The majority of stillbirths occur in normally formed infants, with (retrospective) evidence of placental insufficiency being the commonest clinical finding. Maternal perception of decreased fetal movements appears to be an early biomarker both of placental insufficiency and subsequent stillbirth.

The study proposed here will test the hypothesis that rates of stillbirth will be reduced by introduction of a package of care consisting of strategies for increasing pregnant women's awareness of the need for prompt reporting of decreased fetal movements, followed by a management plan for identification of placental insufficiency with timely delivery in confirmed cases. The odds of stillbirth fell by 30% after the introduction of a similar package of care in Norway but the efficacy of this intervention (and possible adverse effects and implications for service delivery) have not been tested in a randomized trial.

We plan a stepped wedge cluster design trial, in which participating hospitals in the UK will be randomized to the timing of introduction of the care package. Outcomes (including the primary outcome of stillbirth) will be derived from Scotland and Ireland's detailed routinely collected maternity data, allowing us to robustly test our hypothesis. A nested qualitative study will examine the acceptability of the intervention to patients and health care providers and identify process issues (barriers to implementation).

1 INTRODUCTION

1.1 BACKGROUND

Stillbirth (defined in the UK as a baby born dead after 24 weeks of completed pregnancy) remains the major cause of perinatal mortality in resource rich environments, with a recent series of papers in the Lancet on stillbirth issue calling for major action in this area (1). There is no single "cause" of stillbirth, and many stillbirths remain unexplained, but fetal growth restriction, hypertension and low socioeconomic status are amongst the identifiable risk factors (2).

The purpose of this study is to test the efficacy of a package of interventions consisting of strategies for increasing pregnant women's awareness of the need to report early when they perceive a reduction in fetal movements, in combination with a management plan for identification and delivery of the "at risk" fetus in such women. Our primary outcome is stillbirth.

The concept that more can be done to reduce stillbirth in the UK and Ireland is supported by data showing a marked variation in rates between resource rich countries, when similar definitions of stillbirth are used (3). Notably, the UK has the highest rates amongst a group of resource rich countries such as Germany, Spain, New Zealand and Italy, with rates in the UK some 50% greater than those of Germany. Rates of stillbirth in Scotland and Ireland, at 4.9 per 1000 livebirths (Scotland, 2010 and Ireland 2009 (4, 5)) are only marginally better than rates in England and Wales at 5.1 per 1000 livebirths (England and Wales, 2010)(5).

So what can be done to reduce rates of stillbirth further? Scottish ministers see the reduction of avoidable harm for women and babies as a major priority and asked the Scottish Government (SG) Health Department to set up the Stillbirth Working Group in 2011. This group works to implement SG policy within the Scottish Government Refreshed Framework for Maternity Services, and works in partnership with Sands (the Stillbirth and Neonatal Death Society). SG, through the Stillbirth Working Group has provided funding for Sands to improve bereavement services. As a result of this and other initiatives, many Health Boards in Scotland have already invested heavily in applying current best evidence, including addressing social inequalities, encouraging smoking cessation programmes and initiating strategies to prevent and / or manage obesity and to identify and tailor care for those at high risk. The equivalent bodies in England, Wales and Ireland (in Ireland through Perinatal Ireland) are also working on similar strategies. However, many evidence gaps remain.

So what research is needed on prevention of stillbirth? Using a robust priority setting strategy (6) the Lancet Stillbirth's series steering committee identified issues around detection and management of reduced fetal movements amongst the top ten key research questions on prevention and management of stillbirth (3) . In this study, we will test an intervention package aiming to encourage early presentation of women experiencing decreased fetal movement, followed by appropriate investigation and targeted intervention, in order to reduce stillbirth. The intervention package is informed by current understanding of the risk factors / aetiology of stillbirth and will be evaluated in a stepped wedge cluster randomised trial.

Association between decreased fetal movements, placental dysfunction and stillbirth

There is a clear association between maternal perception of decreased strength of fetal movement and late stillbirth. In a recent series of 2000 women, the adjusted OR (95% CI) of late stillbirth in women with decreased fetal movement (compared with controls) was 2.37 (1.29-4.35) (7). Although the mechanisms have not been fully delineated, it is likely that decreased fetal movement and stillbirth are linked by a common pathology, that of placental dysfunction. There is good evidence linking placental dysfunction and decreased fetal movement. Women who have fewer fetal movements on ultrasound immediately prior to caesarean section are more likely to have umbilical cord gas measurements indicative of acidaemia, hypoxaemia, and hypercapnia, compared with controls (8). Applicant Heazell has shown that women delivering within one week of an episode of decreased fetal movement show differences in placental structure and function, including greater signs of infarction (compared to those with normal fetal movements) (9). Additionally, in a series of over 2000

women (conducted by applicant Froen), the odds of fetal growth restriction (FGR, defined as being at less than the 10th centile for gestation adjusted birthweight) were greater in women with decreased fetal movement compared with controls, with adjusted OR of 1.6, 95% CI 1.1–2.2 (10). Taken together these data are strong evidence that placental dysfunction is associated with decreased fetal movement, and a causative pathway seems likely.

The evidence linking placental dysfunction and stillbirth is even stronger. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of placental dysfunction (4). Given that the placenta was examined in only 80% of stillbirths, the true prevalence of placental dysfunction is likely to be higher. Over 20% of stillborn babies had FGR. Additionally, the Lancet reports notes that “placental pathologies accounted for one in four deaths across all gestational ages, and were contributory or causal in more than half of cases” (11). *If decreased fetal movement is a “biomarker” of placental dysfunction, and placental dysfunction itself is associated with stillbirth, then better management of women presenting with decreased fetal movement might reduce the risk of stillbirth.* Although prenatal detection of fetal growth restriction is improved by fetal movement counting (12), a systematic review (13), and a large and influential cluster randomised trial (which dominates the systematic review) showed that routine fetal movement counting had no effect on perinatal mortality (14). Thus after reviewing the literature, the National Institute for Clinical Excellence (NICE) recommended that “Routine formal fetal movement counting should not be offered” (15). Importantly, the large cluster randomised trial tested a specific alarm limit for decreased fetal movement, but did not inform management of women who did present with decreased fetal movement. More women in the fetal movement counting arm came in with a live baby who subsequently died compared with the control arm (19 vs 11), suggesting that the strategy failed because of inadequate investigation and management of those presenting with decreased fetal movements.

