QUIDS

Study Protocol

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

QUIDS

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
CoTS	The Scottish Perinatal Collaborative Transport Study
CRF	Case Report Form
CHaRT	The Centre for Healthcare Randomised Controlled Trials
eCRF	Electronic Case Report Form
fFN	Fetal Fibronectin
GCP	Good Clinical Practice
ISF	Investigator Site File
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
PMG	Project Management Group
qfFN	Quantitative Fetal Fibronectin
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee
TV	Transvaginal ultrasound scan

SUMMARY

The clinical diagnosis of preterm labour that leads to delivery is notoriously challenging. Up to 80% of women who have signs and symptoms of preterm labour remain pregnant after 7 days. This means that many women unnecessarily receive therapies aimed at preventing complications in preterm babies, to ensure benefit for the few babies that are actually born preterm. Possible treatments include steroids given to the mother to help mature preterm babies' lungs; magnesium sulphate to help prevent brain damage in children born preterm; and transfer to a hospital so delivery will occur at a hospital with appropriate neonatal care facilities. In addition, treatments called tocolytics can be given to try to delay delivery until steroids are effective (48 hours) and to allow transfer to a different hospital, but there is little evidence that they improve outcomes for babies. If however, preterm delivery doesn't occur, these treatments are costly and potentially harmful to babies and women. In addition, hospital admission and transfer can be particularly difficult for families, both financially and emotionally.

A test called quantitative fetal Fibronectin (fFN) may help improve diagnosis of preterm labour. The test involves the measurement of fFN in a swab taken at speculum examination (like a smear test), which is part of the assessment of a woman presenting with signs and symptoms of preterm labour. The amount of fFN present in the sample can be measured in an analyser that provides results in less than 10 minutes. The lower the concentration of fFN in the sample, the less likely preterm delivery is to occur. Although another type of fFN test, which provided a positive or negative result, has been available for some time, the ability to measure the absolute amount of fibronectin is new. This new test has the potential to more accurately rule out preterm labour.

The main aim of this research is to see if qfFN can accurately rule out spontaneous preterm delivery within 7 days of testing. Before commencing the QUIDS study, we will analyse previous research data to see if qfFN is likely to be a useful test – either on its own, or in combination with clinical features that may increase the likelihood of preterm delivery (such as history of previous preterm labour or twin pregnancy). We will then determine which combination of features can help diagnose preterm labour most effectively, whilst still being good value to the NHS. In order to ensure that this 'model' works in UK populations, we will test its ability to predict preterm delivery using data collected from women attending at least 8 UK maternity units with

symptoms of preterm labour, and then adapt it as necessary. We will use our findings to develop a decision support tool, to help women and clinicians assess how likely preterm delivery is, and decide whether to start treatment or not. We will ask women, their partners and their caregivers which outcomes are most important when making decisions, and how best to present the decision support, to make sure it is relevant to them. We will make the decision support freely available, most likely as a web-based application.

The work will be carried out over 30 months, by a team with the necessary expertise to complete the research. Public representatives will be involved in trial design, management and interpretation and dissemination of results. Patient advisory groups will also be regularly consulted, and women and their partners will be involved in the needs assessment to design the decision support.

SCIENTIFIC SUMMARY

RESEARCH QUESTION

In women with symptoms suggestive of preterm labour what is the prognostic value of quantitative fetal fibronectin (qfFN) for ruling out preterm labour at different thresholds?

AIM

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 qfFN.

DESIGN

In part 1 of the QUIDS study, we will perform IPD meta-analysis of existing data sets to develop a prognostic model using qfFN and other clinical risk factors. We will also perform focus group consultation with women, their partners and caregivers, to assess decisional needs in relation to threatened preterm labour. These will influence design of a decision support tool. Part 2 of the study we will validate (+/- refine) the prognostic model and decision support tool using data collected in a prospective cohort study in at least eight UK sites.

SETTING

IPD meta-analysis: 5 European studies of women with symptoms of preterm labour. Prospective cohort study: At least 8 UK consultant-led maternity units.

TARGET POPULATION

Women with signs and symptoms of preterm labour at 22^{+0} -34^{+6} weeks gestation in whom admission, transfer or treatment is being considered.

HEALTH TECHNOLOGIES BEING ASSESSED

Quantitative Fetal Fibronectin (qfFN)

MEASUREMENT OF COSTS AND OUTCOMES

Primary outcome will be ability of the prognostic model to rule out spontaneous preterm birth within 7 days. Other endpoints of the model will be influenced by focus groups. IPD meta-analysis will develop a prognostic model including qfFN concentration as a risk factor, in addition to other important risk factors, and evaluate added value of qfFN in prognostic model performance. The prognostic model will be validated using data collected in the prospective cohort and refined as necessary. An economic analysis will be undertaken from an NHS perspective to assess potential cost-effectiveness of the qfFN prognostic model. A decision analytic model will be built and populated with existing data on current practice and resource use and diagnostic outcome data from the prospective cohort study, reporting outcomes in terms of the incremental cost per QALY gained.

SAMPLE SIZE

IPD meta-analysis: 5 studies, 1,783 women and 139 events of preterm delivery within 7 days of testing.

Prospective Cohort Study: 1600 women with estimated 96-192 events of preterm delivery within 7 days of testing

RECRUITMENT AND DATA COLLECTION

A member of clinical staff will identify potentially eligible participants, provide a patient information leaflet and invite consent. Research midwives will collect outcome data from the maternal and neonatal clinical records.

TIMETABLE

Dec 2015 - May 2018

Focus group consultation will be performed in first 3 months. The first iteration of the prognostic model will be prepared by June 2016. The prospective cohort study will commence September 2016 and run for 12 months. Our estimated recruitment rate of 4.45% of all maternities is based on a UK study and a prospective feasibility study.

Full delivery details of participants will be available 20 weeks after recruitment ends to enable final validation of the prognostic model. A decision support tool will be developed and tested alongside the prospective cohort study.

TRANSLATION

If the qfFN based decision support tool is able to rule out preterm labour then it will be rapidly translatable into NHS practice.

EXPERTISE IN TEAM

Members have the required expertise in preterm labour research, including experience with studies of predictors of preterm labour and fFN, diagnostic tests, multicentre trials, IPD meta-analysis, health economic modelling, patient acceptability, and representation from public.

1 INTRODUCTION

1.1 BACKGROUND

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[1,2]. Preterm delivery remains the leading cause of neonatal morbidity and mortality, but timely interventions in women with preterm labour can improve neonatal outcome.

Establishing a diagnosis of preterm labour is, however, challenging, and false positive diagnoses are common. In a large RCT over 80% of women in whom preterm labour was 'diagnosed' on clinical grounds remained undelivered at 7 days post diagnosis[3]. Such diagnostic uncertainty means a large proportion of women with symptoms of preterm labour are treated unnecessarily, to ensure treatment is given to the few women who do actually deliver preterm. Unnecessary interventions result in both a substantial economic burden to health services and potential adverse maternal and neonatal events.

