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Study Protocol: Quantitative Fibronectin to help Decision-making in women with Symptoms of Preterm Labour (QUIDS) Part One- Individual Patient Data Meta-analysis and Health Economic Analysis

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Study Protocol: Quantitative Fibronectin to help Decision-making in women with Symptoms of Preterm Labour (QUIDS) Part One- Individual Patient Data Meta-analysis and Health Economic Analysis

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ABSTRACT

Introduction: The aim of the QUIDS study is to develop a decision support tool for the management of women with symptoms and signs of preterm labour, based on a validated prognostic model using quantitative fetal Fibronectin (fFN) concentration, in combination with clinical risk factors.

Methods and analysis: The study will evaluate the Rapid fFN 10Q System (Hologic, Malborough, MA) which quantifies fFN in a vaginal swab. In part one of the study we will develop and internally validate a prognostic model using an individual participant data (IPD) meta-analysis of existing studies containing women with symptoms of preterm labour alongside fFN measurements and pregnancy outcome. An economic analysis will be undertaken to assess potential cost-effectiveness of the qfFN prognostic model. The primary endpoint will be the ability of the prognostic model to rule out spontaneous preterm birth within seven days. Six eligible studies were identified by systematic review of the literature and five agreed to provide their IPD (n= 5 studies, 1,783 women and 139 events of preterm delivery within 7 days of testing).

Ethics and dissemination: The study is funded by the National Institute of Healthcare Research Health Technology Assessment (HTA 14/32/01). It has been approved by the West of Scotland Research Ethics Committee (16/WS/0068).

Registration details: This IPD Meta-analysis is registered with PROSPERO (PROSPERO 2015:CRD42015027590).

Version: Protocol Version 2, Date 1st November 2016

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- Development of prognostic model and for validation in a separate prospective cohort study

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- Health Economic Analysis to determine cost effectiveness from NHS perspective

Limitations

- Not a randomized control trial to test effectiveness of the model on improved patient outcomes

HOW PATIENTS ARE INVOLVED IN THIS STUDY

Patient representatives were consulted during the protocol development and have been invited to join the Project Management Group and the Trial Steering Committee. Prior to commencing QUIDS, we performed a qualitative study to determine the decisional needs of pregnant women with signs and symptoms of preterm labour, their partners and their caregivers. This is described in the separate protocol "QUIDS Qualitative" (Supplementary Material). The end product of QUIDS will be a decision support aid to help clinicians, women and their partners decide on management of threatened preterm labour, based on the results of the quantitative fFN. In QUIDS Qualitative women and clinicians indicated that they would prefer this to be on web based or mobile app based format, presenting the risk of preterm birth within seven days of testing.

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INTRODUCTION

The overall aim of the QUIDS study is to develop a decision support tool for the management of women with symptoms and signs of preterm labour, based on a validated prognostic model using quantitative fFN testing. The study has been conceptually divided into two parts. In this, the protocol for QUIDS Part One, we detail the protocol for development and internal validation of the prognostic model. In the protocol for QUIDS Part Two we detail the protocol for the prospective cohort for external validation of the prognostic model and acceptability testing.[1]

Preterm delivery (before 37 weeks) occurs in 7.1% of pregnancies in the UK (>50,000 deliveries per annum), with the majority the result of preterm labour.[2,3] It remains the leading cause of neonatal morbidity and mortality, but timely interventions, such as antenatal steroids to promote lung maturity, magnesium sulphate for neuroprotection, and delivery in a unit with appropriate neonatal care facilities can improve neonatal outcome. Establishing a diagnosis of preterm labour is, however, difficult. Clinical signs are non-specific and false positive diagnoses are common, with up to 80% of women with signs and symptoms of preterm labour remaining pregnant after seven days. [4, 5] Such diagnostic uncertainty means a large proportion of women with symptoms of preterm labour are treated unnecessarily to ensure benefits to the small proportion of babies that do actually do deliver preterm.

It is understandable that both clinicians and pregnant women may prefer a 'treat-all' approach in women with symptoms of preterm labour, particularly in a setting remote from an appropriate neonatal unit; and in order to ensure steroid prophylaxis in case preterm delivery occurs. However, unnecessary interventions result in both a substantial economic burden to health services and in potential adverse maternal and neonatal events. Hospital admission and inter-hospital transfer have

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considerable cost implications and can be associated with enormous problems for women and their families due to physical separation and emotional stress.[6,7] Neonatal cots become 'blocked' in order to accept a preterm baby just in case delivery occurs; negatively impacting the efficiency of already stretched neonatal units and networks. This frequently has knock-on effects to other women and babies, who may need transfer to another unit due to lack of cot availability despite an empty, but 'blocked', cot. It also may increase the number of *ex utero* transfers, which are associated with poorer outcomes than *in utero* transfers.[8] If preterm labour has been wrongly diagnosed, and delivery does not occur, steroids may also have adverse long-term consequences for the baby, especially if multiple courses are given.[9] Tocolytic therapy, even when appropriate can have serious side effects for both mother and baby.[10] Lastly, uncertainty of outcome may contribute to the high anxiety scores seen in women with threatened preterm labour and their partners.[11]

Diagnostic tests for preterm labour are available and used in many units in the UK. Fetal Fibronectin (fFN; Hologic, Marlborough, MA, USA) is a biochemical marker of preterm labour that can be measured in samples of cervicovaginal secretions collected at a speculum examination. It has potential to help improve diagnosis of impending preterm delivery.[12] Other biochemical tests which are available include Actim Partus (Medixbiochemica, Espoo, Finland)) which measures phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1), and Partosure (Parsagen Diagnostics, Boston, MA, USA) which measures placental alpha microglobulin-1 (PAMG-1). An alternative approach (which can be combined with fFN) is to measure the cervical length using transvaginal ultrasound, as the longer the cervix is, the less likely a preterm delivery.[12]

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As part of an Health Technology Assessment (HTA) report Honest et al found that a qualitative fFN test (giving a positive or negative result based on a single threshold of 50ng/ml) was potentially useful in the prediction of preterm delivery <34 weeks gestation, with its main benefit relating to its high negative predictive value i.e. its ability to rule out impending delivery.[12] A more recent HTA-funded review found that qualitative fFN testing has moderate accuracy for predicting preterm birth with overall sensitivity and specificity estimates of 76.7% and 82.7% for delivery within 7-10 days.[13] These estimates suggest that qualitative testing on its own would not have the sensitivity to rule out preterm delivery adequately, although in systematic review of clinical trials, no increase in neonatal morbidity or mortality was seen in association with false negative fFN results.[13] The authors concluded that this observation is likely to relate to the multifactorial nature of assessment of the risk of preterm delivery, where, in practice, fFN is just one component of the clinical assessment on which management decisions are based.[13]

Both HTA reviews described above examined the performance of a qualitative fFN test, which provided a positive or negative result on the basis of a single threshold of 50ng/ml. Recently, this test has been replaced in the UK with the Rapid fFN 10Q System, which provides a concentration of fFN within 10 minutes, and thus may be a more useful predictor of preterm delivery (quantitative fFN). We surveyed current practice in UK maternity units (response rate 66% [137/207]; Mar-July 2014).[14] 135/137 units (98.5%) use some sort of diagnostic test of preterm labour. The most common test is fFN (84/137 units; 61.3%). fFN is now only available with a quantitative analyser in the UK, but there is no consensus as to which women to use the test in, or how to interpret the results. Developing and evaluating a decision support for qfFN is thus likely to improve decision making, even if qfFN is already available in clinical practice. Evidence about the potential value of the new

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quantitative fFN is required, along with guidance about how to interpret results. The QUIDS study will address this evidence gap.

METHODS AND ANALYSIS

Aims and Methodologies

The aim of the QUIDS study is to develop a decision support tool for the management of women with symptoms and signs of preterm labour, based on a validated prognostic model using quantitative fFN testing.

The study protocol has been divided into two parts (see flow chart Figure 1). The protocols for Parts One and Two are reported in separate manuscripts.

Part 1: Development and Internal Validation of Prognostic Model

i) Individual Participant Data (IPD) meta-analysis to develop a prognostic model using quantitative fFN and other risk (prognostic) factors and to evaluate the added value of quantitative fFN toward this prognostic model performance. A prognostic model will be developed and internally validated[15,16] based on a meta-analysis of IPD from existing prospective cohort studies where quantitative fFN results and pregnancy outcome details are available. The primary outcome will be prediction will be delivery within 7 days, although other endpoints will be included if recommended by focus groups.

(ii) Economic Analysis: To provide an economic rationale for the prognostic model and analyze its cost-effectiveness from the perspective of the NHS to provide an economic rationale for the prognostic model and the risk factors included in it.

Part 2: Validation And Refinement Of Prognostic Model Involves a prospective cohort study and acceptability testing, with external validation, (and, if necessary, refinement) of the prognostic model, and update of health economic model.[1]

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Endpoints

The primary endpoint is spontaneous preterm delivery within seven days of qfFN test, in women tested at less than 36 weeks gestation. This is both an important endpoint for women and caregivers (determined in QUIDS Qualitative study – a preceding qualitative study to identify the decisional needs of women, their partners and clinicians; Supplementary Material) as well as a clinically important endpoint. Antenatal steroids (which significantly reduce morbidity and mortality in preterm babies[17]) are most effective if delivery occurs within seven days of administration. As repeated doses of antenatal steroids may be harmful, it is crucial to ensure steroids are timed correctly.

A secondary endpoint suggested by the preceding QUIDS Qualitative Study consultation (Supplementary Material), was delivery within 48 hours of qfFN test. This analysis will be performed if feasible to do so within the constraints of the data available for model development.

Health technologies being assessed

The study will evaluate the Rapid fFN 10Q System (Hologic), which provides a concentration of fFN (ng/ml or INVALID) in a vaginal swab sample. Further details about the system and recommended sampling technique are provided in the QUIDS Protocol Part Two. [1]

Target population

The target population is pregnant women attending hospital with signs and symptoms of preterm labour.

Development Of Prognostic Model

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Individual Patient Data Meta-Analysis

The proposed IPD-Meta-analysis was registered on PROSPERO (2015:CRD42015027590). Our IPD meta-analytical approach will follow existing guidelines, and our output will comply with the TRIPOD statement (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement).[18]

Inclusion Criteria

We prespecified inclusion of prospective cohort studies or RCTs of women with signs and symptom of preterm labour (as defined by investigators) that include quantitative fFN results determined by 10Q rapid fFN analyzer system and pregnancy outcome data; and the Principal Investigator of which has agreed to collaborate and provide data.

Exclusion criteria

We will exclude studies where fFN concentration was measured by ELISA and studies where IPD is not available for meta-analysis

Search Strategy

When applying for funding for this study (April 2014) we performed a literature search for completed and ongoing cohort studies of quantitative fFN using search terms for quantitative fetal/foetal fibronectin and preterm birth, including databases (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA)) and clinical trial registries (Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.Gov) general search engines (such as Google: https://www.google.co.uk) and systematic reviews. We also consulted preterm birth

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researchers and networks (RCOG CSG; BMFMS, PREBIC) and the manufacturers of quantitative fFN, (Hologic) to help ensure capture of all relevant studies.

Study manuscripts and/or protocols were screened by two researchers. We identified a total of 10 studies of quantitative fFN that were potentially eligible. Four early datasets (in three manuscripts) used ELISA to determine the concentration of fFN and were excluded as the different method of analysis and earlier period of study would increase heterogeneity.[5,19,20] Therefore, six studies fulfilled the eligibility criteria (see Table 1).

Establishment of the quantitative fFN IPD Collaboration

We contacted the principal investigators (PIs) of the six eligible studies of qfFN invited them to participate (see Table 1). Five of these agreed to provide their IPD as evidenced by their involvement as co-applicants on the funding application and/or co-authorship of this protocol (Mol, van Baaren, Khalil, Shennan, David). The PI of the 6th study (Elovitz) indicated IPD may be available after publication of her study.

The five included studies (Table 1) are European studies of women with symptoms of preterm labour, comprising 1,783 women and 139 events of preterm delivery within 7 days of testing. They are from consultant led maternity units in the UK (three studies) and Europe (two studies). All women in the included trials provided informed consent for participation in clinical trials, and for their IPD to be used in subsequent analyses.

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	PI	Setting	N	Events	Dates	Inclusion	Primary Outcome
Studies with data available							
EQUIPP [21,22]	Prof A Shennan	5 UK centres	452	14	2010-2012	22-35 weeks with symptoms of preterm labour	Delivery <34 weeks gestation
EUFIS* [23]	Prof BW Mol	10 European Hospitals	452	48	2012-2014	24-34 weeks with preterm contractions and intact membranes	Delivery within 7 days of test
APOSTEL I* [24]	van Baaren	10 Dutch Hospitals	528	70	2009 -2012	24-34 weeks with preterm contractions and intact membranes	Days to delivery truncated at 7 days
QFCAPS (unpublished)	Dr A Khalil	London teaching hospital	86	2	2012-2014	24-34 weeks with symptoms of preterm labour Singletons only	Delivery within 7 days of test
UCLH/Whit (unpublished)	Dr A David	2 UK centres	262	5	2009-2010	22-35 weeks with symptoms of preterm labour	Delivery within 7 days of test
	TOTALS	***4 studies***	***1,783***	***139***			
Studies where data may be available in future							
STOP study (http://clinicaltrials.gov/show/NCT01868308)	Prof M Elovitz	USA teaching hospital	700	NK	2011-2015	22 -34 weeks Symptomatic women with singleton pregnancy	Delivery before 37 weeks

Table 1: Details of studies contributing data to IPD meta-analysis.