Efficacy of a package of interventions around decreased fetal movement

Supportive data on the package of interventions we propose comes from a large study observational cohort “clinical quality improvement study” in Norway led by applicant Froen (16). In this study, a significant fall in rates of stillbirth (from 3.0/1000 to 2.0/1000 [OR 0.67 95% CI 0.48–0.93]) was observed after introduction an intervention package consisting of written information for women about detection of decreased fetal movements combined with consensus guidelines for health professionals about their management (16). Although this study was not randomised, and therefore constitutes only level II-3 evidence, it has led to new recommendations from the Royal College of Obstetricians and Gynaecologists that “women should be advised to be aware of their baby’s individual pattern of movements and that if they are concerned about a reduction in or cessation of fetal movementsthey should contact their maternity unit” (17). Importantly, in the Norwegian study, there was no increase in the proportion of women who presented with decreased fetal movement when rates were compared before and after the intervention (16). However, women with decreased fetal movements presented significantly earlier to hospital with decreased fetal movements than they had hitherto. Taken together, these data suggest that a package of interventions encouraging women with decreased fetal movements to present early to hospital, combined with a structured approach to the management of women with decreased fetal movement might reduce rates of stillbirth without contributing to a large increase in admissions antenatally. In the study described in this application we plan to formally test (using gold standard methodologies) whether a similar package of interventions really does decrease stillbirth, whether it does any harm (e.g. by increasing rates of caesarean section or induction of labour) and how it can be implemented to best effect in a very different setting.

Optimal strategy for quantification of decreased fetal movement.

A systematic review has failed to define an optimal strategy for the quantification of decreased fetal movement (13). We are currently in the process of performing an up to date systematic review, although a preliminary literature search (see above) has revealed no new information. There is no uniform threshold of fetal movements above which perinatal morbidity increases (18), so that guidelines from the RCOG (17), informed by the Norwegian study (16) suggest that it is maternal perception of decreased fetal movement which is important. We will use a similar approach, encouraging women to present early if they have this perception. A leaflet will be developed emphasizing the importance of decreased fetal movement as a signal to

seek immediate advice from a midwife / maternity centre. The effects of the leaflet will be amplified by a web based education package developed for midwives and other clinicians to teach them to encourage behaviour change in pregnant women, with re-enforcement at several times during pregnancy. We will also encourage clinicians to take maternal perception of decreased fetal movements seriously, and to follow a structured management plan in further risk stratification to determine which babies should be delivered promptly.

Optimal strategy for investigation and management of women presenting with decreased fetal movement.

As shown in a recent systematic review, there are no proven strategies for the investigation and management of women presenting with decreased fetal movement (19). Cardiotocography (CTG) (either analogue or digital) is routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG guideline around decreased fetal movement (17). However, data from Norway, suggests that ultrasound assessment of fetal size is often the most helpful investigation, performing well on both an absolute basis, and compared with other interventions (20). In a series of over 3000 women with decreased fetal movements, ultrasound (including measurement of liquor volume and growth measurements) was found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in whom an abnormality was found, ultrasound was the only technique that detected an abnormality. Additionally, 85% of abnormalities detected by ultrasound, were important in informing the clinical management of the woman (20). These data are supported by our own recent smaller UK study, where we found that abnormal CTG and abnormal ultrasound scan were the two investigations most strongly associated with poor outcome in women presenting decreased fetal movements, with identification of abnormal estimated fetal growth centile on scan being the test most highly predictive of poor outcome (21). Perhaps this is not surprising, given the strong association between small for gestational age babies and the central importance of ultrasound in the identification and management of such cases (22). Given these data, it is worrying that a survey of clinicians in Scotland (described in detail below) shows that less than 5% would routinely refer women with decreased fetal movements for ultrasound examination. We believe that current investigation of women presenting with decreased fetal movement is inadequate, hence using best available evidence, we have drafted what we consider to be a robust evaluation protocol for investigation of women with decreased fetal movement (attached in Appendix 4). This guideline will be further modified in consensus workshops informed by ongoing cohort studies with all relevant stakeholders (including representatives from each unit, whom we are beginning to identify) before the commencement of the study.

Potential harms of a package of care around increased awareness and optimised management of decreased fetal movements.

Any clinical intervention which aims to improve outcomes also has the ability to do harm. Thus it is essential that the intervention proposed is rigorously evaluated using the gold standard technique of a randomised trial, rather than being introduced as a service development. There is a small window of opportunity to do this, as the Stillbirth Working Group's enthusiasm to improve current management is such that routine introduction of the package of care is unlikely to be delayed much further than the current scheduled end date of this study. Possible harms of a package of care consisting of a management plan for identification and delivery of the "at risk" fetus, together with strategies for increasing pregnant women's awareness of the need to report early include increased maternal anxiety and increased intervention (including hospital admission, induction of labour and caesarean section) which itself is associated with pregnancy related complications. The available evidence is reassuring on some of these issues. Encouraging women to be aware of fetal movement does not increase maternal anxiety (23), and it has a neutral effect on maternal- infant attachment (24), however further research is required. In the Norwegian service development study, the package of care increased rates of follow up of women, but there was no increase in admissions overall, admissions for induction or admissions for emergency caesarean section (16) – again, whilst reassuring these outcomes require formal evaluation in a randomised and relevant setting.

The final possible harm of the package is around increased health care costs. We will not have sufficient resource to perform a formal economic evaluation in this application, but we would be happy to apply for separate funding for this if considered appropriate.

Literature search

A literature search on “decreased fetal movement” and “detection” generated 12 publications, most of which were not relevant, and none of which were randomised trials evaluating different strategies for detection of decreased fetal movement. We are aware of a systematic review on fetal movement counting for assessment of fetal wellbeing (13), which we will update immediately prior to starting this study.

A second literature search on “decreased fetal movement” and “management” generated 30 publications, including a Cochrane systematic review published in April 2012 (19). No randomised trials were identified as suitable for inclusion in this review. The applicants have looked at the remaining 29 papers from this literature search, and many, including the most relevant one of the “clinical quality improvement” unrandomised observational study in Norway by applicant Froen (16) have informed the design of our interventions and are cited in this application.

Results of pilot studies

Applicants Heazell and Froen both have an extensive track record on fetal movement counting - many of these studies have informed the background to this application and are cited in the text. The most relevant is the Norwegian observational cohort study (16). We have conducted two surveys of clinician practice around encouraging maternal fetal movement detection (including seeking advice of perceived movement decreases) and management of women presenting with decreased fetal movements. The first survey conducted in England and Wales in 2008 by Heazell, prior to the introduction of the RCOG guideline (17) had responses from 223 clinicians (58% of whom were obstetricians and the remainder midwives). The survey suggested that clinicians accept “maternal perception of decreased fetal movements” as a reliable indicator of fetal (in)activity with 74% of responders using this definition, in contrast to 2-65% for any numeric definition (25). The second survey (conducted by Dr Oonagh Keog in collaboration with applicants Norman, Calderwood and Ross Davie in Scotland in June 2012) was completed by two hundred clinicians, of whom 68% were midwives and the remainder obstetricians. In this second survey, 80% of clinicians accepted “maternal perception of decreased fetal movements” as a reliable indicator of fetal activity, reflecting concordance with the RCOG guideline. However only 80% advised women to attend when there was a reduction in perception of fetal movement, with less than 10% providing written information about this to women.

