DETAILED PROJECT DESCRIPTION

Which method is best for the induction of labour: A systematic review, network meta-analysis and cost effectiveness analysis

SUMMARY OF RESEARCH

The research question: What is the most cost-effective and safe method for induction of labour in the NHS setting?

Background: More than 140,000 pregnant women in England and Wales will have their labours induced each year. [1,2] There are several different methods available to induce labour with advantages and disadvantages, varying in effectiveness, safety and cost. Clinical guidelines, including NICE,[3] which have made recommendations on this question are now out of date. Moreover, previous reviews of methods to induce labour have assessed comparative effectiveness using informal indirect comparisons between induction methods. This may have led to incorrect and potentially misleading conclusions. As the number of women facing induction increases, and as new evidence from trials becomes available, it is becoming increasingly urgent to address questions about which method of inducing labour is the most cost-effective, safe, and acceptable to women, using a coherent, unified analysis. To achieve this, we propose to carry out a systematic review with network meta-analysis (NMA) and cost-effectiveness analysis to examine all the evidence on different methods for inducing labour. NMA allows evidence synthesis to be performed when there are a range of interventions available, in order to make comparisons across all pairs of interventions in a coherent manner. A NMA is necessary in this context, because there are a range of different methods, routes of administration, and doses available for the induction of labour.

S**cope and Methods of the NMA and cost effectiveness analysis:** Our scoping exercise identified 564 relevant RCTs already included in published Cochrane reviews with a further 277 reports that have not yet been incorporated; most of them have been published since the publication of the last NICE guideline. More than 400 RCTs would contribute to the indirect comparisons of prostaglandins, at least 91 to Foley catheter and 30 to alternative/complementary methods.

We will include RCTs recruiting women due for 3rd trimester labour induction. The NMA will focus on key outcomes that have been selected by a formal iterative process carried out by the multidisciplinary group who prepared the first NICE guideline on induction of labour in 2001, namely: i) vaginal delivery not achieved within 24 hours; ii) uterine hyperstimulation; iii) caesarean section; iv) serious neonatal morbidity or perinatal death; v) serious maternal morbidity or death; vi) maternal satisfaction with the method used; vii) cost, resource use, and utility outcomes to inform the economic model.

We will build a health economic decision model to identify the most cost-effective method (including timing, dose, and mode of administration) and explore whether this differs in different subgroups of women. The model structure will be informed by a systematic review of previous economic models that address this or related questions. Data inputs for efficacy by subgroup will be informed by the NMA, and cost/resource/utility inputs will be informed by data sources identified in previous models and the systematic review.

The output from the project will be a HTA monograph summarising the findings of the systematic review, NMA and cost-effectiveness analysis. In addition, we will publish the results in the Cochrane Library and other high impact peer-review journals: different publications will focus on the overall analysis as well as sections of the network (for example which type, route and dose of prostaglandin works best for which participant groups). The outputs will be of value to clinicians, women, guideline authors and policy makers within the NHS.

BACKGROUND

Induction of labour is carried out for a number of clinical indications. The most common reasons include post-term pregnancy, prelabour rupture of membranes, or when the wellbeing of the woman or baby may be otherwise compromised by prolonging the pregnancy (such as fetal growth restriction or pre-eclampsia). Whilst many women wish to experience a natural onset of labour, occasionally women may request induction of labour for social or psychological reasons. While timely induction may improve outcomes for women and babies, further interventions including caesarean often follow. There is evidence that women are less satisfied with their experience of childbirth if their labour is induced. [4]

The number of labour inductions has increased steadily over the past two decades. Rates in the USA and the UK now exceed 20% of all births. [1.,2,5,6] There is a significant variation in practice in different settings although the reasons for this are not clear. In some hospitals in the USA, up to half of all births follow induction of labour [7]. In the UK there is variation between and within countries. In 2010-11, average rates in England were 21% with some units exceeding 25%. In this context, and with increasing pressure on healthcare resources, it is particularly important to address questions about which methods of inducing labour are most cost-effective, safe, and acceptable to women.

A broad range of pharmacological, mechanical and complementary and alternative methods have been used to induce labour including oxytocin, prostaglandins, prostaglandin analogues and other smooth muscle stimulants, such as castor oil, mechanical methods such as extra-amniotic balloon catheters, laminaria and artificial rupture of the membranes along with acupuncture, homeopathy and other complementary therapies. Currently, there are 24 different reviews in *The Cochrane Library* which share common protocols [8,9] examining different methods, or combinations of methods, for inducing labour. Most reviews include a range of different methods, routes of administration, doses and comparisons with only standard pairwise meta-analyses conducted. In order to make decisions about different treatment options, clinicians, women or policy makers tend to make informal indirect comparisons, which can lead to incorrect and incoherent conclusions [10]. There is, therefore, a need to synthesise evidence in a coherent manner, from reviews in conditions where there are a range of interventions available, in order to support clinicians, women and policy makers to make informed treatment decisions. For the induction of labour such a synthesis is becoming increasingly urgent with the number of trials in this particular topic area increasing. We will use network meta-analysis (NMA) to quantify the effects and safety of different methods and to identify which method (or methods) achieves the best results.