*Study unpublished at time of search in April 2014; manuscript now published

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Study Quality Assessment and Data Collection

IPD will be stored in a bespoke database on a secure server at the University of Edinburgh. PIs will be asked to provide de-identified data, and consider all recorded variables (even if not reported publications). We will assess study quality according to QUADAS-2[25] QUIPS[26] and CHARMS[27] guidelines.

Sample Size Considerations

The size of the IPD meta-analysis is limited by the number of studies with data available (Table 1). In model development the number of covariates that can be considered is limited by the number of events, with guidance suggesting at least ten events required for each covariate.[28,29] In our IPD meta-analysis data we have 139 events (preterm labour within 7 days of testing) and therefore deemed that it was sensible to evaluate quantitative fFN and up to 13 other factors (covariates) for potential inclusion in our model.

Data Items

The following factors which are thought to influence risk of spontaneous preterm birth, will be requested and considered for inclusion as covariates in the prognostic model: quantitative fFN concentration, previous spontaneous preterm labour, gestation at fFN test, age, ethnicity, BMI, smoking, deprivation index, number of uterine contractions in set time period, cervical dilatation, vaginal bleeding, previous cervical treatment for cervical intraepithelial neoplasia, cervical length (measured by transvaginal cervical length), singleton/multiple pregnancy, tocolysis and fetal sex. Up to 13 of these will be prespecified for inclusion, based on available data (we will only use variables which are available in each study), and ranking for likely clinical relevance as agreed by consensus of the project management team.

Data Cleaning

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Prior to analysis data will be checked for outliers and missing data will be identified. Descriptive statistics will be performed to summarise data. Problems identified will be discussed with the PI of the original study, and amended as indicated by consensus discussion.

Data Analysis and Prognostic Model Development

Multivariable logistic regression modelling will be the primary method of analysis. The primary endpoint for the prognostic model will be delivery within seven days. Another endpoint found to be important in focus group consultations performed in QUIDS Qualitative (Supplementary Material) included delivery within 48 hours, and we will use this as a secondary endpoint if feasible (i.e. if sufficient number of cases with delivery within 48 hours). We will develop an initial model with quantitative fFN concentration, and then consider a model with other predefined clinical predictor variables (see *Data Items*, above).

Tocolysis (which may delay onset of labour, although likely not beyond 48 hours) will be included as a categorical variable (administered/not administered). We will explore treatment effect by sensitivity analysis with and without the assumption that tocolysis could delay delivery within 48 hours by a maximum odds ratio of 5.39, 95% credible interval 2.14 to 12.34, based on data in Haas et al.[30].

As the outcome is binary, a logistic regression modelling framework will be used to develop the model. A multi-level structure will be used to account for clustering of patients within studies, and heterogeneity of the effects of included factors (hereafter called 'predictors') will be accounted for using random-effects, with between-study heterogeneity quantified using the estimated variance ('tau-squared') and the I^2 statistic. A separate intercept term per study will be included in the model, to account for the clustering and also guage how predictions may require tailoring to different populations. Predictors with large heterogeneity in the prognostic effect across

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studies may be removed to ensure summary Beta terms in the model are meaningful (accurate) for individual populations.[16]

In the primary analysis, we will use data from the first recorded attendance with signs and symptoms of preterm labour to determine the relationship between that individual episode and outcome. Data from subsequent attendances will be analysed subsequently, and may be included in an appropriate model. As a parsiminous model is sought, to reduce the factors included in the model that may otherwise delay its use, we will use backward stepwise selection based on an information criterion (e.g. Akaike's information criterion $p<0.15$) to identify a parsimonious set of factors to be included in the model; hereafter these are referred to as included 'predictors'. Further, an approach of adding specialist tests, such as cervical length, only after considering simpler clinical assessment will be used, to maximise the utility of the model by ensuring that extra tests with their additional costs are only be included if they add to the predictive power.

Linearity between continuous variables and outcome will be assessed using cubic spline plots and data will transformed where appropriate before inclusion in multivariable analysis (e.g. using fractional polynomial methods). Missing data will be assessed to determine whether missing at random is appropriate, and if so, multiple imputation of observed participant characteristics will be used, with missing data imputed within each original study separately, before the meta-analysis. The results of these analyses will be compared with a complete case analysis.

Assessing Apparent Model Performance

The apparent performance of the model will be assessed by its overall fit, and the observed discrimination and calibration in the IPD used to develop the modle. Overall fit of the models will be expressed with Nagelkerke R^2. The ability of the models to discriminate between women with and without spontaneous preterm birth will be

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determined by the area under the receiver operating characteristics curve (AUC), also known as the *C* statistic. Agreement between predicted and observed proportions of women with spontaneous preterm birth will be visualized using a calibration plot, and measured using calibration slope and calibration-in-the-large.

Internal validation: assessing Optimism In Model Performance

Apparent performance is likely to be optimistic, as it is examined in the same data used for model development. Therefore internal validation will also be undertaken using a non-parametric bootstrap re-sampling technique in which each modelling step is repeated in each bootstrap sample, to obtain a new model in each bootstrap sample, and then its apparent performance (AUC and calibration slope) in the bootstrap sample is compared to its performance in the original dataset. The 'optimism' is the mean difference (across all bootstrap samples) between the apparent value in the bootstrap sample and the observed value in the original dataset. This optimism estimate is then subtracted from the original model's apparent performance, to give an optimism-adjusted estimate of each measure of performance for the original model (e.g. R^2, *C* statistic, Calibration slope).

Production Of Final Model From IPD Meta-Analysis Via Uniform Shrinkage

The optimism-adjusted calibration slope will be used as a uniform shrinkage factor, to adjust the parameter estimates (log odds ratios) of the original model. The beta coefficients in the original model will be multiplied by the shrinkage factor, and the study intercept terms re-estimated to ensure perfect overall calibration is maintained (across all studies and, ideally, in each study separately). This will thereby produce a final model containing the updated intercepts and the shrunken beta coefficients.[31] With multiple intercepts, a strategy (or strategies) will be developed amongst the study investigators for which intercept should be chosen for use when externally validating the model in a new population (e.g. choose intercept from study that most

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closely resembles the population of application); each strategy will be evaluated and compared in the cohort study external validation phase.

Added Value Of Quantitative fFN

The added value of quantitative fFN will be examined throughout the whole model process, in particular its improvement on discrimination, calibration and other meaningful factors (such as clinical decisions) using appropriate techniques (such as net reclassification improvement and decision analysis methods).

Subgroup analyses

Subgroup analysis will be performed for multiple pregnancy, women with a previous preterm labour, gestation and those with criteria that are suggested to indicate preterm labour (number of uterine contractions in a set time period and/or cervical change). This will allow us to do a subgroup-analysis in which we assess whether the predictive capacity of quantitative fFN is similar in all subgroups.

Health Economic Analysis

An early stage decision-analytic model will be built using evidence from current literature and from the IPD meta-analysis to explore the potential cost-effectiveness of different prognostic models including quantitative fFN.

A literature review will be undertaken to inform model design and identify additional model parameters with searches of Medline, Embase, Cochrane Library and the Paediatric Economic Database Evaluation for economic analyses including the use of fFN testing in woman with threatened preterm labour. Any evidence on resource use (test administration, treatments for preterm labour, hospital stay, hospital transfers, etc), quality of life and diagnostic outcome data from the IPD meta-analysis will be synthesized with the wider evidence based on current practice for women attending hospital with signs and symptoms of preterm labour. The economic analysis will be undertaken from the perspective of the UK NHS adhering to good practice guidelines

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and the NICE reference case.[32] A decision tree will be developed to model the clinical pathway. The model will be used to explore potential cost effectiveness of the prognostic model at different thresholds on the Receiver Operator Curve, providing an economic rationale for the chosen prognostic model.

ETHICS AND DISSEMINATION

Trial Management And Oversight Arrangements

Project Management Group

The trial will be coordinated by a Project Management Group (PMG), consisting of the grant holders (Chief Investigator and Co-applicants), the trial manager, representatives from the Study Office and CHaRT (the supporting CTU), plus service user representatives (PAG). The PMG will meet approximately every four months by teleconference or face to face.

Trial Steering Committee and Data Monitoring Committee

A combined Trial Steering Committee and Data Monitoring Committee (TSC/DMC) will oversee the conduct and progress of the study. The terms of reference of the Committee will be developed separately. Members of the TSC/DMC will consist of experts and two patient representatives.

Good Clinical Practice

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP). A favorable ethical opinion has been obtained from the appropriate REC (reference 16/WS/0068) and local R&D approval will be obtained prior to commencement of the study at each site.

Dissemination

On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared. Results will be communicated to the academic

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community via the scientific literature, attendance at conferences and invited presentations. The TRIPOD reporting guidelines will be adhered to.[18] Summaries of results will also be made available to investigators for dissemination within clinics. Social media will be used to signpost publications and conference presentations and highlight important findings. Twitter and Facebook will be used to disseminate findings to professional organizations, charities, stakeholders and the public. Communication to the general public will further be facilitated by our close links with charities such as Tommy's [33].

PEER REVIEW

The study was extensively peer reviewed as part of the process of gaining grant funding from the NIHR HTA (14/32/01).

FUNDING

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CONTRIBUTIONS TO AUTHORSHIP

SJS, KB, RKM, JD, LJ, MC, AD, AK, AS, VHM, TL, KK, SHC, BM, RDR, JN and JEN developed the protocol. SJS, LW, RDR, KB, TL and JN drafted the protocol. RKM, JD, LJ, MC, AD, AK, AS, VHM, KK, SHC, BM and JEN reviewed and commented on the protocol.

COMPETING INTERESTS

SJS and JEN work at the University of Edinburgh, who received £1000 sponsorship from Hologic to support a meeting (The Society of Reproductive Investigation and

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MRC Centre for Reproductive Health Scientific Symposium on Targeting Inflammation to Improve Reproductive Health across the Lifecourse – August 2017).

AS has in the past (over last five years; not in the last three years) received funding for expenses related to advisory board and internal staff education from Hologic.

MC received sponsorship from Hologic to organise an educational teaching focusing on prediction of Preterm Birth at the 2017 annual meeting of the British Maternal and Fetal Medicine Society.

Hologic, the makers of fFN have provided analysers and technical support for their use to sites participating in the QUIDS prospective cohort study. They have no access to the data, or other involvement in the conduct, analysis, interpretation or decision to publish the results of the study.

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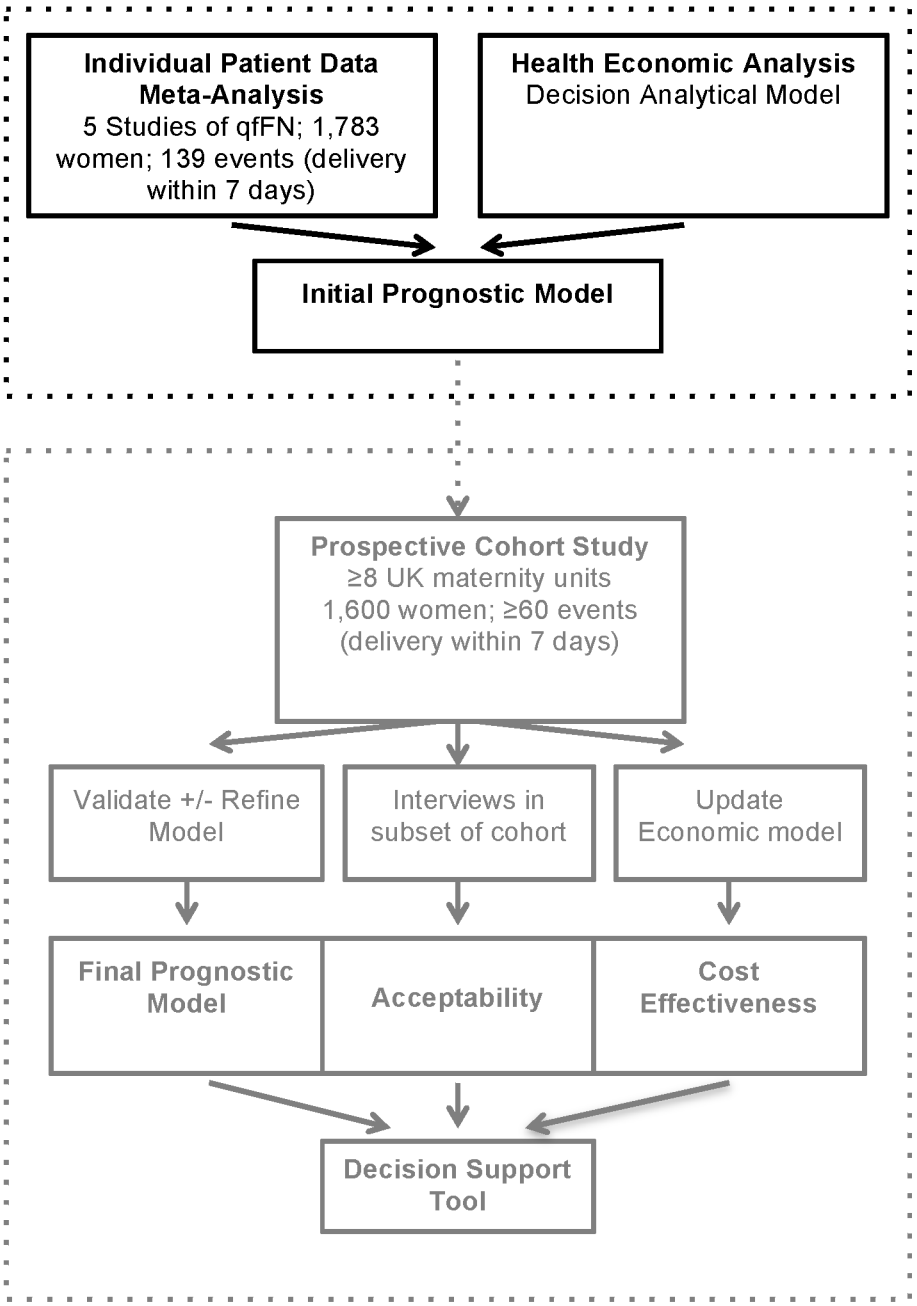
Figure 1