Diagnostic tests for preterm labour are available and used in many units in the UK. Markers of preterm labour can be measured in samples of cervicovaginal secretions collected at a speculum examination (e.g. fFN). An alternative approach (which can be combined with cervicovaginal tests) is to measure the cervical length using transvaginal ultrasound, as the longer the cervix is, the less likely a preterm delivery [4].

fFN is one of the best-researched tests, and recent systematic review has suggested it may have the potential to reduce resource usage[5]. Until recently, only qualitative fFN tests were available for near bedside testing in women with symptom suggestive of preterm labour, which provided a positive or negative result based on a single threshold. However, rapid quantitative fFN (qfFN) tests are now available that measure fFN on a continuous scale and which may better refine clinical decision making.

If effective, the proposed qfFN clinical decision support is likely to decrease unnecessary hospital admissions and often long distance inter-hospital transfers for women with signs and symptoms of preterm labour, but who do not deliver

preterm. These unnecessary admissions are very costly to healthcare services, and carry a significant but often unrecognised financial and emotional burden to women and their families. The Scottish Perinatal Collaborative Transport Study ("CoTS")[6] reported on maternal and neonatal transfers across Scotland and found that threatened preterm labour was the most frequently cited indication for maternal transfer, resulting in approximately 4.4 transfers per 1000 maternities. Only one quarter of transferred women delivered within the subsequent 48 hours. A qualitative study of women who experienced in utero transfer found that hospital admission and transfer had a substantial negative financial and emotional impact on their families [7], Adverse effects particularly related to care of other children and dependents whilst in hospital, travel and accommodation costs for partners and family members near the destination hospital, and employment issues for partners and family members. A recommendation of the CoTS study was to "Establish the feasibility of identifying and introducing rapid bedside testing to predict and/or establish the existence of premature labour."

qfFN has the potential to improve targeting of maternal treatments that improve neonatal outcome in preterm infants, but are potentially harmful to women and their babies if early delivery does not occur. Antenatal steroids decrease neonatal morbidity and mortality, with maximal effectiveness if delivery occurs 48h to 7 days after administration [8]. However, repeated doses of steroids may increase morbidity. In a recently reported 5 year follow-up trial of repeated doses of corticosteroids for women at risk of preterm birth, a sub-analysis of the data suggested that children who had received multiple doses of corticosteroids but were born at term, had a higher incidence of neurosensory disability[9]. Maternal Magnesium Sulphate infusion in the hours immediately prior to delivery can lower the risk of cerebral palsy in preterm neonates, but is safe only within a narrow dosage range, and overdose can cause respiratory depression and cardiac arrest in the mother [10]. Tocolysis also can have serious adverse effects for both mother and baby [11].

The effect of fFN or other tests of preterm labour on maternal anxiety is unclear. Women with signs and symptoms of preterm labour have high anxiety scores and uncertainty of outcome is thought to contribute to antenatal anxiety [12]. fFN may thus help decrease anxiety, particularly if it rules out likely preterm delivery. On the other hand, when fFN is used as a screening test for preterm labour in asymptomatic women it is associated with high anxiety scores [13]. We will evaluate

the effect of fFN on maternal anxiety. This is particularly important as maternal stress can contribute to the risk of preterm delivery.

1.2 RATIONALE AND JUSTIFICATION FOR STUDY

A recent HTA funded systematic review and cost-analysis [4] suggested that fFN testing has a moderate accuracy for predicting preterm birth, but that the main potential role of fFN testing was likely to be through reducing health-care resource use by ruling out likely preterm delivery. Although the economic analysis showed a modest cost benefit in favour of fFN testing, this was largely dependent on whether or not fFN testing reduced hospital admission. The authors concluded that more research was needed to confirm the effect on costs.

Until recently, only qualitative fFN tests were available for near bedside testing of samples from women with signs and symptoms of preterm labour. Rapid quantitative fFN tests are now available that measure fFN on a continuous scale. Qualitative tests based on a single threshold are prone to high false-positive or negative results around the threshold value. Studies that have used quantification of fFN suggest fFN concentration can improve prediction of preterm birth <34 weeks [14]. However, there is little evidence about which thresholds to use and how these relate to outcomes that are important to women with signs and symptoms of preterm labour and their caregivers when deciding on management.

We surveyed current practice in UK maternity units (response rate 66% [137/207]; Mar-July 2014). 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 aid for qfFN is thus likely to improve decision making, even if qfFN is already available in clinical practice.

1.3 INTENDED PURPOSE OF THE INVESTIGATIONAL TOOL

The end product of the investigational study will be a web based or mobile app decision support to help clinicians, women and their partners decide on management of threatened preterm labour. It will be based on the results of the quantitative fetal Fibronectin.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

Primary Objective

The primary aim of the QUIDS study is:

- To develop a mobile app 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.

Specific objectives relating to this are to:
i) Determine the decisional needs of pregnant women with signs and symptoms of preterm labour, their partners and their caregivers (as described in separate protocol “QUIDS Qualitative”).

ii) Develop a prognostic model using quantitative fFN and other risk factors based on IPD meta- analysis of existing data sets from efficacy studies of quantitative fFN, and to evaluate the added value of quantitative fFN toward this prognostic model performance.

iii) Externally validate and, if necessary, refine the prognostic model using data collected in a prospective cohort study of women presenting with symptoms suggestive of preterm labour in UK hospitals, before converting it to a web based or mobile app presented format at the end of the study.

Secondary Objectives

Secondary aims of the study are

- To assess the acceptability of fFN testing.
- To provide an economic rationale for the prognostic model and analyse its cost-effectiveness from the perspective of the NHS.

2.2 ENDPOINTS

Primary Endpoint

Spontaneous preterm delivery within 7 days of fetal Fibronectin test, in women less than 36 weeks gestation.

Secondary Endpoints

Secondary endpoints will be influenced by focus group consultations, but may include delivery within 48 hours of fetal Fibronectin test, delivery before 34 weeks gestational age, time to delivery and any preterm delivery (occurring before 37 weeks) subsequent to signs and symptoms of preterm labour.

3 STUDY DESIGN

3.1 METHODS AND TIMING FOR ASSESSING, RECORDING AND ANALYSING VARIABLES.

Health technologies being assessed

The trial will evaluate the Rapid fFN 10Q System (Hologic, Crawley, West Sussex), which provides a concentration of fFN (ng/ml or INVALID) within 10 minutes. It is now the only commercially available fFN test system, and replaces the TLiQ rapid analyser system, which provided a qualitative fFN result (POSITIVE or NEGATIVE) based on a threshold of 50ng/ml. As per the EQUIPP study [14] , we will use analysers provided by Hologic that produce a positive/negative result in addition to a 3 letter code blinding the clinician from the quantitative result. This will ensure there is no bias in treatment and that clinical care would continue as per current practice. However, if the site wishes not to be blinded, we will accept this decision. The testing procedure will be as per the manufacturer's instructions. Samples will be taken with a fFN specimen collection kit, which consists of a sterile polyester tipped swab and a specimen transport tube containing 1 ml extraction buffer (an aqueous solution containing protease inhibitors and protein preservatives including aprotinin, bovine serum albumin, and sodium azide). During speculum examination the sterile swab will be lightly rotated across the posterior fornix of the vagina for ten seconds to absorb vaginal secretions. Samples will be taken before any other swabs (e.g. for microbiology) or cervical manipulation and the speculum will be lubricated with normal saline as other lubricants may interfere with the antibody-antigen reaction of the test. Following specimen collection the swab will be removed, immersed in extraction buffer, the shaft of the swab snapped off, and the transport tube sealed.