Even though in clinical practice in the UK the choice of method has been restricted to prostaglandins, oxytocin combined with artificial rupture of membranes and occasionally Foley catheter, deciding which method to use

under different clinical circumstances is not simple. Once a method is selected, there are further decisions to be made about route of administration, dose and regimen. Further, women facing decisions about induction of labour should have up to date information about the range of options available, including alternative and complementary methods. To date, there has been no systematic comparison which has examined a broad range of methods for induction, combining all trials that provide evidence on the differential effectiveness of interventions aiming to provide a coherent view of the evidence base as a whole.

CHOOSING THE BEST METHOD FOR INDUCTION OF LABOUR

The choice of method for induction of labour can be influenced by the reason for induction and its urgency. It may also be important to take into account the woman's obstetric and medical history. There is evidence that women may be more sensitive to drugs that stimulate the uterus if they have had a previous birth. In addition, the woman's readiness for labour may influence which method is likely to work best: for example whether or not her membranes have ruptured spontaneously, whether the cervix has started to dilate in preparation for childbirth, and whether or not she is at increased risk of complications due to her obstetric history. Drugs may act differently if the membranes are still intact at the start of the induction process, and the risk of uterine rupture and danger of maternal and fetal death are increased if the woman has a uterine scar from a previous caesarean. Women may also have preferences about which method is used. We will take these important factors into account in the subgroup analyses within the NMA.

WHY IS THE RESEARCH NEEDED NOW?

Choosing the best method for induction is extremely important as adverse effects can be serious, e.g. uterine rupture and fetal mortality. In addition, the choice may have significant implications for NHS resources e.g. if the method increases the risk of complications requiring a caesarean section. Although there is a wealth of trial data, no trial has compared all possible treatment options, and to date, there has been no overall comparison which has examined all induction methods together within a network analysis.

Clinical guidelines in the UK identify vaginal PGE_2 as "the preferred method of induction" for women with intact membranes [3]. This recommendation was not based on a quantitative overview of the evidence of the effects and safety of all available methods, or from synthesis and analysis of data from a range of comparisons. Further, this guideline did not recommend any particular type (gel, tablet or pessary) or dose of PGE_2 as again, trial evidence has infrequently directly compared different PGE_2 preparations. These issues were highlighted as important areas for future investigation in the guideline. NMA allows for such comparisons in a methodologically robust manner that minimises risk of biased conclusions.

Most importantly, the proposed work will consider the most up to date evidence. Since publication of the NICE guideline there has been a growing body of evidence from randomised trials on methods of induction other than vaginal PGE_2; including low dose vaginal misoprostol and mechanical methods of induction, such as Foley catheters. For example, since existing Cochrane reviews have been updated we have identified 37 new trials examining vaginal misoprostol, 36 examining mechanical methods and 12 examining nitric oxide. This new

evidence may have important implications for the NHS. The direct costs associated with different methods of induction of labour vary. The differential effects of different interventions on the time to delivery, need for further intervention (most critically caesarean section) and serious adverse effects for women and babies will all be examined in the NMA and this will underpin the proposed economic decision modelling.

Despite the importance of the question of resource use, this is a relatively under-researched area and there is continuing uncertainty about the costs associated with induction of labour which we will address in the proposed work. There is increasing evidence that inducing labour in women with complications such as pre-eclampsia or with prolonged pregnancy, is associated with lower health service costs compared with expectant management.[11,12,13] On the other hand there is a paucity of evidence on costs associated with particular methods of induction compared with others. Only a few economic analyses have been carried alongside randomised trials where different methods of induction have been compared.[14] The proposed systematic review, NMA and cost-effectiveness modelling will examine the important questions around the relative costs and benefits of different interventions to induce labour.

AIMS AND OBJECTIVES

We plan to carry out a systematic review and NMA of the data from randomised controlled trials to assess the effectiveness and safety of a range of induction methods to determine which method or methods achieves the best outcomes. This work will provide a quantitative summary of the evidence on the relative effects of a broad range of methods to identify which method works best. As part of this analysis we will determine which type of induction agent achieves the best results in terms of positive outcomes for women and babies. We will also develop a decision model to evaluate the cost effectiveness of the different methods for induction in different subgroups of women. The NMA and cost-effectiveness analysis will be of value to clinicians, pregnant women, guideline authors and policy makers within the NHS.