QUIDS Part 1
Individual Patient Data Meta-Analysis
5 Studies of qfFN; 1,783 women; 139 events (delivery within 7 days)
Health Economic Analysis
Decision Analytical Model
Initial Prognostic Model
QUIDS Part 2 [1]
Prospective Cohort Study
≥8 UK maternity units
1,600 women; ≥60 events
(delivery within 7 days)
Validate +/- Refine Model
Interviews in subset of cohort
Update Economic model
Final Prognostic Model
Acceptability
Cost Effectiveness
Decision Support Tool

QUIDS Qualitative

Quantitative Fibronectin to help Decision-making in women with Symptoms of Preterm Labour: determining decisional requirements

Protocol

(October 2015)

White H, O'Brien E, Hodgetts-Moreton V, Stock S, Lavender T

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Background

Preterm birth, defined as birth prior to 37 weeks gestation, occurs in 6-7% of pregnancies in Europe[1] and was recorded as 5.78% in England in 2013/14, equating to over 37,000 births.[2] Preterm birth is associated with a high risk of mortality, wide-ranging short- and long-term morbidities,[3,4] and significant economic costs to the NHS compared with birth at term.[5] Reducing the detrimental impact of preterm birth relies on the provision of timely and appropriate perinatal interventions. However, accurate prediction of preterm birth is challenging, even when the clinical symptoms are suggestive of preterm labour. In randomised trials approximately 80% of women diagnosed with preterm labour remained pregnant after 7 days.[6,7]

Interventions in preterm labour and preparations for preterm birth may include administration of corticosteroids to accelerate fetal lung maturation[8,9] and magnesium sulphate for fetal neuroprotection,[10] in utero transfer to a facility with appropriate maternity and neonatal services, and tocolysis to optimise time before birth to enable these.[11] Whilst such interventions can improve outcomes for mothers and babies who do experience preterm birth, they are not necessarily benign, especially for those in whom preterm birth does not occur.

The maximal beneficial impact of corticosteroids occurs with administration between 48 hours and seven days before birth, thus timing is especially important in optimising benefit for the neonate. For women who remain at risk of preterm birth after seven days of the initial dose, repeated doses reduce respiratory distress in the neonate[9] but have been found to be associated with a dose-dependent reduction in birthweight.[12,13] A five-year follow-up study of women who received repeated doses of antenatal corticosteroids due to risk of preterm birth found an increased risk of neurodevelopment impairment in infants born at term.[14] Therefore developing a strategy to establish the optimal time to give steroids is a research priority.

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Magnesium sulphate administration immediately prior to birth has been shown to reduce cerebral palsy,[10] but there is a risk of magnesium toxicity leading to respiratory depression in the mother and, theoretically, the neonate.[15]

Whilst there is no clear beneficial effect of tocolytics on the incidence or outcome of preterm birth,[16] their use is recommended if the days gained prior to preterm birth can be used appropriately, for example transfer to a suitable maternity unit or the administration of drugs to protect the neonate.[11] Tocolysis is linked with various maternal and neonatal complications,[17] hence the need for therapy targeted only for those at risk of preterm birth and close monitoring of the mother and fetus throughout.

Often, inpatient admission is recommended if preterm labour is suspected. Previous literature has highlighted the social isolation and support needs that women with high-risk pregnancies who are hospitalised experience.[18] In some cases, in-utero transfer is indicated to ensure that birth takes place in a specialist unit with appropriate neonatal care facilities. This policy has been shown to reduce mortality[19,20] and morbidity[21] in preterm neonates, especially those born very premature. Qualitative research has indicated that women generally acknowledge the potential benefit of in utero transfer to their baby and, hence, are willing to endure the inconvenience and upheaval that it entails.[22,23] However, the experience is associated with an emotional, social and financial burden on women and their families, especially for the substantial proportion of women who do not deliver prematurely following in utero transfer. When describing their experiences of in utero transfer, women expressed shock at the prospect of the transfer, feeling socially isolated, and having no control over the situation, in addition to the practical difficulties experienced particularly by women who already had children.[22,24,25] In a large survey of women who had experienced in utero transfer, over a quarter lamented the financial cost[24] particularly with respect to their partner's outlay for travel, food, accommodation, and phone bills, exacerbated with requiring time off work.[22] Furthermore, in utero transfer is costly to maternity services. Securing a maternal and neonatal bed

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in another unit is a time-consuming task that often falls to delivery suite midwives to arrange, whilst also continuing to provide care to the woman.[26] In a large observational study of all in utero transfers that took place in Scotland in a six-month period, nearly one third of all transfers were due to threatened preterm labour.[27] Under half of the women transferred from one consultant-led unit to another gave birth within 48 hours.[27] Such unnecessary transfers are costly to women, their families and maternity services. Qualitative research into women's experiences of preterm labour have highlighted the need for caregivers to create an environment where women are enabled to discuss their fears[28] and exert control over how they manage their preterm labour care.[25]

Accurate prediction of preterm birth could reduce the burdens and risks associated with unnecessary interventions, and enable women and their clinicians to make informed decisions regarding their care. Numerous diagnostic tests have been used in preterm labour, including biochemical tests of vaginal secretions and cervical length.[29] One such test is fetal fibronectin, a near-bedside test that provides a positive or negative result and has excellent negative predictive value.[30] Thus fetal fibronectin can identify which women will not benefit and may be put at risk by the interventions described previously, and reduce costs to maternity services.[31] Developments in fetal fibronectin testing have led to a quantitative test that provides a concentration of fetal fibronectin in vaginal secretions, giving women and clinicians more information on which to base their management decisions.[32]

Qualitative evidence has indicated that women feel a sense of increased responsibility to their babies and themselves during a high risk pregnancy, such as threatened preterm labour.[33] Women want to be involved in decision making about their care to different degrees and feel most satisfied when their caregiver supports them to make decisions in the way they felt most comfortable.[33]

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Previous literature on decision making and preterm birth has focussed on diagnostic tests[6,28–32,34] and the care of the preterm infant.[35,36] To date, there has been no investigation of what women, their partners and caregivers would like to know in order to make informed decisions about the care that is provided following the signs and symptoms of preterm labour.

Funding has been received from the National Institute for Health Research Health Technology Assessment Programme for a large, multicentre trial to develop a mobile application decision support tool for the management of women with symptoms and signs of preterm labour, based on a validated model using quantitative fetal fibronectin testing. This study is the precursor to that trial, with the aim of determining the decisional needs of pregnant women with the symptoms and signs of preterm labour, their families and caregivers, using a qualitative framework approach. The outcomes of this qualitative study will inform the development of the mobile application decision support tool, using the findings from an individual patient data meta-analysis. The tool will then be externally validated and refined in the multi-centre trial, QUIDS.

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Methods

A qualitative framework approach will be used, based on data collected from focus groups and semi-structured telephone interviews.

Setting

Focus groups will take place in three maternity units: Liverpool Women's NHS Foundation Trust, Birmingham Women's NHS Foundation Trust and Royal Edinburgh Hospital, NHS Lothian. There will be focus groups for women and a separate focus group for partners. Clinicians who care for women with threatened preterm birth will be interviewed by telephone.

Sample

A purposive sample of women and partners will be recruited to cover a variety of experiences of preterm labour and birth. Women will be stratified by their prior experience and relevant characteristics, including ethnicity, previous obstetric history, living in an urban or rural setting and proximity to a tertiary neonatal referral centre. Two focus groups of 4–8 women will be conducted at each site; one for pregnant women who are at high risk of preterm birth, and one for postnatal women who have recently experienced preterm birth. One partners' focus group will be conducted at one of the sites. If women or partners are unable to attend a focus group but still wish to participate, a semi-structured telephone interview will be offered.

Up to 10 obstetricians, including trainees, midwives, and neonatologists will be purposefully recruited to cover a range of professional backgrounds and experience. Semi-structured telephone interviews will be used to collect the data.

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Eligibility

Principal inclusion criteria for women's antenatal focus groups

Women who are currently pregnant who:

- Have previously experienced preterm birth following preterm labour,
- Have experienced threatened preterm labour in this pregnancy,
- Are at high risk of preterm birth for another clinical reason, such as prior cervical surgery.

Principal inclusion criteria for women's postnatal focus groups

Women who have experienced preterm birth following preterm labour at <34 weeks whose babies **are stable and well** and are receiving care on the special care baby unit or neonatal intensive care unit.

Principal inclusion criteria for partners' focus groups

Partners of women who fit the eligibility criteria for either focus group.

Principal exclusion criteria for the focus groups

Non-English speaking individuals.

Principal inclusion criteria for clinician interviews

Clinicians who care for pregnant women i.e. obstetricians (including trainees), neonatologists and midwives.

Principal exclusion criteria for clinician interviews

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Researchers in QUIDS or QUIDS qualitative.

Recruitment

Women and partners

Eligible women will be identified by clinicians in the preterm birth clinic and other antenatal clinics, and antenatal, triage or labour wards (for the antenatal focus groups) and the special care baby unit or postnatal clinics (for the postnatal focus groups) at each site. Eligible partners will be identified by the same method. Clinicians who are aware of and understand the research aims will approach women and partners to request consent for a researcher to contact them. Importantly, only postnatal parents whose babies are being cared for on the SCBU who are considered stable and well by the clinicians will be approached. With consent the researcher will make contact to talk to the women and/or their partners about the research, either face-to-face or over the telephone. Potential participants will be given the participant information sheet (PIS) (appendix _) that is relevant to them and given verbal information about the study. Each participant will be given time to read the information and the opportunity to have any questions answered. Willing participants will be asked to provide their written consent prior to the focus groups.

Clinicians

Eligible clinicians will be approached by the researchers, via email or face-to-face. Clinicians will be given the clinician PIS (appendix _) and the opportunity to read the information and have any questions answered. Willing clinicians will be asked to provide their written consent prior to the interviews.

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All participants (women, partners and clinicians) will be reassured that they are not compelled to participate, that they can withdraw from the study at any time, and that non-participation will not affect their care or employment in any way.

Data collection

The primary aim of this research is to determine the decisional requirements of women, their partners and clinicians for the management of preterm labour. Qualitative semi-structured interviews, in a focus-group setting or individual telephone interviews, provide a means of collecting rich, in-depth data with a specific focus.[37] Hence, structured topic guides will be used to initiate and concentrate the discussion (appendices 7–10).

Focus groups are the preferred format for eliciting the view of women and women's partners. Encouraging discussion among a homogenous group with a shared interest is likely to provide rich insight and understanding into the group's experiences, beliefs and norms as a result of their social interaction.[38] Conversely, interviewing clinicians individually avoids the potential pitfall of professional embarrassment stifling ideas in a group setting. Interviewing individual clinicians with a range of professional experience should ensure that the decisional requirements of clinicians at all levels of experience are understood.

Demographic details and baseline characteristics will be collected prior to the interviews, either as a self-completion questionnaire, or questions asked by the researcher over the telephone. All interviews will be audio recorded, with the participants' consent, and field notes taken. The focus groups will be facilitated by at least two researchers. This is to ensure that all pre-specified areas of interest are covered and that non-verbal communication and group interactions are documented within the field-notes, which will provide context for the data analysis. Recapping will be used to

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clarify aspects and avoid misinterpretation. To enable all participants to talk freely, the researchers will be unknown to the participants and not working clinically in the unit where the interview is conducted. Clinicians will be interviewed by a researcher who is unknown to them.