Regarding investigation and management of women presenting with decreased fetal movements, our first survey showed wide variation in clinical practice, with the majority (90%), but not all clinicians performing a CTG and with only 20% routinely requesting an ultrasound scan to assess fetal growth and liquor volume (25). Our second survey identified that, despite the introduction of RCOG guidelines in 2011, only 68% of responders had a policy to investigate women who report reduced fetal movements. Only a very small minority (less than 5%) would *routinely* request ultrasound in women presenting with reduced fetal movements, with the majority reserving ultrasound for women with further additional risk factors. The second survey also showed that access to ultrasound for women with decreased fetal movement with or without risk factors was suboptimal, with only 52% able to access within a 24hr period. Enthusiasm for induction of labour at term for women with more than one episode of decreased fetal movements was low, with nearly 25% of respondents suggesting that they would *never* offer induction of labour before 41 weeks in this scenario.

Taken together, the data from these two surveys suggest that that a trial based on increasing maternal awareness of decreased fetal movement would be acceptable to clinicians. Importantly, by standardizing management, greater access to scanning would occur, allowing identification of a greater number of women with FGR. Additionally, standardization of management around early delivery for those with identified fetal compromise or those at additional risk should improve outcomes.

1.2 RATIONALE FOR STUDY

The aim of this study is to test the hypothesis that a package of interventions consisting of strategies for increasing pregnant women's awareness of the need to report early when they perceive a reduction in fetal movements, followed with a management plan for identification and delivery of the "at risk" fetus in such women, will reduce rates of stillbirth.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary objective is to answer the research question: Q1. Does the introduction of a protocol for detection and management of decreased fetal movements reduce rates of stillbirth?

2.1.2 Secondary Objectives

The secondary objectives are to answer the research questions:

Q2. What is the effect of the above intervention on rates of caesarean section and induction of labour?

Q3. What is the effect of the above intervention on rates of admission to the neonatal intensive care unit?

Q4. What is the effect of the above intervention on the proportion of women with fetal growth restriction remaining undelivered by 40 weeks gestation?

Q5. What is the acceptability of such a package of care to pregnant women and their health care providers?

Q6. What other process outcomes are influenced by the intervention, such as health care provider/patient interactions?

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The primary endpoint is stillbirth (antepartum and intrapartum). We will use the CEMACH definition of stillbirth which is "a baby delivered without signs of life after 23⁺⁶ weeks". Where gestation is uncertain we will include all babies with a birth weight of 500g or more.

2.2.2 Secondary Endpoints

Other measures of perinatal mortality including:

- Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
- Stillbirth at 22 weeks gestation and above
- Stillbirth at 37 weeks gestation and above
- Stillbirths amongst normally formed infants of 22 weeks gestation and above, 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks gestation and above
- Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and deaths in the first seven days of life)
- Rates of caesarean section
- Rates of induction of labour (overall)
- Rates of elective delivery (induction of labour and caesarean section prior to the onset of labour) overall
- Rates of induction of labour at 39 weeks 0 days gestation or later
- Rates of elective delivery (induction of labour and caesarean section prior to the onset of labour) in women delivered at 39 weeks 0 days gestation or later
- Mean gestation at delivery for women having induction of labour

- Rates of admission to the neonatal unit (and their reasons)
- Rates of admission to the neonatal unit for more than 48 hours
- Rates of admission to the neonatal unit for term babies (those born at 37 weeks 0 days or greater)
- Proportion of women with fetal growth restriction (less than the 10th centile, customised for gender) remaining undelivered at or after 40 weeks gestation
- Rates of spontaneous vaginal delivery

Other secondary outcomes are the baby parameters:

- Gestation at delivery
- Proportion of babies born preterm (\leq 37 weeks and 0 days gestation)
- Sex baby
- Birthweight of baby
- Birthweight centile (according to the Intergrowth birthweight centile calculator at <https://intergrowth21.tghn.org>)
- Apgar score at 5 minutes
- Proportion of babies with 5 minute Apgar score $<$ 4
- Proportion of babies with 5 minute Apgar score $<$ 7
- Resuscitation required at birth

We will also collect the following data:

maternal age, maternity unit of delivery, birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever), maternal BMI, number of babies (one or more), ethnicity (to allow a customised birthweight centile to be generated), method of delivery, Scottish index of multiple deprivation (or other deprivation scores) (where available) other neonatal variables: Apgar score, resuscitation required at birth, encephalopathy etc.

Adjustment will be made for the following variables: (maternal age, maternity unit of delivery, parity, smoking status, maternal BMI, number of babies [one or more] and ethnicity)

3 STUDY DESIGN

This is a multicentre, stepped wedge cluster randomised trial of a package of care consisting of a management plan for identification and delivery of the 'at risk' fetus, together with strategies for increasing pregnant women's awareness of the need to report decreased fetal movements early. A nested qualitative study will examine the acceptability of the intervention to patients and health care providers and identify process issues (barriers to implementation). Clinical audit (before and after the change in practice) will be used to determine the effect of interventions on process outcomes (eg number of ultrasound scans, number of admissions for induction of labour). The study will take place in participating hospitals in the UK.

The interventions will be introduced over a 33 month period. Data will be collected over a 36 month period.

Data in the 'active phase' after introduction of the intervention will be compared to data in the 'control phase' – the time from study start to the time of introduction of the intervention. Given

that it will take individual units some time (a) to effect change in management in their unit from time of introduction of the intervention and (b) that it will take some time for this change in practice to impact on clinical outcomes, we plan a “washout” period after the introduction of the intervention during which data will not be included in either group for analysis. We anticipate that this washout period will be of two months duration – this will be finalised in the statistical analysis plan.

Outcomes will be measured from routinely collected data. For consistency, we will normally only include data items which become available within four months after the delivery date in question, although we may seek advice from the TSC about exceptions as they arise.

A diagram indicating randomisation of hospital groupings in the stepped wedge design is shown below:

Table 1: Stepped wedge design. Shaded areas indicate periods in which the interventions are being implemented. The order in which hospital groupings implement the interventions will be determined via randomization.

Hospital groupings	Month								
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36
1-3									
4-6									
7-9									
10-12									
13-15									
16-18									
19-21									
22-24									

This is a cluster randomised trial and individual patient consent is not required for the package of care. However, participants’ will be asked to sign a study specific ethically approved consent form for the qualitative interviews which are planned with both women and health care professionals. . There are no stopping rules for the study.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

Participants will be those delivering at all the sites described in Appendix 2 over the study period (36 months).

All eligible women will be recruited to the cluster RCT (Q1-4). Based on previous delivery numbers, after accounting for a washout period of two months (and assuming no withdrawals or losses to follow up) this is a total of around 300,000 women.

A subset of around 30 participating women and 30 midwives, sonographer and obstetricians will be recruited to address Q5.

4.2 INCLUSION CRITERIA

For Q1-4, we will include all women delivering at one of the maternity units involved in for the duration of the study. Women who have been seen at any of the maternity units but who deliver at home will not be included. The duration of the study will be 42 months from the start of the trial. The precise start date of the trial will be formally recorded and published in a future version of this protocol.