METHODS FOR EVIDENCE SYNTHESIS

Types of studies

Clinical trials comparing any method of third trimester cervical ripening or labour induction, with placebo/no treatment, with the same method but using different routes or doses, with different types of the same class of drugs or with other methods. The trials should include some form of random allocation to either group and they should report one or more of the pre-stated outcomes. We will include multi-arm trials and, if identified and otherwise eligible, cluster randomised trials. We will carry out any necessary adjustments to account for cluster design effect if trialists have not already done this.

Types of participants

The population of interest includes pregnant women due for third trimester induction of labour, carrying a viable fetus. We will include trials recruiting women with a range of indications for labour induction. We will carry out planned subgroup analysis examining:

- reason for induction,
- parity,
- previous caesarean section,
- ripe/unripe cervix,
- intact/ruptured membranes.

Interventions

All pharmacological and mechanical methods for 3rd trimester induction of labour or cervical ripening in current use that have been examined in randomised trials. We will include methods less commonly used in NHS settings, but used in comparable settings in other countries. We will include complementary and alternative methods as information on the effects and safety of such methods may be important for women. The inclusion of all relevant comparisons will strengthen the NMA by increasing statistical power, allowing us to investigate potential inconsistencies in the evidence, and make our conclusions about the most effective and safe method more robust.

Outcomes

The NMA will focus on 7 key outcomes that have been selected by a formal iterative process carried out by the Cochrane Pregnancy and Childbirth Group and the multidisciplinary group who prepared the first NICE guideline on induction of labour in 2001.

1. vaginal delivery not achieved within 24 hours (or period specified by trial authors);
2. uterine hyperstimulation with fetal heart rate (FHR) changes;
3. caesarean section;
4. serious neonatal morbidity or perinatal death;
5. serious maternal morbidity or death;
6. maternal satisfaction with the method used;
7. cost, resource use, and utility outcomes to inform the economic model.

Five primary outcomes (1-5) have been used in all Cochrane reviews of labour induction interventions. For this NMA, we have added two key outcomes which were identified as 'secondary', namely maternal satisfaction and health economic outcomes. We will also record information relating to intervention setting, participant characteristics (such as parity, reason for induction, previous caesarean section) and where relevant dose. This information will be used in subgroup analyses.

Search methods for identification of studies

To identify trials for inclusion in the NMA we will work with an Information Specialist who will search the CPC Group's Specialist Register (which incorporates pregnancy and postpartum searches of CENTRAL, MEDLINE, EMBASE, NHS EED, relevant journals and conference proceedings). We will also search NHS NICE Technology Appraisals and Clinical Guidelines and the NIHR HTA series for previous cost-effectiveness analyses and economic data.

The search strategy will be finalised as part of the early consultative stages of the project.

We have already carried out a scoping exercise to provide a sense of the number of trials that are likely to contribute data to the NMA. Many of the trials are already included in published Cochrane reviews, but we have carried out further searches to identify more recent trials which may contribute data to the analysis. Below we have indicated, for each review how many trials already contribute data and (in brackets) the number of new reports which have not yet been incorporated into reviews.

1. vaginal prostaglandins; 63 (10)[15]
2. intracervical prostaglandins; 56 (12)[16]
3. intravenous oxytocin; 61 (8)[17]
4. amniotomy; 2 (2)[18]
5. intravenous oxytocin with amniotomy; 16 (4)[19]
6. vaginal misoprostol; 121 (45)[20]
7. oral misoprostol; 51 (22)[21]
8. mechanical methods including extra-amniotic Foley catheter; 71 (20)[22]
9. membrane sweeping; 22 (15)[23]
10. extra-amniotic prostaglandins; 12 (0)[24]
11. intravenous prostaglandins; 13 (2)[25]
12. oral prostaglandins; 19 (2)[26]
13. mifepristone; 10 (1)[27]
14. estrogens; 7 (0)[28]
15. corticosteroids; 1 (6)[29]
16. relaxin; 4 (3)[30]
17. hyaluronidase; 1 (1)[31]
18. castor oil, bath, and/or enema; 1 (6)[32]
19. acupuncture; 3 (15)[33]
20. breast stimulation; 6 (1)[34]
21. sexual intercourse; 1 (2)[35]
22. homoeopathic methods; 2 (0)[36]
23. nitric oxide 10 (4)[37]
24. buccal or sublingual misoprostol; 3 (25)[38]
25. hypnosis; (1)
26. combined and other methods for induction of labour. (31)
27. different oxytocin infusion regimens (40)[39]