	Site	Interviewers
Women and partners' focus groups	Liverpool	HW and EO
	Birmingham	HW and VH-M
	Edinburgh	HW and LM
Clinician interviews	Telephone	HW (and EO?)

Analysis plan

A framework approach to data analysis will be used. This approach was developed to manage and interpret large volumes of data collected to inform health policy, meaning they had focussed aims and objectives.[37] Likewise, this research has clear aims, as described previously, in addition to the methodological aim of collecting rich data about the experiences and beliefs of women, their partners and clinicians in relation to managing preterm labour.

Framework analysis follows specific, clearly documented stages of analysis that are transparent so that others can review the interpretation processes and understand how the findings were reached.[39] Transparency is particularly important in this study as the findings will inform the development of an application to aid management decisions in clinical practice. Following verbatim transcription of the interview recordings, the researchers will become familiar with the data by reading the transcripts and field-notes several times. The next stage is to develop a theoretical framework by re-reading the transcripts and making notes as recurring characteristics are

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recognised. The characteristics will then be collated into themes, which are based on the text itself, supported by the field-notes. The resulting thematic framework will be applied back to the transcripts and field-notes to check that it reflects the context of the original data. The transcripts will be coded, so that portions of text are linked to a discrete theme. A sample of transcripts will be independently coded by two people. The data will be charted and indexed to identify the preterm labour or professional experience of the participant, thus enabling the attribution of themes to a particular group. Finally, the content of the charts will be interpreted and mapped against each other to devise themes and sub-themes categories. Once again, this will involve review of the original data. Explanatory accounts will be developed to clarify the data and quotable sections of data will be identified. The final categories will be discussed between the researchers until consensus is met. The researchers will maintain reflexive journals throughout the data collection and analysis stages, recognising and ameliorating, as far as possible, the fact that their presence and assumptions impact on the data and the findings.[40]

This method of data analysis creates a clear audit trail thus ensuring rigour. Each stage of analysis refers back to the original data so that context and meaning is not lost in the final framework of themes and subthemes. The data analysis process will be managed using NVivo software, a qualitative data analysis tool.

Participant withdrawal

Participants may withdraw from the study at any point. However, they will not be able to withdraw use of their data once the prognostic tool is developed.

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Safety

The physical safety of participants will be ensured through adhering to the health and safety policies of the host units where the focus groups take place.

The emotional wellbeing of the participants will be safeguarded by following the Distress Policy (see appendix 11). The Supervisors of Midwives (SOM) team in each unit will be informed of the study and women and their partners will be given the SOM team contact details, should they become distressed or upset as a result of talking about their experiences. Participants will also be given the contact details for accessing local counselling services.

Good clinical practice

Informed consent

All participants will be fully informed about the study and the subsequent QUIDS trial via verbal and written communication. All eligible individuals will be given the participant information sheet (appendix __) and provided with an opportunity to have any questions answered. Written consent will then be gained prior to the commencement of the focus groups/interviews.

Confidentiality

Demographic information will be collected from participants to attribute themes from the data to particular groups within the analysis and dissemination of findings. Demographic information, which will contain potentially identifiable information, will be kept in a secure lockable cabinet. Audio recordings will be stored on an encryptable audio device only until they are transcribed. Once transcribed the audio recordings will be deleted. Transcription services are provided by '1st Class Secretarial', who subscribe to the Data Protection Act and have also signed the Code of Practice on Data Handling. Hard copies of audio transcripts and field-notes will be kept in a separate secure

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lockable cabinet to the demographic information. The transcripts and field-notes will be coded to identify which participant provided that data; the codes will only be known by the researchers. Participant's data will not be used for any purpose other than this study and the subsequent QUIDS trial.

Data Protection

Participants will be informed that publications from this study will contain direct quotes from the focus groups/interviews and categorisation of their experience of preterm labour (e.g. experienced preterm birth), which could enable personal identification.

All researchers involved in 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 uphold the Act's core principles. All computers used for processing data are password protected and subject to the strict data protection policies of the researcher's institution.

Good clinical practice training

All researchers involved in this study must hold evidence of recent Good Clinical Practice training.

Additional ethical considerations

Expenses and reimbursement

Participants will be reimbursed for all out of pocket expenses, for example travelling to the interview site. Participants will be informed of this and how to apply for expenses reimbursement, including keeping receipts for travel.

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Safety of researchers

An individualised risk assessment will be conducted to identify any risks to researchers or participants involved in this study. The lone working policy of the institution will be adhered to at all times. The only anticipated lone working will be during travel to and from the interview sites.

The lone working policy of the researcher's institutions mandates that researchers wear a GPS tracking and audio transmitting device during all lone-working, off-site research activity with participants. Participants will be informed if this device is being used.

Insurance / Indemnity

The researcher's institution holds public liability insurance and professional indemnity insurance (appendices 12, 13 and 14).

Timeline

The anticipated start date for the focus groups and interviews is 1st January 2016, to be completed within 3 months.

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Appendices

Appendix 1: PIS women

Appendix 2: PIS partners

Appendix 3: PIS clinicians

Appendix 4: Consent form women

Appendix 5: consent form partners

Appendix 6: consent form clinicians

Appendix 7: Interview schedule AN women

Appendix 8: Interview schedule PN women

Appendix 9: Interview schedule partners

Appendix 10: Interview schedule clinicians

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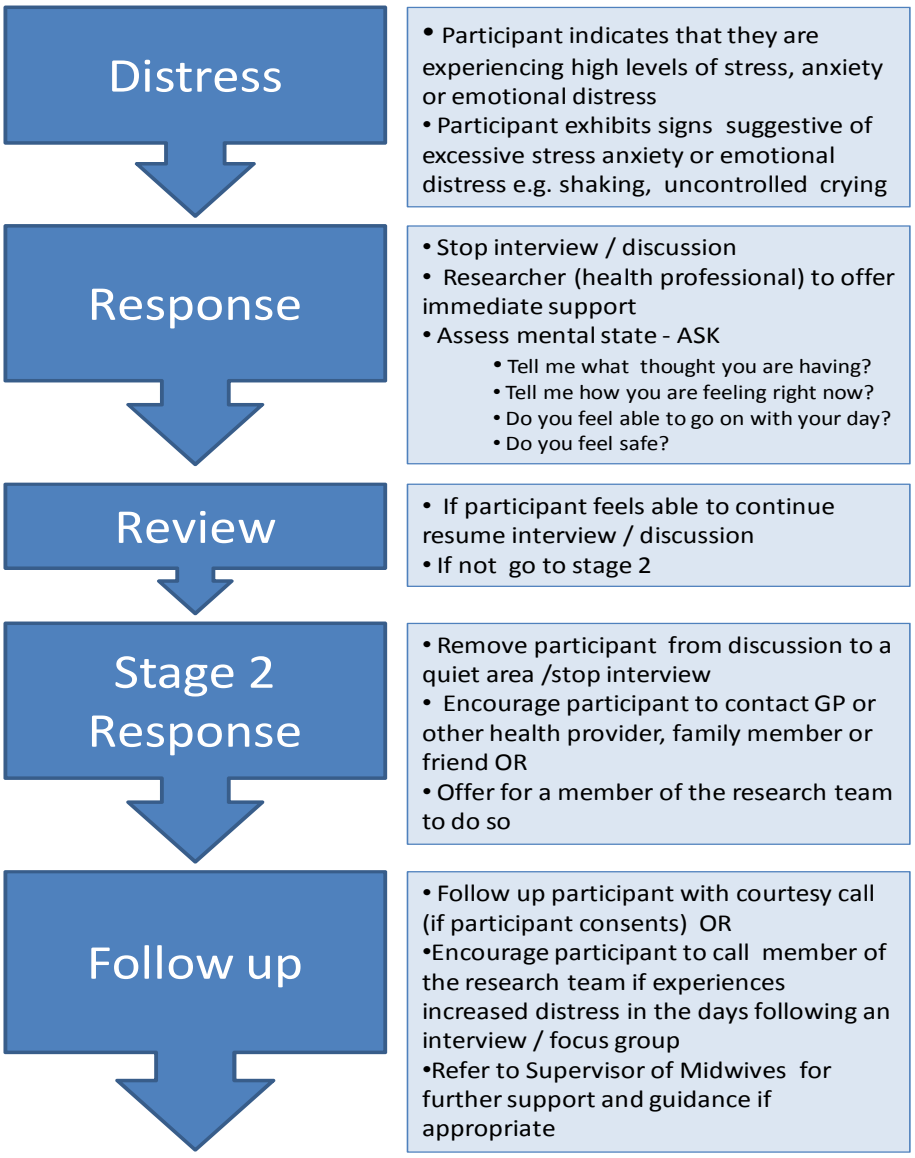
Appendix 11: Distress policy



Adapted from Haigh and Witham (2010)[41]

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Appendix 12: Public Liability insurance

ZURICH MUNICIPAL

To Whom It May Concern

Our ref: SP/IND 3 June, 2015

Zurich Municipal Customer: The University of Manchester

This is to confirm that The University of Manchester have in force with this Company Public Liability Insurance until the policy expiry on 31 May 2016:

Policy Number: NHE-07CA03-0013

Limit of Indemnity: £ 50,000,000 any one claim

Excess: Nil any one claim

Yours faithfully

Underwriting Services
Zurich Municipal
Farnborough

Zurich Municipal
Zurich House
2 Gladiator Way
Farnborough
Hampshire
GU14 6GB

Telephone 0870 2418050
Direct Phone 01252 387859
Direct Fax 01252 375893
E-mail alison.cliff@uk.zurich.com

Communications will be monitored regularly to improve our service and for security and regulatory purposes

Zurich Municipal is a trading name of Zurich Insurance Group Ltd

A public limited company incorporated in Ireland. Registration No. 13460 Registered Office: Zurich House, Ballsbridge Park, Dublin 4, Ireland.

UK branch registered in England and Wales Registration No. BR7985. UK Branch Head Office: The Zurich Centre, 3000 Parkway, Whiteley, Fareham, Hampshire PO15 7JZ

Authorised by the Central Bank of Ireland and subject to limited regulation by the Financial Conduct Authority. Details about the extent of our regulation by the Financial Conduct Authority are available from us on request.

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Appendix 13: Employers' Liability insurance

ZURICH MUNICIPAL

Certificate of Employers' Liability Insurance(a)

(Where required by regulation 5 of the Employers' Liability (Compulsory Insurance) Regulations 2008 (the Regulations), a copy of this certificate must be displayed at all places where you employ persons covered by the policy or an electronic copy of the certificate must be retained and be reasonably accessible to each employee to whom it relates).

Policy No.	NHE-07CA03-0013
1. Name of policyholder	The University of Manchester
2. Date of commencement of insurance policy	01 June 2015
3. Date of expiry of insurance policy	31 May 2016

We hereby certify that subject to paragraph 2:

1. The policy to which this certificate relates satisfies the requirements of the relevant law applicable in Great Britain, Northern Ireland, the Isle of Man, the Island of Jersey, the Island of Guernsey and the Island of Alderney **(b)**

2. **(a)** the minimum amount of cover provided by this policy is no less than £5 million **(c)**

Signed on behalf of Zurich Insurance plc (Authorised Insurer).

Signature

S. Lewis

Stephen Lewis

Chief Executive Officer, Zurich Insurance plc (UK Branch)

Zurich Municipal is a trading name of Zurich Insurance plc
A public limited company incorporated in Ireland
Registration No.13460 Registered Office Zurich House, Ballsbridge Park ,Dublin 4 Ireland.
UK branch registered in England and Wales Registration No. BR 7985
UK Branch Head Office The Zurich Centre, 3000 Parkway, Whiteley, Fareham, Hampshire PO15 7JZ

Authorised by the Central Bank of Ireland and subject to limited regulation by the Financial Conduct Authority. Details about the extent of our regulation by the Financial Conduct Authority are available from us on request

Notes

(a) Where the employer is a company to which regulation 3(2) of the Regulations applies, the certificate shall state in a prominent place, either that the policy covers the holding company and all its subsidiaries, or that the policy covers the holding company and all its subsidiaries except any specifically excluded by name, or that the policy covers the holding company and only the named subsidiaries.

(b) Specify applicable law as provided for in regulation 4(6) of the Regulations.