Participants for Q5 will be recruited from the participating units.

4.3 EXCLUSION CRITERIA

We will exclude women as follows:

- Women for whom data on delivery outcomes is still unavailable four months after the date of delivery

- Women delivering in the “washout” period in each unit.

Members of the trial management group and participants who do not speak/understand English will be excluded from those participating in Q5.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Women will be identified from those whose data is included in routine data returns from each unit.

Participants for Q5 will be identified from those attending antenatal clinics in participating hospitals, and/or local staff.

5.2 CONSENTING PARTICIPANTS

Q1-4 is a cluster randomised trial of a package of care which would be introduced in many of the participating units regardless of whether the trial was on-going or not. As such, it is not considered that formal individual patient consent is necessary.

Q5 will require individual patient / participant consent.

5.3 SCREENING FOR ELIGIBILITY

No specific screening tests will be performed for Q1-4 of this project.

Participants for Q5 will be

(i) Pregnant women attending hospitals (who are participating in the main trial) in Scotland. Purposive sampling will ensure that the final sample set includes women who have and who have not experienced decreased fetal movement, both before and after the introduction of the intervention.

(ii) Hospital staff (including midwives, ultrasonographers and obstetricians/radiologists) working in participating hospitals in Scotland.

There will be no specific screening tests for eligibility for Q5, other than a policy whereby women who have experienced a stillbirth in the index pregnancy will not be approached.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Potential participants for Q5 who are not approached or who decline will have no specific interventions / procedures.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

This is a cluster-randomised, stepped-wedge design trial wherein maternity units rather than individual patients are randomised. All units will implement the fetal movement monitoring intervention at some point during the trial; the random element is the time point at which this will occur, the so-called “step” of the stepped-wedge design.

Participating maternity units will be blinded to their randomly allocated time point until the time this is required to be revealed to enable the necessary training in the implementation of the intervention to be delivered. Primary and secondary outcomes of the trial will be gathered in a blinded manner via routinely collected data sources.

Groups of units which are in close proximity to each other will be treated as strata for the purposes of randomisation (see section 9.1). This will assist with the feasibility of delivering the training for and implementation of the intervention as the units will be near one another. Furthermore, this local synchronisation of the intervention implementation will minimise the chances of contamination from maternity units which have already implemented the intervention to those not yet randomised.

The order in which the strata of units step in to implement the intervention will be determined by computer generated random numbers from a uniform distribution.

The randomisation list will be held by the ECTU. The identities of the research team staff whose roles in the trial require them to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

5.5.2 Treatment Allocation

Centres will be randomised to “active” or conventional treatment. All units will be providing conventional treatment at baseline according to local practice– this is the treatment established before the study starts. Centres will be randomised to “active” treatment in turn as described above. Active treatment will consist of a package of care consisting of a management plan for identification and delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s awareness of the need to report decreased fetal movements early. A draft management plan for identification and delivery of the “at risk” fetus is shown in Appendix 4 Practice change in the active units will be achieved by: (i) written/email information to all clinicians (doctors, midwives and ultrasonographers) in each unit about the study protocol and amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the study protocol (ii) a short web-based training package taking approximately one hour to complete for all clinicians in each centre and (iii) training /information sessions to run in each unit and (iv) posters in each unit to describe the practice change.

Strategies for encouraging clinicians to increase pregnant women’s awareness of fetal movement will include all the above and also a fetal movement leaflet for pregnant women.

Once units have begun active treatment it is not anticipated that they will return to conventional treatment.

Units will be informed about treatment allocation as near as possible to the implementation of the “active” treatment. For practical purposes, we anticipate that each unit will need around three months’ notice before the “active” treatment is introduced, hence units will be informed of the timing of their treatment allocation (step) three months before the active treatment is due to start.

5.5.3 Emergency Unblinding Procedures

The treatment allocation will not be administered blind, hence there is no need for emergency unblinding.

5.5.4 Withdrawal of Study Participants

The nature of a cluster randomised study is such that it is not possible for the participant to withdraw from the “cluster” (Q1-4) unless she changes the hospital of delivery part way through the pregnancy. The delivery hospital will be considered to be the relevant hospital when calculating treatment allocation – no specific allowance will be made for those who have some antenatal care in one hospital and then transfer to another hospital with a different treatment allocation.

We plan to collect routinely recorded anonymised data. Patients have the right to opt out of having their data used – if this happens their data would be withdrawn (eg under the Confidentiality and Security advisory Group Report 2002 and the Data Protection Act requirements for fair processing of data). Of note, only two individuals have ever contacted ISD asking for their data to be removed, with none within the last three years.

Participants in Q5 who wish to withdraw will be allowed to do so. Their data will be retained and used, unless they additionally indicate that they wish to withdraw their data.

6 STUDY ASSESSMENTS

6.1 SAFETY ASSESSMENTS

Not applicable.

6.2 STUDY ASSESSMENTS

There will be no specific study related assessments. All data in Scotland and Ireland will be routinely collected data. In other areas in the UK it may be necessary to collect data specifically for the purpose of this study. Such data will be collected from hospital patient records. No additional assessments will be required to collect outcome data.

7 DATA COLLECTION

For Q1-4, data will be routinely collected during the clinical management of the patient. Data will be accessed from this routine collection. Different data sources will be used for different regions of the study.

- (i) In Scotland the source data will be SMR2 and the Scottish Birth record
- (ii) In Ireland the source data will be the National Perinatal Reporting system (NRPS http://www.esri.ie/health_information/nprs).
- (iii) In Northern Ireland, the source data will be the Northern Ireland maternity Statistics database (NIMATS).
- (iv) In England and Wales, the source data will be ONS, or other relevant body.

Data will be collected retrospectively on an annual basis from all sources. We will assume that data unavailable four months after the woman delivered is likely to be unobtainable (but see note in section 3 above). Thus, data on the first year of the study will be collected at month four; data on the second year will be collected at month 16 etc.

Data are routinely collected. A formal request for data access will be made at the start of the study. This will require (i) in Scotland - PAC approval and a formal approach to ISD (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in England and Wales a formal approach will be made to the relevant bodies.

Data will then be sent to the eDRIS National Safe Haven (NHS National Services Scotland) by SFTP (or other similar) for storage and subsequent analysis within a secure project area (the AFFIRM study database). Further information on the National Safe Haven is available at <http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven>. Briefly, the National Safe Haven is located on a secure server, in which trusted and authorised researchers can analyse individual level data while maintaining the utmost confidentiality. Researchers meeting the necessary criteria may remotely access a secure project area on the server where their data is held. It is not possible to download or print out information from the Safe Haven. Final output is only available for release after an eDRIS Research Coordinator has checked the output to ensure that it does not contain information which could be used either on its own or in conjunction with other data to breach an individual's privacy. It is anticipated that all study analysis will be done within the Safe Haven, using one of the available statistical packages (e.g. R, SPSS).