Within some of these reviews there are a number of comparisons that will be explored separately, for example the vaginal prostaglandin review includes an analysis of PGE_2 and PGF_2alpha, in vaginal tablet, gel, pessary and slow release pessary form, compared with placebo or other treatments. We will separate these different types of prostaglandin in our NMA to see whether the relative effects of different preparations differ, and if so, to what

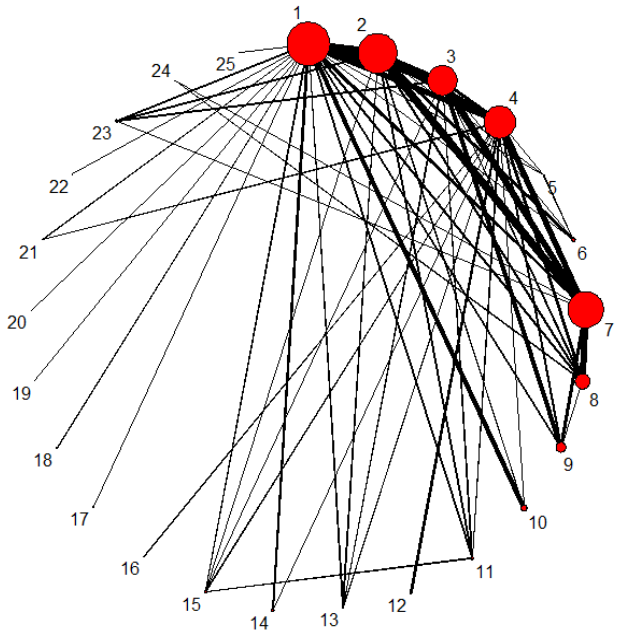
extent. Similarly we will separate out high and low-dose oral misoprostol as for this intervention dose may have an important effect on outcomes.

The scope of the NMA

The NMA will allow us to synthesise data for all relevant comparisons. Figure 1 shows a treatment network map; lines between different methods of induction of labour indicate that there have been direct comparisons between these methods in one or more trials. This map is based on comparisons from trials already included in Cochrane reviews, however, it provides a good illustration of the main comparisons that have been examined, and highlights the need for NMA methods to provide a coherent synthesis of all the available evidence. We anticipate that there may be some new comparisons to add to the network from more recent trials which have not yet been incorporated into reviews.

Figure 1.

Network diagram* for all RCT of different induction regimens with available data for caesarean section rates.



1 = placebo/no treatment
2 = vaginal prostaglandins
3 = intracervical prostaglandins
4 = intravenous oxytocin
5 = amniotomy
6= intravenous oxytocin and amniotomy
7 = vaginal misoprostol
8 = oral misprostol
9 = mechanical methods
10 = membrane sweeping
11 = extra-amniotic prostaglandins
12 = intravenous prostaglandins
13 = oral prostaglandins
14 = mifepristone
15 = oestrogens
16 = corticosteroids
17 = relaxin
18 = hyaluronidase
19 = castor oil
20 = acupuncture
21 = breast stimulation
22 = homeopathy
23 = nitric oxide
24 = buccal/sublingual misoprostol
25 = hypnosis

The width of the lines is proportional to the number of trials making that comparison, and the size of the circles corresponds to the number of trials.

Assessing trial eligibility, data extraction and assessing risk of bias

We will use Cochrane Methods to assess whether trials are eligible for inclusion in the network, to carry out data extraction in preparation for data analysis. We will work in close collaboration with the Cochrane Multiple

Interventions Methods Group (of which DMC is co-convenor) which is actively developing methodology in conducting overviews where there are disparate interventions for the same condition.

Two investigators will independently assess whether trials use random allocation to groups, examine one or more of the selected interventions and comparisons, and include data on at least one of our primary outcomes. We will include a PRISMA diagram to set out the results of the search and to indicate the number of included and excluded trials. The reasons for excluding any studies identified by the search from the NMA will be documented in tables.

Data extraction will be carried out by one investigator and checked by a second. Some of the data has already been extracted as part of existing reviews and is included in Review Manager Tables; this data will be copied over into new data extraction spreadsheets. For new trial reports data extraction for our primary outcomes will be carried out for each report and will be checked.

We will record whether the randomisation method was at high or low risk of bias; we will record in the spreadsheet whether methods used to conceal allocation to comparison groups were likely to introduce bias (where methods are unclear the assumption will be that methods were at high risk of bias). This assessment will be used as part of sensitivity analysis.

For all included trials we will extract data on trial characteristics and this will be summarised in tables. We will describe study settings, methods and the types of intervention/s (dose, mode of administration, type of preparation eg, slow release pessary vs gel, regimen and any co-interventions). We will also describe comparison arms (placebo or "usual care/no treatment"). For women we will report important obstetric characteristics such as parity, previous caesarean section, state of cervix and whether or not amniotic membranes are intact along with the indication for induction.