Samples will be analysed by lateral flow; solid-phase immunochromatographic assay called the Rapid fFN Cassette, and interpreted in the 10Q Rapid analyser. Before analysis samples will be gently mixed and as much liquid as possible expressed from the swab by rolling the tip against the inside of the tube. 200 µL of the sample will be pipetted into the sample application well of the Rapid fFN Cassette using a polypropylene or polyethylene pipette. The sample will then flow from an absorbent pad across a nitrocellulose membrane via capillary action through a reaction zone containing murine monoclonal anti-fetal fibronectin antibody conjugated to blue microspheres (conjugate). The conjugate, embedded in the membrane, will be mobilized by the flow of the sample. The sample will then flow through a zone containing goat polyclonal antihuman fibronectin antibody that captures the fibronectin-conjugate complexes. The remaining sample will flow through a zone containing goat polyclonal anti-mouse IgG antibody that captures unbound conjugate, resulting in a control line. After 10 minutes of reaction time, the intensities of the test line and control line will be interpreted with the TLiIQ analyzer. A printed result will be provided for use in audit. Test results will be reported as a concentration in ng/ml (0->500ng/ml) or INVALID. The result is invalid if the test does not meet internal quality controls that are performed automatically with every test. In the event of an invalid result, the test can be repeated with any remaining clinical specimen. Evidence from previous studies of fFN carried out by the applicants has shown a rate of invalid results of less than <1% after repeat testing [14].

The Rapid fFN 10Q system is designed to be a point of care test, and clinical staff can easily perform analysis. All reagents for fFN testing can be stored at room and specimen collection kits, reagents, cassettes and the 10Q analyzer can be kept in clinical areas where women with symptoms of preterm labour are assessed so they can be conveniently accessed. A daily quality control should be performed using the reusable Rapid fFN 10Q QCette® QC Device, which verifies that the analyser performance is within specification with results in 3 minutes.

Target population

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

Design and theoretical/conceptual framework

See flow chart APPENDIX 1

The primary aim of the 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, outlined below. Subsequent sections of the protocol have been divided into parts 1 and 2 for clarity.

3.2 PART 1: DEVELOPMENT OF PROGNOSTIC MODEL AND DECISION SUPPORT TOOL

The prognostic model will be developed into a decision support tool, presented in a format for use by clinicians, women and their families. This will likely be paper based initially, and will be validated+/- refined with data from the prospective cohort study. We will convert it to web based or mobile app based presentation at the end of the study.

Focus group consultation: *To determine the decisional needs of pregnant women with signs and symptoms of preterm labour, their caregivers and clinicians.*

This work is being led by professor Dame Tina Lavender, and sponsored by the University of Manchester, described in separate protocol “QUIDS Qualitative” (appendix 2). A qualitative framework approach will be used, based on data collected from focus groups and semi-structured telephone interviews.

Individual Participant Data (IPD) meta-analysis: *To develop a prognostic model using quantitative fFN and other risk factors and to evaluate the added value of quantitative fFN toward this prognostic model performance.*

A prognostic model will be developed based on IPD meta-analysis of 5 existing datasets (n=1,783 with 139 events of preterm labour within seven days) from prospective cohort studies where quantitative fFN results and pregnancy outcome details are available. The primary outcome of the model will be delivery within 7 days, although other endpoints will be included if recommended by focus groups.

We will include an economic analysis from an early stage to provide an economic rationale for the prognostic model and the risk factors included in it prior to its validation in the prospective cohort study.

3.3 PART 2: VALIDATION AND REFINEMENT OF PROGNOSTIC MODEL AND DECISION AID

Prospective cohort study

A prospective cohort study will be performed in at least 8 UK hospitals with different settings (rural/urban) and different levels of neonatal care facilities to externally validate, and if necessary refine, the prognostic model using the data collected

We will also assess the potential cost-effectiveness of the final prognostic model/decision support tool compared to clinical assessment only. This additional analysis allows us to model the full costs and effect impacts of the different prognostic models and compare these in a cost-effectiveness analysis to provide an evidence-based economic rationale for implementing the diagnostic tool in the NHS.

4 QUIDS PART 1 (*development of prognostic model and decision support*)

4.1 FOCUS GROUPS

A brief summary is written below. Please refer to appendix 2 for the full “QUIDS Qualitative” protocol.

STUDY POPULATION

Two focus groups of 4–8 women will be conducted at each of 3 sites (Liverpool Women’s NHS Foundation Trust, Birmingham Women’s NHS Foundation Trust and Royal Infirmary of Edinburgh, NHS Lothian) one for pregnant women who are at high risk of preterm birth, and one for postnatal women who have recently experienced preterm birth. This qualitative approach has been chosen as focus groups have the advantage of encouraging discussion amongst homogenous groups, thus providing insight and understanding on a topic of shared interest.

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. Hence, structured topic guides will be used to initiate and concentrate the discussion.

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. 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.

STATISTICS AND DATA ANALYSIS

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. 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.

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.

4.2 INDIVIDUAL PATIENT DATA META-ANALYSIS

STUDY POPULATION

NUMBER OF PARTICIPANTS:

5 European studies of women with symptoms of preterm labour, comprising 1,783 women and 139 events of preterm delivery within 7 days of testing. The studies to be

included in the IPD meta-analysis are from consultant led maternity units in the UK (3 studies) and Europe (2 studies).

A prognostic model will be developed based on IPD meta-analysis of 5 existing datasets (n=1,783 with 139 events of preterm labour within seven days). The primary outcome of the model will be delivery within seven days. This is a clinically important time point, because antenatal steroids (which significantly reduce morbidity and mortality in preterm babies) are most effective if delivery occurs within seven days of administration. As repeated doses of antenatal steroids may be harmful, only one course of antenatal steroids is given in any pregnancy, even if there are subsequent episodes of suspected preterm labour. It is thus crucial to ensure steroids are timed correctly and not given unnecessarily if delivery within seven days is unlikely. Other endpoints may be identified in consultation with focus groups and we will include these if feasible to do so within the constraints of the data available for model development.

We will include an economic analysis from an early stage to provide an economic rationale for the prognostic model and the value of the information included in it prior to its validation in the prospective cohort study. We will also assess the potential cost-effectiveness of the final prognostic model/decision support tool compared to clinical assessment only.

INCLUSION CRITERIA

Prospective cohort studies or RCTs of women with signs and symptom of preterm labour (as defined by investigators) identified by literature search and contact through networks and professional organizations in March 2014; which 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

Studies where quantitative fFN is measured by ELISA. Studies where IPD is not available for meta-analysis.