(c) See regulation 3(1) of the Regulations and delete whichever of paragraphs 2(a) or 2(b) does not apply. Where 2(b) is applicable, specify the amount of cover provided by the relevant policy

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Appendix 14: Professional indemnity insurance

Cliffe Crowther
Marsh Ltd
Belvedere
12 Booth Street
Manchester
M2 4AW
+44 (0) 161 954 7317
Fax +44 (0) 161 954 7210
Cliffe.crowther@marsh.com
www.marsh.com

To whom it may concern

29th May 2015

Dear Sirs,

CONFIRMATION OF INSURANCE – The University of Manchester and Subsidiary Companies

As requested by the above client, we are writing to confirm that we act as Insurance Brokers to the client and that we have arranged insurance(s) on its behalf as detailed below:

PROFESSIONAL INDEMNITY INSURANCE

INSURERS	Novae Underwriting Ltd.
POLICY NUMBER	003210MMA15C
PERIOD OF INSURANCE	01 June 2015 to 31st May 2016, both dates inclusive.
LIMIT OF INDEMNITY	GBP10,000,000 any one claim and in the aggregate any one insurance period plus costs and expenses.
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Study Protocol: Quantitative Fibronectin to help Decision-making in women with Symptoms of Preterm Labour (QUIDS) Part One- Individual Patient Data Meta-analysis and Health Economic Analysis

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Study Protocol: Quantitative Fibronectin to help Decision-making in women with Symptoms of Preterm Labour (QUIDS) Part One- Individual Patient Data Meta-analysis and Health Economic Analysis

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ABSTRACT

Introduction: The aim of the QUIDS study is to develop a decision support tool for the management of women with symptoms and signs of preterm labour, based on a validated prognostic model using quantitative fetal Fibronectin (fFN) concentration, in combination with clinical risk factors.

Methods and analysis: The study will evaluate the Rapid fFN 10Q System (Hologic, Malborough, MA) which quantifies fFN in a vaginal swab. In part one of the study we will develop and internally validate a prognostic model using an individual participant data (IPD) meta-analysis of existing studies containing women with symptoms of preterm labour alongside fFN measurements and pregnancy outcome. An economic analysis will be undertaken to assess potential cost-effectiveness of the qfFN prognostic model. The primary endpoint will be the ability of the prognostic model to rule out spontaneous preterm birth within seven days. Six eligible studies were identified by systematic review of the literature and five agreed to provide their IPD (n= 5 studies, 1,783 women and 139 events of preterm delivery within 7 days of testing).

Ethics and dissemination: The study is funded by the National Institute of Healthcare Research Health Technology Assessment (HTA 14/32/01). It has been approved by the West of Scotland Research Ethics Committee (16/WS/0068).

Registration details: This IPD Meta-analysis is registered with PROSPERO (PROSPERO 2015:CRD42015027590).

Version: Protocol Version 2, Date 1st November 2016

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- Development of prognostic model and for validation in a separate prospective cohort study

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- Health Economic Analysis to determine cost effectiveness from NHS perspective

Limitations

- Not a randomized control trial to test effectiveness of the model on improved patient outcomes

HOW PATIENTS ARE INVOLVED IN THIS STUDY

Patient representatives were consulted during the protocol development and have been invited to join the Project Management Group and the Trial Steering Committee. Prior to commencing QUIDS, we performed a qualitative study to determine the decisional needs of pregnant women with signs and symptoms of preterm labour, their partners and their caregivers. This is described in the separate protocol "QUIDS Qualitative" (Supplementary Material). The end product of QUIDS will be a decision support aid to help clinicians, women and their partners decide on management of threatened preterm labour, based on the results of the quantitative fFN. In QUIDS Qualitative women and clinicians indicated that they would prefer this to be on web based or mobile app based format, presenting the risk of preterm birth within seven days of testing.

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INTRODUCTION

The overall aim of the QUIDS study is to develop a decision support tool for the management of women with symptoms and signs of preterm labour, based on a validated prognostic model using quantitative fFN testing. The study has been conceptually divided into two parts. In this, the protocol for QUIDS Part One, we detail the protocol for development and internal validation of the prognostic model. In the protocol for QUIDS Part Two we detail the protocol for the prospective cohort for external validation of the prognostic model and acceptability testing.[1]

Preterm delivery (before 37 weeks) occurs in 7.1% of pregnancies in the UK (>50,000 deliveries per annum), with the majority the result of preterm labour.[2,3] It remains the leading cause of neonatal morbidity and mortality, but timely interventions, such as antenatal steroids to promote lung maturity, magnesium sulphate for neuroprotection, and delivery in a unit with appropriate neonatal care facilities can improve neonatal outcome. Establishing a diagnosis of preterm labour is, however, difficult. Clinical signs are non-specific and false positive diagnoses are common, with up to 80% of women with signs and symptoms of preterm labour remaining pregnant after seven days. [4, 5] Such diagnostic uncertainty means a large proportion of women with symptoms of preterm labour are treated unnecessarily to ensure benefits to the small proportion of babies that do actually do deliver preterm.

It is understandable that both clinicians and pregnant women may prefer a 'treat-all' approach in women with symptoms of preterm labour, particularly in a setting remote from an appropriate neonatal unit; and in order to ensure steroid prophylaxis in case preterm delivery occurs. However, unnecessary interventions result in both a substantial economic burden to health services and in potential adverse maternal and neonatal events. Hospital admission and inter-hospital transfer have

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considerable cost implications and can be associated with enormous problems for women and their families due to physical separation and emotional stress.[6,7] Neonatal cots become 'blocked' in order to accept a preterm baby just in case delivery occurs; negatively impacting the efficiency of already stretched neonatal units and networks. This frequently has knock-on effects to other women and babies, who may need transfer to another unit due to lack of cot availability despite an empty, but 'blocked', cot. It also may increase the number of *ex utero* transfers, which are associated with poorer outcomes than *in utero* transfers.[8] If preterm labour has been wrongly diagnosed, and delivery does not occur, steroids may also have adverse long-term consequences for the baby, especially if multiple courses are given.[9] Tocolytic therapy, even when appropriate can have serious side effects for both mother and baby.[10] Lastly, uncertainty of outcome may contribute to the high anxiety scores seen in women with threatened preterm labour and their partners.[11]

Diagnostic tests for preterm labour are available and used in many units in the UK. Fetal Fibronectin (fFN; Hologic, Marlborough, MA, USA) is a biochemical marker of preterm labour that can be measured in samples of cervicovaginal secretions collected at a speculum examination. It has potential to help improve diagnosis of impending preterm delivery.[12] Other biochemical tests which are available include Actim Partus (Medixbiochemica, Espoo, Finland)) which measures phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1), and Partosure (Parsagen Diagnostics, Boston, MA, USA) which measures placental alpha microglobulin-1 (PAMG-1). An alternative approach (which can be combined with fFN) is to measure the cervical length using transvaginal ultrasound, as the longer the cervix is, the less likely a preterm delivery.[12]

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As part of an Health Technology Assessment (HTA) report Honest et al found that a qualitative fFN test (giving a positive or negative result based on a single threshold of 50ng/ml) was potentially useful in the prediction of preterm delivery <34 weeks gestation, with its main benefit relating to its high negative predictive value i.e. its ability to rule out impending delivery.[12] A more recent HTA-funded review found that qualitative fFN testing has moderate accuracy for predicting preterm birth with overall sensitivity and specificity estimates of 76.7% and 82.7% for delivery within 7-10 days.[13] These estimates suggest that qualitative testing on its own would not have the sensitivity to rule out preterm delivery adequately, although in systematic review of clinical trials, no increase in neonatal morbidity or mortality was seen in association with false negative fFN results.[13] The authors concluded that this observation is likely to relate to the multifactorial nature of assessment of the risk of preterm delivery, where, in practice, fFN is just one component of the clinical assessment on which management decisions are based.[13]

Both HTA reviews described above examined the performance of a qualitative fFN test, which provided a positive or negative result on the basis of a single threshold of 50ng/ml. Recently, this test has been replaced in the UK with the Rapid fFN 10Q System, which provides a concentration of fFN within 10 minutes, and thus may be a more useful predictor of preterm delivery (quantitative fFN). We surveyed current practice in UK maternity units (response rate 66% [137/207]; Mar-July 2014).[14] 135/137 units (98.5%) use some sort of diagnostic test of preterm labour. The most common test is fFN (84/137 units; 61.3%). fFN is now only available with a quantitative analyser in the UK, but there is no consensus as to which women to use the test in, or how to interpret the results. Developing and evaluating a decision support for qfFN is thus likely to improve decision making, even if qfFN is already available in clinical practice. Evidence about the potential value of the new

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quantitative fFN is required, along with guidance about how to interpret results. The QUIDS study will address this evidence gap.

METHODS AND ANALYSIS

Aims and Methodologies

The aim of the QUIDS study is to develop a decision support tool for the management of women with symptoms and signs of preterm labour, based on a validated prognostic model using quantitative fFN testing.

The study protocol has been divided into two parts (see flow chart Figure 1). The protocols for Parts One and Two are reported in separate manuscripts.

Part 1: Development and Internal Validation of Prognostic Model

i) Individual Participant Data (IPD) meta-analysis to develop a prognostic model using quantitative fFN and other risk (prognostic) factors and to evaluate the added value of quantitative fFN toward this prognostic model performance. A prognostic model will be developed and internally validated[15,16] based on a meta-analysis of IPD from existing prospective cohort studies where quantitative fFN results and pregnancy outcome details are available. The primary outcome will be prediction will be delivery within 7 days, although other endpoints will be included if recommended by focus groups.

(ii) Economic Analysis: To provide an economic rationale for the prognostic model and analyze its cost-effectiveness from the perspective of the NHS to provide an economic rationale for the prognostic model and the risk factors included in it.

Part 2: Validation And Refinement Of Prognostic Model Involves a prospective cohort study and acceptability testing, with external validation, (and, if necessary, refinement) of the prognostic model, and update of health economic model.[1]

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Endpoints

The primary endpoint is spontaneous preterm delivery within seven days of qfFN test, in women tested at less than 36 weeks gestation. This is both an important endpoint for women and caregivers (determined in QUIDS Qualitative study – a preceding qualitative study to identify the decisional needs of women, their partners and clinicians; Supplementary Material) as well as a clinically important endpoint. Antenatal steroids (which significantly reduce morbidity and mortality in preterm babies[17]) are most effective if delivery occurs within seven days of administration. As repeated doses of antenatal steroids may be harmful, it is crucial to ensure steroids are timed correctly.

A secondary endpoint suggested by the preceding QUIDS Qualitative Study consultation (Supplementary Material), was delivery within 48 hours of qfFN test. This analysis will be performed if feasible to do so within the constraints of the data available for model development.

Health technologies being assessed

The study will evaluate the Rapid fFN 10Q System (Hologic), which provides a concentration of fFN (ng/ml or INVALID) in a vaginal swab sample. Further details about the system and recommended sampling technique are provided in the QUIDS Protocol Part Two. [1]

Target population

The target population is pregnant women attending hospital with signs and symptoms of preterm labour.

Development Of Prognostic Model

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Individual Patient Data Meta-Analysis

The proposed IPD-Meta-analysis was registered on PROSPERO (2015:CRD42015027590). Our IPD meta-analytical approach will follow existing guidelines, and our output will comply with the TRIPOD statement (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement).[18]

Inclusion Criteria

We prespecified inclusion of prospective cohort studies or RCTs of women with signs and symptom of preterm labour (as defined by investigators) that include quantitative fFN results determined by 10Q rapid fFN analyzer system and pregnancy outcome data; and the Principal Investigator of which has agreed to collaborate and provide data.

Exclusion criteria

We will exclude studies where fFN concentration was measured by ELISA and studies where IPD is not available for meta-analysis

Search Strategy

When applying for funding for this study (April 2014) we performed a literature search for completed and ongoing cohort studies of quantitative fFN using search terms for quantitative fetal/foetal fibronectin and preterm birth, including databases (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA)) and clinical trial registries (Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.Gov) general search engines (such as Google: https://www.google.co.uk) and systematic reviews. We also consulted preterm birth

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researchers and networks (RCOG CSG; BMFMS, PREBIC) and the manufacturers of quantitative fFN, (Hologic) to help ensure capture of all relevant studies.

Study manuscripts and/or protocols were screened by two researchers. We identified a total of 10 studies of quantitative fFN that were potentially eligible. Four early datasets (in three manuscripts) used ELISA to determine the concentration of fFN and were excluded as the different method of analysis and earlier period of study would increase heterogeneity.[5,19,20] Therefore, six studies fulfilled the eligibility criteria (see Table 1).

Establishment of the quantitative fFN IPD Collaboration

We contacted the principal investigators (PIs) of the six eligible studies of qfFN invited them to participate (see Table 1). Five of these agreed to provide their IPD as evidenced by their involvement as co-applicants on the funding application and/or co-authorship of this protocol (Mol, van Baaren, Khalil, Shennan, David). The PI of the 6th study (Elovitz) indicated IPD may be available after publication of her study.

The five included studies (Table 1) are European studies of women with symptoms of preterm labour, comprising 1,783 women and 139 events of preterm delivery within 7 days of testing. They are from consultant led maternity units in the UK (three studies) and Europe (two studies). All women in the included trials provided informed consent for participation in clinical trials, and for their IPD to be used in subsequent analyses.