Statistical Methods

We will conduct standard meta-analyses for each pairwise comparison of treatments and each outcome. We will present results of both fixed- and random-effects meta-analyses in forest plots: where these estimates differ we will consider possible reasons for the heterogeneity, such as risk of bias indicators and other potential effect modifiers. Between-study heterogeneity will be quantified using the between-study variance (τ^2) and the I^2 statistic.

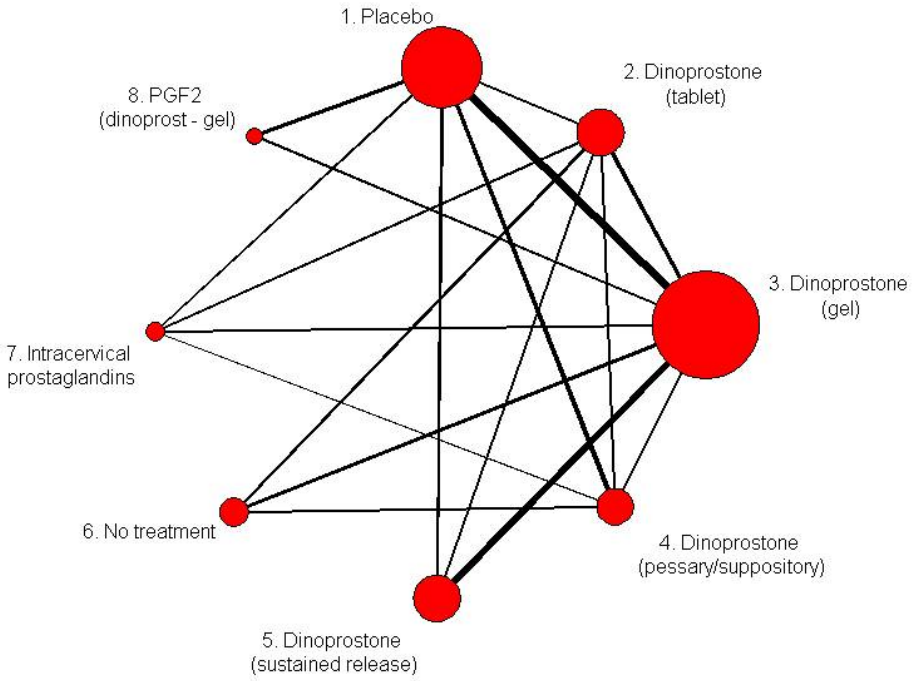
For each separate outcome, we will also construct a NMA [40] which will be compared to the pair-wise results. NMA will enable estimation of relative intervention effect estimates for every pair-wise contrast in a connected evidence network, even if they have not been compared directly in an RCT. It also enables the ranking of treatments according to the probability that each is the best, or worst, for a given outcome. All analyses will be performed within a Bayesian framework, using freely-available WinBUGS software (version 1.4.3).

A prerequisite for NMA is that the network of treatment comparisons is connected. A preliminary network diagram constructed using the data from the scoping exercise is shown in the figure 2 below, and demonstrates the way the network is connected for the outcome caesarean section in RCTs of vaginal dinoprostone. The links

in the network will vary between outcomes: if parts of the network are unconnected we will perform the analysis on each sub-network that is connected.

Figure 2.

Network diagram for vaginal dinoprostone for the outcome caesarean section



The width of the lines is proportional to the number of trials making that comparison, and the size of the circles corresponds to the number of trials.

We will assume homogeneous between-study variability across studies, and will report the estimated value of τ (the standard deviation of underlying effects across studies). We will also report the effective number of parameters, P_D, [41] which increases with the degree of heterogeneity in random effect models, and so also reflects the extent of heterogeneity.

Goodness of fit (of the model to the observed data) will be assessed by calculating the posterior mean residual deviance.[43] This is defined as the difference between the deviance for the fitted model and the saturated model, where the deviance measures the fit of the model using the likelihood function. The Deviance Information Criterion (DIC),[41] which is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters P_D, will be used as a basis for model comparison. The DIC penalises the posterior mean

residual deviance (a measure of model fit) by the effective number of parameters in the model (as measure of complexity) and can, therefore, be viewed as a trade-off between the fit and complexity of the model.

Validity of a NMA depends on the assumption that there is no effect modification of the pair-wise intervention effects or, that the prevalence of effect modifiers is similar in the different studies. This key assumption has been referred to variously as transitivity, similarity and consistency).[42] A clinical and epidemiological judgement of the plausibility of this assumption requires assessment of the inclusion/exclusion criteria of every trial in the network, to assess whether the patients, trial protocols, doses, administration etc. are similar in ways that might modify treatment effect. We will compile a table of important trial and patient characteristics and visually inspect the 'similarity' of factors we consider likely to modify treatment effect.