CO-ENROLMENT

Not applicable

PARTICIPANT SELECTION AND ENROLLEMENT

IDENTIFYING TRIALS FOR INCLUSION

We performed a literature review and searched clinical trial databases and registries for completed and ongoing cohort studies of quantitative fFN, and consulted preterm birth researchers and networks and the manufacturers of quantitative fFN, (Hologic) to ensure capture of all relevant studies. We identified five studies using the clinical platform available for quantitative fFN testing, the Rapid fFN 10Q System, and have completed recruitment. These are summarized in ***Table 1***. We contacted the PIs of the 6 studies in April 2014 to invite them to collaborate. The PIs of 5 studies have committed to providing data for the IPD meta-analysis as evidenced by their involvement as co-applicants on this application (Mol, van Baaren, Khalil, Shennan, David). The PI of the 6th study (Elovitz) has agreed to be a collaborator, and data may be available after publication of her study, for which recruitment is ongoing. An additional 4 earlier datasets, which used ELISA to determine the concentration of fFN were also identified ([[15]; containing 2 trial datasets], [16,17]). However, these will not be included, as the different method of analysis and earlier period of study would increase heterogeneity between the studies.

TABLE 1

	PI	*Setting*	*N*	*Events*	*Dates*	*Inclusion*	*Primary Outcome*	*Notes*
Studies with data available								
EQUIPP [14] 1 1	Prof A Shennan	5 UK centres	452	14	(study completed)	22-35 weeks with symptoms of preterm labour	Delivery <34 weeks gestation	
EUFIS [18]	Prof BW Mol	10 European Hospitals	452	48	2012-2014 (recruitment completed Jun 2014)	24-34 weeks with preterm contractions and intact membranes	Delivery within 7 days of test	Includes cervical length
APOSTEL I [19]	van Baaren	10 Dutch Hospitals	528	70	2009 -2012 (study completed)	24-34 weeks with preterm contractions and intact membranes	Days to delivery truncated at 7 days	Includes cervical length
QFCAPS	Dr A Khalil	London teaching hospital	86	2	2012-2014 (recruitment ongoing through November 2014)	24-34 weeks with symptoms of preterm labour	Delivery within 7 days of test	Includes cervical length Singletons only
UCLH/Whit	Dr A David	2 UK centres	262	5	(study completed)	22-35 weeks with symptoms of preterm labour	Delivery within 7 days of test	
	TOTALS	***4 studies***	***1,783***	***139***				
Other studies in which data may become available in future								
STOP study (http://clinicaltrials.gov/show/NCT01868308)	Prof M Elovitz	USA teaching hospital	700	NK	2011-2014 (recruitment ongoing through December 2014)	22 -34 weeks Symptomatic women with singleton pregnancy	Delivery before 37 weeks	

CONSENTING PARTICIPANTS

All women in the included trials provided informed consent for participation in clinical trials, and for their data to be used in subsequent analyses.

SCREENING FOR ELIGIBILITY

Trials for inclusion were screened by the investigators to ensure they fulfilled eligibility criteria.

STATISTICS AND DATA ANALYSIS

SAMPLE SIZE CALCULATION

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 at least ten events required for each covariate [20] In our IPD meta-analysis data we have 139 events so far (preterm labour within 7 days of testing) therefore we can explore the influence of quantitative fFN and up 14 other covariates [21].

PROPOSED ANALYSES

The following factors which have been shown to influence risk of preterm labour, will be considered for inclusion as covariates in the prognostic model: quantitative fFN concentration, singleton/multiple pregnancy, 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, fetal sex, tocolysis, cervical length.

We will assess study quality according to QUADAS-2[22], QUIPS [37] and CHARMS [38] guidelines

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 Principal Investigator of the original study, and amended as indicated by consensus discussion.

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. Other endpoints will be considered if found to be important in focus group consultations, and might include delivery <48 hours and delivery <34 weeks. We will develop an initial model with quantitative fFN concentration, and then add clinical predictor variables (e.g. gestation, number of uterine contractions in a set time period, cervical dilatation) and cervical length measurement (where available [2 studies]). Tocolysis (which may delay onset of labour, although likely not beyond 48 hours) will be included as a categorical variable. 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 [23]. 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. We will use backward stepwise selection based on an information criterion (e.g. Akaike's information criterion) to identify a parsimonious set of included predictors. The approach of adding specialist tests such as cervical length only after considering simpler clinical assessment will maximise the utility of the model by ensuring that extra tests with their additional costs will 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, and if so, multiple imputation of observed participant characteristics will be used, with missing data imputed within each original study, before pooling of study data. The results of these analyses will be compared with a complete case analysis. Heterogeneity of included studies will be assessed using I2 and random-effect meta-analysis techniques. Heterogeneity between studies and dependency of data originating from the same study will be taken into account by random effects as appropriate (e.g. in terms of the predictor effects) and a separate intercept term per study. Predictors with large heterogeneity in the prognostic effect across studies may be removed to ensure summary Beta terms in the model are meaningful (accurate) for individual populations [39]. 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.

ASSESSING APPARENT MODEL PERFORMANCE

The apparent performance of the model will be assessed by overall fit, discrimination and calibration in the IPD. Overall fit of the models will be expressed with Nagelkerke R2. The ability of the models to discriminate between women with and without spontaneous preterm birth will be determined by the area under the receiver operating characteristics curve (AUC). 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.

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 the 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.

PRODUCTION OF FINAL MODEL FROM IPD META-ANALYSIS VIA UNIFORM SHRINKAGE

The optimism-adjusted calibration slope from 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 thereby produces a final model produced containing the updated intercepts and the shrunken beta coefficients [24]. With multiple intercepts, a strategy (or strategies) will be developed amongst the study investigators for which intercept should be chosen for use (e.g. choose intercept from study that most closely resembles the population of

application); each strategy can be 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).

ECONOMIC ANALYSIS

An early stage decision 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. 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 model will also enable us to explore potential cost effectiveness of the prognostic model at different thresholds on the ROC curve, providing an economic rationale for the chosen prognostic for the cohort study.

DECISION SUPPORT DEVELOPMENT

We will develop the decision support tool in accordance with the guidelines produced by the International Patient Decision Aid Standards (IPDAS) Collaboration (http://ipdas.ohri.ca). Scoping of decisional requirements and how data should be presented will be performed during focus group consultation. A prototype decision support tool will be designed incorporating the initial prognostic model developed as part of the IPD-meta-analysis. 'Alpha' testing will be performed with women and clinicians, again in focus groups, in an iterative process to ensure comprehensibility and usability.

5 QUIDS PART 2: VALIDATION +/- REFINEMENT OF PROGNOSTIC MODEL AND DECISION SUPPORT

5.1 STUDY POPULATION

NUMBER OF PARTICIPANTS

The study will include women with signs and symptoms of preterm labour at 22^{+0} – 34^{+6} weeks gestation in whom admission, transfer or treatment is being considered. Target is 1600 women with estimated 96-192 events of preterm delivery within 7 days of testing. These will be recruited from at least 8 sites with a mix of rural/urban settings, and have different levels of neonatal care facilities. The recruitment period is anticipated to last 12 months.

INCLUSION CRITERIA

The following inclusion criteria apply at <u>screening assessment</u> (all apply):

- Women who are 22^{+0} – 34^{+6} weeks (or earlier gestation if the fetus is considered potentially viable).
- Women showing signs and symptoms of pre-term labour which may include any or all of back pain, abdominal cramping, abdominal pain, light vaginal bleeding, vaginal pressure, uterine tightenings or contractions and cervical effacement or dilatation.
- Women where hospital admission, interhospital transfer or treatment (antenatal steroids, tocolysis or magnesium sulphate) is being considered due to signs of pre-term labour.
- Women aged 16 years or above.