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	PI	Setting	N	Events	Dates	Inclusion	Primary Outcome
Studies with data available							
EQUIPP [21,22]	Prof A Shennan	5 UK centres	452	14	2010-2012	22-35 weeks with symptoms of preterm labour	Delivery <34 weeks gestation
EUFIS* [23]	Prof BW Mol	10 European Hospitals	452	48	2012-2014	24-34 weeks with preterm contractions and intact membranes	Delivery within 7 days of test
APOSTEL I* [24]	van Baaren	10 Dutch Hospitals	528	70	2009 -2012	24-34 weeks with preterm contractions and intact membranes	Days to delivery truncated at 7 days
QFCAPS (unpublished)	Dr A Khalil	London teaching hospital	86	2	2012-2014	24-34 weeks with symptoms of preterm labour Singletons only	Delivery within 7 days of test
UCLH/Whit (unpublished)	Dr A David	2 UK centres	262	5	2009-2010	22-35 weeks with symptoms of preterm labour	Delivery within 7 days of test
	TOTALS	***4 studies***	***1,783***	***139***			
Studies where data may be available in future							
STOP study (http://clinicaltrials.gov/show/NCT01868308)	Prof M Elovitz	USA teaching hospital	700	NK	2011-2015	22 -34 weeks Symptomatic women with singleton pregnancy	Delivery before 37 weeks

Table 1: Details of studies contributing data to IPD meta-analysis.

*Study unpublished at time of search in April 2014; manuscript now published

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Study Quality Assessment and Data Collection

IPD will be stored in a bespoke database on a secure server at the University of Edinburgh. PIs will be asked to provide de-identified data, and consider all recorded variables (even if not reported publications). We will assess study quality according to QUADAS-2[25] QUIPS[26] and CHARMS[27] guidelines.

Sample Size Considerations

The size of the IPD meta-analysis is limited by the number of studies with data available (Table 1). In model development the number of covariates that can be considered is limited by the number of events, with guidance suggesting at least ten events required for each covariate.[28,29] In our IPD meta-analysis data we have 139 events (preterm labour within 7 days of testing) and therefore deemed that it was sensible to evaluate quantitative fFN and up to 13 other factors (covariates) for potential inclusion in our model.

Data Items

The following factors which are thought to influence risk of spontaneous preterm birth, will be requested and considered for inclusion as covariates in the prognostic model: quantitative fFN concentration, previous spontaneous preterm labour, gestation at fFN test, age, ethnicity, BMI, smoking, deprivation index, number of uterine contractions in set time period, cervical dilatation, vaginal bleeding, previous cervical treatment for cervical intraepithelial neoplasia, cervical length (measured by transvaginal cervical length), singleton/multiple pregnancy, tocolysis and fetal sex. Up to 13 of these will be prespecified for inclusion, based on available data (we will only use variables which are available in each study), and ranking for likely clinical relevance as agreed by consensus of the project management team.

Data Cleaning

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Prior to analysis data will be checked for outliers and missing data will be identified. Descriptive statistics will be performed to summarise data. Problems identified will be discussed with the PI of the original study, and amended as indicated by consensus discussion.

Data Analysis and Prognostic Model Development

Multivariable logistic regression modelling will be the primary method of analysis. The primary endpoint for the prognostic model will be delivery within seven days. Another endpoint found to be important in focus group consultations performed in QUIDS Qualitative (Supplementary Material) included delivery within 48 hours, and we will use this as a secondary endpoint if feasible (i.e. if sufficient number of cases with delivery within 48 hours). We will develop an initial model with quantitative fFN concentration, and then consider a model with other predefined clinical predictor variables (see *Data Items*, above).

Tocolysis (which may delay onset of labour, although likely not beyond 48 hours) will be included as a categorical variable (administered/not administered). We will explore treatment effect by sensitivity analysis with and without the assumption that tocolysis could delay delivery within 48 hours by a maximum odds ratio of 5.39, 95% credible interval 2.14 to 12.34, based on data in Haas et al.[30].

As the outcome is binary, a logistic regression modelling framework will be used to develop the model. A multi-level structure will be used to account for clustering of patients within studies, and heterogeneity of the effects of included factors (hereafter called 'predictors') will be accounted for using random-effects, with between-study heterogeneity quantified using the estimated variance ('tau-squared') and the I^2 statistic. A separate intercept term per study will be included in the model, to account for the clustering and also guage how predictions may require tailoring to different populations. Predictors with large heterogeneity in the prognostic effect across

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studies may be removed to ensure summary Beta terms in the model are meaningful (accurate) for individual populations.[16]

In the primary analysis, we will use data from the first recorded attendance with signs and symptoms of preterm labour to determine the relationship between that individual episode and outcome. Data from subsequent attendances will be analysed subsequently, and may be included in an appropriate model. As a parsiminous model is sought, to reduce the factors included in the model that may otherwise delay its use, we will use backward stepwise selection based on an information criterion (e.g. Akaike's information criterion p<0.15) to identify a parsimonious set of factors to be included in the model; hereafter these are referred to as included 'predictors'. Further, an approach of adding specialist tests, such as cervical length, only after considering simpler clinical assessment will be used, to maximise the utility of the model by ensuring that extra tests with their additional costs are only be included if they add to the predictive power.

Linearity between continuous variables and outcome will be assessed using cubic spline plots and data will transformed where appropriate before inclusion in multivariable analysis (e.g. using fractional polynomial methods). Missing data will be assessed to determine whether missing at random is appropriate, and if so, multiple imputation of observed participant characteristics will be used, with missing data imputed within each original study separately, before the meta-analysis. The results of these analyses will be compared with a complete case analysis.

Assessing Apparent Model Performance

The apparent performance of the model will be assessed by its overall fit, and the observed discrimination and calibration in the IPD used to develop the modle. Overall fit of the models will be expressed with Nagelkerke R^2. The ability of the models to discriminate between women with and without spontaneous preterm birth will be

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determined by the area under the receiver operating characteristics curve (AUC), also known as the *C* statistic. Agreement between predicted and observed proportions of women with spontaneous preterm birth will be visualized using a calibration plot, and measured using calibration slope and calibration-in-the-large.

Internal validation: assessing Optimism In Model Performance

Apparent performance is likely to be optimistic, as it is examined in the same data used for model development. Therefore internal validation will also be undertaken using a non-parametric bootstrap re-sampling technique in which each modelling step is repeated in each bootstrap sample, to obtain a new model in each bootstrap sample, and then its apparent performance (AUC and calibration slope) in the bootstrap sample is compared to its performance in the original dataset. The 'optimism' is the mean difference (across all bootstrap samples) between the apparent value in the bootstrap sample and the observed value in the original dataset. This optimism estimate is then subtracted from the original model's apparent performance, to give an optimism-adjusted estimate of each measure of performance for the original model (e.g. R^2, *C* statistic, Calibration slope).

Production Of Final Model From IPD Meta-Analysis Via Uniform Shrinkage

The optimism-adjusted calibration slope will be used as a uniform shrinkage factor, to adjust the parameter estimates (log odds ratios) of the original model. The beta coefficients in the original model will be multiplied by the shrinkage factor, and the study intercept terms re-estimated to ensure perfect overall calibration is maintained (across all studies and, ideally, in each study separately). This will thereby produce a final model containing the updated intercepts and the shrunken beta coefficients.[31] With multiple intercepts, a strategy (or strategies) will be developed amongst the study investigators for which intercept should be chosen for use when externally validating the model in a new population (e.g. choose intercept from study that most

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closely resembles the population of application); each strategy will be evaluated and compared in the cohort study external validation phase.

Added Value Of Quantitative fFN

The added value of quantitative fFN will be examined throughout the whole model process, in particular its improvement on discrimination, calibration and other meaningful factors (such as clinical decisions) using appropriate techniques (such as net reclassification improvement and decision analysis methods).

Subgroup analyses

Subgroup analysis will be performed for multiple pregnancy, women with a previous preterm labour, gestation and those with criteria that are suggested to indicate preterm labour (number of uterine contractions in a set time period and/or cervical change). This will allow us to do a subgroup-analysis in which we assess whether the predictive capacity of quantitative fFN is similar in all subgroups.

Health Economic Analysis

An early stage decision-analytic model will be built using evidence from current literature and from the IPD meta-analysis to explore the potential cost-effectiveness of different prognostic models including quantitative fFN.

A literature review will be undertaken to inform model design and identify additional model parameters with searches of Medline, Embase, Cochrane Library and the Paediatric Economic Database Evaluation for economic analyses including the use of fFN testing in woman with threatened preterm labour. Any evidence on resource use (test administration, treatments for preterm labour, hospital stay, hospital transfers, etc), quality of life and diagnostic outcome data from the IPD meta-analysis will be synthesized with the wider evidence based on current practice for women attending hospital with signs and symptoms of preterm labour. The economic analysis will be undertaken from the perspective of the UK NHS adhering to good practice guidelines

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and the NICE reference case.[32] A decision tree will be developed to model the clinical pathway. The model will be used to explore potential cost effectiveness of the prognostic model at different thresholds on the Receiver Operator Curve, providing an economic rationale for the chosen prognostic model.

ETHICS AND DISSEMINATION

Trial Management And Oversight Arrangements

Project Management Group

The trial will be coordinated by a Project Management Group (PMG), consisting of the grant holders (Chief Investigator and Co-applicants), the trial manager, representatives from the Study Office and CHaRT (the supporting CTU), plus service user representatives (PAG). The PMG will meet approximately every four months by teleconference or face to face.

Trial Steering Committee and Data Monitoring Committee

A combined Trial Steering Committee and Data Monitoring Committee (TSC/DMC) will oversee the conduct and progress of the study. The terms of reference of the Committee will be developed separately. Members of the TSC/DMC will consist of experts and two patient representatives.

Good Clinical Practice

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP). A favorable ethical opinion has been obtained from the appropriate REC (reference 16/WS/0068) and local R&D approval will be obtained prior to commencement of the study at each site.

Dissemination

On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared. Results will be communicated to the academic

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community via the scientific literature, attendance at conferences and invited presentations. The TRIPOD reporting guidelines will be adhered to.[18] Summaries of results will also be made available to investigators for dissemination within clinics. Social media will be used to signpost publications and conference presentations and highlight important findings. Twitter and Facebook will be used to disseminate findings to professional organizations, charities, stakeholders and the public. Communication to the general public will further be facilitated by our close links with charities such as Tommy's [33].

PEER REVIEW

The study was extensively peer reviewed as part of the process of gaining grant funding from the NIHR HTA (14/32/01).

FUNDING

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CONTRIBUTIONS TO AUTHORSHIP

SJS, KB, RKM, JD, LJ, MC, AD, AK, AS, VHM, TL, KK, SHC, BM, RDR, JN and JEN developed the protocol. SJS, LW, RDR, KB, TL and JN drafted the protocol. RKM, JD, LJ, MC, AD, AK, AS, VHM, KK, SHC, BM and JEN reviewed and commented on the protocol.

COMPETING INTERESTS

SJS and JEN work at the University of Edinburgh, who received £1000 sponsorship from Hologic to support a meeting (The Society of Reproductive Investigation and

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MRC Centre for Reproductive Health Scientific Symposium on Targeting Inflammation to Improve Reproductive Health across the Lifecourse – August 2017).

AS has in the past (over last five years; not in the last three years) received funding for expenses related to advisory board and internal staff education from Hologic.

MC received sponsorship from Hologic to organise an educational teaching focusing on prediction of Preterm Birth at the 2017 annual meeting of the British Maternal and Fetal Medicine Society.

Hologic, the makers of fFN have provided analysers and technical support for their use to sites participating in the QUIDS prospective cohort study. They have no access to the data, or other involvement in the conduct, analysis, interpretation or decision to publish the results of the study.