Evidence of inconsistency can be considered an additional layer of heterogeneity that occurs in networks of evidence when there is a discrepancy between a direct and indirect estimate of treatment effect, i.e. when the consistency assumption described above is violated. Therefore, inconsistency is a property of 'closed loops' of evidence. We will visually inspect the network diagram to identify the extent of potential inconsistency (the number of loops) and use model fit and selection statistics to informally assess whether it is evident. If inconsistency is suspected, we will explore it formally using a "node-splitting" approach.[43]

For the individual dichotomous outcomes we will assume binomial likelihood with the logit link function.[44] If there is differential follow-up times in the included studies, we will use the complementary log-log link which assumes a constant hazard of the outcome over time. [44] We will fit a hierarchical model with individual treatments nested within treatment classes so that we can look at variability in treatment effects within and between treatment classes. [45]

We will use subgroup and meta-regression analyses to examine the extent to which study characteristics explain between-study heterogeneity, if present. We aim to assess the evidence that treatment effects vary according to key participant characteristics: such as reason for induction, parity, previous caesarean section and whether or not membranes are intact at the commencement of induction. Other potential covariates identified by the systematic review will also be considered. We will also stratify analyses according to the summary assessment of risk of bias for each outcome.

HEALTH ECONOMIC MODELLING

We will build a health economic decision model to address the question: which is the most cost-effective method (including timing, dose, and mode of administration) for the induction of labour in different patient subgroups (reason for induction, parity, previous caesarean, ripe/unripe cervix, intact/ruptured membranes). The model structure will be informed by a systematic review of previous economic models that address this or related questions. Data inputs for efficacy by subgroup will be informed by the NMA, and cost/resource/utility inputs will be informed by data sources identified in previous models and also from the systematic review results. We will develop a Markov model to represent costs and utilities over time. A similar model was used in the NICE Guidelines (2008)[46] to explore the timing of induction – however, the method of induction and patient subgroups were not included in that model. We will present results as incremental cost-effectiveness ratios,

expected net benefit and produce cost-effectiveness acceptability curves. We will also calculate the expected value of perfect information in order to assess the potential value of conducting further research. We will calculate the expected value of partial perfect information for various subsets of parameters in the economic model and, if further research appears warranted, the expected value of sample information to identify the value of running new studies of different possible designs, in order to establish the optimal design.

There may be very little evidence to inform some of the parameters. In this case we will discuss with clinical experts their opinion on minimum and maximum values for such parameters. We will then take two approaches: (a) assign "flat" distributions between these limits in a probabilistic sensitivity analysis and (b) perform threshold analyses to identify values of the parameters where the optimal strategy may change."

DISSEMINATION AND PROJECT OUTPUTS

We propose to disseminate findings in a number of ways. We will register our research protocol with Prospero (http://www.crd.york.ac.uk/prospero/). We will produce a report describing our methods and setting out the relative effects, safety and cost-effectiveness of each method used for the induction of labour to identify which methods work best, to be published as an HTA monograph and also a series of articles in peer reviewed journals. There will be a Plain Language Summary for lay people and the public. We will disseminate findings via local, national and international meetings and conferences. In addition to the findings of the analysis we also aim to publish details of the methodological process in appropriate journals as this approach to evidence synthesis is relatively new and still developing. We believe women will be particularly interested in the findings of this research, as induction of labour a topic often discussed by women. We will liaise with the National Childbirth Trust (NCT), the Association for Improvements in Maternity Services (AIMS) and websites relating to Pregnancy and Childbirth to disseminate the findings (e.g. Baby Centre, Netmums and Mumsnet) with the aim to disseminate through their channels. With NCT, we will discuss writing articles for their publications, and plan to target antenatal teachers for dissemination through antenatal classes. We will also ask Maternity Services Liaison Committees (MSLC) representatives to disseminate the information to MSLC meetings with the aim of getting information to antenatal clinics. Use of social media will be utilised to disseminate key findings.

We will work with other groups such as COMET (Core outcome measures in effectiveness trials), also based in Liverpool, to ensure the widespread dissemination and adoption of relevant outcomes. It is important that our findings are disseminated in order to help inform the development of core outcome sets, so that outcomes in trials of induction of labour interventions may be more easily compared, contrasted and combined.