The broad inclusion criteria reflects current clinical practice and enables the generalisability of the results of the trial for routine clinical care. We will include women who re-attend 7 days or more after initial recruitment with signs and symptoms of preterm labour and also women who remain symptomatic but undelivered 7 days later in whom repeat testing by the clinician is deemed to be appropriate. This will be in line with manufacturer's recommendation for fFN testing.

The following inclusion criteria apply on <u>speculum examination</u>:

- Cervical dilation ≤ 3cm
- Intact membranes

- No significant vaginal bleeding, as judged by the clinician.
- fFN swab taken.

The potential participant must meet all criteria at screening and speculum examination to be able to be fully enrolled on the study.

EXCLUSION CRITERIA

The following exclusion criteria apply:

- Contraindication to vaginal examination (e.g. placenta praevia).
- Multiple Pregnancy of triplets or more.
- Moderate or severe vaginal bleeding.
- Cervical dilatation greater than 3cm.
- Confirmed rupture of membranes.
- Sexual intercourse, vaginal examination or transvaginal ultrasound in the preceding 24 hours factors can invalidate results. These women will be initially excluded from the study, but can be included if still symptomatic after 24 hours, when fFN accuracy will be restored.

CO-ENROLEMENT

This trial involves validating a decision support tool relating to a test that is currently commonly used in clinical practice. As such, there are no additional interventions. Co-enrolment in other non-interventional trials will be allowed. Co-enrolment in trials of tocolytic treatments or other management strategies that may influence timing of delivery as a primary outcome will not be allowed. Participation in QUIDs would not preclude babies being subsequently involved in interventional trials. Co-enrolment will be recorded in eCRF.

5.2 PARTICIPANT SELECTION AND ENROLMENT

IDENTIFYING PARTICIPANTS

Women with signs and symptoms of preterm labour will be identified on presentation to obstetric services. A member of clinical staff, usually the doctor or midwife assessing the woman, will identify potentially eligible participants, provide a participant information leaflet and invite consent.

CONSENTING PARTICIPANTS

A suitably trained member of clinical staff (doctor or midwife) or research team will consent participants.

Posters and leaflets will be situated in antenatal areas of participating hospitals to alert women that the study is taking place, and women will be allowed as much time as possible to consider participation without unduly delaying further clinical assessment. Participants will receive adequate oral and written information and appropriate Participant Information and Informed Consent Forms will be provided. The participant will be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. Due to the time critical and potentially stressful clinical situation, a summary leaflet will be provided initially and then followed up with a more detailed information sheet after the fFN swab has been taken. The participant and the consenter will sign the consent form to confirm that consent has been obtained. The participant will receive a copy of this document and a copy will be filed in the investigator site file.

SCREENING FOR ELIGIBILITY

The clinical likelihood of preterm delivery is usually evaluated by history and examination, which includes abdominal palpation, to assess strength and frequency of uterine contractions. If preterm labour is suspected, a vaginal speculum examination is usually performed where the cervix is inspected for dilatation, and evidence of vaginal bleeding and membrane rupture assessed. Swabs for fFN are usually taken at this point. Potential participants in the QUIDS study will be identified after the initial assessment and provided with information about the study. The combined Screening and Consent Form will be used as a self-screening tool for potentially eligible participants. Informed consent will take place before speculum examination and the fFN swab has been taken. This approach means that samples are collected at routine speculum examination, as they would be if fFN is implemented in clinical practice, and participants avoid an additional vaginal examination.

INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Certain exclusion criteria can only be assessed at speculum examination (for example vaginal bleeding or evidence of ruptured membranes) so a proportion of women will become ineligible for participation at this time. In all other women a swab for quantitative fFN testing will be taken. The reason for exclusion of potentially eligible participants will be recorded where possible for input into study metrics. This data will be entered onto the eCRF Screening Log and delivery outcomes collected for these participants.

WITHDRAWAL OF STUDY PARTICIPANTS

Women will be able to withdraw consent for us of their data at any time until the end of the study.

5.3 STUDY ASSESSMENTS

ELIGIBILITY ASSESSMENT (Screening and Recruitment)

Women presenting with signs and symptoms of pre-term labour will be identified on presentation to obstetric services. The doctor or midwife assessing the woman will identify potentially eligible participants and provide an invitation letter and short information leaflet.

After the woman has had the opportunity to consider whether she would like to participate, she will be asked to complete the Screening/Consent Form. This will be done before the speculum examination and the fFN test is done. It is at this point, if required, the woman will undergo the speculum examination. The clinician will then decide whether the fFN test can be carried out. If the test can be carried out (according to manufacturer's guidelines) then the participant will be fully enrolled on the study. If the swab cannot be taken, the participant will be provided with a letter explaining why they cannot be fully enrolled and thanking them for their interest in taking part in the study.

If the woman declines to participate and she is willing to provide a reason for this, the reason given will be entered on to an anonymous log. There will be no personal identifiable data held in the log. Baseline demographics will be collected on consenting women, together with height and weight, information on medical history, obstetric history, estimated date of delivery together with the signs and symptoms they are presenting with. The original consent form will be stored in the Investigator Site File (ISF) file, a copy is given to the woman, a copy added to the medical notes and a copy sent to the Trial Office.

After providing consent, the participant will be asked to complete a short State Trait Anxiety Inventory (STAI) questionnaire and complete a contact details form. They will also be issued with a letter thanking them for taking part in the trial and giving details of the second questionnaire to be completed.

REPEAT fFN TESTS

Should the participant require further fFN tests to be carried out, the results will also be collected and recorded on the CRF/eCRF.

DELIVERY DETAILS

Labour/Delivery/ Neonatal Assessments

Admission for delivery will not be a formal study visit but data will be collected using information recorded in the participant's notes. Delivery data will be collected on the maternal outcomes of delivery, including method of delivery, indication for delivery method, onset of labour, date and gestation of delivery and blood loss.

QUESTIONNAIRES

All participants who are eligible to participate will be asked to complete a State Trait Anxiety Inventory (STAI) questionnaire after consenting and before the speculum examination. The same questionnaire will be repeated 24-48 hours post examination. The second questionnaire will be provided on paper with a pre-paid envelope to be returned by post to the Trial Office. Should we not receive the second questionnaire, the Trial Office will try to contact the participant, (with the contact details provided), to see if the questionnaire can be completed over the phone.