Identifiers on Scottish data within the National Safe Haven are concealed from researchers. Data from outwith Scotland will be anonymised before submission to the National Safe Haven. Thus the trial team will not at any stage have access to identifiable patient data. We have carefully considered how we might maximise patient confidentiality whilst maintaining the integrity and the usefulness of the study.

We propose that data submitted to the National Safe Haven will be "anonymised" by the data provider. This will happen automatically for Scottish data. Data from other areas will be anonymised before submission to the National Safe Haven. Thus data stored in the AFFIRM project area in the National Safe Haven will not include names, addresses or CHI (or equivalent) numbers. In other words, it would not be possible to use the AFFIRM project area data to identify individuals. However, we propose that the anonymisation link will be retained at the source so that it will be possible to re-link data retrospectively. Such re-link would require co-operation by the data source (e.g. ISD for Scottish data, or other local clinicians /data guardians for other data), and, depending on the mechanism by which this was done, may require an amendment to ethics / research governance approvals. A similar strategy will be implemented with other data providers.

The rationale for retaining the ability of local data guardians to re-link data is because we believe that it is important to retain the possibility of identifying individual patients retrospectively. Examples include: (i) It is possible that some additional important data may be available at a late stage on individual participants – e.g. in the scenario where the woman or baby had a major adverse event and spent a long time in hospital before discharge or death. Given that data recording is linked to date of discharge from hospital, these data may not be available until some time after our planned four month cut off period. We may therefore have transferred a large block of data from ISD (or other data provider) into the AFFIRM study National Safe Haven database prior to information about this important individual and her/his outcomes. If it is not possible to retrospectively identify individual patients, it will not be possible to amend this single individual's data in the AFFIRM study database. (ii) Although our protocol and outcome analysis does not require identifiable data, we believe this will be a 'once in a lifetime' study, and that subsequent secondary analyses could yield important information for patients and for policy makers. If retrospective identification is not possible, this will limit further analysis. One likely example of future analyses is to determine the effect of the intervention on different causes of stillbirth. This is outwith the scope of the current protocol, but could be done relatively straightforwardly, by linking nationally recorded information on "cause" of stillbirth to our study database. We anticipate that such additional analyses would require additional ethics approval, but if all identifiers are stripped, it will not be possible to perform such subsequent analyses.

We acknowledge that the nature of the data is that it may be possible for a determined and unscrupulous person to identify some individuals with uncommon events, e.g. from the date of delivery. However, the National Safe Haven has extensive processes in place to minimise access to datasets to prevent this happening, and we believe that date of delivery required facilitating analysis of important outcomes (e.g. age of the baby in cases of neonatal death). Given that postcode data will be used exclusively to determine deprivation score, we will convert postcodes into deciles of deprivation (e.g. Scottish Index of Multiple Deprivation Score) at source (eg ISD).

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK) with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Published results will not contain any personal data that could allow identification of individual participant.

In addition to the data recorded above, all centres will be asked to provide a copy of their guidelines around (i) maternal awareness of decreased fetal movement and (ii) management of women presenting with decreased fetal movement. Copies of guidelines will be sought by the study office (a) at the start of the study (b) immediately before initiation of the intervention in each specific unit and (c) six months after initiation of the intervention in each specific unit.

For Q5, we will perform interviews of healthcare workers and a small nested cohort of pregnant women about their experiences of fetal movement and of this intervention. We shall ensure a diversity of age and include primi and multigravida women (n=30 in total). Ten interviews will be conducted with each of the following groups of health care providers: obstetricians, midwives and sonographers/radiologists. The interviews will take a semi-structured format (sensitising and piloting interviews will be conducted prior to the commencement of the trial and in the first month of the nested qualitative study). This format will ensure the same categories of data will be obtained from each participant but also allow individual responses to be fully explored.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

The sample size is the number of women delivering in hospitals participating in the study. Scotland has around 58,000 deliveries per year with 16 consultant led maternity units, 20 smaller units each delivering less than 350 babies per year, and seven units delivering less than five births per year (Appendix 2). The units involved in Perinatal Ireland (an all-Ireland research consortium across 7 academic centres in Ireland currently funded by the Health

Research Board, Ireland) have 50,000 births per year with seven large centres (Appendix 2). Combining one or two of the smaller units and one larger unit into a single “hospital group” for each local area could provide 24 hospital “groups” – the details of hospital groupings will be reviewed and finalised immediately prior to randomisation.

We calculated statistical power using the methodology for stepped wedge designs proposed in Hussey and Hughes (2007) (26). First, we analysed stillbirth event data from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR) covering years 2005-2010 (4) to determine estimates of between- and within-unit variability in stillbirth rate. Analysis was by generalized linear mixed model for binary outcomes. The power calculation, as per equations (#7) and (#8) in (26) assumed: significance level 5%; analysis by generalized linear mixed model; deliveries equally distributed across hospital groupings; baseline stillbirth rate 0.438% (4); cluster coefficient of variation 0.333.

Finally, the statistical power depends on the number of groups in which the intervention is implemented at each stage of the stepped wedge design and the duration of recruitment at each “step”. Our study design proposes sequential introduction of the intervention into three hospital groups at a time at four month intervals over a 32 month period. This would give 92.4% power to detect a 30% relative risk reduction under the intervention and 80.7% power to detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and 30% relative reduction take into account that the intervention will not have the power to reduce all stillbirths, since 20% of stillbirths in Ireland (5) and 15% in Scotland (4) are associated with congenital anomaly.

The power actually achieved in the study will be slightly lower, as deliveries during the two month “washout” period following implementation of the intervention in a site will not be included in the analysis. The effect of this was explored using the Stata function steppedwedge (27), which showed the statistical power would become 88.2% (30% risk reduction) and 74.6% (25% risk reduction). It is anticipated that unavailability of data and women asking to withdraw their data will be less than 1%.

8.2 PROPOSED ANALYSES

For the binary outcomes being addressed in research questions Q1-Q4, data will be analysed by generalized linear mixed model with a random effect for hospital group and fixed effects for the intervention implementation and study time period. Data will be analysed on an intention to treat basis (the design of the trial means it is not possible to determine individual patient /caregiver compliance with the intervention). There will be no imputations for missing data. Subgroup analyses will include those with and without congenital anomalies. No interim analyses will be performed other than those requested by the trial steering committee, who will be the only group to view the interim analyses. A full statistical analysis plan will be developed and signed off prior to locking of the study database.

For research question Q5, the qualitative data will be audio recorded and transcribed. The data will be coded thematically and an analytical framework developed to make sense of patient experience of fetal movement and the intervention and also health care providers’ perspectives and experiences. NVivo will be utilised to support the analysis. The RA and SCB will work together to ensure rigour and validity.

The process outcomes being assessed in Q6 (rates of induction of labour, number of women presenting with decreased fetal movements, interval between perceiving fetal movements and presenting to hospital) will be analysed using the same methods as for Q1-Q4, with the exception of the continuous outcome (interval between perceiving fetal movements and presenting to hospital) which will be analysed in a normal linear mixed model.