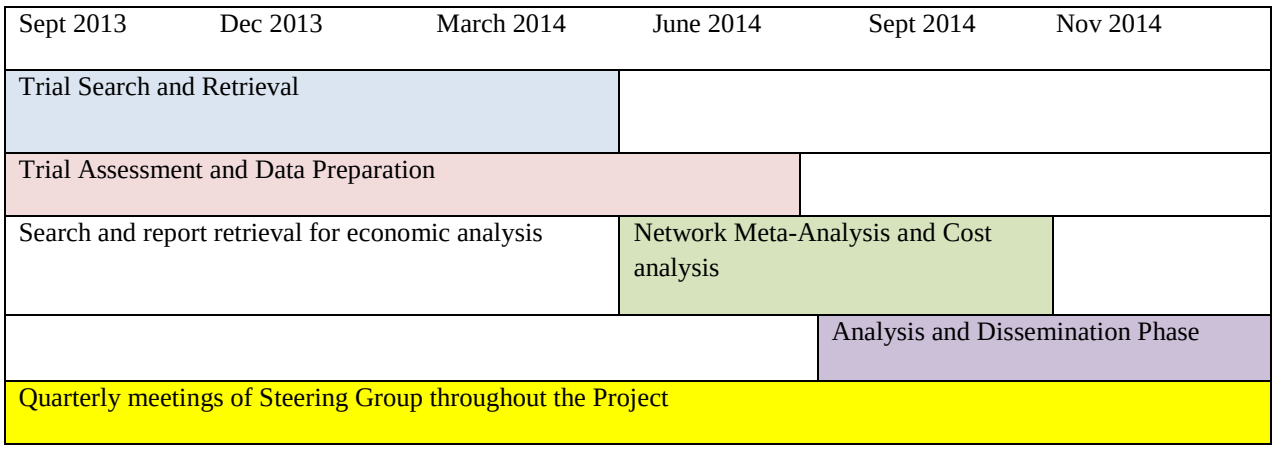
PROJECT MANAGEMENT AND TIMETABLE

We propose a 15 month project beginning in September 2013. We have set out main project phases in the table below. We anticipate quarterly meetings of the Project Steering Group.

Key Dates:

1. September 1st 2013. Project commences in Liverpool. Named Research Associate takes up FT appointment. Search and data preparation activities begin.
2. December 1st 2013. Project commences in Bristol. Researcher takes up FT appointment and preparation for NMA and cost analysis begins.

3. July 1st 2014. Data available and NMA completed for all outcomes.
4. September 1st 2014. Cost modelling and analysis completed.



PROJECT MANAGEMENT

Day to day management of the Project will be the responsibility of TD, the named Research Associate; general supervision will be provided by ZA in Liverpool and by NW in Bristol. We plan quarterly meetings of the project team to review progress. In view of the developing methodology in conducting NMA and the complexity of some of the analysis, we have also requested support for other project applicants. Throughout the period of the proposed work project staff are likely to draw on the experience and expertise of the team.

Project Steering Group:

Oversight of the project will be provided by a Steering Group which will meet quarterly. Final membership has not been confirmed but we envisage the Group will include a representative of the National Childbirth Trust, NICE, Royal college of Midwives (RCM) and Royal College of Obstetricians and Gynaecologists (RCOG).

INVOLVING CONSUMERS AND NHS STAFF

The Cochrane Pregnancy and Childbirth Group (CPCG) has an active consumer panel (CP) established in 1998 and members comment on all reviews as part of the peer-review process. The PCG has a Consumer Editor who is a collaborator on this research project and has contributed to drafting the application. Induction of labour is known to be of great interest to pregnant women, in particular, women are interested in self administered ways of initiating labour and so these topics are included in the proposed work. We anticipate that women will wish to actively contribute to this project. For the development of a common protocol for Cochrane reviews on methods of induction of labour and for subsequent reviews, 22 consumers from the PCG consumer panel contributed comments.

The PCG Consumer Editor will be on the project steering group. She will coordinate the involvement of members of the PCG CP, NCT and AIMS who are interested in participating. Members of these groups will be

asked for comments to inform steering group meetings e.g. on whether all relevant outcomes are included, on the interpretation of the findings, the papers to be published and on most appropriate ways of disseminating the findings to women and the wider NHS.

Women will be interested in the findings of this research, as induction of labour is a topic often discussed by pregnant women. We will target midwifery journals as midwives provide antenatal care to women. We will liaise with the National Childbirth Trust (NCT), the Association for Improvements in Maternity Services (AIMS) and websites relating to Pregnancy and Childbirth to disseminate the findings (e.g. Baby Centre, Netmums and Mumsnet) with the aim to disseminate through their channels. With NCT, we will discuss writing articles for their publications, and plan to target antenatal teachers for dissemination through antenatal classes. We will also ask Maternity Services Liaison Committees (MSLC) representatives to disseminate the information to MSLC meetings with the aim of getting information to antenatal clinics. Use of social media will be utilised to disseminate key findings.