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Figure Legends

Figure 1

Flow chart illustrating the design of QUIDS study and conceptual division into Part 1 and Part 2

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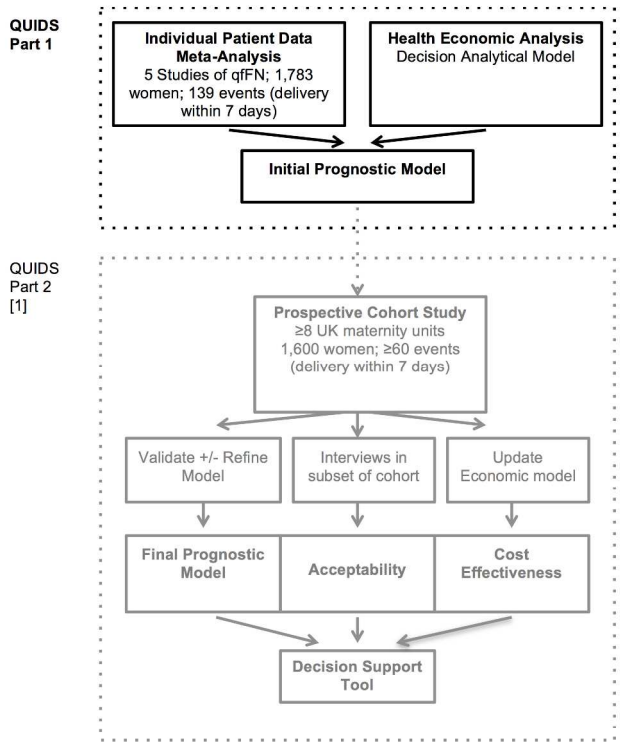
Figure 1



Flow chart illustrating the design of QUIDS study and conceptual division into Part 1 and Part 2

209x297mm (300 x 300 DPI)

QUIDS Qualitative

Quantitative Fibronectin to help Decision-making in women with Symptoms of Preterm Labour:

determining decisional requirements

Protocol

(October 2015)

White H, O'Brien E, Hodgetts-Moreton V, Stock S, Lavender T

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Background

Preterm birth, defined as birth prior to 37 weeks gestation, occurs in 6-7% of pregnancies in Europe[1] and was recorded as 5.78% in England in 2013/14, equating to over 37,000 births.[2] Preterm birth is associated with a high risk of mortality, wide-ranging short- and long-term morbidities,[3,4] and significant economic costs to the NHS compared with birth at term.[5] Reducing the detrimental impact of preterm birth relies on the provision of timely and appropriate perinatal interventions. However, accurate prediction of preterm birth is challenging, even when the clinical symptoms are suggestive of preterm labour. In randomised trials approximately 80% of women diagnosed with preterm labour remained pregnant after 7 days.[6,7]

Interventions in preterm labour and preparations for preterm birth may include administration of corticosteroids to accelerate fetal lung maturation[8,9] and magnesium sulphate for fetal neuroprotection,[10] in utero transfer to a facility with appropriate maternity and neonatal services, and tocolysis to optimise time before birth to enable these.[11] Whilst such interventions can improve outcomes for mothers and babies who do experience preterm birth, they are not necessarily benign, especially for those in whom preterm birth does not occur.

The maximal beneficial impact of corticosteroids occurs with administration between 48 hours and seven days before birth, thus timing is especially important in optimising benefit for the neonate. For women who remain at risk of preterm birth after seven days of the initial dose, repeated doses reduce respiratory distress in the neonate[9] but have been found to be associated with a dose-dependent reduction in birthweight.[12,13] A five-year follow-up study of women who received repeated doses of antenatal corticosteroids due to risk of preterm birth found an increased risk of neurodevelopment impairment in infants born at term.[14] Therefore developing a strategy to establish the optimal time to give steroids is a research priority.

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Magnesium sulphate administration immediately prior to birth has been shown to reduce cerebral palsy,[10] but there is a risk of magnesium toxicity leading to respiratory depression in the mother and, theoretically, the neonate.[15]

Whilst there is no clear beneficial effect of tocolytics on the incidence or outcome of preterm birth,[16] their use is recommended if the days gained prior to preterm birth can be used appropriately, for example transfer to a suitable maternity unit or the administration of drugs to protect the neonate.[11] Tocolysis is linked with various maternal and neonatal complications,[17] hence the need for therapy targeted only for those at risk of preterm birth and close monitoring of the mother and fetus throughout.

Often, inpatient admission is recommended if preterm labour is suspected. Previous literature has highlighted the social isolation and support needs that women with high-risk pregnancies who are hospitalised experience.[18] In some cases, in-utero transfer is indicated to ensure that birth takes place in a specialist unit with appropriate neonatal care facilities. This policy has been shown to reduce mortality[19,20] and morbidity[21] in preterm neonates, especially those born very premature. Qualitative research has indicated that women generally acknowledge the potential benefit of in utero transfer to their baby and, hence, are willing to endure the inconvenience and upheaval that it entails.[22,23] However, the experience is associated with an emotional, social and financial burden on women and their families, especially for the substantial proportion of women who do not deliver prematurely following in utero transfer. When describing their experiences of in utero transfer, women expressed shock at the prospect of the transfer, feeling socially isolated, and having no control over the situation, in addition to the practical difficulties experienced particularly by women who already had children.[22,24,25] In a large survey of women who had experienced in utero transfer, over a quarter lamented the financial cost[24] particularly with respect to their partner's outlay for travel, food, accommodation, and phone bills, exacerbated with requiring time off work.[22] Furthermore, in utero transfer is costly to maternity services. Securing a maternal and neonatal bed

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in another unit is a time-consuming task that often falls to delivery suite midwives to arrange, whilst also continuing to provide care to the woman.[26] In a large observational study of all in utero transfers that took place in Scotland in a six-month period, nearly one third of all transfers were due to threatened preterm labour.[27] Under half of the women transferred from one consultant-led unit to another gave birth within 48 hours.[27] Such unnecessary transfers are costly to women, their families and maternity services. Qualitative research into women's experiences of preterm labour have highlighted the need for caregivers to create an environment where women are enabled to discuss their fears[28] and exert control over how they manage their preterm labour care.[25]

Accurate prediction of preterm birth could reduce the burdens and risks associated with unnecessary interventions, and enable women and their clinicians to make informed decisions regarding their care. Numerous diagnostic tests have been used in preterm labour, including biochemical tests of vaginal secretions and cervical length.[29] One such test is fetal fibronectin, a near-bedside test that provides a positive or negative result and has excellent negative predictive value.[30] Thus fetal fibronectin can identify which women will not benefit and may be put at risk by the interventions described previously, and reduce costs to maternity services.[31] Developments in fetal fibronectin testing have led to a quantitative test that provides a concentration of fetal fibronectin in vaginal secretions, giving women and clinicians more information on which to base their management decisions.[32]

Qualitative evidence has indicated that women feel a sense of increased responsibility to their babies and themselves during a high risk pregnancy, such as threatened preterm labour.[33] Women want to be involved in decision making about their care to different degrees and feel most satisfied when their caregiver supports them to make decisions in the way they felt most comfortable.[33]

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Previous literature on decision making and preterm birth has focussed on diagnostic tests[6,28–32,34] and the care of the preterm infant.[35,36] To date, there has been no investigation of what women, their partners and caregivers would like to know in order to make informed decisions about the care that is provided following the signs and symptoms of preterm labour.

Funding has been received from the National Institute for Health Research Health Technology Assessment Programme for a large, multicentre trial to develop a mobile application decision support tool for the management of women with symptoms and signs of preterm labour, based on a validated model using quantitative fetal fibronectin testing. This study is the precursor to that trial, with the aim of determining the decisional needs of pregnant women with the symptoms and signs of preterm labour, their families and caregivers, using a qualitative framework approach. The outcomes of this qualitative study will inform the development of the mobile application decision support tool, using the findings from an individual patient data meta-analysis. The tool will then be externally validated and refined in the multi-centre trial, QUIDS.

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Methods

A qualitative framework approach will be used, based on data collected from focus groups and semi-structured telephone interviews.

Setting

Focus groups will take place in three maternity units: Liverpool Women's NHS Foundation Trust, Birmingham Women's NHS Foundation Trust and Royal Edinburgh Hospital, NHS Lothian. There will be focus groups for women and a separate focus group for partners. Clinicians who care for women with threatened preterm birth will be interviewed by telephone.

Sample

A purposive sample of women and partners will be recruited to cover a variety of experiences of preterm labour and birth. Women will be stratified by their prior experience and relevant characteristics, including ethnicity, previous obstetric history, living in an urban or rural setting and proximity to a tertiary neonatal referral centre. Two focus groups of 4–8 women will be conducted at each site; one for pregnant women who are at high risk of preterm birth, and one for postnatal women who have recently experienced preterm birth. One partners' focus group will be conducted at one of the sites. If women or partners are unable to attend a focus group but still wish to participate, a semi-structured telephone interview will be offered.

Up to 10 obstetricians, including trainees, midwives, and neonatologists will be purposefully recruited to cover a range of professional backgrounds and experience. Semi-structured telephone interviews will be used to collect the data.

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Eligibility

Principal inclusion criteria for women's antenatal focus groups

Women who are currently pregnant who:

- Have previously experienced preterm birth following preterm labour,
- Have experienced threatened preterm labour in this pregnancy,
- Are at high risk of preterm birth for another clinical reason, such as prior cervical surgery.

Principal inclusion criteria for women's postnatal focus groups

Women who have experienced preterm birth following preterm labour at <34 weeks whose babies **are stable and well** and are receiving care on the special care baby unit or neonatal intensive care unit.

Principal inclusion criteria for partners' focus groups

Partners of women who fit the eligibility criteria for either focus group.

Principal exclusion criteria for the focus groups

Non-English speaking individuals.

Principal inclusion criteria for clinician interviews

Clinicians who care for pregnant women i.e. obstetricians (including trainees), neonatologists and midwives.

Principal exclusion criteria for clinician interviews

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Researchers in QUIDS or QUIDS qualitative.

Recruitment

Women and partners

Eligible women will be identified by clinicians in the preterm birth clinic and other antenatal clinics, and antenatal, triage or labour wards (for the antenatal focus groups) and the special care baby unit or postnatal clinics (for the postnatal focus groups) at each site. Eligible partners will be identified by the same method. Clinicians who are aware of and understand the research aims will approach women and partners to request consent for a researcher to contact them. Importantly, only postnatal parents whose babies are being cared for on the SCBU who are considered stable and well by the clinicians will be approached. With consent the researcher will make contact to talk to the women and/or their partners about the research, either face-to-face or over the telephone. Potential participants will be given the participant information sheet (PIS) (appendix _) that is relevant to them and given verbal information about the study. Each participant will be given time to read the information and the opportunity to have any questions answered. Willing participants will be asked to provide their written consent prior to the focus groups.

Clinicians

Eligible clinicians will be approached by the researchers, via email or face-to-face. Clinicians will be given the clinician PIS (appendix _) and the opportunity to read the information and have any questions answered. Willing clinicians will be asked to provide their written consent prior to the interviews.

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All participants (women, partners and clinicians) will be reassured that they are not compelled to participate, that they can withdraw from the study at any time, and that non-participation will not affect their care or employment in any way.

Data collection

The primary aim of this research is to determine the decisional requirements of women, their partners and clinicians for the management of preterm labour. Qualitative semi-structured interviews, in a focus-group setting or individual telephone interviews, provide a means of collecting rich, in-depth data with a specific focus.[37] Hence, structured topic guides will be used to initiate and concentrate the discussion (appendices 7–10).

Focus groups are the preferred format for eliciting the view of women and women's partners. Encouraging discussion among a homogenous group with a shared interest is likely to provide rich insight and understanding into the group's experiences, beliefs and norms as a result of their social interaction.[38] Conversely, interviewing clinicians individually avoids the potential pitfall of professional embarrassment stifling ideas in a group setting. Interviewing individual clinicians with a range of professional experience should ensure that the decisional requirements of clinicians at all levels of experience are understood.

Demographic details and baseline characteristics will be collected prior to the interviews, either as a self-completion questionnaire, or questions asked by the researcher over the telephone. All interviews will be audio recorded, with the participants' consent, and field notes taken. The focus groups will be facilitated by at least two researchers. This is to ensure that all pre-specified areas of interest are covered and that non-verbal communication and group interactions are documented within the field-notes, which will provide context for the data analysis. Recapping will be used to

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clarify aspects and avoid misinterpretation. To enable all participants to talk freely, the researchers will be unknown to the participants and not working clinically in the unit where the interview is conducted. Clinicians will be interviewed by a researcher who is unknown to them.

	Site	Interviewers
Women and partners' focus groups	Liverpool	HW and EO
	Birmingham	HW and VH-M
	Edinburgh	HW and LM
Clinician interviews	Telephone	HW (and EO?)

Analysis plan

A framework approach to data analysis will be used. This approach was developed to manage and interpret large volumes of data collected to inform health policy, meaning they had focussed aims and objectives.[37] Likewise, this research has clear aims, as described previously, in addition to the methodological aim of collecting rich data about the experiences and beliefs of women, their partners and clinicians in relation to managing preterm labour.

Framework analysis follows specific, clearly documented stages of analysis that are transparent so that others can review the interpretation processes and understand how the findings were reached.[39] Transparency is particularly important in this study as the findings will inform the development of an application to aid management decisions in clinical practice. Following verbatim transcription of the interview recordings, the researchers will become familiar with the data by reading the transcripts and field-notes several times. The next stage is to develop a theoretical framework by re-reading the transcripts and making notes as recurring characteristics are

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recognised. The characteristics will then be collated into themes, which are based on the text itself, supported by the field-notes. The resulting thematic framework will be applied back to the transcripts and field-notes to check that it reflects the context of the original data. The transcripts will be coded, so that portions of text are linked to a discrete theme. A sample of transcripts will be independently coded by two people. The data will be charted and indexed to identify the preterm labour or professional experience of the participant, thus enabling the attribution of themes to a particular group. Finally, the content of the charts will be interpreted and mapped against each other to devise themes and sub-themes categories. Once again, this will involve review of the original data. Explanatory accounts will be developed to clarify the data and quotable sections of data will be identified. The final categories will be discussed between the researchers until consensus is met. The researchers will maintain reflexive journals throughout the data collection and analysis stages, recognising and ameliorating, as far as possible, the fact that their presence and assumptions impact on the data and the findings.[40]

This method of data analysis creates a clear audit trail thus ensuring rigour. Each stage of analysis refers back to the original data so that context and meaning is not lost in the final framework of themes and subthemes. The data analysis process will be managed using NVivo software, a qualitative data analysis tool.