STUDY ASSESSMENTS

	Attendance with signs and symptoms preterm labour			
Visit	**Screening and Recruitment**	**24-48h**	**1-6 months**	**DELIVERY**
Responsibility of Site PI and Local teams				
Inc/Exc Criteria	**X**			
PIS	**X**			
Consent Form	**X**			
Demographics	**X**			
Obstetric History	**X**			
Symptoms and Signs	**X**			
Quantitative ffN	**X**			
Cervical length/ TV scan (only if IPD meta-analysis suggests value)	**X**			
STAI Questionnaire	**X**	**X**		
Delivery details				**X**
Neonatal outcomes				**X**
Finalise eCRF data				**X**
Responsibility of Qualitative Research Team				
Qualitative Acceptability Questionnaires (subgroup n=30)			**X**	

SAFETY ASSESSMENTS

Hologic analyser

The Hologic Rapid fFN 10Q analyzer has integrated quality control measures, and we will keep records of these as well as staff training logs. A daily pre-calibrated reusable quality control cassette must be inserted and analysed every 24 hours to verify that the analyser performance is within specification. Logs of results are stored on the machine and will be downloaded, and we will also keep a paper log of printed results. Each patient test has an internal quality control, with a procedural control line that verifies the threshold level of signal by the instrument. Sample flow detection ensures the sample travels across the cassette properly, and confirms absence of conjugate aggregation. We believe that these measures will help ensure the validity of results. However, to provide further evidence of integrity and comparability of results from each site we will request that all participating sites enroll in the WEQAS Point of Care Quality Assurance Scheme for preterm labour markers at a cost of £180 (+ VAT) per site. WEQAS will provide a sample for analysis to each site bimonthly, and provide reports on analyser performance and variability (http://www.weqas.co.uk/index.html).

5.4 DATA COLLECTION

DATA FOR PROGNOSTIC MODEL VALIDATION

In the prospective cohort the CRF and database will be based on those developed for the OPPTIMUM study. We will collect data on all of the candidate predictors considered for inclusion in the prognostic model developed in the IPD meta-analysis. Outcome data will include gestational age at delivery, date and time of delivery, administration of treatments for preterm labour (steroids, antibiotics, tocolysis, magnesium sulphate) duration hospital admission, hospital transfer, onset of labour (preterm prelabour rupture of membranes; idiopathic preterm birth; medically indicated preterm birth [and indication]), place of delivery (base hospital, other hospital, outwith hospital), mode of delivery, neonatal admission, neonatal complications, perinatal mortality, congenital anomaly, sex and birthweight.

Baseline data and data about quantitative fFN testing will be collected on paper based CRFs and research midwives or trial administrator will input these into the web based electronic database. Clinical outcome data will mainly be collected from case notes and recorded on electronic case report forms by research midwives.

MATERNAL ACCEPTABILITY

Maternal anxiety will be measured pre and post-test (24-48h) using the validated State Trait Anxiety Inventory (STAI) questionnaire. Acceptability of fFN testing and the decision aid will be assessed using follow up interviews (face to face or telephone, according to maternal preference) which will be conducted with a sub-group of participants (n=30) purposively sampled and stratified according to geographical location, outcome (preterm labour or not) and anxiety scores. Acceptability will also be assessed in a cohort of clinicians (n=30).

QUALITY CONTROL

The trial administrator and manager based in Edinburgh will liaise with Centre for Healthcare Randomised Trials (CHaRT) about data queries with missing data being collected and fed-back from study centres by the local research team. A subset of individual data items will be checked at site visits.

5.5 STATISTICS AND DATA ANALYSIS

SAMPLE SIZE CALCULATION

We aim to recruit 1,600 women in the prospective cohort study. A UK study has shown that 8.9% of pregnant women present with symptoms of preterm labour and are eligible for quantitative fFN and a 50% recruitment rate is achievable, thus overall 4.5% of maternities could be recruited [25]. The 8 proposed units for inclusion in the cohort study have a combined delivery rate of approximately 36,000 per annum. We will achieve target recruitment within 12 months (1 year * 36,000 * 0.089 * 0.5 = 1,602). Our prospective feasibility study has confirmed that this recruitment is realistic. The study ran over 51 days between 2nd May and 17th June 2014 at the Centre for Reproductive Health in Edinburgh. Over this period of time there were 860 deliveries. 40 women were recruited which equates to 4.7% of women overall, providing evidence of the feasibility of our estimated recruitment rate. All of the participants were identified and invited to provide consent by members of the clinical team caring for women. We anticipate that recruitment could be higher in participating units, where research midwife support will be available and resources allocated to the study.

Vegouwe et al [26] suggest that at least 100 events (preterm labour within 7 day) and 100 non-events (no delivery within 7 days) are required for the validation of a prognostic model. Data from the cohorts included in our IPD meta-analysis suggests an event rate of between 6 [14] and 12% [20] i.e. we expect between 96 and 192 events

(deliveries within 7 days of quantitative fFN testing) within the prospective cohort study. This will ensure validation of the model, even if our event rate is at the lower end of our estimates.

It is possible that the IPD meta-analysis finds there is potential added value of combining quantitative fFN testing with cervical length measurement [20, 27]. As cervical length measurement has significant resource requirement (estimated NHS cost £68.16 per test) and lack of out of hours provision further limits availability in many NHS hospitals, we think it is very unlikely that cervical length scanning will improve performance of the prognostic model to such a degree as to make it cost effective. We will assess the incremental costs and effects of cervical length measurement in the proposed health economic model performed in parallel with the IPD meta-analysis, and will feed into design considerations during the first iteration of the prognostic model. In the unlikely scenario that inclusion of cervical length ultrasound is found to be potentially cost-effective, we will discuss with the board whether we should include it in the prospective cohort study. We would anticipate that including cervical length measurement in the prospective cohort study would decrease recruitment rate (due to need for additional transvaginal ultrasound examination) and also require additional resources to support provision of scans, and application for additional funding would be made.

PROPOSED ANALYSES

VALIDATION OF PROGNOSTIC MODEL

The prognostic model developed in the IPD will be externally validated using data collected in the prospective cohort data, using the measures of discrimination and calibration described above (section 4.2 – Proposed Analysis). The average performance of the model will be summarised across the centers in the cohort study. Between-center heterogeneity in performance will also be summarised, and reduced (if necessary) by recalibration techniques regarding the strategy for the choice of baseline risk (intercept). That is, the predictor effects will not be modified from the IPD meta-analysis model, but the intercept may need to be tailored to improve validation in UK centers (e.g. for rural settings). Based on the findings, a final model and its implementation strategy will then be recommended for use.

ECONOMIC ANALYSIS

The economic model will be refined, integrated and updated with data from the prospective study cohort, so as the most up to date and validated evidence is used to inform a cost-effectiveness decision. Such an iterative approach to economic

evaluation is now well established [28, 29]. The care pathway following diagnosis will be included in the economic analysis, using data from the cohort study such as the diagnostic test accuracy data, resource use data (i.e. steroid use, other medications, time in hospital, hospital transfer) and secondary outcome data (i.e., treatment of side-effects, morbidity, mortality) so as to capture the full costs and effect impacts (quality of life, morbidity and mortality) for both the mother and baby. Resource use data will be combined with unit cost information from the British National Formulary [30] and NHS reference costs [31, 32]. Outcomes will be reported as the incremental cost per correct diagnosis, and incremental cost per Quality Adjusted Life Year (QALY) gained of the qfFN prognostic model compared to current practice (no qfFN model). The analysis will adhere to the NICE reference case [33] and the recommended guidelines for decision modeling and reporting of economic analyses [34]. Probabilistic sensitivity analysis will be undertaken to explore how uncertainty in the model inputs impact on the cost-effectiveness outcome [35].

DECISION SUPPORT DEVELOPMENT

Testing of the prototype decision support will be performed alongside the prospective cohort study to determine feasibility of the prototype. The final version will be updated with the validated (and, if necessary revised) prognostic model generated from the prospective cohort study. The multidisciplinary trial steering committee will oversee the development process, and decide how material is selected for inclusion.