The experience of consumers contributing to the work of PCG was evaluated and demonstrated additional value in terms of clarifying the language; contributing to the discussions on the rationale for the reviews; suggesting outcomes important to women and suggesting interventions for future research and review topics. Consumers in this project will be actively supported by the Consumer Editor to perform their role.

RESEARCH TEAM EXPERTISE

The multidisciplinary team has a wide range of expertise in relevant clinical and HTA disciplines, including systematic review and evidence synthesis, network meta-analysis and biostatistics, cost-effectiveness analysis and clinical and obstetric practice.

ZA is a clinically active obstetrician and joint co-ordinating editor of the Cochrane PCG with 20 years of experience in research synthesis. He is the author of published Cochrane reviews on induction of labour. He was also member of the NICE guideline development group for induction of labour (2008).

DC is a research fellow in population health science and holds an MRC post-doctoral fellowship developing methodology for network meta-analysis. She has experience in applied network meta-analysis in a wide range of applications and is co-convenor of the Cochrane Comparing Multiple Interventions Methods Group.

SD is a research fellow in biostatistics and Scientific Coordinator of the NICE Clinical Guidelines Technical Support Unit based in Bristol. She has extensive experience of network meta-analysis in a wide range of applications and has developed methods for modelling bias and checking for consistency in network meta-analysis. She is Statistical editor of the Cochrane Menstrual Disorders and Sub-fertility Group.

NW is a senior lecturer in biostatistics and holds an MRC methodology fellowship on methods for value of information (VOI) analyses. She is co-lead of the Evidence Synthesis and VOI theme of the ConDuCT Hub for

Trials Methodology Research. She has a wide experience of methods for evidence synthesis (including network meta-analysis) to inform cost-effectiveness models and cost-effectiveness modelling.

TD is an experienced health services researcher and has considerable experience in evidence synthesis. She is an author on more than 20 published Cochrane intervention reviews, on a generic protocol for induction of labour reviews and on an overview of reviews.

LJ is a researcher with over 10 years experience of evidence synthesis. She is an author on 6 published Cochrane intervention reviews, one methodology review, a generic protocol for overviews and an overview of reviews of pain management for women in labour.

We have the support of an Information Specialist with expertise in developing optimal search strategies for identifying trials for systematic reviews in the area of pregnancy and childbirth.

We also have the support of a Consumer member of the National Childbirth Trust (NCT), with 24 years of experience teaching NCT antenatal classes and Consumer Editor of the Cochrane Pregnancy and Childbirth Group with over 10 years experience of co-ordinating consumer input in Cochrane systematic reviews.

JUSTIFICATION OF COSTS

An experienced research associate will be required for 15 months to co-ordinate the project and to have day to management responsibility. We have requested support for a named researcher (TD) who is already working in the Cochrane PCG and would be available to take up this full-time post. The research associate will assess trial eligibility, assess risk of bias, extract relevant outcome data and prepare the dataset for the NMA. She will prepare and populate the network diagram. The research associate will also co-ordinate the production of outputs from the project and will be responsible for day-to-day management.

We have requested support for an information specialist (20% FTE) who will be involved in identifying and retrieving relevant trial reports for the NMA during the first 9 months of the project.

A health economist (research fellow) will be required for the duration of the project. We aim to appoint an experienced health economist at Grade K on the academic and research staff scale. The health economist will undertake reviewing of the literature to parameterise the economic model. They will also develop the structure of the cost-effectiveness model and coding of it. They will carry out the cost-effectiveness analyses and contribute to the writing of the report and journal papers.

Supervision will be provided by ZA(0.05 for the duration of the project) and LJ (0.05 for the duration of the project). LJ will be involved in data checking and contributing to project outputs. DMC will supervise the systematic review methodology required for network meta-analyses. SD will supervise the statistical analyses. NJW (10% for the duration of the project) will supervise the economic modelling and provide overall management for the Bristol team.

We have requested support for consumer input into the project and for staff to attend face to face meetings.

We have included costs for two computers (one in Bristol and one in Liverpool) and for essential project related consumables (e.g. library costs for retrieval of reports not readily available through other means).

INTELLECTUAL PROPERTY

While the outputs from the project are not likely to have commercial value, however, there is considerable potential for patient benefit. We will ensure that the findings of the network meta-analysis along with the economic analysis will be made available to guideline authors so that they can be used to underpin guideline development and recommendations on labour induction methods. NICE guidelines on labour induction are currently being updated and the lead applicant (ZA) is a member of the guideline panel. We will also make findings available through our network of contacts at the World Health Organisation (WHO) so that there is potential for findings to be incorporated into updates of international guidelines. The involvement of consumer organisations in the project and our plans for dissemination to patient networks also offers potential for patient benefit as a summary of the relative effects and safety of all available methods of labour induction will inform patient choice.

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