Participant withdrawal

Participants may withdraw from the study at any point. However, they will not be able to withdraw use of their data once the prognostic tool is developed.

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Safety

The physical safety of participants will be ensured through adhering to the health and safety policies of the host units where the focus groups take place.

The emotional wellbeing of the participants will be safeguarded by following the Distress Policy (see appendix 11). The Supervisors of Midwives (SOM) team in each unit will be informed of the study and women and their partners will be given the SOM team contact details, should they become distressed or upset as a result of talking about their experiences. Participants will also be given the contact details for accessing local counselling services.

Good clinical practice

Informed consent

All participants will be fully informed about the study and the subsequent QUIDS trial via verbal and written communication. All eligible individuals will be given the participant information sheet (appendix __) and provided with an opportunity to have any questions answered. Written consent will then be gained prior to the commencement of the focus groups/interviews.

Confidentiality

Demographic information will be collected from participants to attribute themes from the data to particular groups within the analysis and dissemination of findings. Demographic information, which will contain potentially identifiable information, will be kept in a secure lockable cabinet. Audio recordings will be stored on an encryptable audio device only until they are transcribed. Once transcribed the audio recordings will be deleted. Transcription services are provided by '1st Class Secretarial', who subscribe to the Data Protection Act and have also signed the Code of Practice on Data Handling. Hard copies of audio transcripts and field-notes will be kept in a separate secure

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lockable cabinet to the demographic information. The transcripts and field-notes will be coded to identify which participant provided that data; the codes will only be known by the researchers. Participant's data will not be used for any purpose other than this study and the subsequent QUIDS trial.

Data Protection

Participants will be informed that publications from this study will contain direct quotes from the focus groups/interviews and categorisation of their experience of preterm labour (e.g. experienced preterm birth), which could enable personal identification.

All researchers involved in 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 uphold the Act's core principles. All computers used for processing data are password protected and subject to the strict data protection policies of the researcher's institution.

Good clinical practice training

All researchers involved in this study must hold evidence of recent Good Clinical Practice training.

Additional ethical considerations

Expenses and reimbursement

Participants will be reimbursed for all out of pocket expenses, for example travelling to the interview site. Participants will be informed of this and how to apply for expenses reimbursement, including keeping receipts for travel.

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Safety of researchers

An individualised risk assessment will be conducted to identify any risks to researchers or participants involved in this study. The lone working policy of the institution will be adhered to at all times. The only anticipated lone working will be during travel to and from the interview sites.

The lone working policy of the researcher's institutions mandates that researchers wear a GPS tracking and audio transmitting device during all lone-working, off-site research activity with participants. Participants will be informed if this device is being used.

Insurance / Indemnity

The researcher's institution holds public liability insurance and professional indemnity insurance (appendices 12, 13 and 14).

Timeline

The anticipated start date for the focus groups and interviews is 1st January 2016, to be completed within 3 months.

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Appendices

Appendix 1: PIS women

Appendix 2: PIS partners

Appendix 3: PIS clinicians

Appendix 4: Consent form women

Appendix 5: consent form partners

Appendix 6: consent form clinicians

Appendix 7: Interview schedule AN women

Appendix 8: Interview schedule PN women

Appendix 9: Interview schedule partners

Appendix 10: Interview schedule clinicians

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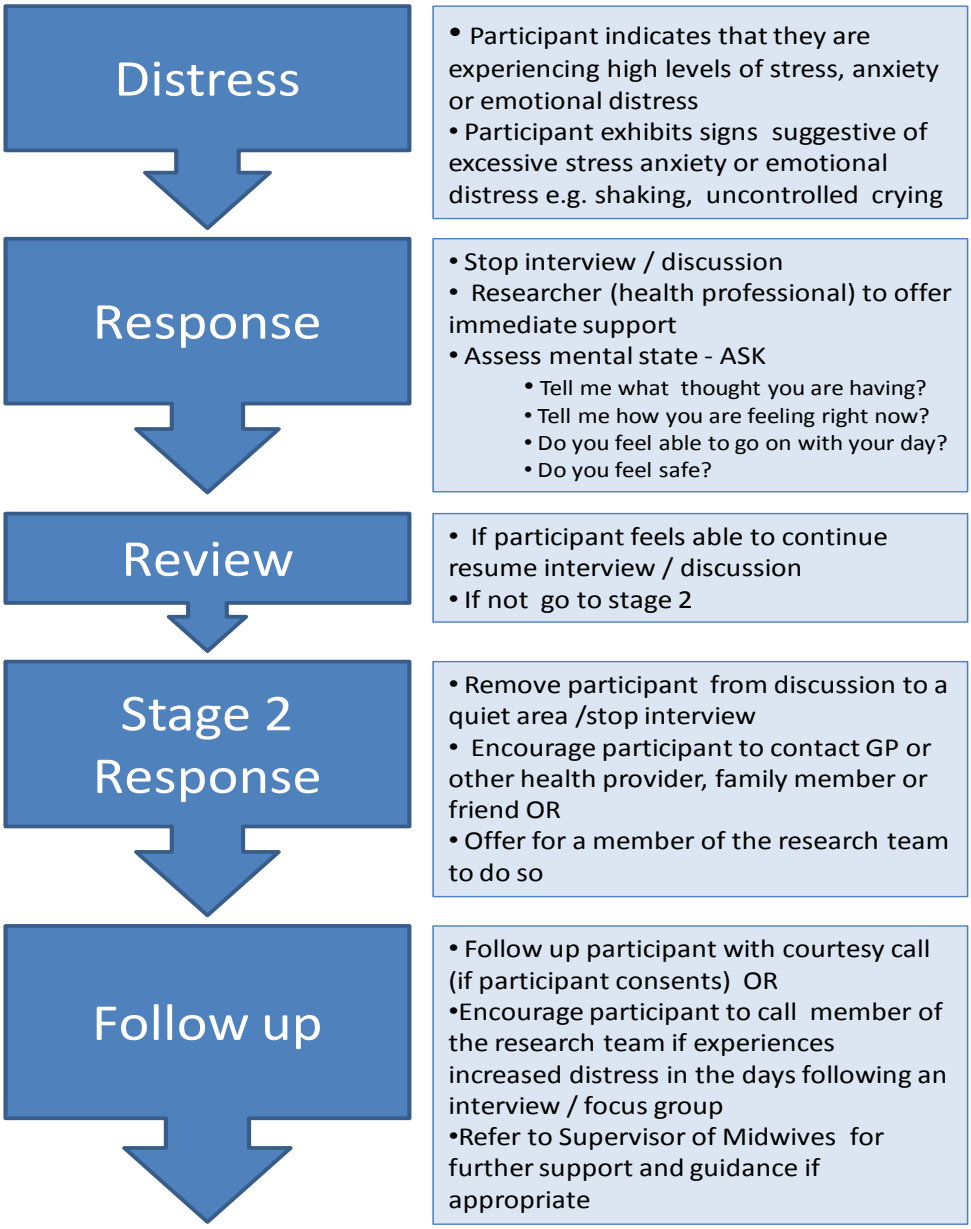
Appendix 11: Distress policy



Adapted from Haigh and Witham (2010)[41]

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Appendix 12: Public Liability insurance

ZURICH MUNICIPAL

To Whom It May Concern

Our ref: SP/IND 3 June, 2015

Zurich Municipal Customer: The University of Manchester

This is to confirm that The University of Manchester have in force with this Company Public Liability Insurance until the policy expiry on 31 May 2016:

Policy Number: NHE-07CA03-0013

Limit of Indemnity: £ 50,000,000 any one claim

Excess: Nil any one claim

Yours faithfully

Underwriting Services
Zurich Municipal
Farnborough

Zurich Municipal
Zurich House
2 Gladiator Way
Farnborough
Hampshire
GU14 6GB

Telephone 0870 2418050
Direct Phone 01252 387859
Direct Fax 01252 375893
E-mail alison.cliff@uk.zurich.com

Communications will be monitored regularly to improve our service and for security and regulatory purposes

Zurich Municipal is a trading name of Zurich Insurance Group Ltd

A public limited company incorporated in Ireland. Registration No. 13460 Registered Office: Zurich House, Ballsbridge Park, Dublin 4, Ireland.

UK branch registered in England and Wales Registration No. BR7985. UK Branch Head Office: The Zurich Centre, 3000 Parkway, Whiteley, Fareham, Hampshire PO15 7JZ

Authorised by the Central Bank of Ireland and subject to limited regulation by the Financial Conduct Authority. Details about the extent of our regulation by the Financial Conduct Authority are available from us on request.

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Appendix 13: Employers' Liability insurance

ZURICH MUNICIPAL

Certificate of Employers' Liability Insurance(a)

(Where required by regulation 5 of the Employers' Liability (Compulsory Insurance) Regulations 2008 (the Regulations), a copy of this certificate must be displayed at all places where you employ persons covered by the policy or an electronic copy of the certificate must be retained and be reasonably accessible to each employee to whom it relates).

Policy No.	NHE-07CA03-0013
1. Name of policyholder	The University of Manchester
2. Date of commencement of insurance policy	01 June 2015
3. Date of expiry of insurance policy	31 May 2016

We hereby certify that subject to paragraph 2:

1. The policy to which this certificate relates satisfies the requirements of the relevant law applicable in Great Britain, Northern Ireland, the Isle of Man, the Island of Jersey, the Island of Guernsey and the Island of Alderney **(b)**

2. **(a)** the minimum amount of cover provided by this policy is no less than £5 million **(c)**

Signed on behalf of Zurich Insurance plc (Authorised Insurer).

Signature

S. Lewis

Stephen Lewis

Chief Executive Officer, Zurich Insurance plc (UK Branch)

Zurich Municipal is a trading name of Zurich Insurance plc
A public limited company incorporated in Ireland Registration No.13460 Registered Office Zurich House, Ballsbridge Park ,Dublin 4 Ireland.
UK branch registered in England and Wales Registration No. . BR 7985
UK Branch Head Office The Zurich Centre, 3000 Parkway, Whiteley, Fareham, Hampshire PO15 7JZ

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Notes

(a) Where the employer is a company to which regulation 3(2) of the Regulations applies, the certificate shall state in a prominent place, either that the policy covers the holding company and all its subsidiaries, or that the policy covers the holding company and all its subsidiaries except any specifically excluded by name, or that the policy covers the holding company and only the named subsidiaries.

(b) Specify applicable law as provided for in regulation 4(6) of the Regulations.

(c) See regulation 3(1) of the Regulations and delete whichever of paragraphs 2(a) or 2(b) does not apply. Where 2(b) is applicable, specify the amount of cover provided by the relevant policy

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Appendix 14: Professional indemnity insurance

Cliffe Crowther
Marsh Ltd
Belvedere
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+44 (0) 161 954 7317
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Cliffe.crowther@marsh.com
www.marsh.com

To whom it may concern

29th May 2015

Dear Sirs,

CONFIRMATION OF INSURANCE – The University of Manchester and Subsidiary Companies

As requested by the above client, we are writing to confirm that we act as Insurance Brokers to the client and that we have arranged insurance(s) on its behalf as detailed below:

PROFESSIONAL INDEMNITY INSURANCE

INSURERS	Novae Underwriting Ltd.
POLICY NUMBER	003210MMA15C
PERIOD OF INSURANCE	01 June 2015 to 31st May 2016, both dates inclusive.
LIMIT OF INDEMNITY	GBP10,000,000 any one claim and in the aggregate any one insurance period plus costs and expenses.
DEDUCTIBLE	GBP20,000 each & every claim including costs and expenses

Registered in England Number: 1507274, Registered Office: 1 Tower Place West, Tower Place, London EC3R 5BU. Marsh Ltd is authorised and regulated by the Financial Conduct Authority

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MARSH

We have placed the insurance which is the subject of this letter after consultation with the client and based upon the client's instructions only. Terms of coverage, including limits and deductibles, are based upon information furnished to us by the client, which information we have not independently verified.

This letter is issued as a matter of information only and confers no right upon you other than those provided by the policy. This letter does not amend, extend or alter the coverage afforded by the policies described herein. Notwithstanding any requirement, term or condition of any contract or other document with respect to which this letter may be issued or pertain, the insurance afforded by the policy (policies) described herein is subject to all terms, conditions, limitations, exclusions and cancellation provisions and may also be subject to warranties. Limits shown may have been reduced by paid claims.

We express no view and assume no liability with respect to the solvency or future ability to pay of any of the insurance companies which have issued the insurance(s).

We assume no obligation to advise yourselves of any developments regarding the insurance(s) subsequent to the date hereof. This letter is given on the condition that you forever waive any liability against us based upon the placement of the insurance(s) and/or the statements made herein with the exception only of wilful default, recklessness or fraud.

This letter may not be reproduced by you or used for any other purpose without our prior written consent.

This letter shall be governed by and shall be construed in accordance with English law.

Yours faithfully

Cliffe Crowther

MARSH & McLENNAN COMPANIES

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