9 ADVERSE EVENTS

This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse events will not be formally reported. Stillbirth and other measures of fetal and maternal morbidity are outcomes of the study. The purpose of the intervention is to reduce such adverse events. If

required, the Trial Steering committee (TSC) may review unblinded data for the study, including morbidity and mortality indices. No other adverse event reporting will be undertaken.

10. PREGNANCY

Pregnancy is an inclusion criterion for participation in the trial.

11 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders and the Trial Manager (Sonia Whyte). The Chief Investigator - Prof Jane Norman will lead the project management group.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator.

11.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The names and contact details of the TSC are detailed in Appendix 1; their terms of reference and a draft template for reporting will be ratified in one of their early meetings.

11.3 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.4 RISK ASSESSMENT

An independent risk assessment will be performed by ACCORD to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by ACCORD to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

11.5 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan if required. Investigator sites will be risk assessed by the ACCORD QA Manager, or designee, in order to determine if audit by the ACCORD QA group is required.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the research governance framework operational in the relevant country.

A favorable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

12.2 REGULATORY COMPLIANCE

As this trial is not a CTIMP, there is no requirement for approval from the MHRA.

12.3 INVESTIGATOR RESPONSIBILITIES

Local study investigator(s) will be appointed to each site (or, for small centres, groups of sites). S/he will be responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. The following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

12.3.1 Informed Consent

Informed consent will only be required for Q5 – the following statements apply to this part of the study only.

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and (if the participant is a patient) agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

12.3.2 Study Site Staff

The local study investigator is expected to be familiar with the protocol and the study requirements and to publicise the study in their centre. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

12.3.3 Confidentiality

All evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.3.4 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Access to collated participant data will be restricted.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator and Sponsor.

Amendments to the protocol must be submitted in writing to the appropriate REC and local R&D for approval prior to participants being enrolled into an amended protocol.

13.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Investigators will not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC and R&D approval except where necessary to eliminate an immediate hazard to trial participants.

In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

13.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

- (a) the safety or physical or mental integrity of the participants of the trial; or
- b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and, if so, report it to the REC.

All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria for a serious breach. If the sponsor(s) deem the incident to be a violation that does not constitute a serious breach from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within the TMF and ISF.

13.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.5 END OF STUDY

The end of study date will be finalised in the protocol once the study starts

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

13.6 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with GCP guidelines.

14.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

14.3 PEER REVIEW

This project has been peer reviewed internally, and was externally peer reviewed during the process of securing funding from the CSO.

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AFFIRM

Version 6_ 27th February 2017

APPENDIX 1: TRIAL STEERING COMMITTEE

Chair – Prof Gordon Smith, University of Cambridge - gcss2@cam.ac.uk

Obstetric member – Mr Kim Hinshaw, Sunderland Royal Hospital - kim.hinshaw@lineone.net

Lay member – Mrs [Louise Fenton - louisefenton78@icloud.com](mailto:louisefenton78@icloud.com)

Sponsor's representative – Dr Ray French – Ray.French@ed.ac.uk

CI – Prof Jane Norman, University of Edinburgh – Jane.Norman@ed.ac.uk

Trial Manager – Mrs Sonia Whyte – Sonia.Whyte@ed.ac.uk

Invited members of the Trial Management Group (TMG)

The Trial Steering Committee will act according to guidelines from the NIHR Clinical Trials toolkit (see <http://www.ct-toolkit.ac.uk/glossary/trial-steering-committee-tsc>).

APPENDIX 2: PARTICIPATING SITES (UPDATED 09/01/2015)

Maternity unit	Births 2013 figures
A. Large consultant led units (Scotland)	
New Royal Infirmary of Edinburgh	6462
Princess Royal Maternity Hospital, Glasgow	6900
Wishaw General Hospital, Lanarkshire	5000
Aberdeen Maternity Hospital, Grampian	5009
Ninewells Hospital, Tayside	4281
Crosshouse Hospital, Ayrshire	3733
Forth Park Maternity Hospital, Kirkcaldy, Fife	4171
Southern General Hospital, Glasgow	6000
Forth Valley Royal, Larbert	3339
Royal Alexandra Hospital, Paisley	3700
St. John's at Howden, Livingston	2995
Raigmore Hospital, Inverness	3107
Dumfries and Galloway Royal Infirmary, Dumfries	1373
Borders General Hospital, Borders	1214
Dr Gray's Hospital, Elgin	1156
B. Perinatal Ireland consortium	
Rotunda Hospital, Dublin	9000
University College Hospital, Galway	2500
Royal Jubilee Maternity Hospital, Belfast	5000
National Maternity, Dublin	9000
C. Large consultant led units (Wales)	
Ysbyty Gwynnedd Hospital	2200
Glan Clwyd Hospital	2450
Wrexham Maelor	2650
Nevill Hall Hospital	2250
Royal Gwent Hospital	3450
D. Large consultant led units (England)	
St Richard's Hospital, Chichester	2600
Worthing and Southlands Hospital, Chichester	2700
Birmingham Women's Hospital	8000
Leeds General Infirmary	4800
St George's Hospital, London	5400
Royal Preston Hospital	4800
Blackpool Victoria Hospital	2900
St Mary's Hospital, Manchester	8400
Stepping Hill Hospital, Stockport	3800
Royal Albert Edward Infirmary, Wigan	2800
Total number of deliveries per year	143140

APPENDIX 3: INFORMATION FOR WOMEN ABOUT FETAL MOVEMENTS

<p>One of the easiest ways to tell if your baby is healthy is to see how often you can feel her or his movements. Every baby is different, so it is a good idea if you can become familiar with your baby's usual movements and activity, and report to us if you notice a reduction in them. The number of kicks you want to feel per</p> 	<p>18-24 WEEKS</p> <p>Most people begin to feel movements between 18-24 weeks if this is a second baby, then you may be aware of these earlier. It may feel like bubbles, flutters or 'the wags'. There are often irregular 'cannys' and gaps. Later you can be sure of more regular hits.</p> <p>Everyone is different. There are many reasons for not feeling movements as early as you expect, including your body weight, your baby's position and the location of your placenta. As long as the baby is growing well at your 22-week check, then you should not worry.</p>
<p>If you feel big, you should become aware of what babies do every day. You should feel movements every day.</p> 	<p>24-36 WEEKS</p> <p>'Kicking, punching, stretching and squirming' - these are all words women use to describe their baby's movements. Usually you are more aware of movements when lying down, or at night time, when you are still and often not at all. When you are busy and on your feet.</p> <p>During these weeks, it would be good if you could become aware of what time of day you are most likely to feel movements so you can notice if these become absent or reduced.</p> <p>None of these do not count as movements.</p>
<p>This number of movements may change, but the frequency should not decrease.</p> 	<p>36-42 WEEKS</p> <p>At 36-42 weeks, your baby will have less room to wiggle around, and when you get ready to feel the baby, you may notice big movements, and rolling.</p> <p>There will be the nature of the movements may change. But the frequency should not decrease. It should be the same as you feel in the weeks before the date of the check.</p> <p>Some people may tell you that your baby will kick less frequently in late pregnancy and before you go into labour. This is not so. It is important that you report any change, as it might be a sign that your baby is unwell.</p>

APPENDIX 4: UPDATED 09/01/2015

SUGGESTED MANAGEMENT PLAN FOR WOMEN PRESENTING WITH REDUCED FETAL MOVEMENTS

Guideline for management of women presenting with reduced fetal movements at more than 28 weeks gestation.