ACCEPTABILITY OF FFN TESTING AND THE DECISION SUPPORT TOOL

Maternal anxiety will be measured pre and post test using the validated State Trait Anxiety Inventory (STAI) 51. The State-Trait Anxiety Inventory Form Y (STAI) is a widely used tool for measuring both temporary "state anxiety" and the more general, long-standing "trait anxiety". The STAI is designed for the self-reported assessment of the intensity of feelings of apprehension, tension, nervousness, and worry. STAIS-Anxiety scores increase in response to physical danger and psychological stress, making it highly appropriate for this study. The use of STAI in pregnancy studies is discussed in [36] and we will interpret the results accordingly.

The questionnaire will be administered prior to fFN testing (baseline) and 24-48 hrs after the test, to assess early reactions to the test and any acute anxiety prompted by the result of the test. We will also be able to assess any differences in those presented with a high risk or low risk result. Although it might be interesting to assess anxiety again in the latter stages of pregnancy, it is likely that, in this population, many pregnancies will not reach full term. Thus we believe our strategy of repeat

questionnaire administration will allow measurement of longer term anxiety induced or alleviated by the test, whilst minimising bias due to preterm or term delivery itself or loss to follow up.

The follow up interviews with a sub-group of participants (n=30) will enable deeper exploration of women's views, to gain insight into the rationale for responses given in the questionnaires. Interviews will be conducted following confirmation of pregnancy status. All interviews will be audio recorded with consent, and field notes taken to ensure an audit trail.

6 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

6.1 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.

The Trial Manager based in Edinburgh will oversee the study and will be accountable to the Chief Investigator. The Trial Manager supported by the trial administrator(s) will take responsibility for the day-to-day transaction of study activities. They will be supported by the CTU at CHaRT to provide expertise and guidance. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

6.2 PATIENT ADVISORY GROUP (PAG)

We will set up a public involvement advisory group (PAG) with parents recruited from existing groups, including parents who have experienced preterm birth and threatened preterm labour.

The group will meet every 6-9 months to discuss the project and will communicate via email/phone as necessary between these meetings. Workshops will be set up to introduce the project and to get parents' views key issues identified by the team,

through the CI. The group will also contribute to focus groups, and further development of the patient information sheet and consent form and suggest strategies to improve the acceptability of the decision support.

Two representatives are included in the Project Management Group and the Trial Steering Committee. They will help to ensure appropriate involvement in the project between PAG meetings. Support for these representatives will be primarily through teleconferencing and email. Between these meetings the group will receive email updates about the conduct of the project.

6.3 DIVISION OF RESPONSIBILITIES

The responsibilities of the investigators are as follows:

- Chief Investigator, Stock: overall responsibility for the design, conduct, analyses and reporting of the trial; assisted by the PMG.
- The Chief Investigator, Trial Manager and Trial Administrator will be based at the central trial office at the Lothian site (Royal Infirmary of Edinburgh). The Chief Investigator will be responsible for the general running of the trial, supported by the Trial Manager and Trial Administrator.
- The Trial Manager will liaise with the Co-Investigators, Principal Investigators and study teams at each site. The Trial Manager will also prepare drafts of reports to the ethics committee, sponsor and the funder in collaboration with the Chief Investigator.
- The central trial team will provide:

  • Clear communication: they will plan, arrange and manage project meetings; provide frequent status reports; act as central point-of-contact for clients, internal teams, and site staff, responding rapidly and comprehensively to requests.

  • Prepare project plans with detailed timelines.

  • Anticipate and address issues that may affect the achievement of study objective.

  • Oversee the performance of all teams, services, and technologies affecting the project.

  • Monitor contract fulfilment and compliance with the protocol and standard operating procedures.

  • Maintain and archive all Trial Master File project documentation.

• Assist the trial sites by preparing trial files for the teams to maintain locally

• Be responsible for robust planning and ensuring that, as far as possible, the team stays within the budget.

• The Trial Manager and Trial Administrator will support each site with trial-related issues.

- The central trial team will be supported by CHaRT, University of Aberdeen, Clinical Trials Unit (CTU) who will provide additional expertise and guidance, and will provide statistical expertise and programming, and quality assurance throughout the trial.
- Statistical analysis. See table below for responsibilities.

Task	**Person Responsible**	**Supervision**
Receipt of individual datasets	Meta-analyst / modeller (Edinburgh)	John Norrie
Creation of prognostic model	Meta-analyst / modeller (Edinburgh) Aberdeen statistician	Richard Riley John Norrie
Build validation model at 8 sites, 1600 patients	Aberdeen statistician	Richard Riley John Norrie
Refine prognostic model (allow site specific intercepts)	Aberdeen statistician	Richard Riley John Norrie
Final HTA Report – monograph	Aberdeen statistician	John Norrie (Richard Riley)

- Shennan, Mol and Khalil responsible for provision of data sets for IPD meta-analysis
- Boyd overall responsibility for the design, analysis and reporting of health economic outcomes.
- Lavender overall responsibility for focus groups and qualitative research components.
- The remaining members include the trial clinicians and scientists and participating centres will have responsibilities for the conduct of the trial in their hospital.

6.4 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 trial. The terms of reference of the Committee will be developed separately. Members of the TSC/DMC will consist of experts and two patient representatives. The names and contact details of the TSC/DMC are detailed in Appendix 3.

6.5 INSPECTION OF RECORDS

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

6.6 STUDY MONITORING AND RISK ASSESSMENT

The level of monitoring required for this study will be assessed during ACCORD Sponsorship review. Where deemed necessary a monitoring plan will be developed and monitoring will be conducted in accordance with this plan by an ACCORD Clinical Trials Monitor or designee. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties will be performed if deemed necessary by the co-sponsors.

Wherever possible study start-up will be completed remotely prior to recruitment commencing. Teams will be required to provide evidence of training and local approvals to the project team. Ongoing monitoring will be performed remotely during recruitment to verify eligibility, consent and trial data quality. At the end of the trial and prior to closure each site will be required to complete a checklist and provide confirmation to the project team that the local site file is complete.

7 GOOD CLINICAL PRACTICE

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP).

7.1 ETHICAL CONDUCT

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

7.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

INFORMED CONSENT

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

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

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

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

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

STUDY SITE STAFF

The Investigator must be familiar with the fetal fibronectin test procedure, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the fetal fibronectin test,

protocol and their trial related duties. An eLearning package will be developed to assist with on-site staff training. It will include sponsor requirements for safety reporting and protocol training. All staff will be expected to complete the training prior to the site initiation visit and the certificate provided following completion should be added to the ISF. Any new staff will also be required to undertake the study specific training.

Participants will be approached and recruited by staff delegated by the investigator who will obtain informed consent. The investigator/delegated physician must undertake a review of eligibility and confirm suitability prior to randomisation. The fetal fibronectin test will only be done by qualified and trained staff. Trial obstetricians will be responsible for the women whilst participating and for obtaining information until study closure.