Suggested management plan is based on that employed in the Tveit study where an intervention was associated with a reduction in stillbirth rates. Given that decreased FM is a risk factor for SGA (OR ranging from 1.6 (1), to 3), these guidelines are also informed by the revised RCOG guidelines on SGA <http://www.rcog.org.uk/files/rcog-corp/GTG31SGA23012013.pdf>. The management plan described here depends very heavily on ultrasound, given data that ultrasound performs well both on an absolute basis and compared with other interventions (with a. ultrasound perceived as useful in detecting abnormalities in 11.6% of scans, b. detection of the identified abnormality being perceived as useful after ascertainment in 86.2% of women and c. the ultrasound being the only modality to detect abnormality in 71.3%). Ultrasound examinations (whether for LV or AC / EFW or umbilical artery Doppler) should only be performed by a trained individual (e.g. RCOG ultrasound module 2 “signed off”), and a formal report issued. Note there is no formal definition of decreased fetal movement – previous studies have suggested that the woman’s perception of decreased fetal movements are the most helpful criterion definition of decreased fetal movement, so that an arbitrary reference range for movements is not recommended).

Single episode of presenting with reduced fetal movement.

i. 37 weeks gestation or more

Assess for risk factors. Perform CTG within 2 hours and USS for LV within 12 hours.

- If CTG abnormal or LV reduced (deepest vertical pool \leq 2cm), arrange delivery, with input from senior obstetrician on timing, and certainly within 48 hours.
- If CTG and LV normal perform USS for EFW /AC next working day (+/-Dopplers as per local protocol).
 - If EFW/AC $>$ 10th centile, growth trajectory normal AND fetal movements have returned to normal, discharge back to routine care.
 - If AC or EFW \leq 10th centile or there is decreased growth velocity or abnormal Doppler deliver with input from senior obstetrician on timing, and certainly within 48 hours.
 - If all investigations are normal but fetal movements have not returned to normal within 24 hours follow recurrent reduced fetal movement pathway.
- If \geq 40 weeks, consider delivery within 48 hours as an alternative to USS.

ii If 27+0 – 36+6 weeks.

Assess for risk factors. Perform CTG within 2 hours and USS for LV within 12 hours.

- If CTG abnormal or LV reduced (deepest vertical pool \leq 2cm), involve senior obstetrician in management plan.
- If CTG and LV normal perform USS for EFW /AC next working day (+/- Dopplers as per local protocol).
 - If EFW/AC $>$ 10th centile, growth trajectory normal AND fetal movements have returned to normal discharge back to routine care.
 - If AC or EFW \leq 10th centile or there is decreased growth velocity or abnormal Doppler review by senior obstetrician as per local protocol for suspected FGR. The revised RCOG guidelines for SGA <http://www.rcog.org.uk/files/rcog-corp/GTG31SGA23012013.pdf> should also be consulted. Consider delivery by 37 weeks for women with suspected fetal growth restriction.

- If all normal but fetal movements have not returned to normal within 24 hours, follow recurrent reduced fetal movement pathway.

iii. If 24+0 – 26+6 weeks.

Assess for risk factors. Confirm fetal viability. Perform fetal anomaly scan if not already completed. If risk factors or FGR and stillbirth present, arrange serial growth USS as per local policy/RCOG guideline.

Recurrent episodes of reduced fetal movement.

Recurrent reduced fetal movement is defined as persistent reduced fetal movement for more than 24 hours or second or subsequent episode within 21 days of first presentation. If previous attendance \geq 21 days ago follow single episode guidance above.

iv. 37+0 weeks gestation or more

Perform CTG within 2 hours. Offer delivery (eg induction of labour) with input from senior obstetrician on timing (and certainly within 48 hours) if woman wishes delivery.

v. 27+0 – 36+6 weeks inclusive.

Perform CTG within 2 hours and LV within 12 hours of presentation. Schedule repeat USS scan for EFW/AC if it is \geq 21 days after previous USS (+/- Dopplers as per local protocol) and perform twice weekly CTG monitoring and weekly LV until then. Thereafter, manage according to repeat scan results. If measurements of EFW/AC are \leq 10th centile, or if there is decreased growth velocity, or abnormal Doppler review by senior obstetrician. If EFW/AC are $>$ 10th centile, return to routine care.

vi. 24+0 – 26+6 weeks inclusive.

Assess for risk factors for stillbirth and FGR. Confirm fetal viability. Perform anomaly scan, if not already done. If high risk of FGR arrange serial growth USS as per local policy /RCOG guideline.

What would the impact of this be on the clinical service?

In addition to a reduction in stillbirth, Tveit (1) showed that a policy of encouraging women to attend quickly after perception of decreased fetal movements had no significant increase in the total proportion of women attending with 6.2% of women presenting with decreased FM in third trimester prior to intervention and 6.6% of women after the intervention

However, it had a significant decrease in the proportion of women who waited more than 48 h to come to hospital (49% vs 54%) significant reduction in admission for induction (4.9% vs 7%) significant decrease in the number of admissions (11% vs 14%) non significant increase in the proportion of women with no follow up (69% vs 63%) a significant increase in the proportion of consultations which had ultrasound (94% compared with 86%).

In two other studies looking at the number of people attending with recurrent decreased fetal movements after 37 weeks, the figures were 0.2 – 0.5% of the obstetric population (2) (3). Again, Tveit showed that his intervention did not increase the number of women presenting, so the figure of 0.2 – 0.5% of the obstetric population should be robust. Even assuming an increase in the proportion of women presenting (at worst a doubling), this would result in only a modest increase in the proportion of women undergoing induction of labour (at worst, 0.4 - 1% of the obstetric population). In practice, the majority may have abnormal growth monitoring, so may already be undergoing induction of labour. These data suggest that, with the exception of the need for ultrasound, these policies should not increase the need for service delivery. Regarding ultrasound, in the worst case scenario (assuming that no woman presenting with reduced FM currently has USS, but that all women will in the future, and assuming that 6-7% of all women will present at some point in the third trimester after the intervention, then a hospital with 7000 deliveries per year will do no more than 2 - 8 extra scans per week. For induction of labour, a hospital with 7000 women would have no more than 0.4 – 1.3 inductions per week.

References:

1. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth*. 2009;9:32. PubMed PMID: 19624847. Pubmed Central PMCID: 2734741. Epub 2009/07/25. eng.
2. Dutton P, Warrander LK, Roberts S, Bernatavicius G, Byrd L, Gaze D, et al. Predictors of poor perinatal outcome following maternal perception of reduced fetal movement - a prospective cohort study. *PLOS One*. 2012;7:e39784.
3. O'Sullivan O, Stephen G, Martindale E, Heazell AE. Predicting poor perinatal outcome in women who present with decreased fetal movements. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology*. 2009 Nov;29(8):705-10. PubMed PMID: 19821662. Epub 2009/10/14. eng.

APPENDIX 5: AUDIT OF COMPLIANCE ADDED 17th July 2017

An audit of compliance with the affirm management protocol (appendix 4: updated 09/01/2015) for women presenting with reduced fetal movements will be determined by two means:

A) **QUESTIONNAIRE** Via Telephone or email contact with Principal Investigators at each site to determine which aspects of the AFFIRM protocol have been implemented effectively.

This will involve email contact with Principal Investigators to alert them to the request for information, detailing the information required, followed by a phone call to elicit the information (unless it had already been supplied). Investigators will be asked which of the following elements they had implemented locally:

- Issuing leaflets to all pregnant women,
- Cardiotocography within 2 hours of presentation,
- Measurement of amniotic fluid volume within 12 hours of presentation,
- Growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours),
- Induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation.

Compliance (effective implementation) will be defined as 4/5 of the above management elements for 80% or more of the time.

AUDIT PART A: STAFF QUESTIONNAIRE



Dear (PI Name)

You very kindly agreed to answer some questions regarding your unit's compliance with the AFFIRM audit. We would be most grateful to receive your views on the following:

1. In your opinion, were the following aspects of the AFFIRM audit implemented at least 80% of the time at [Insert site name]?

Unit name: (Hospital name)	Yes	Partially	No	If Partially or NO, What proportion of women do you estimate received these?
Leaflets about RFM issued to women				
eLearning completed by staff				
CTG within 2 hours of presentation with RFM				
Growth scans for RFM (next working day)				
IOL for women 37 weeks and above with recurrent RFM (within 48hrs)				

2. If you could turn back time to 1st January 2014, and (with the benefit of experience) would you agree to participate in the AFFIRM study again? YES/NO

If NO, please could you explain why not?

We would be most grateful to receive your answers by **XX/ XXX/XXXX** If you haven't already given us your best address for sending out your vouchers, please don't forget to include this.

As always, thank you so much for your help with AFFIRM.

Best Wishes

Prof Jane Norman and Dr Sarah Stock
On behalf of the AFFIRM Study

NB: If you wish to print and fax your completed sheet to us, the number is 0131-242-6441

B) **CLINICAL AUDIT** to determine whether the perception of the site Principal Investigator is supported by review of actual decision making will be performed for the following elements:

- Cardiocography within 2 hours of presentation,
- Measurement of amniotic fluid volume within 12 hours of presentation,
- Growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours),
- Induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation.

This will be conducted by asking sites to complete an audit of the management of all women presenting with reduced fetal movement over the course of one calendar month. Sites will be asked to complete an audit form for each participant.

The audit form template (see below) has been generated by the central AFFIRM study team; anonymized forms will be analysed centrally. There will not be an attempt to corroborate Principal Investigator perception of the proportion of women who were given leaflets, nor will there be any attempt to incorporate the proportion of staff who had completed the e-learning package into analysis of whether any specific site has implemented the intervention or not.

AUDIT PART B: CLINICAL AUDIT FORM - One month data collection AUDIT [Month & Year] Unit name: [Name of Hospital]

If you assess a woman with reduced fetal movements (RFM), please complete the questions below. Do not worry if the woman has been seen in other areas of the hospital by other staff, we would rather have multiple reports for the same woman than miss episodes of RFM.

INSERT Patient Sticker (or WRITE name and CHI /NHS number)				AREA WHERE SEEN (CIRCLE)						
				Triage / Labour ward / Day Assessment Unit (DAU)						
				Other (specify area i.e. antenatal ward): _____						
Date and time of presentation with reduced fetal movements.	DATE: ____/____/____ TIME ____:____ am / pm			GESTATION AND EDD:	____ WEEKS ____ DAYS EDD: _____					
Referred by (TICK BOX):	Self	Community Midwife	GP	ANC	Triage	DAU	Other (specify: _____)			
What was the primary reason for attending/phoning? (TICK BOX):	Reduced Fetal Movements			Other (specify: _____)						
How many times has the woman attended before this visit, with RFM? (TICK BOX):	None – first attendance		Once previously	Unknown	Multiple times (please provide the gestation at each presentation i.e. 30+6)	1	2	3	4	5
What was the time interval from the woman first being aware of reduced fetal movements and attending the hospital (in hours)?					HOURS: _____					
Has she been given a leaflet "Your baby's movements in pregnancy"? (TICK BOX):	Yes – she already has one		Yes – I have given one to her today		Locally Created Leaflet Given			NO		
Has this woman had a growth USS in this pregnancy? (TICK BOX):	No, she has not had a growth scan		Yes, within the last 3 weeks (date of scan): DATE: ____/____/____		Yes, but more than 3 weeks ago (date of scan): DATE: ____/____/____					

Can Promoting **A**wareness of **F**etal movements and **F**ocussing **I**nterventions **R**educe **F**etal **M**ortality - a stepped wedge cluster randomised trial? **AFFIRM**

CONTINUATION: NHS/ CHI NUMBER:

Are any of the following risk factors for Fetal growth restriction present (CIRCLE all that apply)?							
Age ≥40 or ≤16	Smoker ≥20cpd	Known or suspected growth restriction	Congenital anomaly	Raised BP (essential hypertension, pre-eclampsia or pregnancy induced hypertension)	Previous pre-eclampsia	Diabetes or gestational diabetes	Previous FGR or stillbirth
What investigations were conducted during this episode of reduced fetal movement?							
Please record below the date and time that these investigations were completed or indicate if not performed.					Please provide the results (CIRCLE):		
CTG	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / Suspicious / Pathological		
					Computerised CTG: YES / NO (CIRCLE)		
Liquor volume assessment on scan	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / Reduced / Increased		
Growth scan	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / EFW < 10 th centile / AC < 10 th centile / EFW and AC < 10 th centile		
Umbilical Artery Doppler	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / > 95 th centile / absent EDF / reversed EDF		
MCA Doppler	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / < 5 th centile		
DELIVERY METHOD (If available)							
Was the woman offered induction of labour	YES / NO (CIRCLE)			DATE: ____/ ____/ ____			
	IF Yes, please provide date, time and method of the induction:			TIME: ____:____ am/pm			
Was the woman offered elective caesarean section as a result of the reduced fetal movement?	YES / NO (CIRCLE)			DATE: ____/ ____/ ____		Please provide the reason for the elective Caesarean section:	
	IF Yes, please provide date, time and reason:			TIME: ____:____ am/pm			