DATA RECORDING

The Principal Investigator is responsible for the quality of the data recorded in the eCRF at each Investigator Site. The eCRF manual created by CHaRT identifies which source data correspond to eCRF data and states which data are recorded directly into the eCRF.

INVESTIGATOR DOCUMENTATION

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the trial office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- Evidence of training for cervical length measurements for all staff delegated for this study task.

The Trial Office will ensure all other documents required by GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available for the local ISFs.

GCP TRAINING

A GCP Certificate should be provided at the start of the trial, if available, for all staff detailed on the delegation log. Although GCP is not a requirement for a non-CTIMP study it is preferred that this is undertaken by the investigator and delegated team members prior to, or immediately after, the start of the study. GCP should be updated

as per local requirements; when updates are undertaken a copy of the certificate should be provided to the trial manager.

CONFIDENTIALITY

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

DATA PROTECTION

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

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

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

8 STUDY CONDUCT RESPONSIBILITIES

8.1 PROTOCOL AMENDMENTS

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

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

8.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 24 hours of becoming aware of the violation.

8.3 SERIOUS BREACH REQUIREMENTS

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

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

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

8.4 STUDY RECORD RETENTION

This is a study involving pregnant women and research records should be retained according to NHS Guidelines for the retention of documentation involving pregnant women. All medical records will be retained for at least 25 years, where possible, after publication of the final study report. Guidelines on retention of other research related documents are continually under review. We plan to retain all documents for 5 years and then review according to current guidance at that time.

8.5 END OF STUDY

The end of study is defined as the last participant's last visit.

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

The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform

participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

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

8.6 INSURANCE AND INDEMNITY

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

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

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

9 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

9.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the Co-Investigators and any others who fulfil the criteria for Authorship as determined by the Chief Investigator. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with GCP guidelines.

For reports which specifically arise from the trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to the named individual(s) for the QUIDS Study Group.

9.2 PUBLICATION

We intend to maintain interest in the study by publication of QUIDS newsletters at intervals for staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final QUIDS Newsletter to all involved in the trial.

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

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

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the Project Management Group.

9.3 PEER REVIEW

The study was extensively peer reviewed as part of the process of gaining grant funding.

9.4 POTENTIAL SATELLITE STUDIES

It is recognised, that the value of the trial may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advanced with the Project Management Group. REC approval will be sought for any new proposal, if appropriate.

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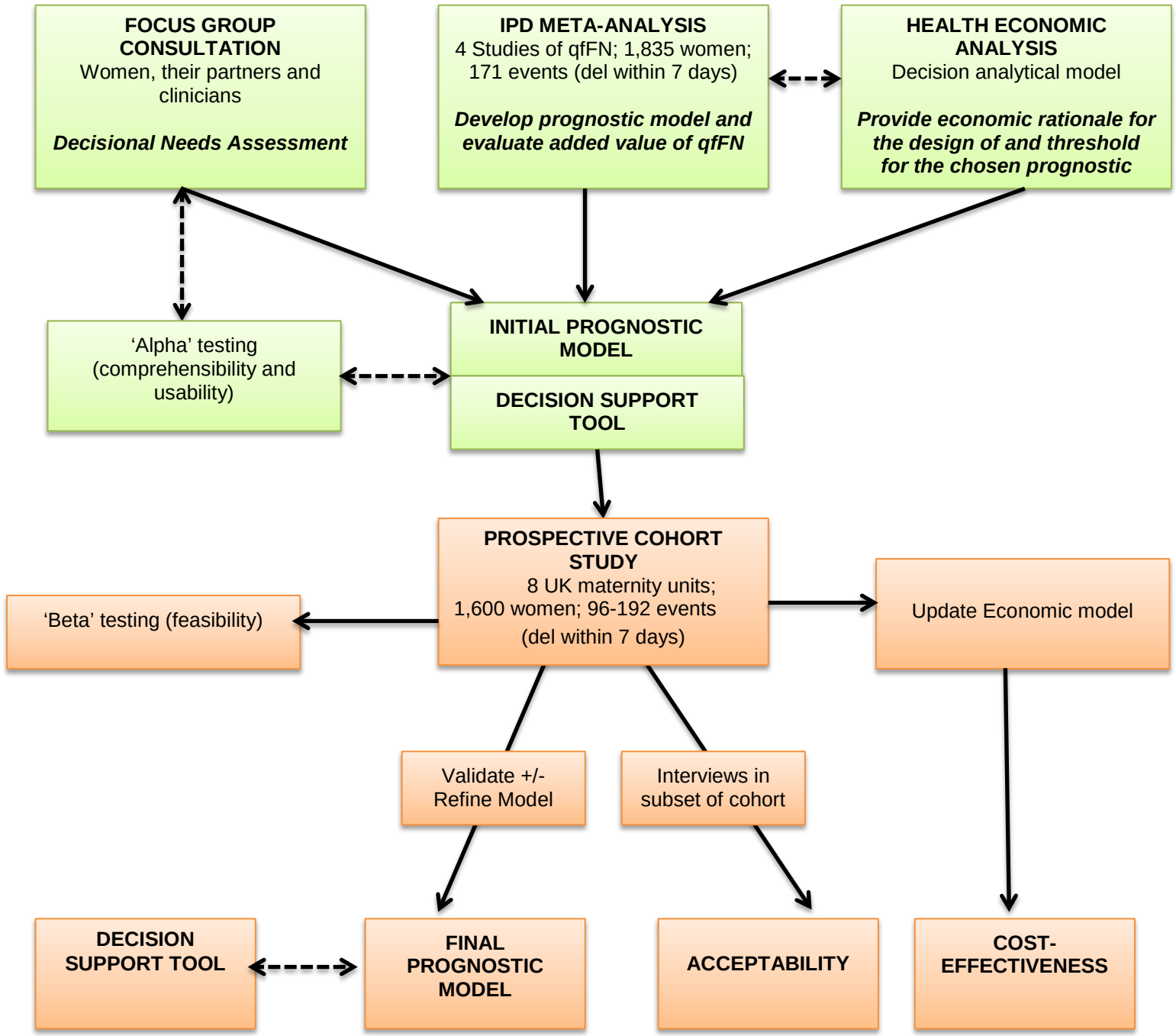
10.1 APPENDIX 1: FLOWCHART


FOCUS GROUP CONSULTATION
Women, their partners and clinicians
Decisional Needs Assessment
IPD META-ANALYSIS
4 Studies of qfFN; 1,835 women; 171 events (del within 7 days)
Develop prognostic model and evaluate added value of qfFN
HEALTH ECONOMIC ANALYSIS
Decision analytical model
Provide economic rationale for the design of and threshold for the chosen prognostic
'Alpha' testing (comprehensibility and usability)
INITIAL PROGNOSTIC MODEL
DECISION SUPPORT TOOL
PROSPECTIVE COHORT STUDY
8 UK maternity units; 1,600 women; 96-192 events (del within 7 days)
'Beta' testing (feasibility)
Update Economic model
Validate +/- Refine Model
Interviews in subset of cohort
DECISION SUPPORT TOOL
FINAL PROGNOSTIC MODEL
ACCEPTABILITY
COST-EFFECTIVENESS

10.2 Appendix 3: QUIDS Qualitative Protocol

10.3 Appendix 3: Details of TSC/DMEC

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